

## Discovery of hormones

1889

Oskar Minkowski & Josef von Mering

Role of pancreas (with lipases) in fat digestion

Remove pancreas from dog

More fat in urine

Pancreas extract injection

Unsuccessful

1921

Frederick G. Banting & Charles Best

Purified extract of pancreas

Cured the symptoms of diabetes in dogs

1922

Frederick G. Banting & Charles Best

Extract was injected into Leonard Thompson

Cured the symptoms of diabetes mellitus in him.

1923

Frederick G. Banting & Macleod

Discovered insulin – chemical produced from insula or island of cells of pancreas

## *How is a hormone detected & isolated????????*

- Discovery that a physiological process in one tissue depends on the signals from other tissues.  
Eg. Insulin is produced from pancreas and affects glucose level in muscles.
- Injecting the extracts from pancreas into experimental animals and glucose level of blood/urine was quantified.
- To isolate hormone: solvent fractionation, chromatography, electrophoresis (Eg. TRH – hypothalamus from million of sheep and pigs by Schally & Guillemin)
- Determination of the structure.
- Chemical synthesis of the hormone.
- Radioimmunoassay to study hormone actions (Rosalyn Yellow & Solomon A. Berson)
- ELISA using hormone-specific antibodies.

*Need to know!!!!*

## ABBREVIATIONS

<b>ACTH</b>	Adrenocorticotrophic hormone
<b>ANF</b>	Atrial natriuretic factor
<b>cAMP</b>	Cyclic adenosine monophosphate
<b>CBG</b>	Corticosteroid-binding globulin
<b>CG</b>	Chorionic gonadotropin
<b>cGMP</b>	Cyclic guanosine monophosphate
<b>CLIP</b>	Corticotropin-like intermediate lobe peptide
<b>DBH</b>	Dopamine -hydroxylase
<b>DHEA</b>	Dehydroepiandrosterone
<b>DHT</b>	Dihydrotestosterone
<b>DIT</b>	Diiodotyrosine
<b>DOC</b>	Deoxycorticosterone
<b>EGF</b>	Epidermal growth factor
<b>FSH</b>	Follicle-stimulating hormone
<b>GH</b>	Growth hormone
<b>IGF-I</b>	Insulin-like growth factor-I
<b>LH</b>	Luteotropic hormone
<b>LPH</b>	Lipotropin
<b>MIT</b>	Monoiodotyrosine
<b>MSH</b>	Melanocyte-stimulating hormone
<b>OHSD</b>	Hydroxysteroid dehydrogenase
<b>PNMT</b>	Phenylethanolamine- <i>N</i> -methyltransferase
<b>POMC</b>	Pro-opiomelanocortin
<b>SHBG</b>	Sex hormone-binding globulin
<b>StAR</b>	Steroidogenic acute regulatory (protein)
<b>TBG</b>	Thyroxine-binding globulin
<b>TEBG</b>	Testosterone-estrogen-binding globulin
<b>TRH</b>	Thyrotropin-releasing hormone
<b>TSH</b>	Thyrotropin-stimulating hormone

# Classification of hormones

- **Depending upon chemical nature**
  - Amines or amino acid derivatives
    - Catecholamines, thyroid hormones
  - Proteins & polypeptides
    - Posterior pituitary hormones: oxytocin, vasopressin
    - Insulin, glucagon, PTH, other anterior pituitary hormones
  - Steroid hormones
    - Glucocorticoids, mineralocorticoids, sex steroids, Vit D
- **Depending on Mechanism of action**
  - Group I & Group II hormones
- **Site of synthesis**

1. Chemical composition
2. Solubility properties
- Mechanism of action
3. Location of receptors
4. Nature of the signal used to mediate hormonal action within the cell

