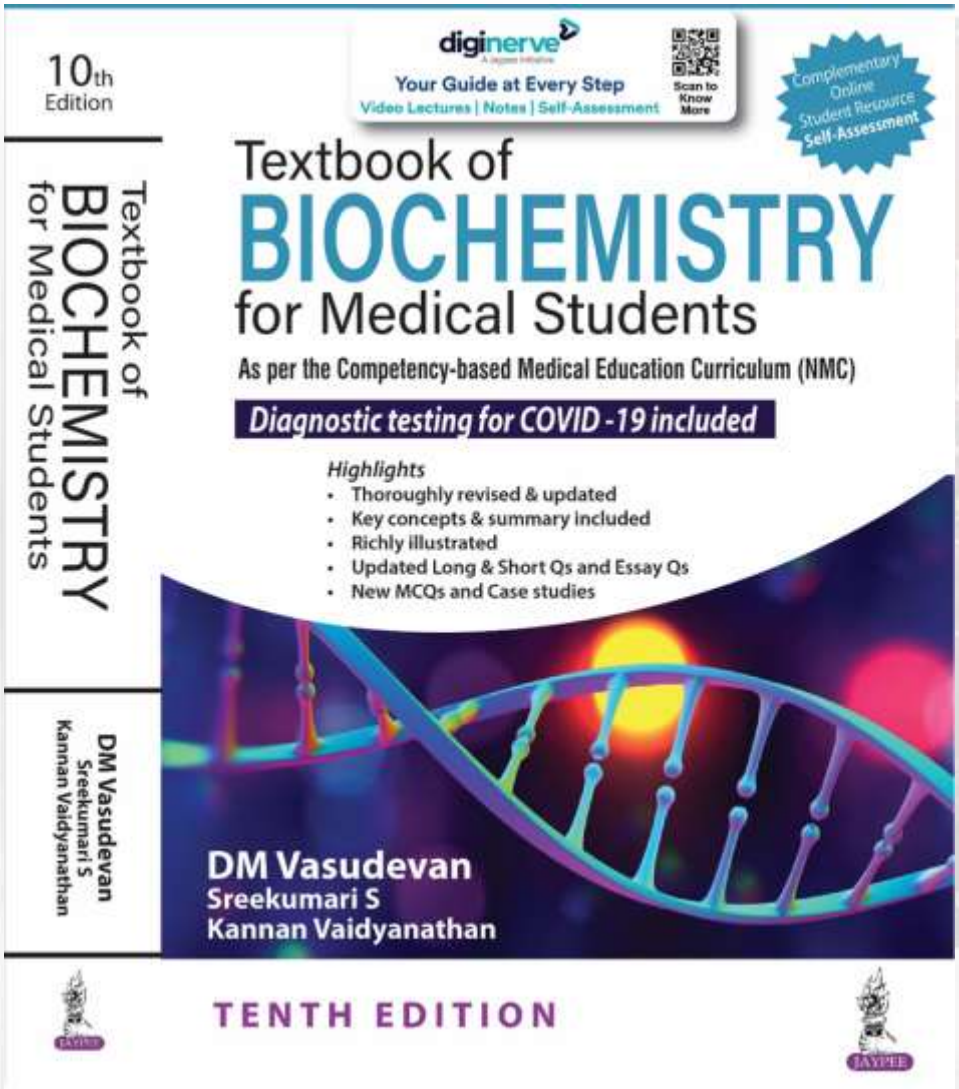


Chapter 44:

Mechanisms of Action of Hormones

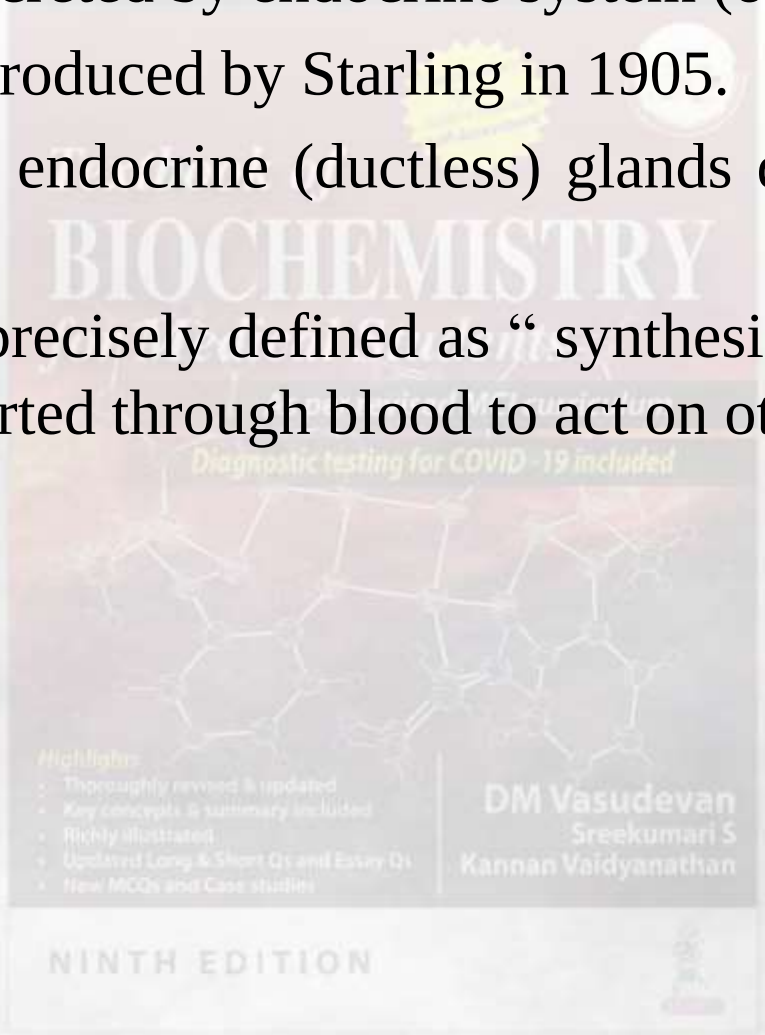
Textbook of
BIOCHEMISTRY
for Medical Students

