



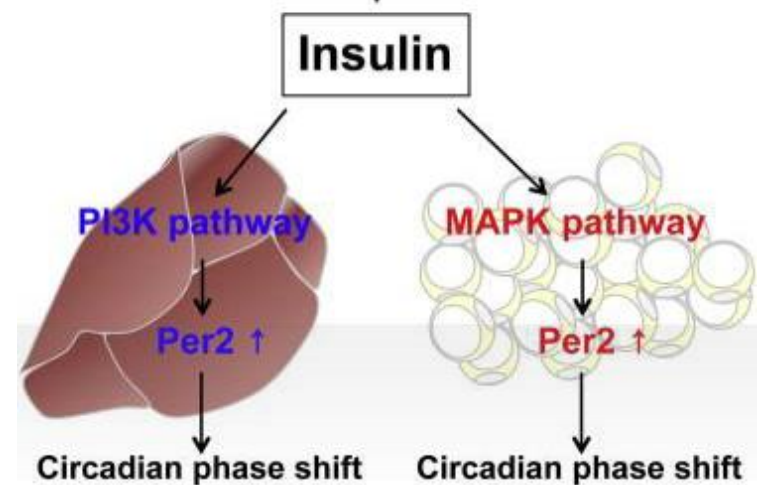
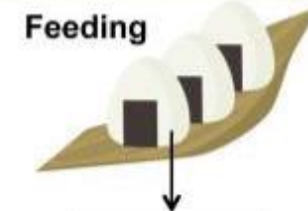
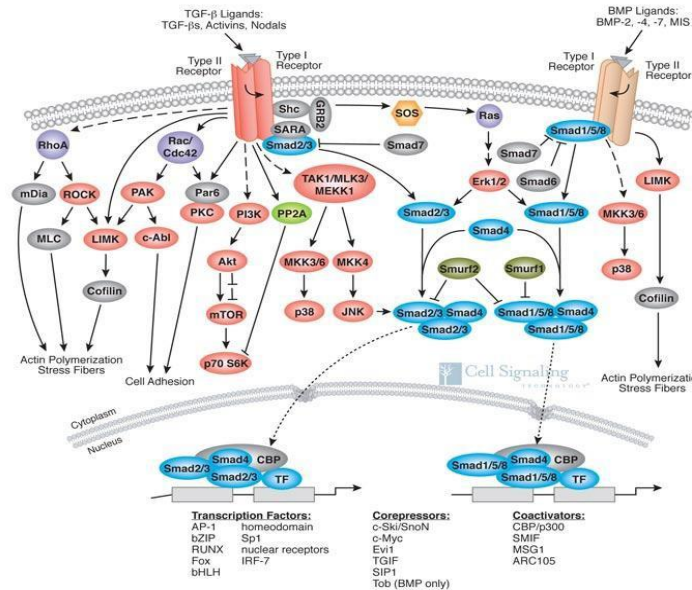
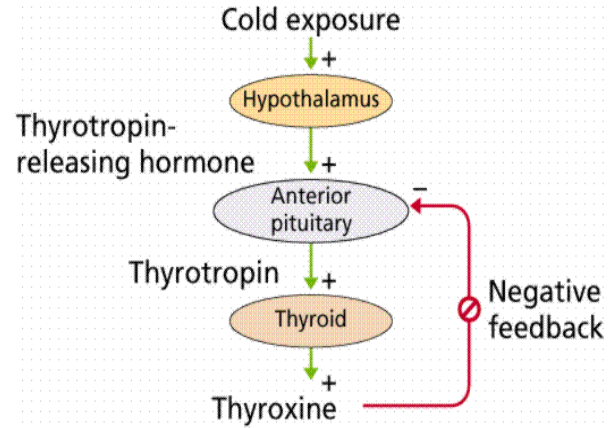
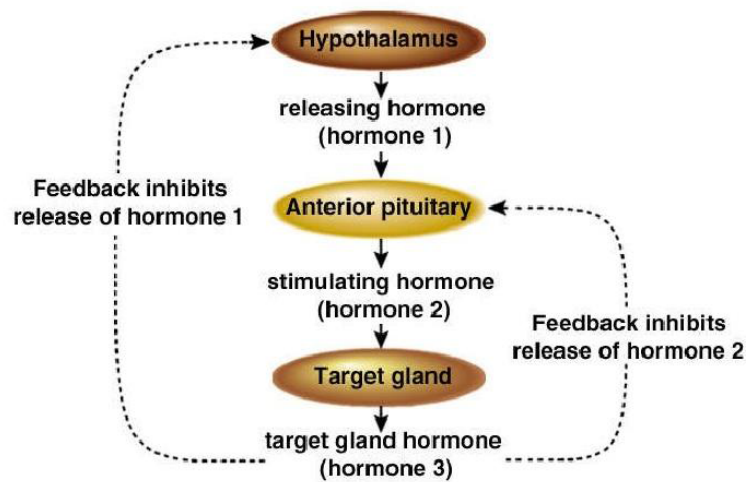
Nafith Abu Tarboush DDS, MSc, PhD

natarboush@ju.edu.jo www.facebook.com/natarboush

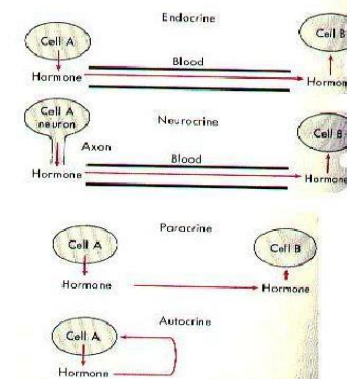
Integration of Metabolism: hormones & Cellular Signaling

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Endocrine Glands



Types of cell-to-cell signaling



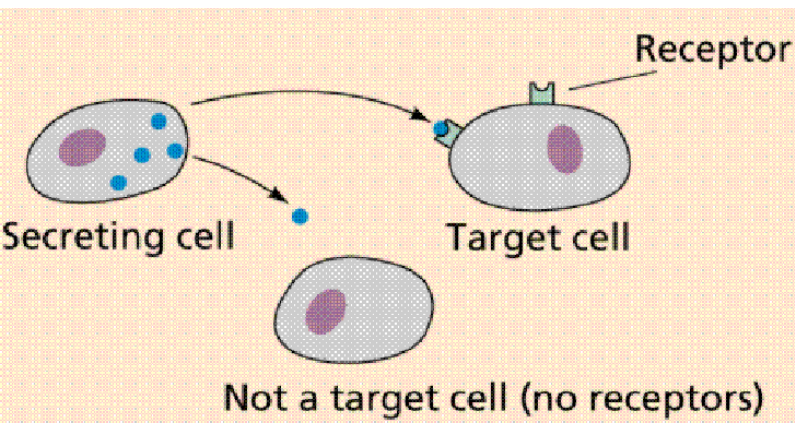
Endocrine Hormones: travel via bloodstream to target cells

Neurocrine hormones: released from nerve terminals

Paracrine hormones: act on adjacent cells

Autocrine hormones: Released and act on the cell that secreted them.