## (1) Chemical composition

Steroid Based	Non-Steroid Based		
Steroids, lipid-like compounds derived from cholesterol <ul style="list-style-type: none"><li>• <u>Lipid-soluble</u> can <u>pass through cell membrane</u></li><li>• requires <u>intracellular receptors</u> (bind to receptors within the cell) and can directly affect the structure or function of the cell, via affect on protein synthesis &amp;/or energy production</li></ul>	Amino Acid Derivatives	Peptide hormones	Other: Prostaglandins <ul style="list-style-type: none"><li>• Local, or tissue, hormones</li><li>• Derived from lipid molecules</li><li>• Do not travel in the bloodstream</li><li>• Target tissues are located close by</li><li>• Produced by organs such as<ul style="list-style-type: none"><li>Kidneys</li><li>Heart</li><li>Stomach</li><li>Uterus</li><li>Brain</li></ul></li></ul>
	<ul style="list-style-type: none"><li>• <u>Water soluble</u> and <u>do not enter the cell</u></li><li>• requires <u>membrane receptors</u> –(bind to receptors on cell membrane) triggering a cascade of biological activity</li><li>• enzymes catalyzes a reaction that produced a second messenger molecule that oversees additional intracellular changes that promotes a response of the target cell</li></ul>		

# Chemical Classification of Hormones

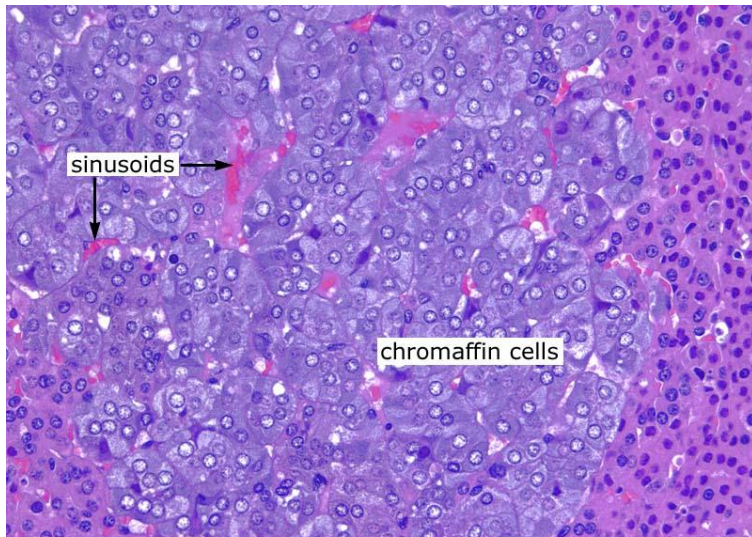
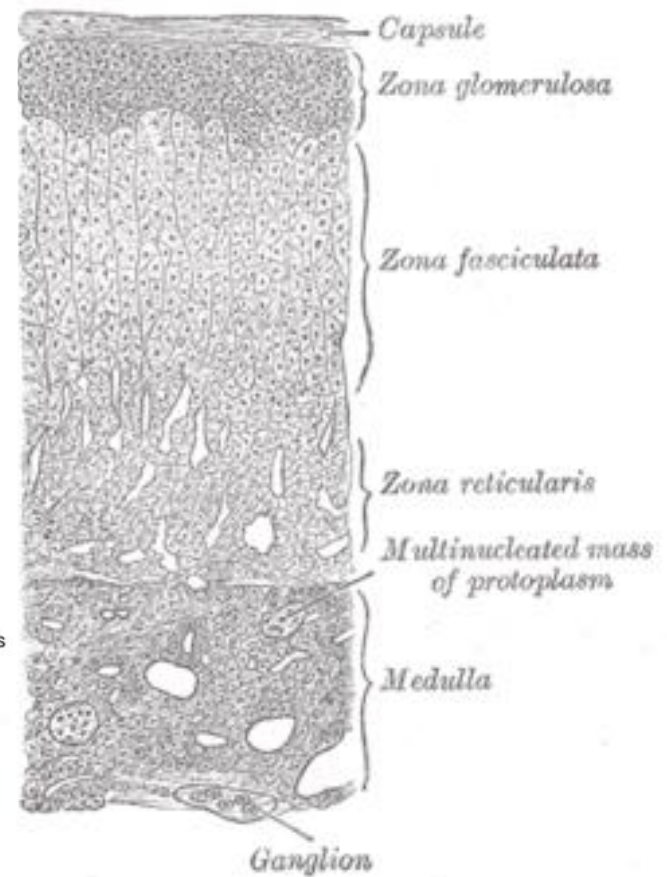
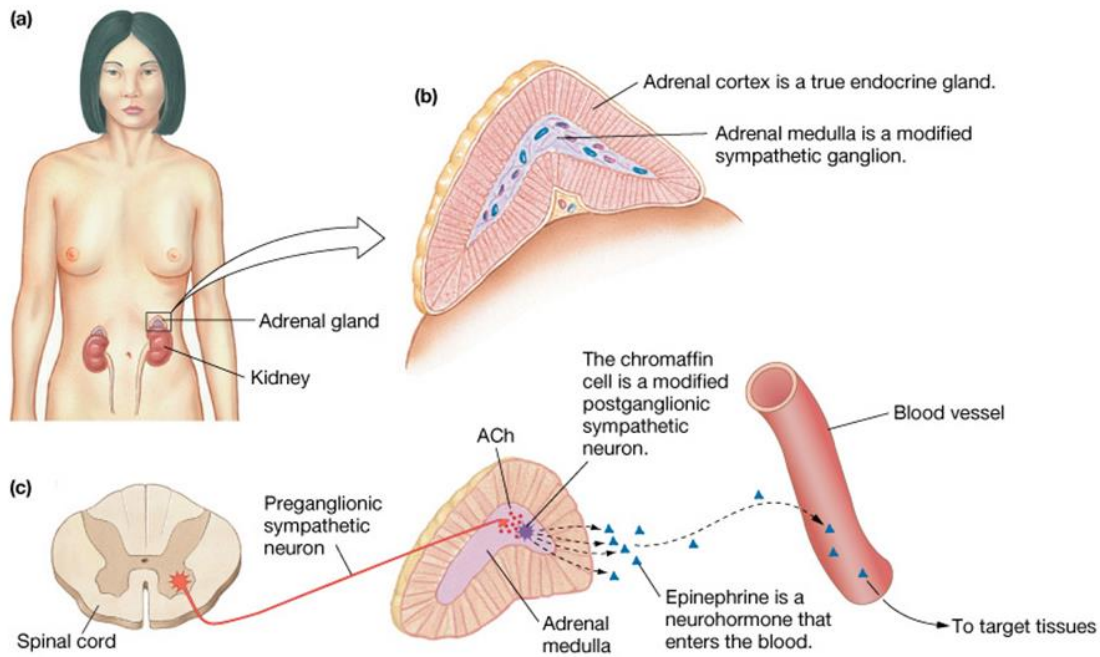
- Amine hormones are derived from tyrosine or tryptophan
  - Include NE, Epi, thyroxine, melatonin
- Polypeptide/protein hormones are chains of amino acids
  - Include ADH, GH, insulin, oxytocin, glucagon, ACTH, PTH
- Glycoproteins
  - Long polypeptide bound to a carbohydrate group
  - Include LH, FSH, TSH
- Steroids are lipids derived from cholesterol
  - Include testosterone, estrogen, progesterone & cortisol

<u>Source of synthesis</u>	Hormone	Synthetic pathway	Site of synthesis
	Steroids	Cholesterol	Adrenal Glands, Testis, Ovary, Placenta
	Retinoids	Vitamin A	Liver
	Calcitrol (1-alpha, 25-dihydroxycalcitriol)	Vitamin D	Liver & Kidneys
	Iodothyronine	Iodine + Tyrosine	Thyroid gland
	Prostaglandins	Arachidonic acid (20:4 fatty acids)	Most tissues
	Peptides/proteins	Pro-hormone cleavage – 3-200 aa residues	Hypothalamus, Pituitary, Thyroid, Pancreas
	Catecholamines (E,NE)	Tyrosine	Brain, adrenal gland