By DM Vasudevan, *et al.*

TENTH EDITION

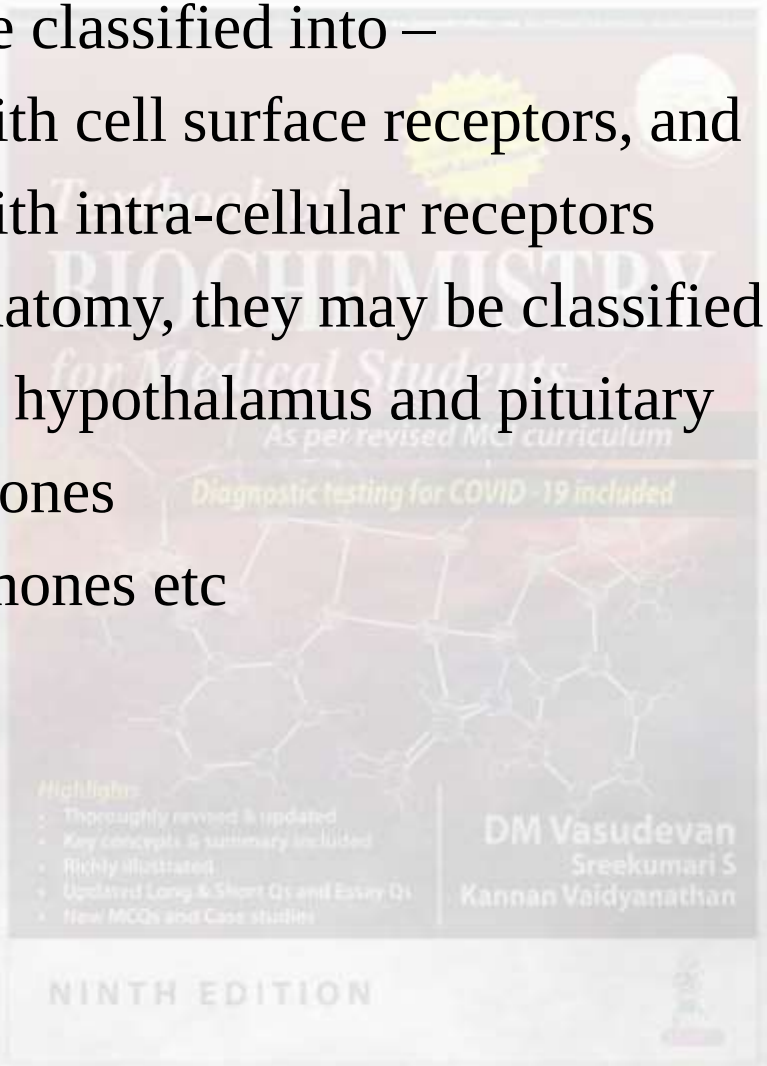
Introduction

- Hormones are secreted by endocrine system (organs).
- The term was introduced by Starling in 1905.
- It is secreted by endocrine (ductless) glands directly into blood stream.
- It may be more precisely defined as " synthesized by one type of cells and transported through blood to act on other type of cells".



Classification

- Hormones can be classified into –
  - Hormones with cell surface receptors, and
  - Hormones with intra-cellular receptors
- Depending on anatomy, they may be classified into –
  - Hormones of hypothalamus and pituitary
  - Steroid hormones
  - Thyroid hormones etc