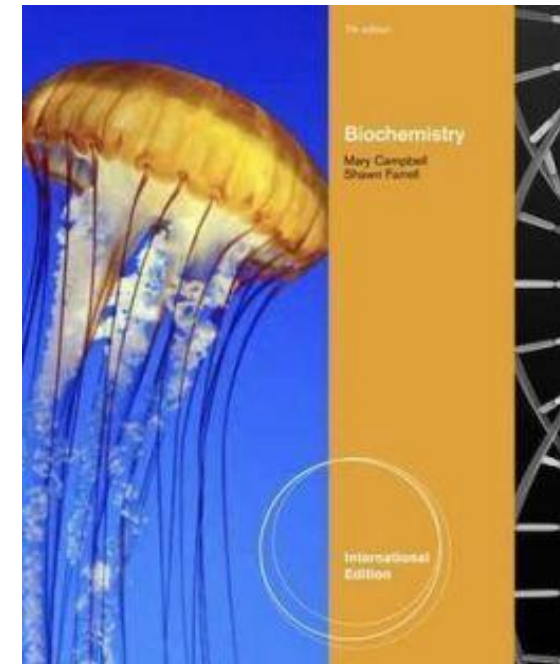
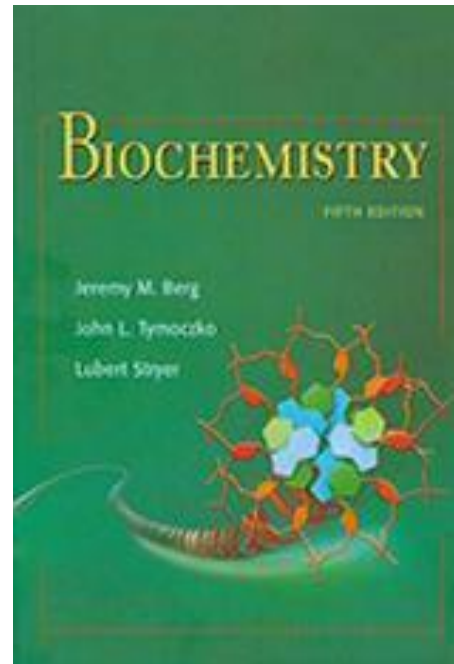
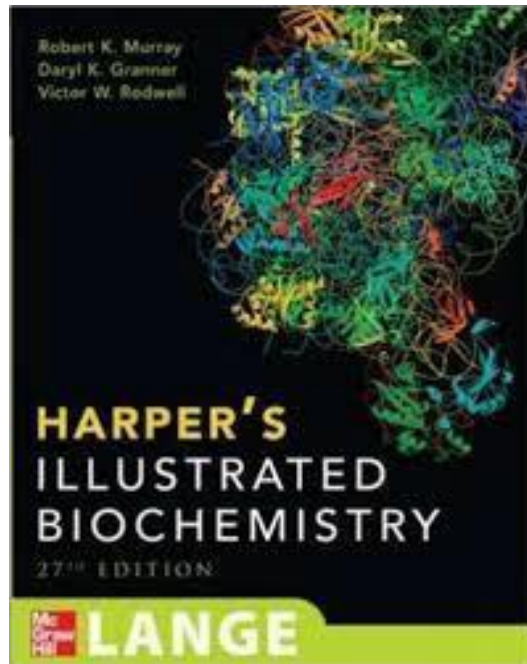
Intracrine Hormones: act within the cell that produces them.





Resources for the lectures

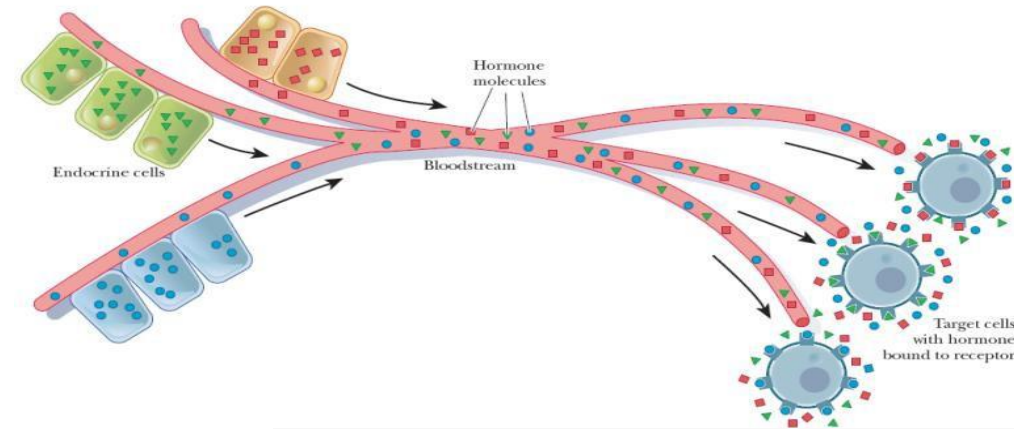
- Harper's Illustrated Biochemistry
- Stryer's Biochemistry
- Campbell's Biochemistry





Hormones: The Remote Controllers

- **What are hormones?** Organic, blood, low amounts, source & target
- **Functions:**
 - They help maintain homeostasis
 - Mediate responses to external stimuli
 - Play roles in growth and development
- **Classes:**
 - Endocrine hormones
 - Distance; stability; & concentration
 - Paracrine hormones
 - Autocrine hormones

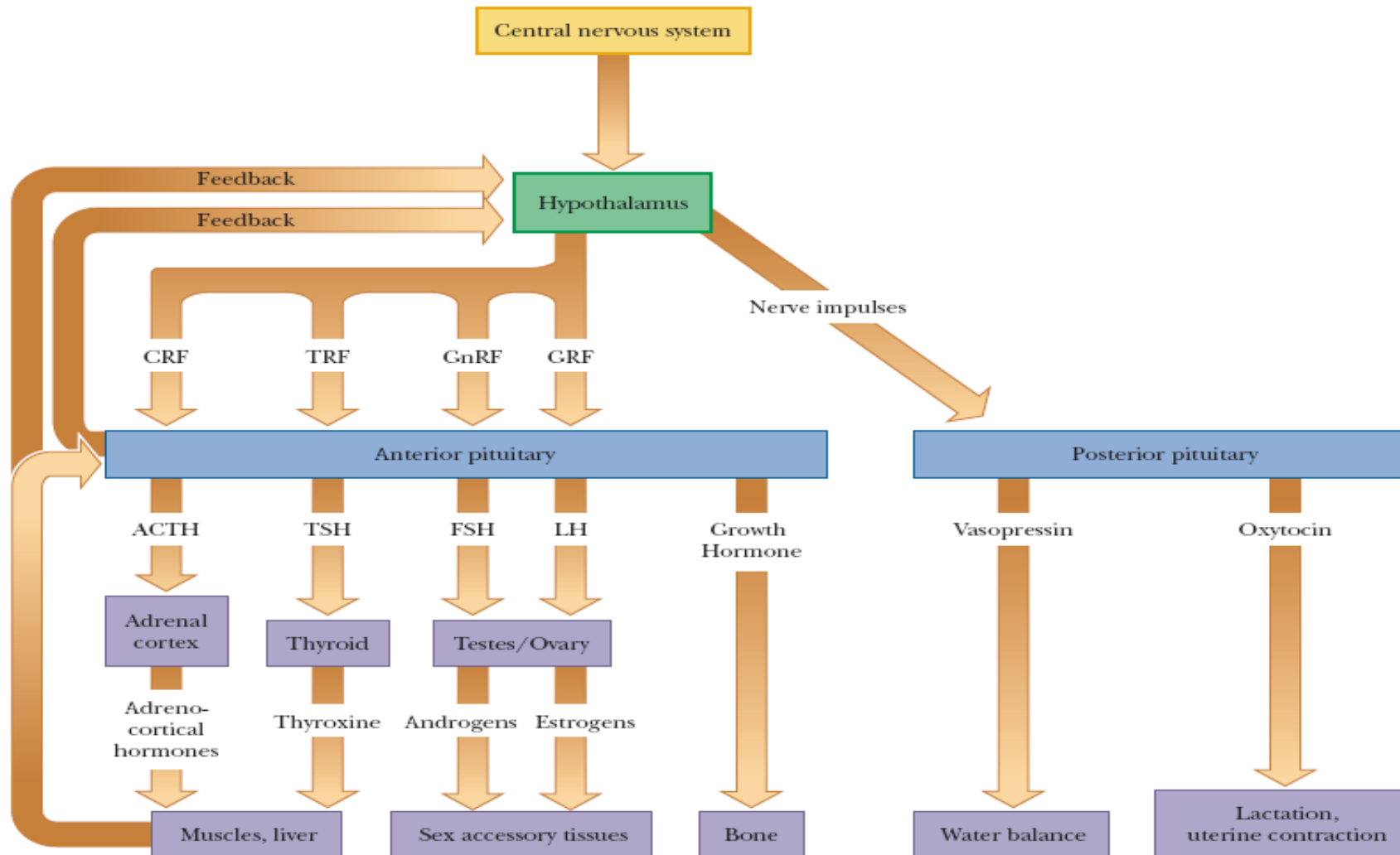


Signaling by Secreted Molecules



Nervous vs./& Endocrine

Two systems act individually and together in regulating the human physiology





The Target Cell Concept

- The definition of a target has been expanded to include any cell in which the hormone (ligand) binds to its receptor, regardless of the action
- **200 types** of differentiated cells in humans
- Only a few produce hormones! (**<50 known hormones**)
- All of **75 trillion cells** in a human are targets to one or more
- One hormone → several cell types
- One cell type → several hormones
- One hormone → several effects