Hormone	Supply Stored in Cell
Steroids and 1,25(OH) <sub>2</sub> -D3	None
Catecholamines and PTH	Hours
Insulin	Days
T <sub>3</sub> and T <sub>4</sub>	Weeks

<u>Form of storage</u>
(1) NR
(2) Granules in the chromaffin cells in the adrenal medulla
(3) Storage vesicles of parathyroid gland
(4) B-cells of pancreas (proinsulin to insulin)
(5) Thyroglobulin in colloid in the lumen of the thyroid follicles

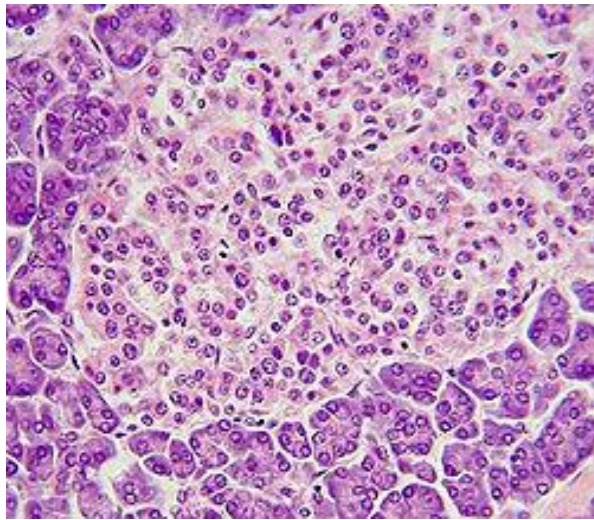




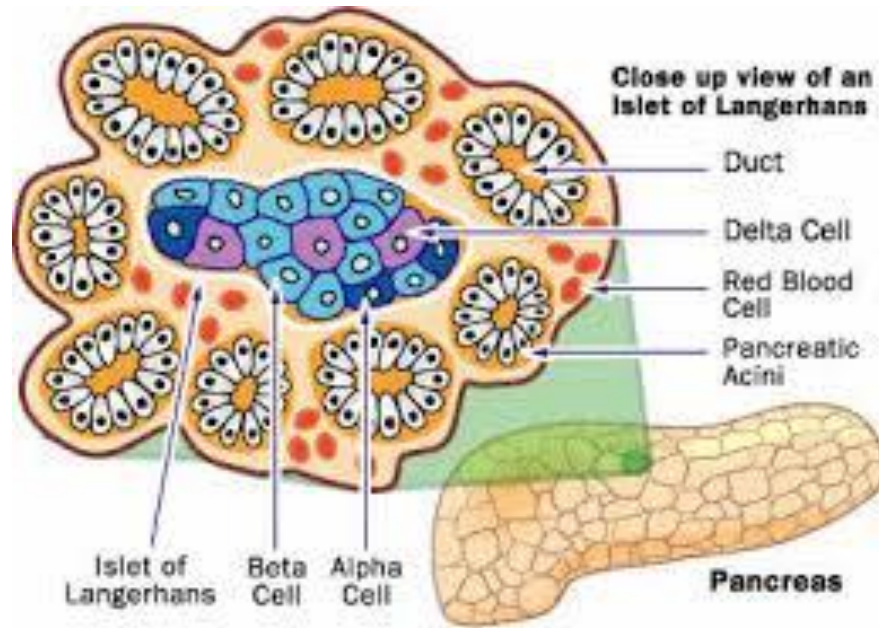
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## Adrenal Gland structure