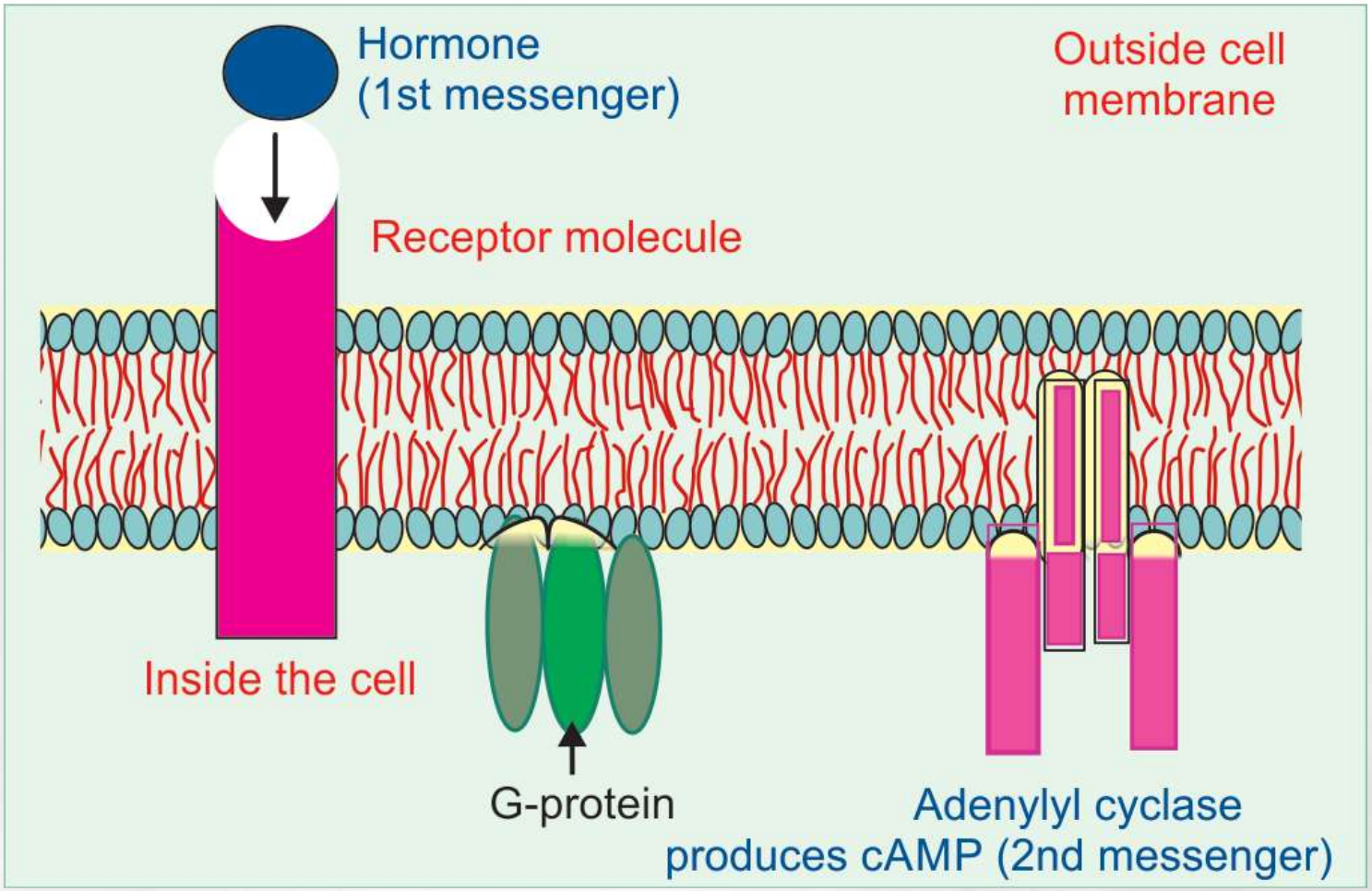
Mechanism of Action of Hormones

Group	Mechanism of action	Examples of hormone
I	Hormones that bind to the intracellular receptors	Glucocorticoids, Mineralocorticoids, Estrogens, Progesterone, Androgens, Calcitriol, Thyroxine
II A	Hormones bind with cell surface receptors with cAMP as the second messenger	ACTH, ADH, FSH, HCG, LH, TSH, MSH, PTH, CRH, Glucagon, Calcitonin, Catecholamines, Vasopressin
II B	Hormones having cell surface receptors; cGMP as second messenger	ANF (atrial natriuretic factor), NO (nitric oxide)