The Target Cell Concept

- Several factors determine the response of a target cell to a hormone:

Factors affect the concentration of the hormone at the target cell

- ✓ The rate of synthesis and secretion of the hormone
- ✓ The proximity of the target cell to the hormone source (dilution)
- ✓ The K_d of the hormone – receptor complex
- ✓ The rate of conversion of inactive form to the fully active form
- ✓ The rate of clearance from the plasma



The Target Cell Concept

- Several factors determine the response of a target cell to a hormone:

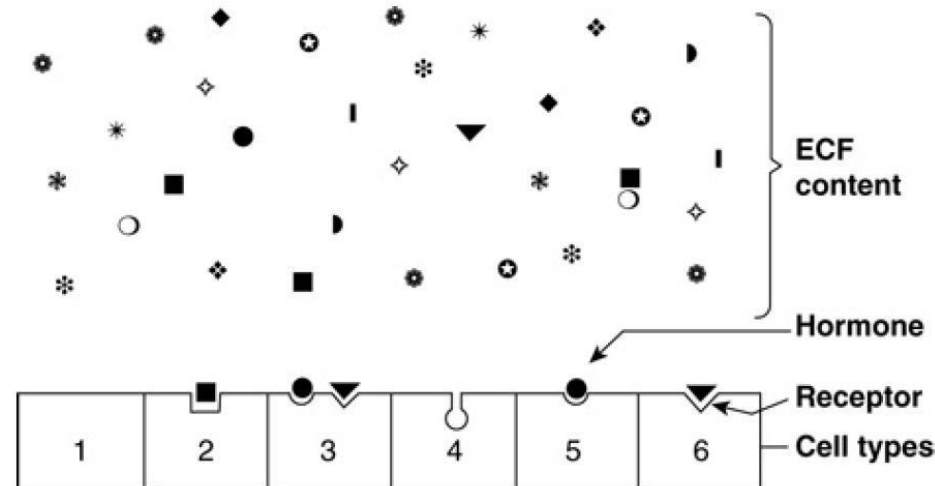
Factors affecting the target cell response	
✓	The number, relative activity, and state of occupancy of receptors
✓	The metabolism (activation / inactivation) of the hormone in the target cell
✓	The presence of factors within target cell necessary for the response
✓	Up- or down-regulation of the receptors upon interaction with ligand
✓	Post-receptor desensitization of the cell



Receptors Discriminate Precisely

- **Major challenge:**

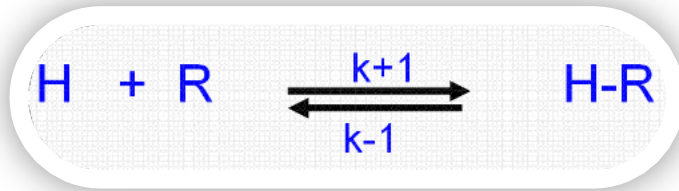
- Atto- to nano-molar range (10^{-15} to 10^{-9} mol/L) vs. Structurally similar molecules (sterols, amino acids, peptides, and proteins): micro- to milli-molar (10^{-6} to 10^{-3} mol/L) range



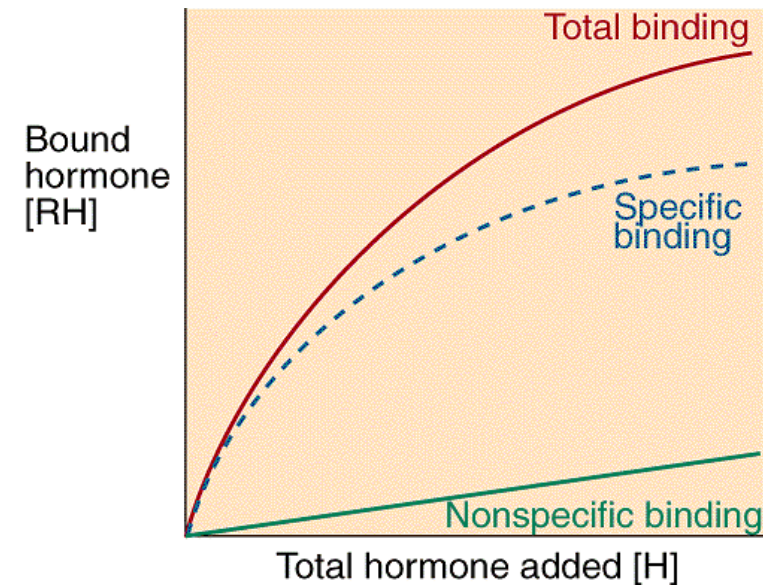


Accordingly; Hormone-Receptor Interactions

- Should be specific: displaceable by agonist or antagonist
- Should be saturable
- Should occur within the concentration range provided



- Dissociation constant K_d
- $K_d = \{[\text{H}] \times [\text{R}]\} / [\text{H-R}]$

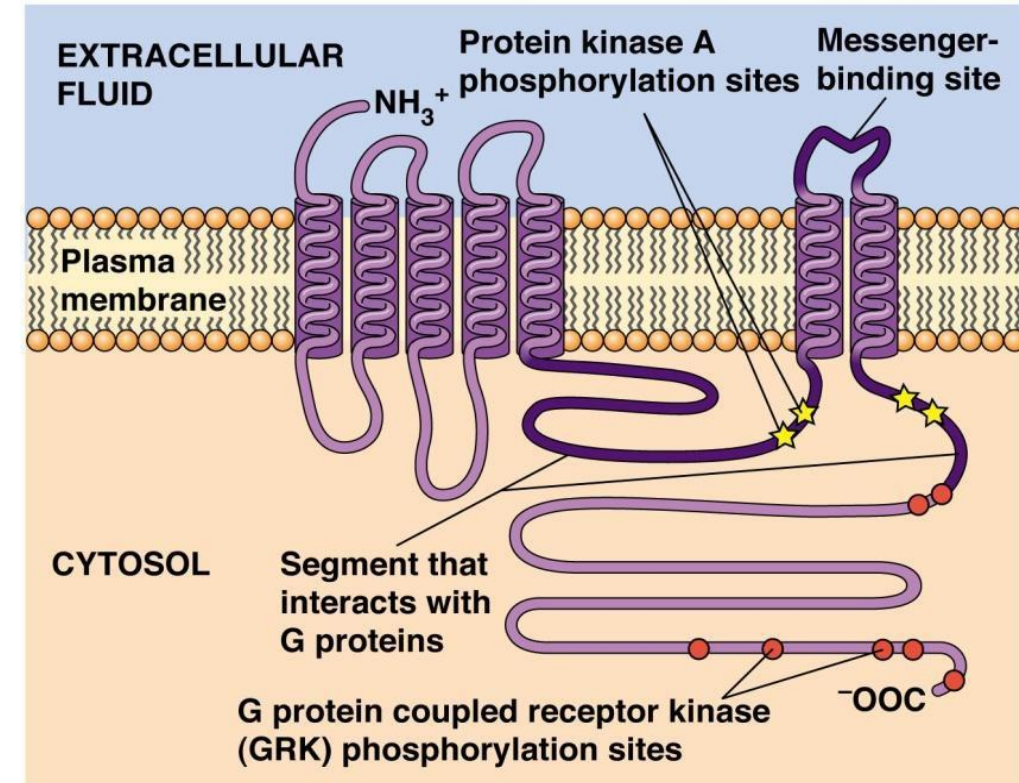


- 20 X dissociation constant is enough to saturate the receptor
- K_d values for many hormone range from 10^{-9} to 10^{-11} M