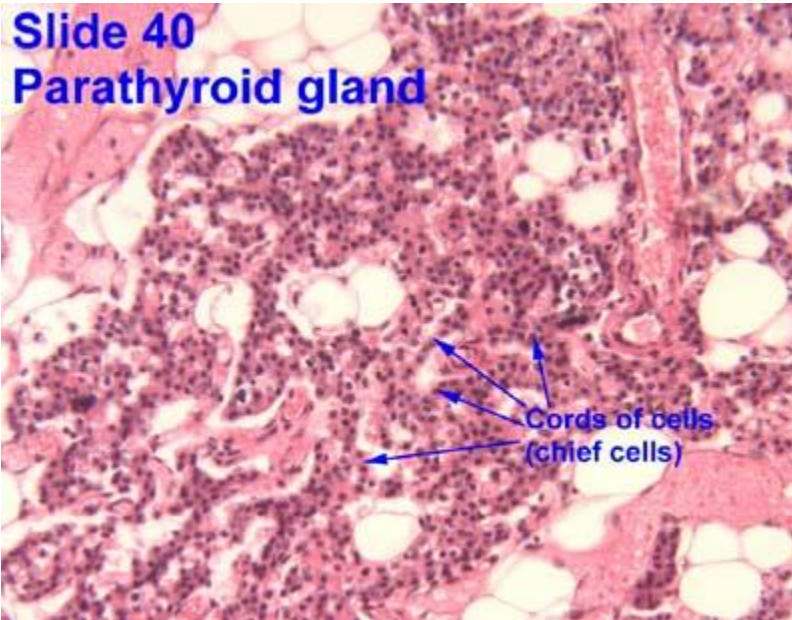




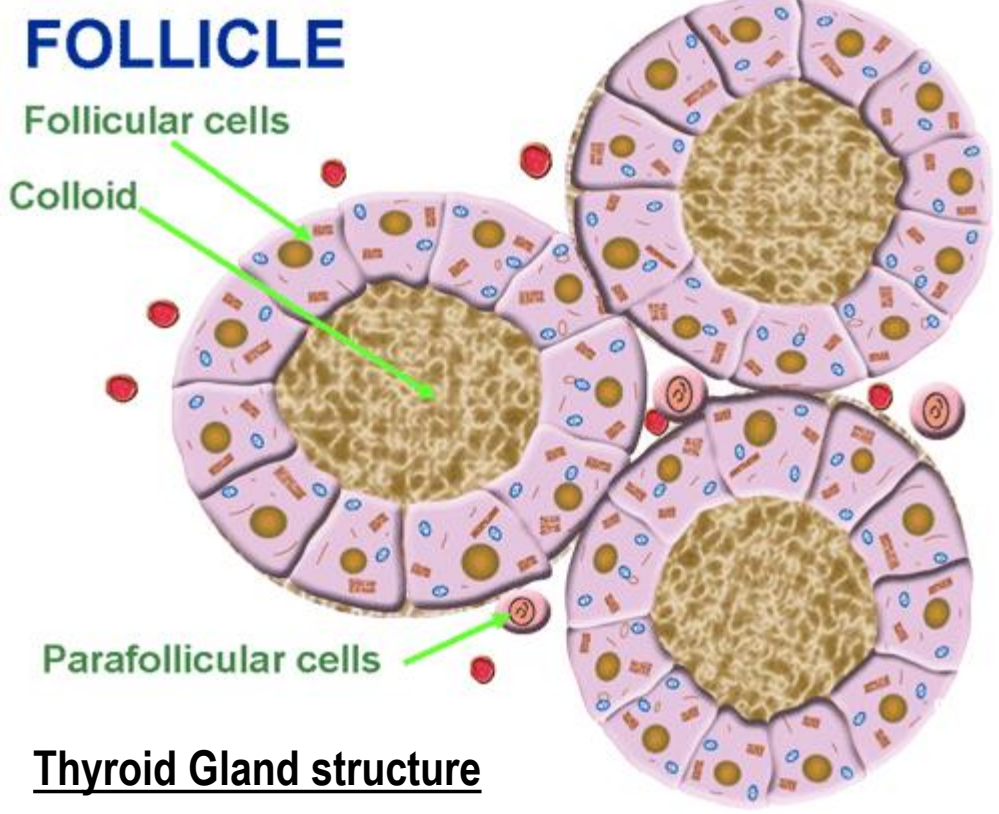
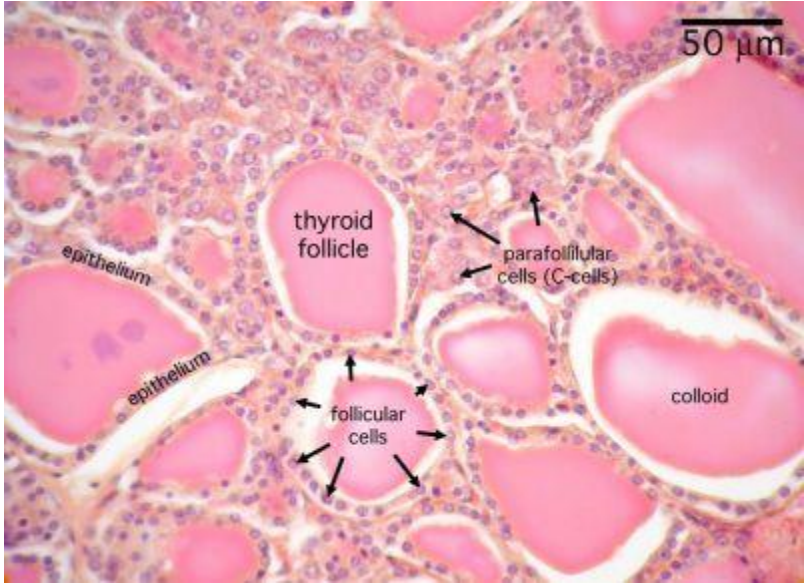
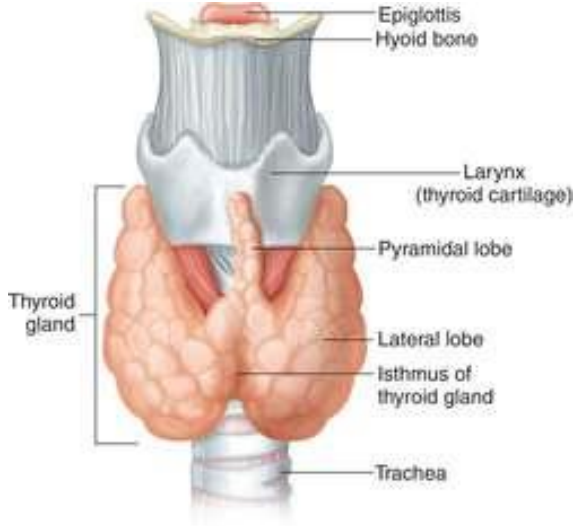
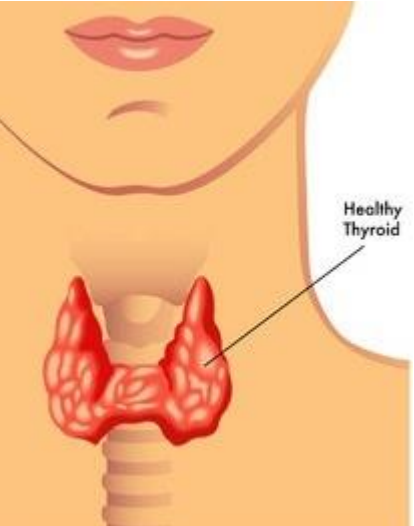
Islets of Langerhans



Pancreas



Parathyroid Gland structure





## (2) Mechanism of action

	<b>Group I</b>	<b>Group II</b>
Types	Steroids, iodothyronines, calcitriol, retinoids	Polypeptides, proteins, glycoproteins, catecholamines
Solubility	Lipophilic	Hydrophilic
Transport proteins	Yes	
Plasma half-life	Long (hours to days)	Short (minutes)
Receptor	Intracellular	Plasma membrane
Mediator	Receptor-hormone complex	cAMP, cGMP, $\text{Ca}^{2+}$ , metabolites of complex phosphoinositols, kinase cascades

### ***(1) Hormones that bind to intracellular receptors***

Androgens  
Calcitriol (1,25[OH]<sub>2</sub>-D<sub>3</sub>)  
Estrogens  
Glucocorticoids  
Mineralocorticoids  
Progestins  
Retinoic acid  
Thyroid hormones (T<sub>3</sub> and T<sub>4</sub>)