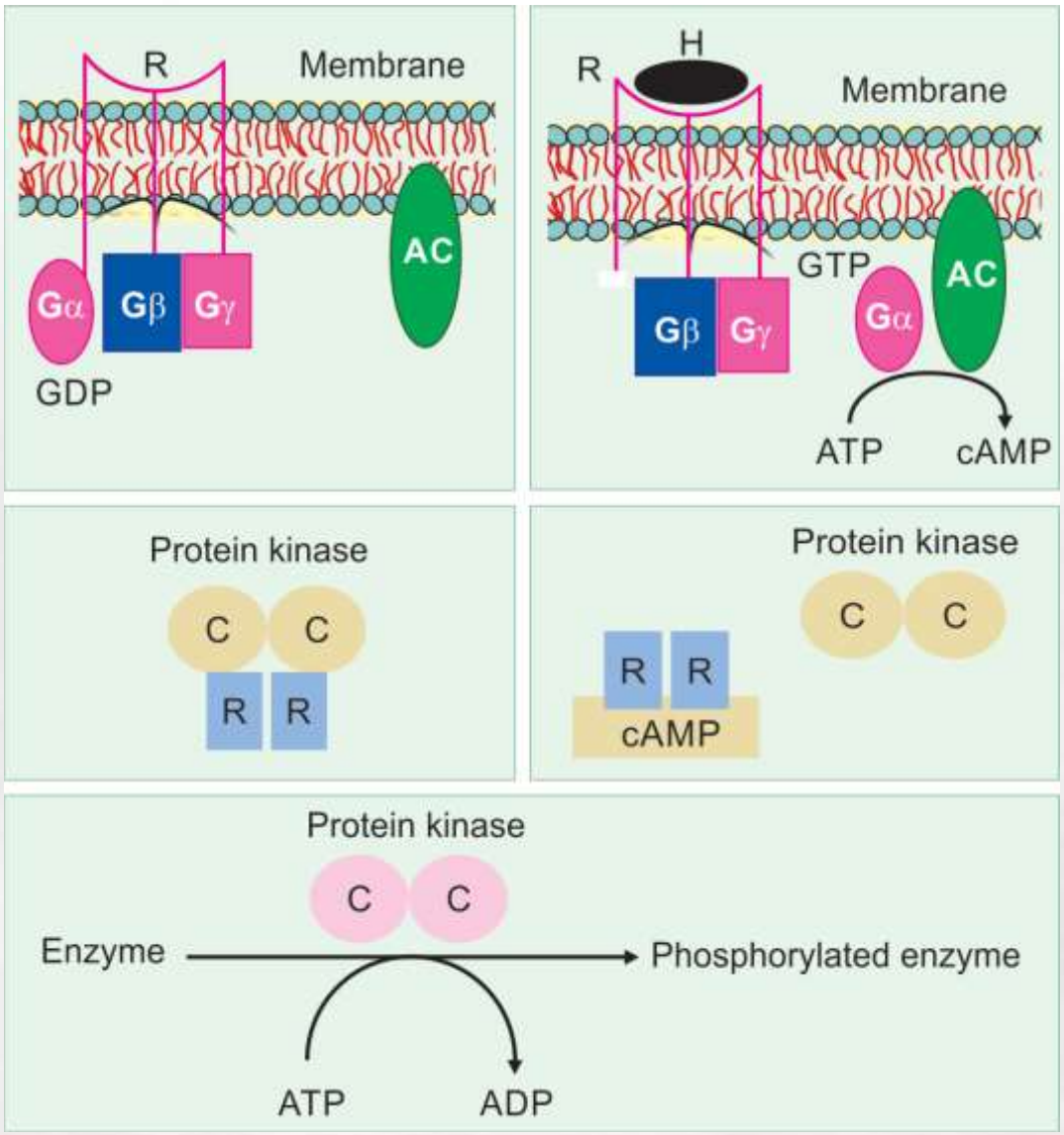
Group	Mechanism of action	Examples of hormone
II C	Hormones having cell surface receptors; second messenger is calcium or phosphatidyl inositol (PIP_2)	**TRH, GnRH, Acetylcholine, CCK, Gastrin Vasopressin Oxytocin, PDGF**
II D	Hormones having cell surface receptors and mediated through tyrosine kinase	**Insulin, EGF, FGF PDGF, NGF, IGF**
II E	**Hormones having cell surface receptors, but intracellular messenger is a kinase or utilise phosphatase cascade**	**IL, GH, PRL, TNF, Adiponectin, Leptin, Resistin, Erythropoietin**

G proteins

- Many hormones acting via cAMP involves G proteins.
- When hormone-receptor complex is formed, activated receptor stimulates G protein, and it carries excitation signal to adenylate cyclase.
- It takes place in the plasma membrane and adenyl cyclase is also found there.
- Once action is over, G proteins are inactivated.
- Second messengers activates protein kinases.
- Protein kinases pass the signal to various downstream pathways, which depend on type of molecule activated.
- About 30 G proteins are identified, may be stimulatory (Gs) or inhibitory (Gi).
- Protein kinases are also of many types – calmodulin dependent, cAMP dependent (I and II), EGF-dependent tyrosine kinases, insulin dependent, myosin light chain kinase etc.

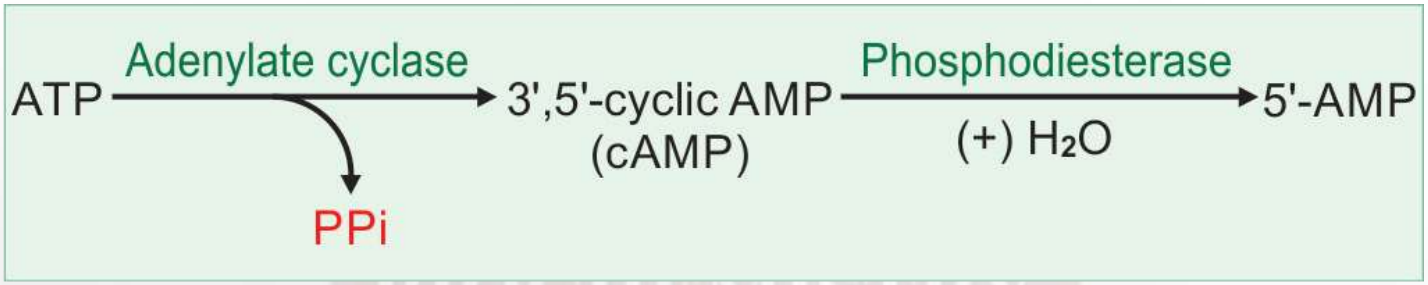


Hormone binding activates G-protein.