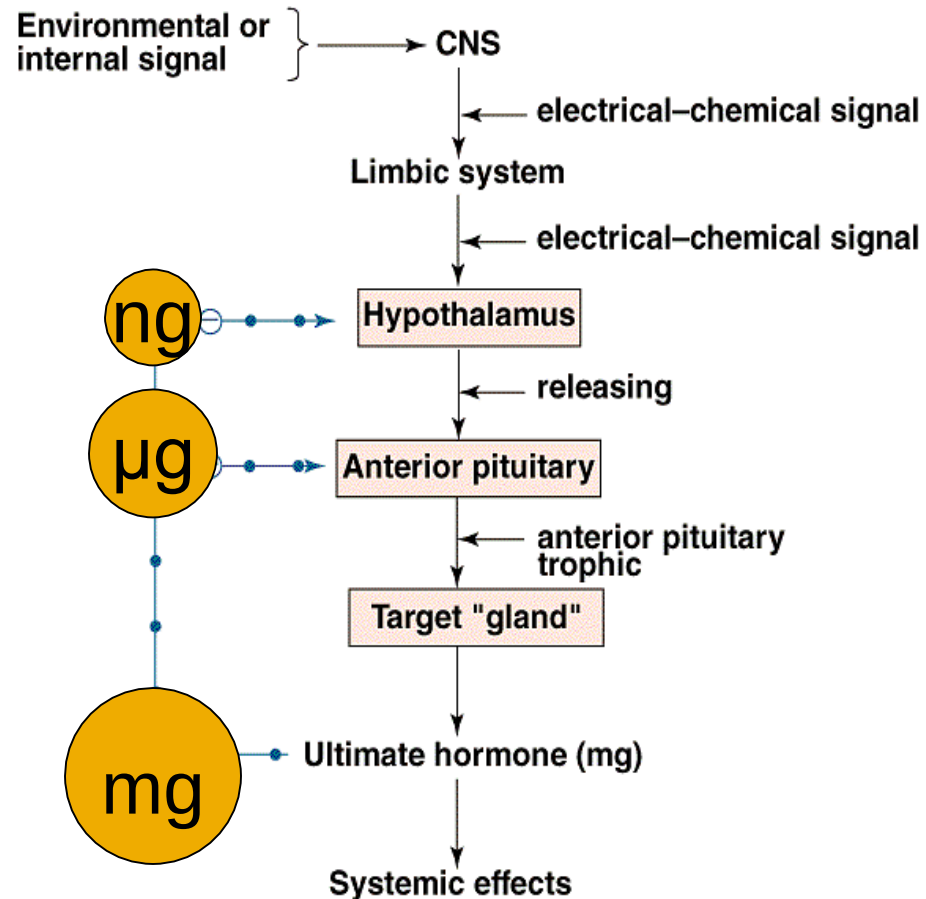
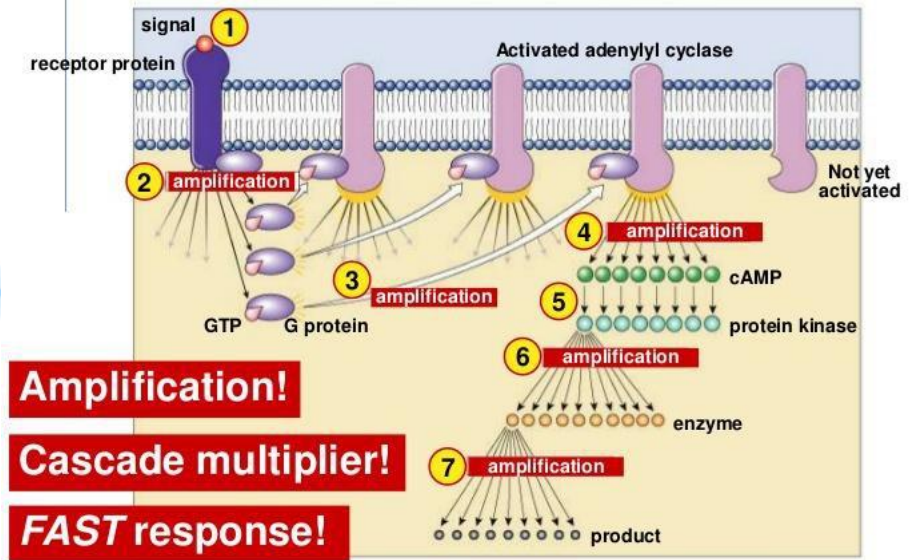
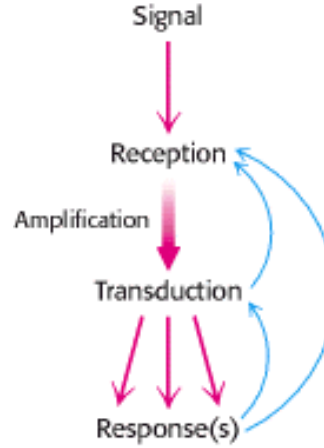
Receptor domains

- All receptors have at least two functional domains:
 - **Recognition domain**
 - **Coupling or signal transduction domain**
- Coupling occurs in two general ways:
 - Changing the activity of an enzyme (Polypeptide & catecholamines, plasma membrane)
 - Direct (steroids, retinoids, and thyroid hormones, intracellular)
- Steroid, thyroid, and retinoid hormone receptors:
 - Hormone binding site ; DNA binding site; co-regulator proteins binding site, cellular trafficking proteins binding site
- Receptor–effector coupling provides the first step in amplification





Signal Amplification



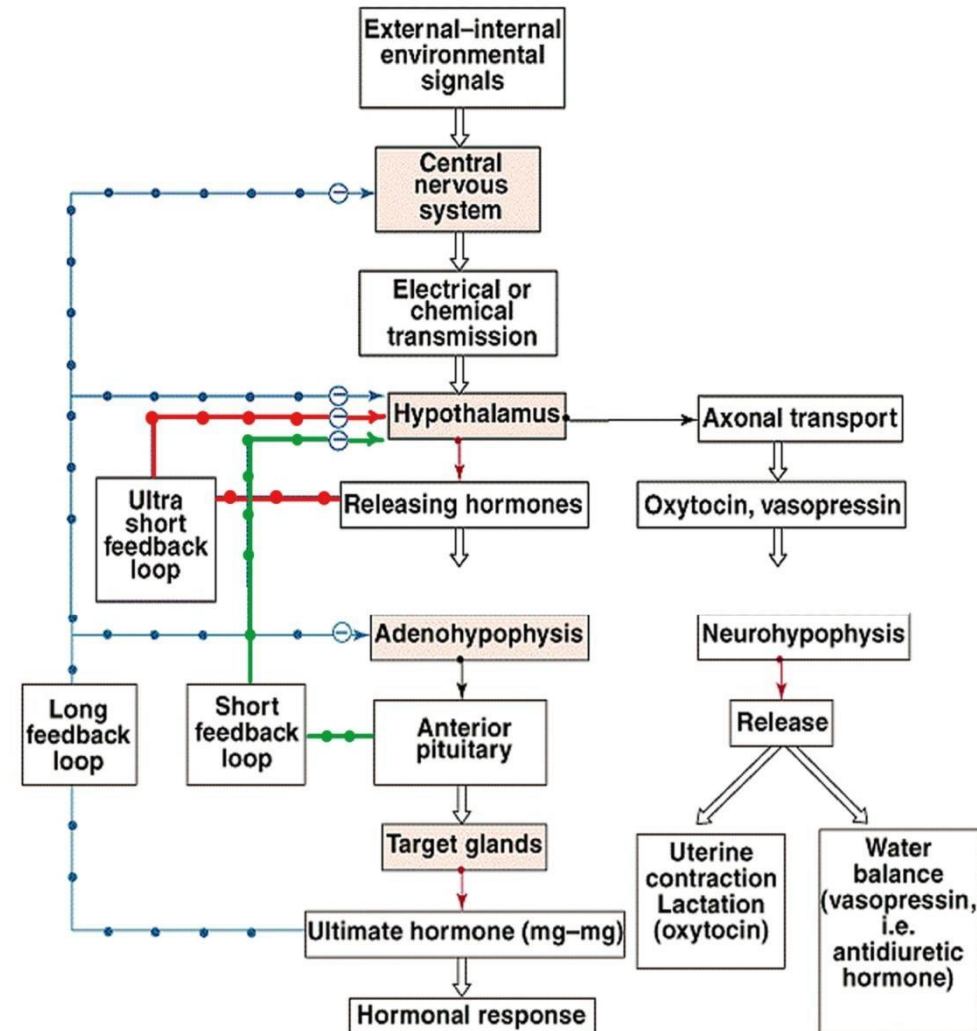
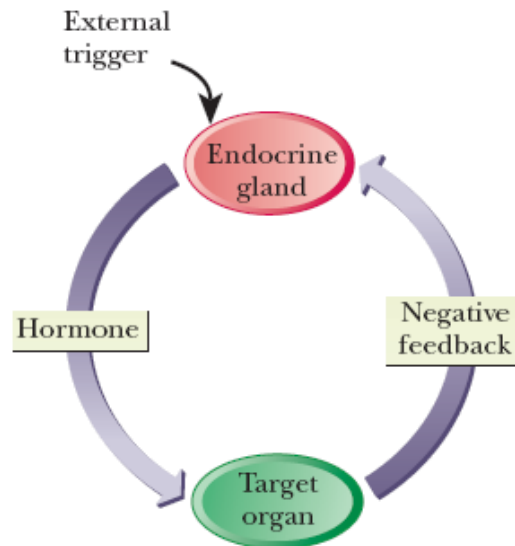
(a) Signaling pathway	(b) Number of molecules activated
RECEPTION Binding of epinephrine to G protein-linked receptor	1 molecule
TRANSDUCTION Inactive G protein → Active G protein	10^2 molecules
Inactive adenylyl cyclase → Active adenylyl cyclase	10^2 molecules
ATP → Cyclic AMP	10^4 molecules
Inactive protein kinase A → Active protein kinase A	10^4 molecules
Inactive phosphorylase kinase → Active phosphorylase kinase	10^5 molecules
Inactive glycogen phosphorylase → Active glycogen phosphorylase	10^6 molecules
RESPONSE Glycogen → Glucose-1-phosphate	10^8 molecules