### ***2. Hormones that bind to cell surface receptors***

#### **1. cAMP**

Alpha & Beta Adrenergic catecholamines  
Adrenocorticotrophic hormone (ACTH)  
Antidiuretic hormone (ADH/vasopressin)  
Calcitonin  
Chorionic gonadotropin human (CG)  
Corticotropin-releasing hormone (CRH)  
Follicle-stimulating hormone (FSH)  
Glucagon  
Lipotropin (LPH)  
Luteinizing hormone (LH)  
Melanocyte-stimulating hormone (MSH)  
Parathyroid hormone (PTH)  
Somatostatin/Growth Hormone (GH)  
Thyroid-stimulating hormone (TSH)

### **3. cGMP**

Atrial natriuretic factor

Nitric oxide

### **4. Calcium (Ca) or phosphatidylinositols (PI, PtdIns) or both**

Acetylcholine (muscarinic)

Alpha-Adrenergic catecholamines

Angiotensin II

Antidiuretic hormone (ADH/vasopressin)

Cholecystokinin

Gastrin

Gonadotropin-releasing hormone

Oxytocin

Platelet-derived growth factor (PDGF)

Substance P

Thyrotropin-releasing hormone (TRH)

### **5. Kinase or phosphatase cascade**

Adiponectin

Chorionic somatomammotropin

Epidermal growth factor (EGF)

Erythropoietin (EPO)

Fibroblast growth factor (FGF)

Growth hormone (GH)

Insulin

Insulin-like growth factors I and II (IGF)

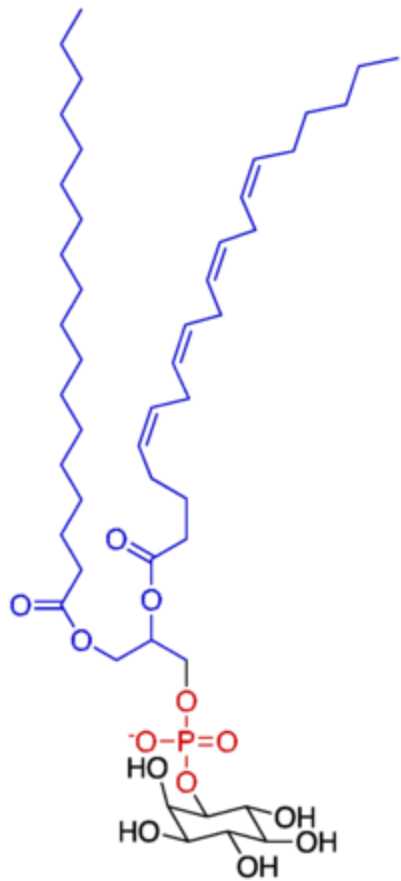
Leptin

Nerve growth factor (NGF)

Platelet-derived growth factor (PDGF)

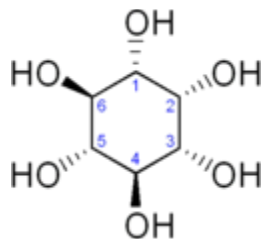
Prolactin (PL)

- Phosphatidylinositol can be phosphorylated to form **phosphatidylinositol phosphate** (PI-4-P, referred to as PIP in close context or informally), **phosphatidylinositol bisphosphate** (PIP<sub>2</sub>) and **phosphatidylinositol trisphosphate** (PIP<sub>3</sub>).
- All lipids based on phosphatidylinositol are known as inositides, or sometimes phosphoinositides.