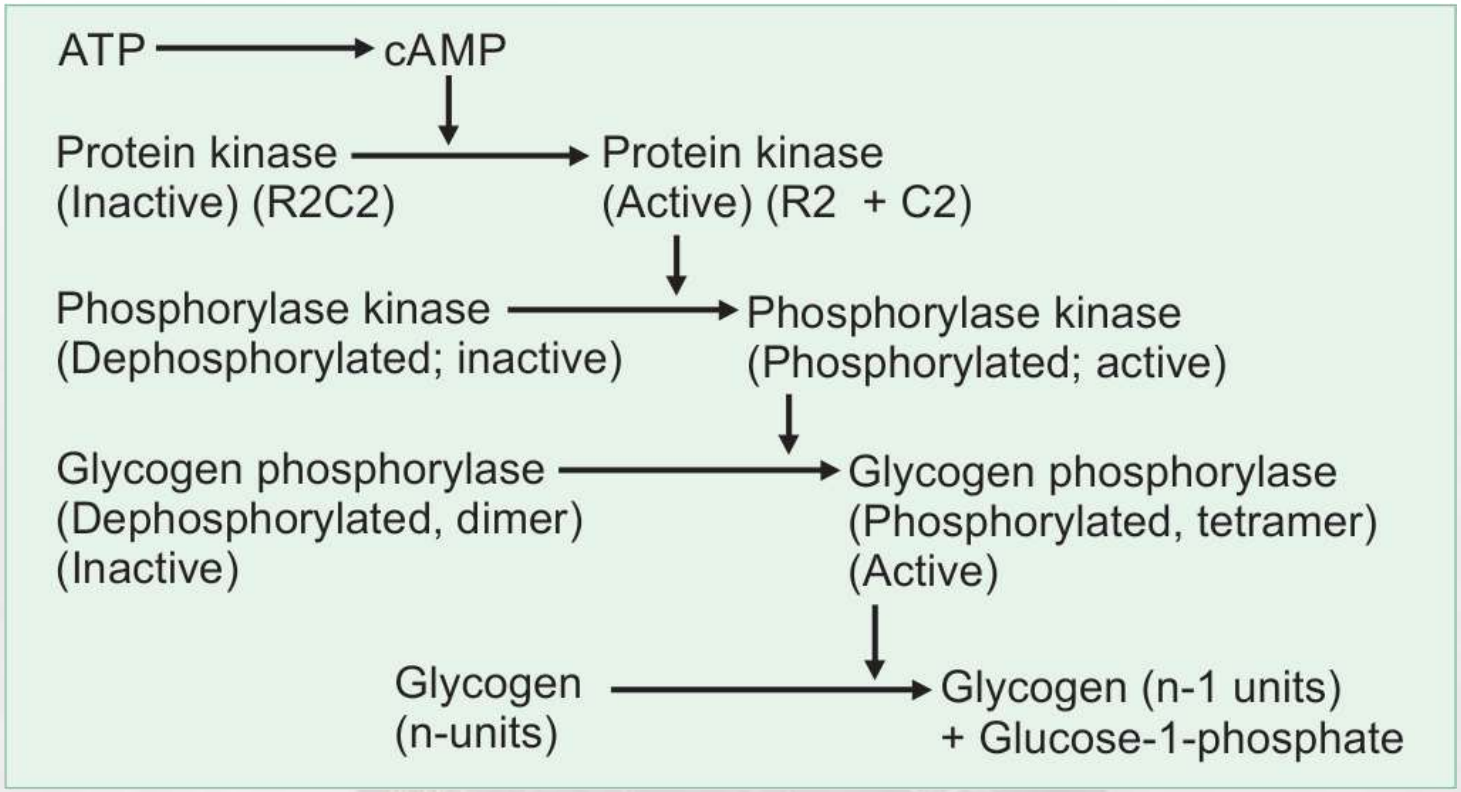

R
Membrane
AC
Gα
Gβ
Gγ
GDP
H
R
Membrane
GTP
Gβ
Gγ
Gα
AC
ATP
cAMP
Protein kinase
C
C
R
R
Protein kinase
C
C
R
R
cAMP
Protein kinase
C
C
Enzyme
Phosphorylated enzyme
ATP
ADP

Action of hormone through G-protein.

(A): Receptor is attached to the G protein, which has a, b, g subunits. It is bound with DP, and is inactive. These are membrane bound; (B): When the hormone attaches, alpha subunit detaches, then GTP is bound, Ga-GTP activates adenylyl cyclase, so cAMP is generated; (C): Protein kinase contains two catalytic units, but these are attached to two regulatory units, and are inactive; (D): The cAMP binds with the regulatory units; now catalytic units are free and kinases is now active; (E): Active protein kinase phosphorylates the enzyme proteins. (R: receptor; G: G protein with a, b, g subunits; AC: adenylyl cyclase; H: hormone; C: catalytic unit; R: regulatory unit; cAMP: cyclic AMP).



Synthesis and degradation of cyclic AMP.