How the release is controlled?

■ Feedback inhibition

- Ultrashort loop
- Short loop
- Long loop





Classification of Hormones

Chemical Structure

- Chemical composition; solubility; location of receptors; nature of the signal used to mediate hormonal action
- ✓ **Polypeptides:** Pituitary hormones; Hypothalamic releasing hormones; Insulin, Growth factors...
- ✓ **Amino acid derivatives:** Adrenalin, Thyroid hormones
- ✓ **Steroids**



Classification of Hormones

Mechanism of Action

- Hormones that bind to intracellular receptors

- Steroids
- Thyroid hormones
- Calcitriol, retinoic acid

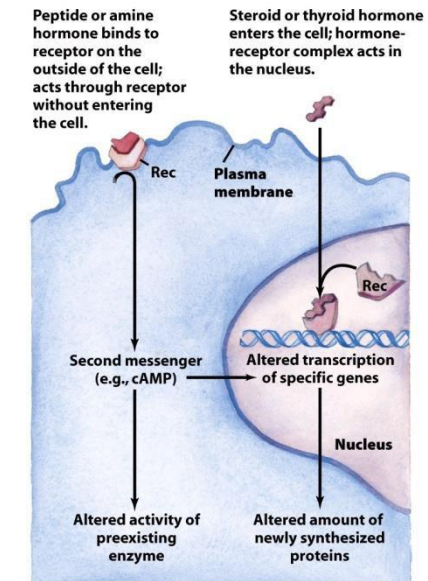
Long Half- life
(hrs-days)

Transport
proteins

KOSH
EDUTECH PVT LTD



compilation of knowledge





Classification of Hormones

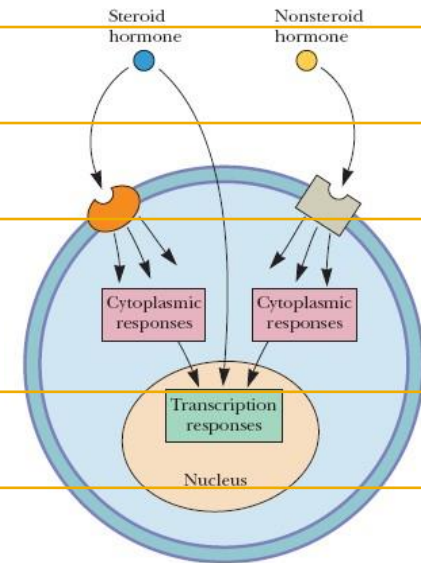
Mechanism of Action

- Hormones that bind to cell surface receptors
 - (According to second messenger):
 - cAMP (β adrenergic factor, glucagon, ACTH)
 - cGMP (atrial natriuretic factor, Nitric oxide)
 - Calcium or phosphatidyl inositol (oxytocin, TRH)
 - Kinase or phosphatase cascade (insulin, GH)



General Features of Hormone Classes

	Group I	Group II
Types	Steroids, iodothyronines, calcitriol, retinoids	Polypeptides, proteins, glycoproteins, catecholamines
Action	Slow	Fast
Solubility	Lipophilic	Hydrophilic
Transport proteins	Yes	No
Plasma $t_{1/2}$	Long (hrs - days)	Short (minutes)
Receptor	Intracellular	Plasma membrane
Mediator	Receptor-hormone complex	cAMP, cGMP, Ca^{2+} , kinase cascades, metabolites of phosphoinositols





Hormones Classes

Steroid hormones

- A. Sex hormones - are divided into 3 groups
 - 1. Male sex hormones or Androgens
 - 2. Female sex hormones or Estrogens
 - 3. Pregnancy hormones or Progestines

- B. Hormones of Adrenal Cortex
 - 1. Mineralocorticoids: aldosterone. ...
 - 2. Glucocorticoids: cortisol. ...
 - 3. Adrenal androgens: male sex hormones mainly dehydroepiandrosterone (DHEA) and testosterone



Hormones Classes

Non steroid hormones

A. Peptide and protein hormones

- ✓ All hypothalamic, pituitary, digestive hormones
- ❖ All pituitary hormones are made from single polypeptide chains **EXCEPT**: TSH; FSH; LH (homodimers) – glycoproteins (≈ 25 kDa)

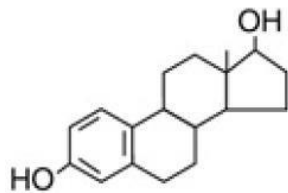
B. Amino acid derivatives

- ✓ Amines - derived from tyrosine or tryptophan: TH, dopamine, epinephrine, melatonin

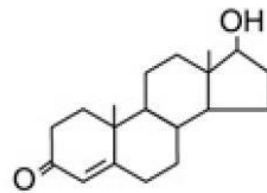


- Lipid – soluble hormones:

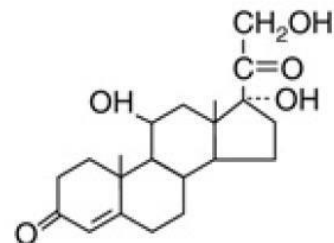
A. Cholesterol derivatives



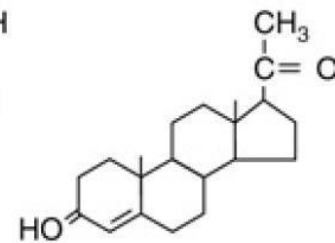
17β-Estradiol



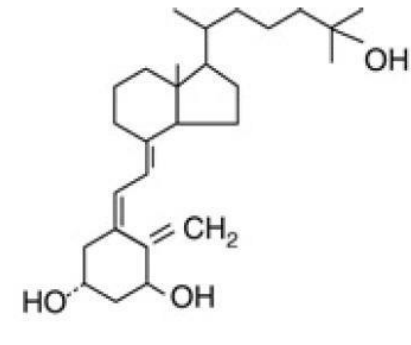
Testosterone



Cortisol



Progesterone

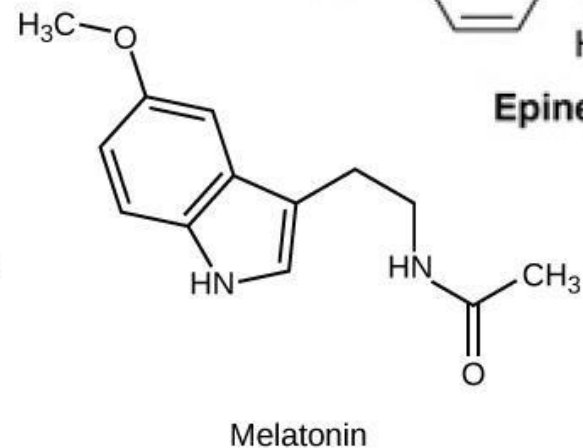
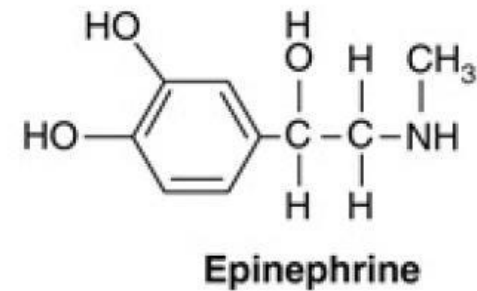
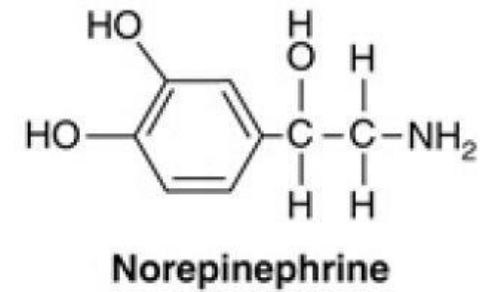
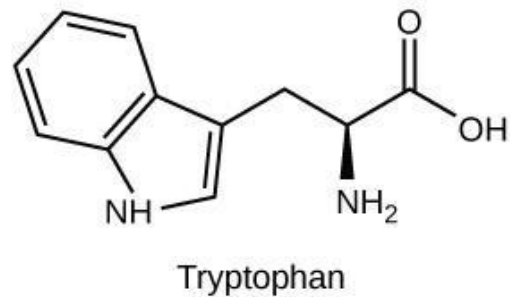
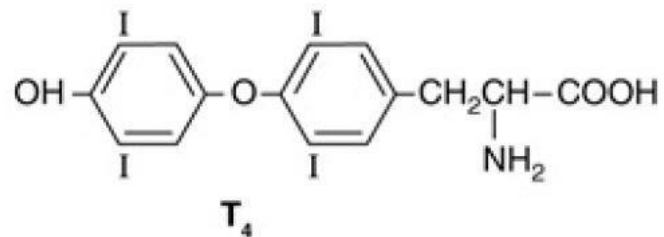
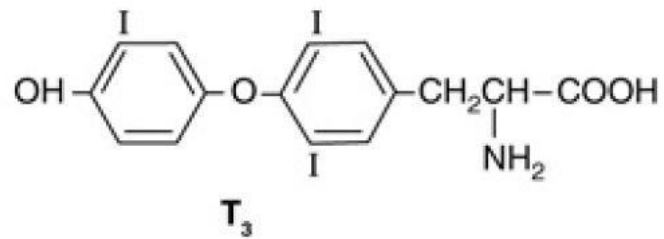


1,25(OH)₂-D₃



■ Amino Acid-Derived Hormones

Tyrosine derivatives

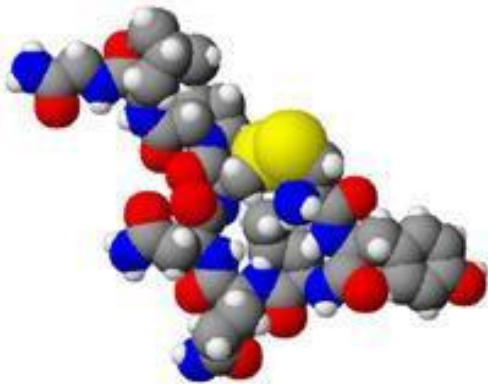




Structure of Hormones

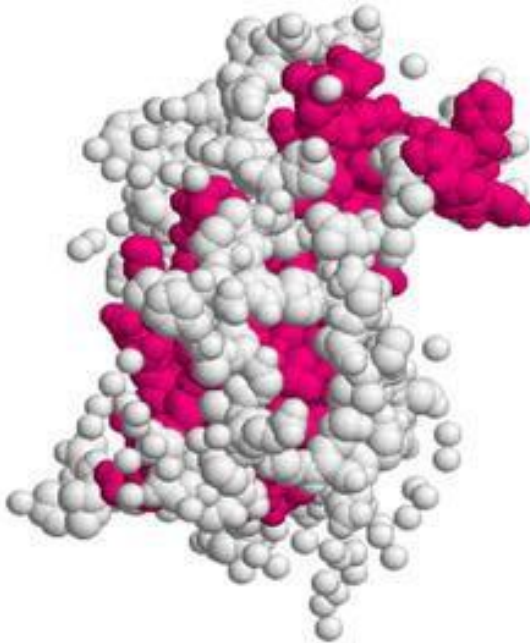
- Peptide & Protein Hormones

Oxytocin



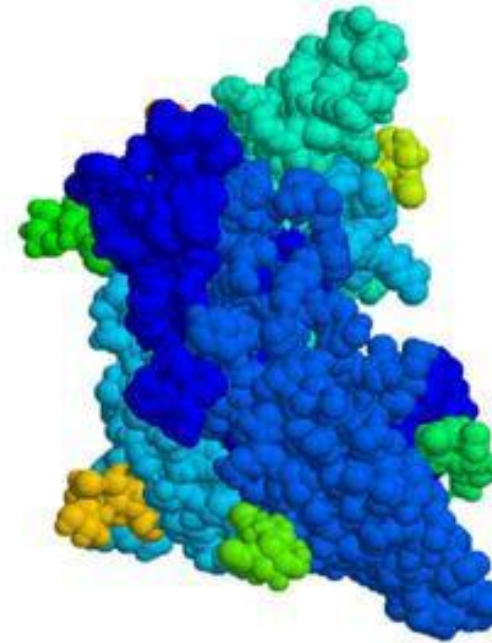
(a)

GH



(b)

FSH

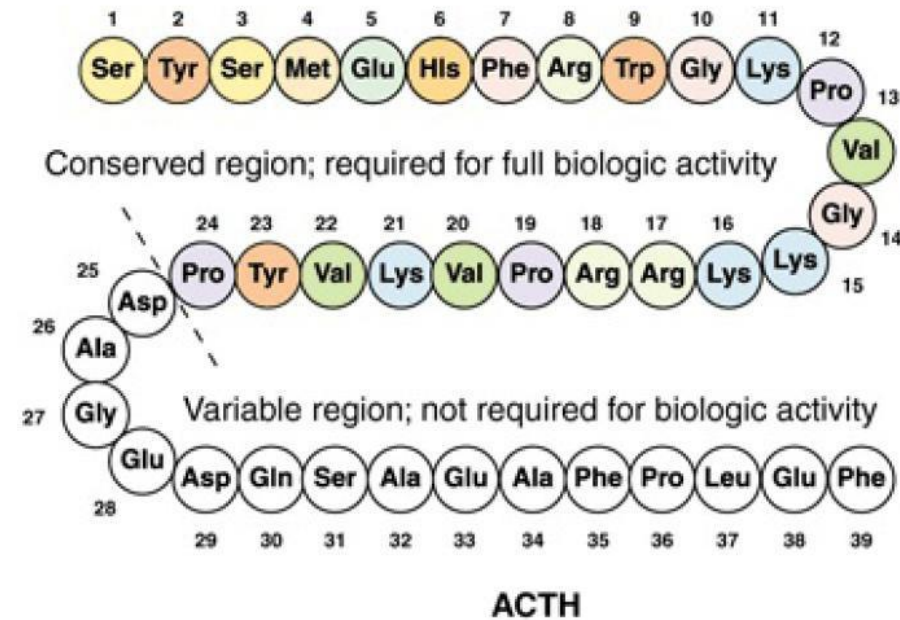
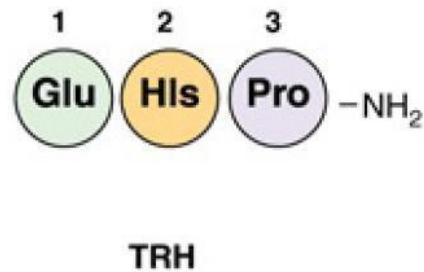