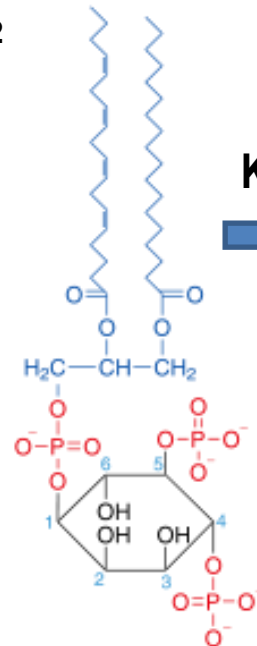
**PtdIns - phosphatidylglyceride**

**Inositol or cyclohexane-1,2,3,4,5,6-hexol**



**PIP<sub>2</sub>**

**Phosphatidylinositol 4,5 bisphosphate**  
or **PtdIns(4,5)P<sub>2</sub>**

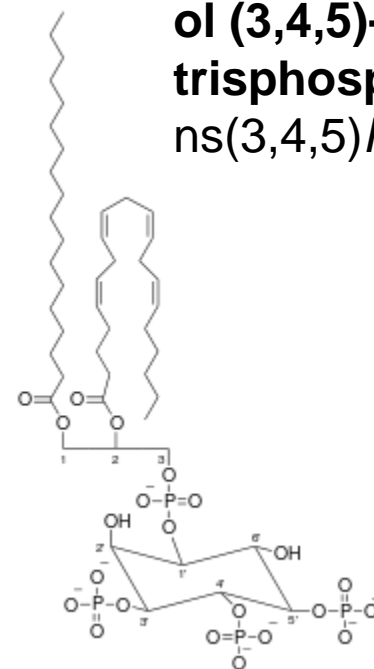


**Kinase**



**PIP<sub>3</sub>**

**Phosphatidylinositol (3,4,5)-trisphosphate** (PtdIns(3,4,5)P<sub>3</sub>)



## Key enzyme in signal transduction

**Kinase:** Enzyme that catalyzes the transfer of phosphate groups from high-energy, phosphate-donating molecules to specific substrates (phosphorylation)

**High energy phosphate group** – ATP



**Dephosphorylation:** when the phosphorylated substrate donates a phosphate group and ADP gains a phosphate group.



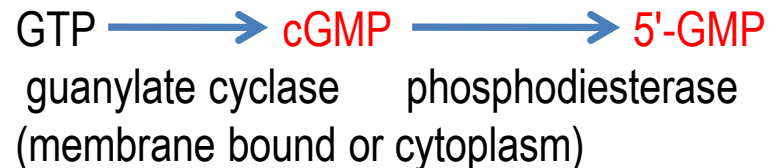
**Phosphorylases** are enzymes that catalyze the addition of a phosphate group from an inorganic phosphate (phosphate+hydrogen) to an acceptor (**do not confuse with kinase**)

**Cyclic adenosine monophosphate** (cAMP or 3',5'-cyclic adenosine monophosphate)



(on the inner side of the plasma membrane & anchored at various locations in the interior of the cell)

**Cyclic guanosine monophosphate** (cGMP)





## **SUMMARY- Key points for Lecture1 & Lecture2**

- **Endocrine system is a controlling mechanism** of the body mediated by chemical messengers called hormones which move through blood from the **site of synthesis/secretion to site of action** (target cells)
- The presence of a **specific receptor** defines the target cells for a given hormone. Receptors are proteins that bind specific hormones and generate an intracellular signal (receptor–effector coupling).
- Hormone-receptor binding affinity is inversely proportional to dissociation constant.
- Hormones are named according to their **site of synthesis/secretion** (hypothalamic hormones; anterior pituitary and posterior pituitary hormones; adreno-cortical and adreno-medullary hormones; thyroid and parathyroid hormones; gonadal hormones (testicular & ovarian hormones)).
- Hormones are also named according to the **structures/functions** (like adrenocorticosteroids/adrenocorticoids/adrenocorticosterones; trophic or stimulatory hormones and releasing hormones).
- Receptors may be **intracellular** (steroid-derived hormones) or **transmembrane** (non-steroid hormones like peptide/protein hormones).
- **Plasma transport proteins** bind to steroid hormones.
- Hormones are synthesized from a number of **precursor molecules**, including cholesterol, amino acids like tyrosine and all the constituent amino acids of peptides and proteins.
- A number of **modification processes** alter the activity of hormones. For example, many hormones are synthesized from larger precursor molecules.
- The **complement of enzymes** in a particular cell type allows for the production of a specific class of steroid hormone.