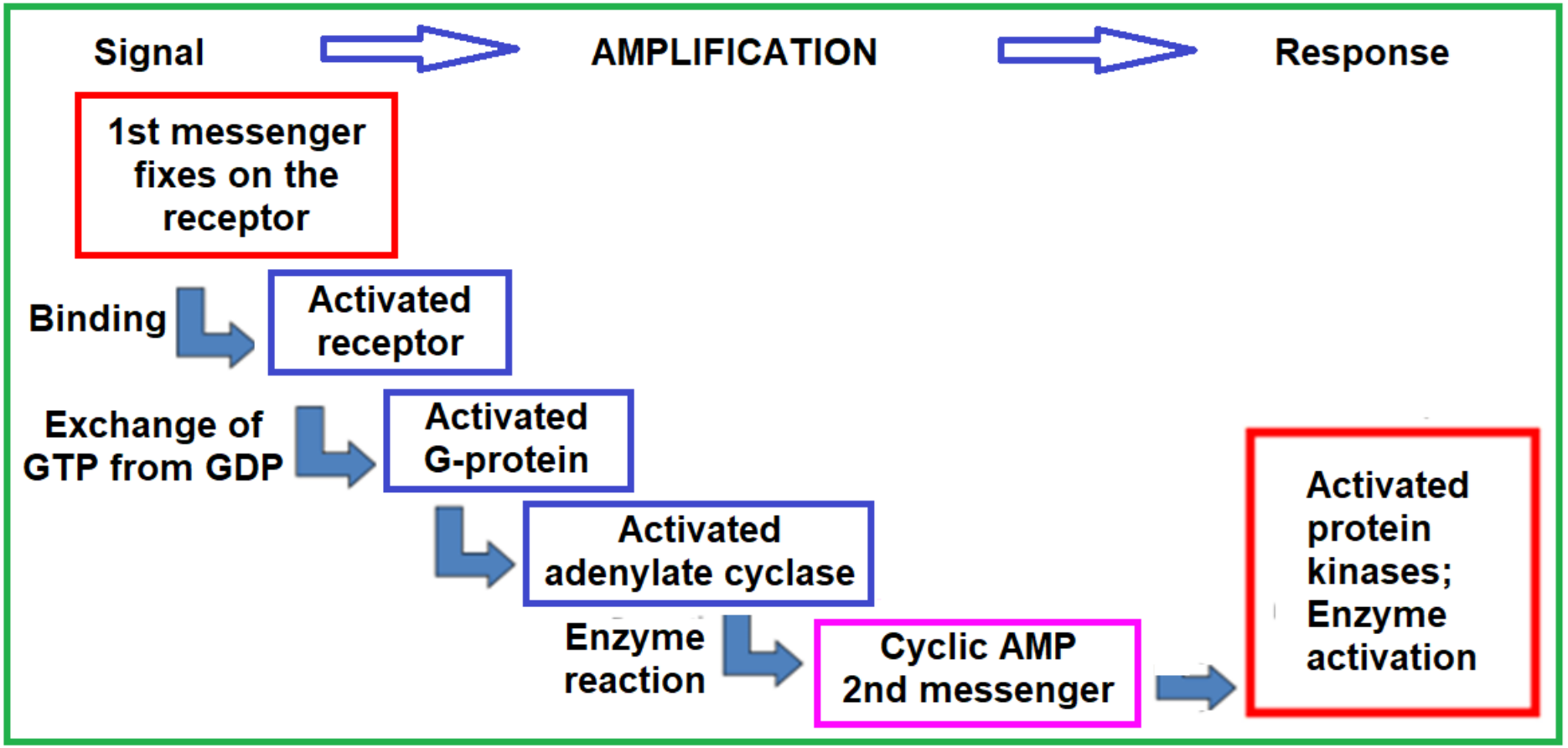


The cAMP mediated cascade.

Hormones acting through adenyl cyclase

Hormones which stimulate adenyl cyclase:
ACTH, ADH, Calcitonin, CRH, FSH, Glucagon, epinephrine, hCG, LH, LPH, MSH, PTH and TSH.

Hormones which inhibit adenyl cyclase:
Acetylcholine, Angiotensin II and Somatostatin



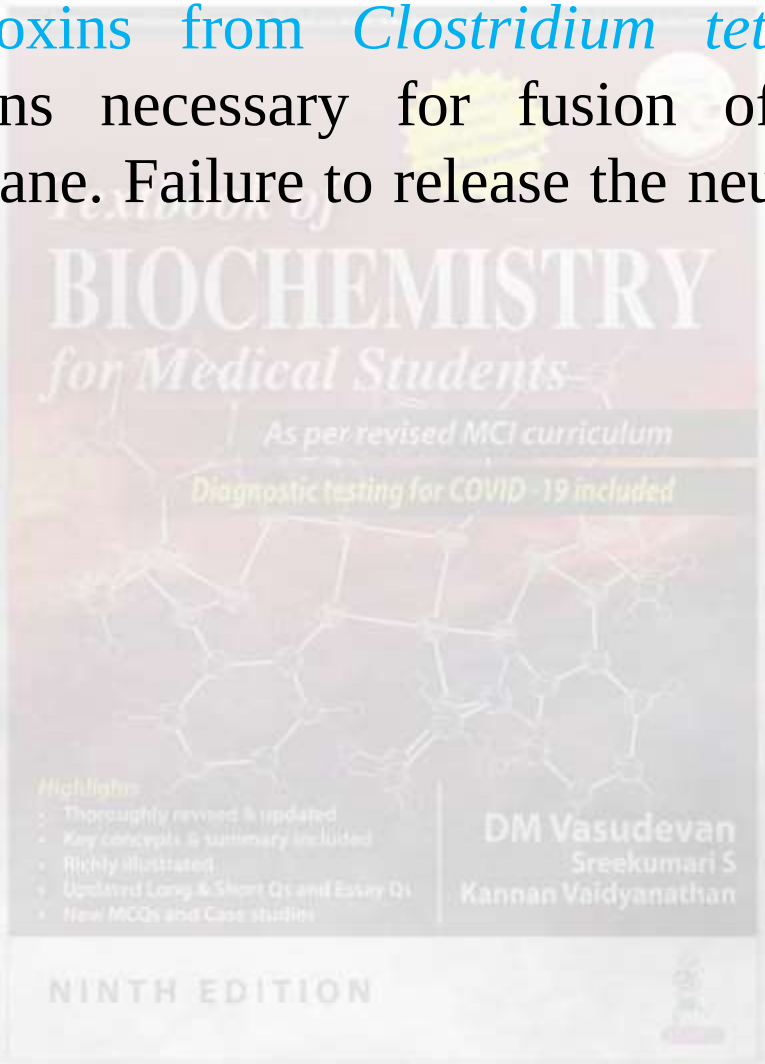
Summary of Signal Transduction Pathway.
In each step, the signal is amplified.