(c)



■ Peptide & Protein Hormones

C. Peptides of various sizes





Structure of Hormones

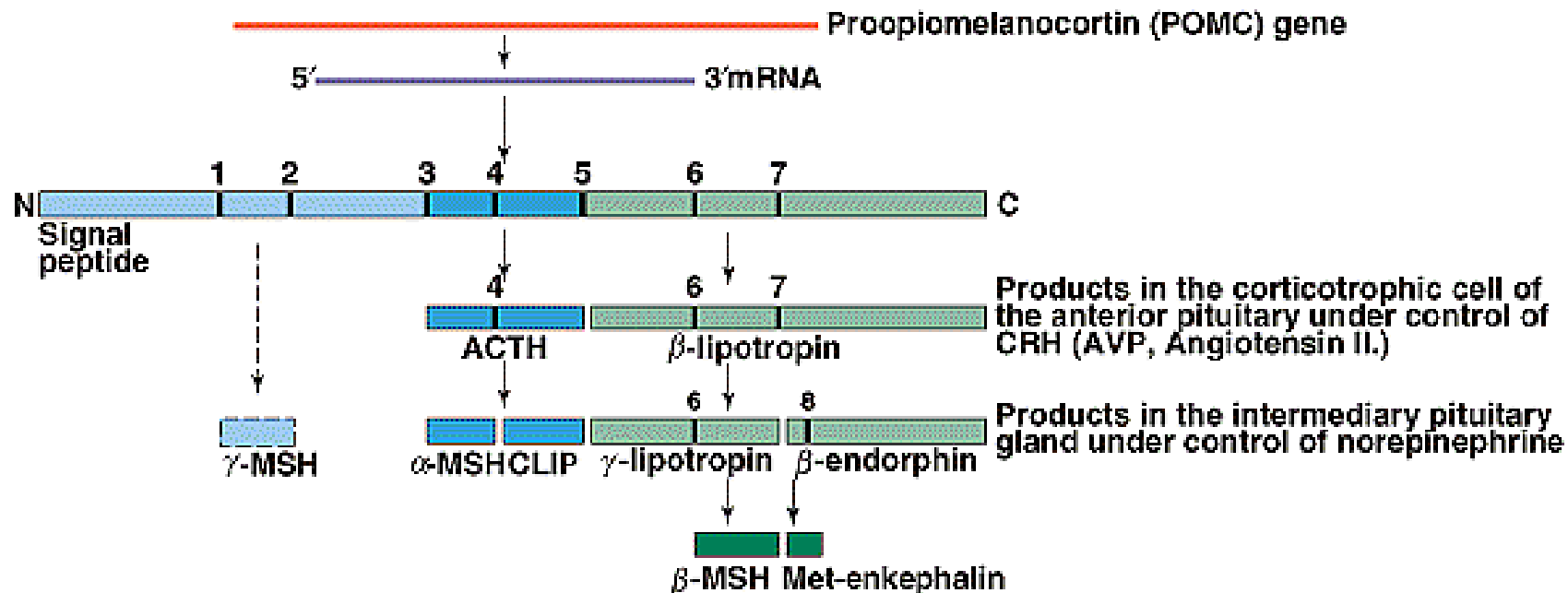
Peptide & Protein Hormones

Hormone	Structure
GHRH	44
TRH	3
GnRH	10
CRH	41
ADH	9
Vasopressin	9
Angiotensin I	10
Angiotensin II	8
Insulin	51
Glucagon	29



Synthesis of Peptide Hormones

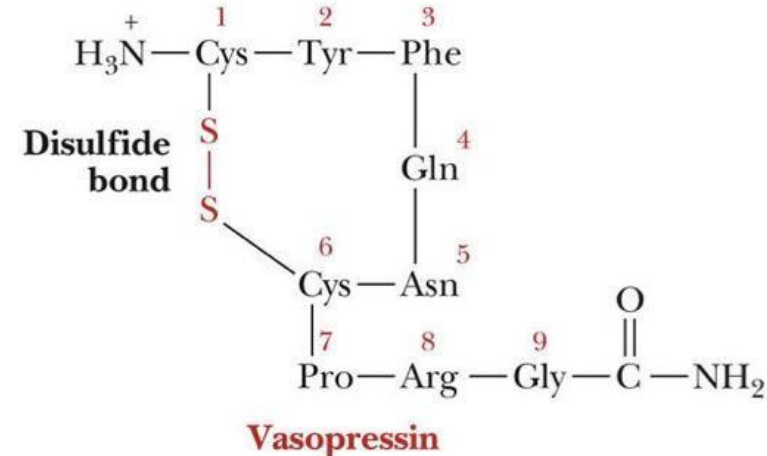
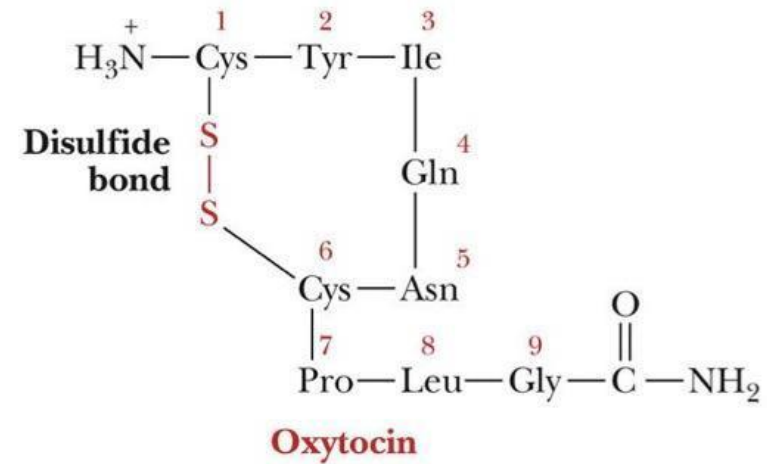
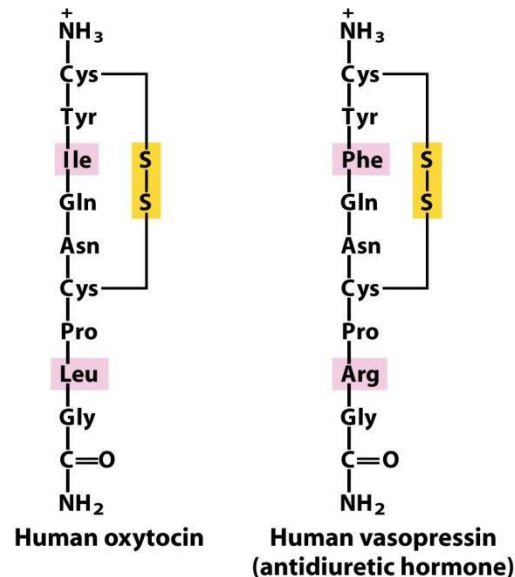
- From precursor polypeptides
 - One gene may code more than one hormone (POMC)
 - The cleavage depends on specific enzymes