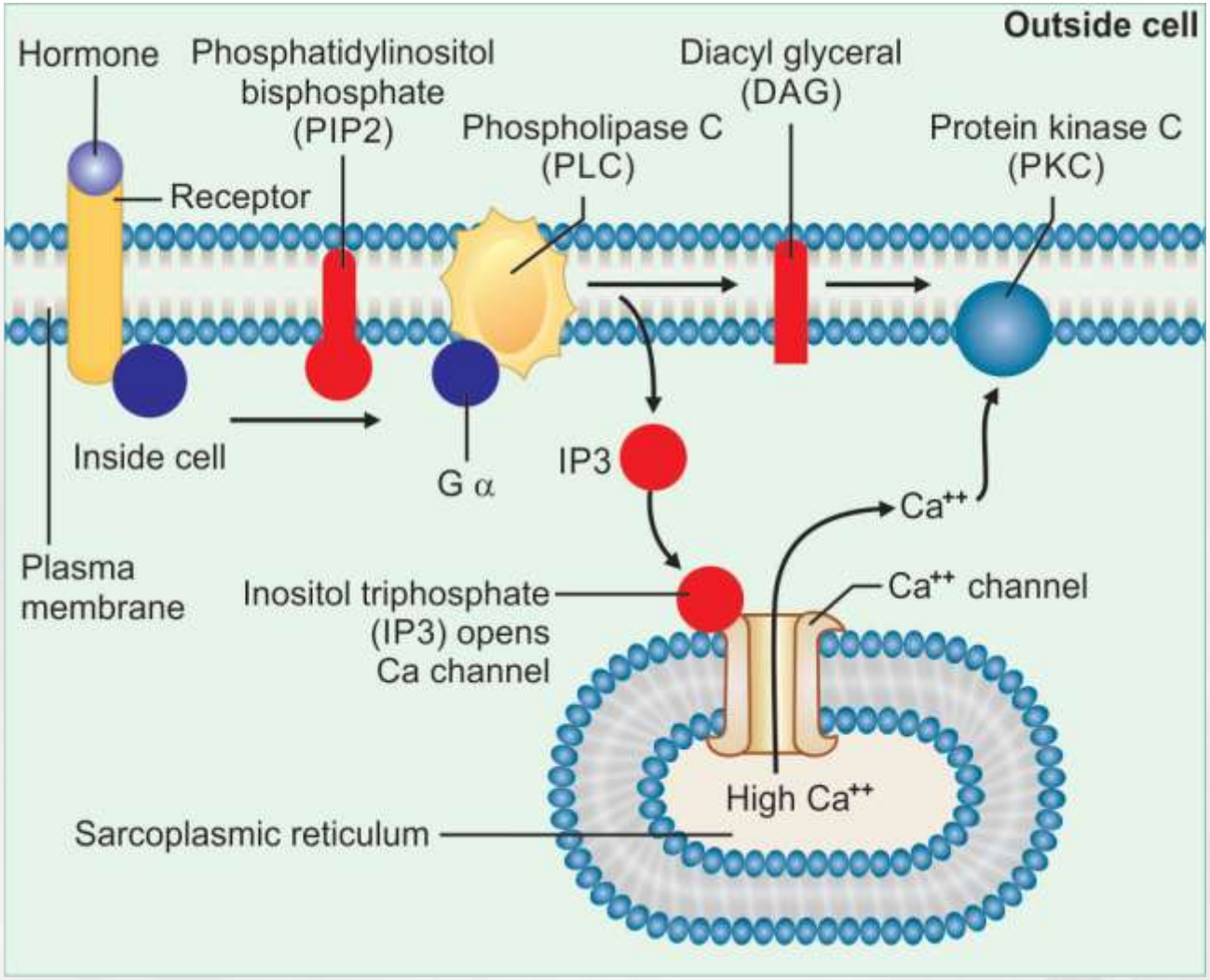
Mechanism of Action of some Toxins

Cholera toxin of the bacteria *Vibrio cholerae* contains two A subunits and 5 B subunits. The B subunit binds to a ganglioside GM1 on the surface of intestinal mucosal cell. The A subunit then enters into the inner part of the membrane, which leads to ribosylation of the alpha subunit of Gs protein. Hence the effect of hormones acting through Gi is inhibited. Therefore, adenylyl cyclase remains continuously active and keeps cyclic AMP levels high and prevents absorption of salts from intestine leading to watery diarrhea and loss of water from body.

Pertussis toxin ribosylates the alpha subunit of Gi protein and prevents the Gi-GDP complex from interacting with the activated receptor. Hence, the action of hormones acting through Gi is inhibited.

Bacterial toxins from *Clostridium tetani* are proteases that attack proteins necessary for fusion of synaptic vesicle and plasma membrane. Failure to release the neurotransmitter leads to fatal paralysis.