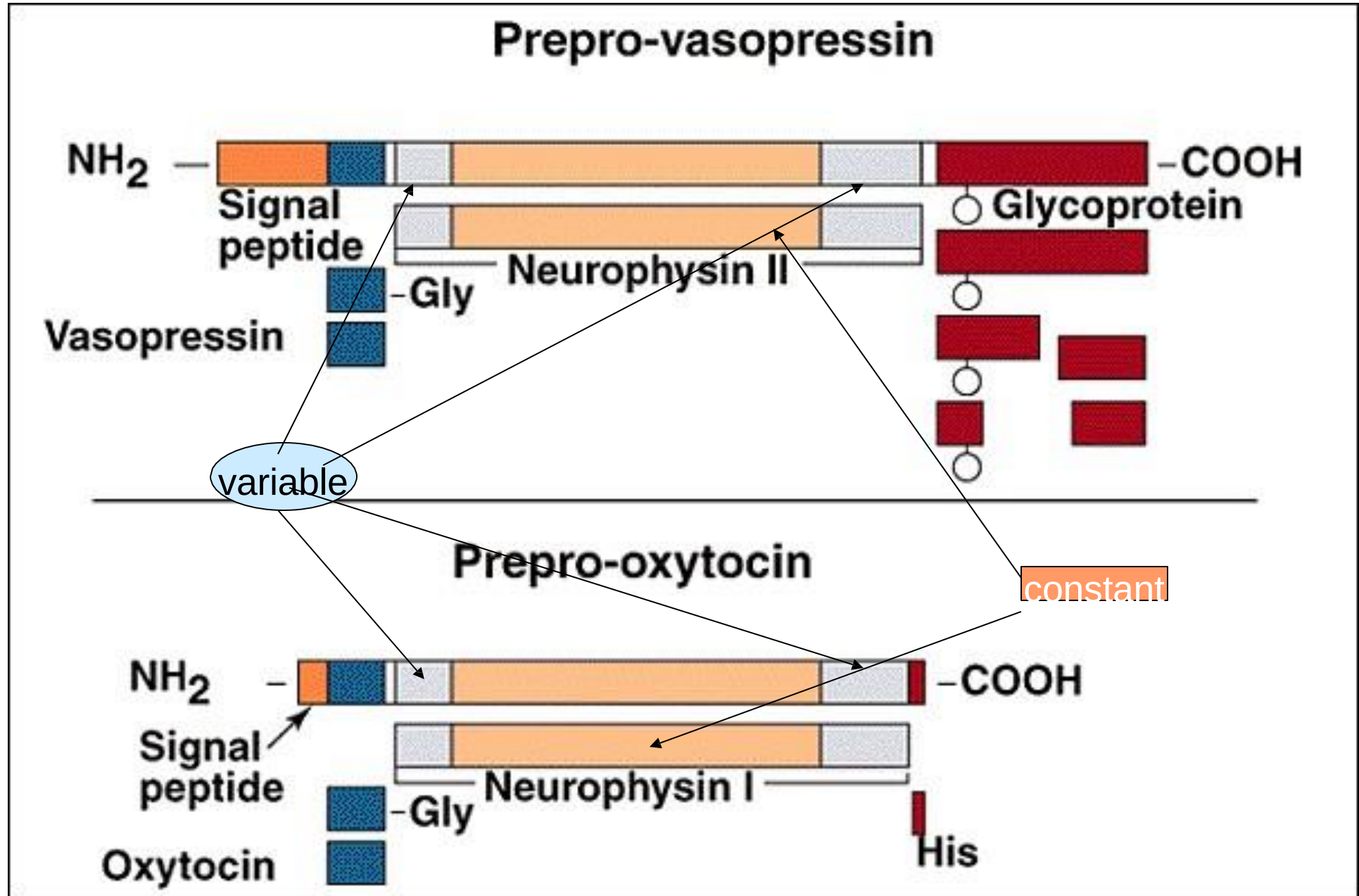




Synthesis of Peptide Hormones

- From precursor genes
 - Vasopressin and oxytocin
 - Synthesis in separate cell bodies of hypothalamic neurons



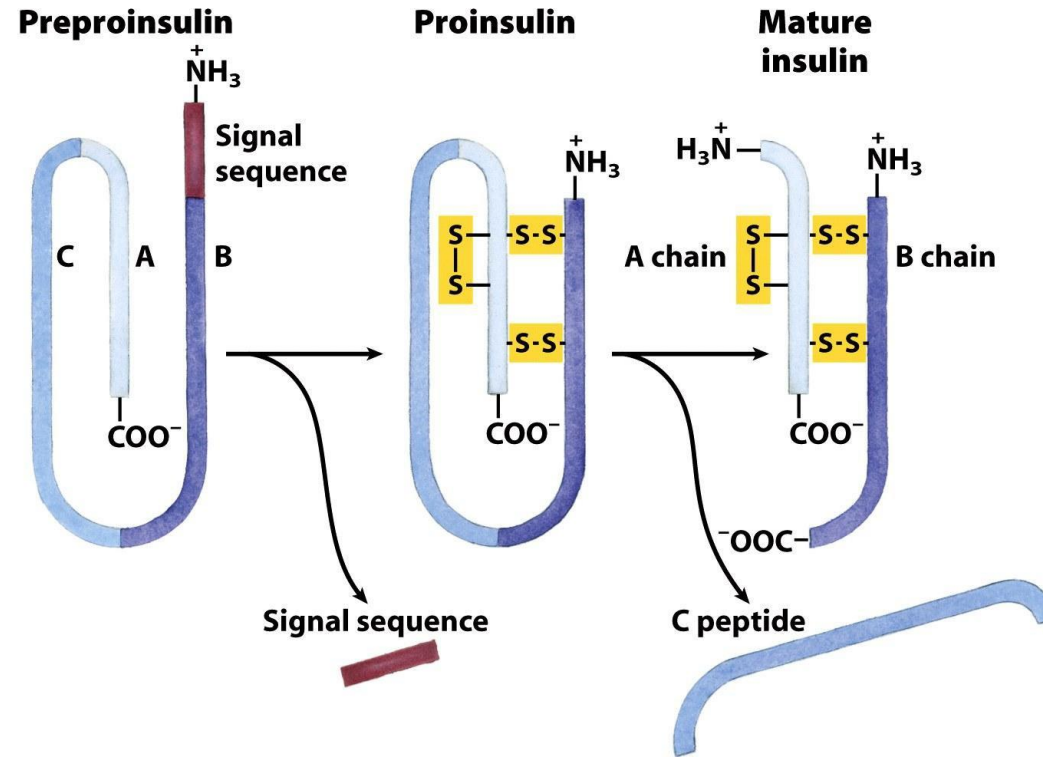
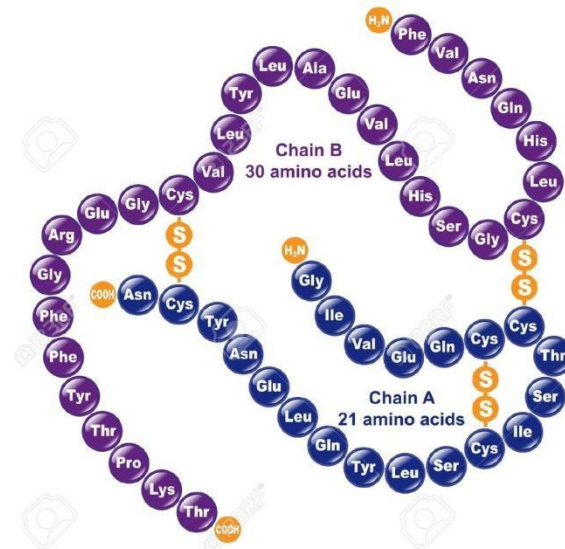




Synthesis of Peptide Hormones

- Peptide & Protein Hormones
- From Pre-pro-hormones
- A larger precursor preproinsulin
 - 23 aa signal sequence
 - 3 disulfide bonds
- Proinsulin
 - Remove the C peptide
- Mature insulin
 - A and B chains

Human Insulin





Target cells interactive effects

1. **Permissive effects** – one hormone enhances the effect of a later hormone
 - ✓ **Estrogen up-regulates progesterone receptors** in uterus
 - ✓ **Thyroid hormone increases the effect of epinephrine** on breakdown of triglycerides in adipocytes
2. **Integrative effects** – hormones produce complementary effects on different tissues
 - ✓ **PTH and calcitriol increase ECF calcium**



Target cells interactive effects

3. Synergistic effects:

- ✓ Both **FSH** and **estrogen** necessary for **normal oocyte development**
- ✓ **FSH** and **testosterone** together increase **spermatogenesis**

4. Antagonistic effects:

- ✓ **Insulin** and **glucagon**