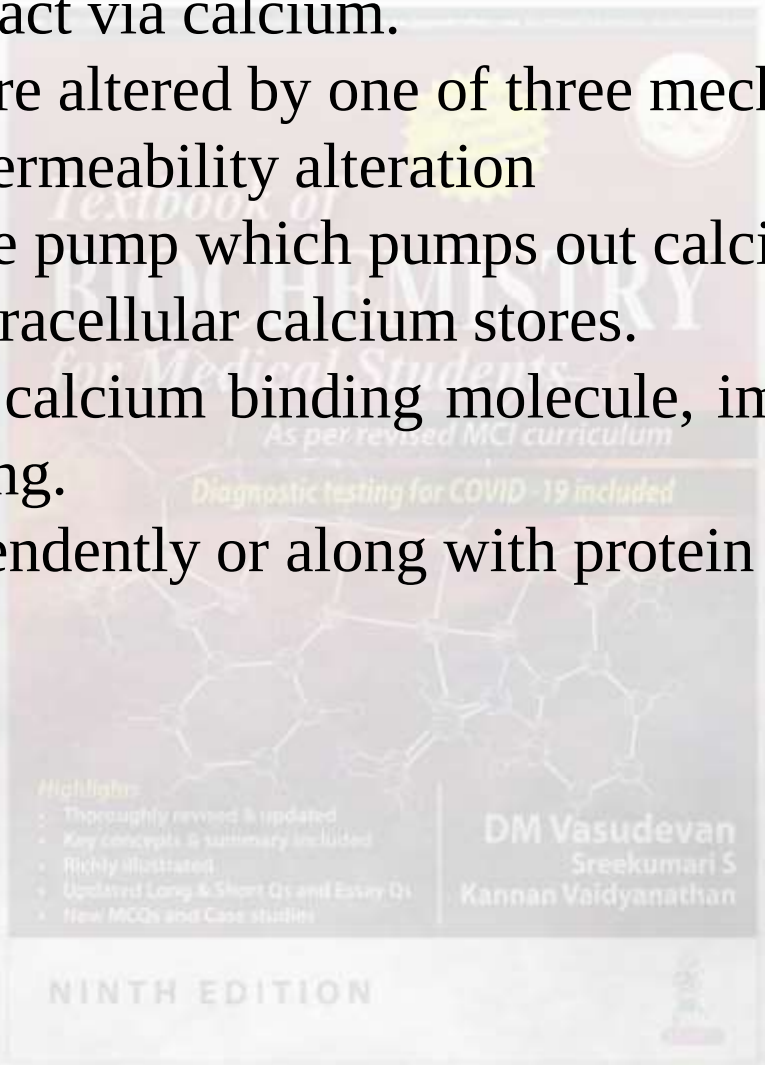




PIP2 and DAG acting as second messengers.

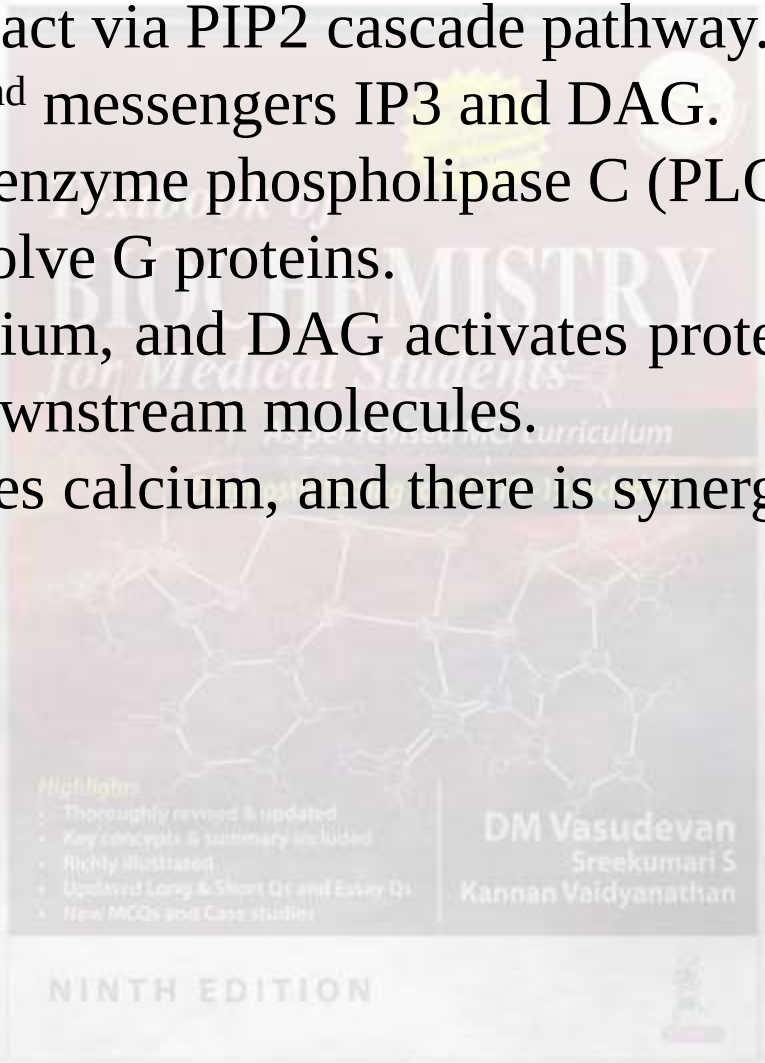
Calcium

- Some hormones act via calcium.
- Calcium levels are altered by one of three mechanims –
  - Membrane permeability alteration
  - Ca-H-ATPase pump which pumps out calcium
  - Releasing intracellular calcium stores.
- Calmodulin is a calcium binding molecule, important in calcium mediated signaling.
- It may act independently or along with protein kinases.



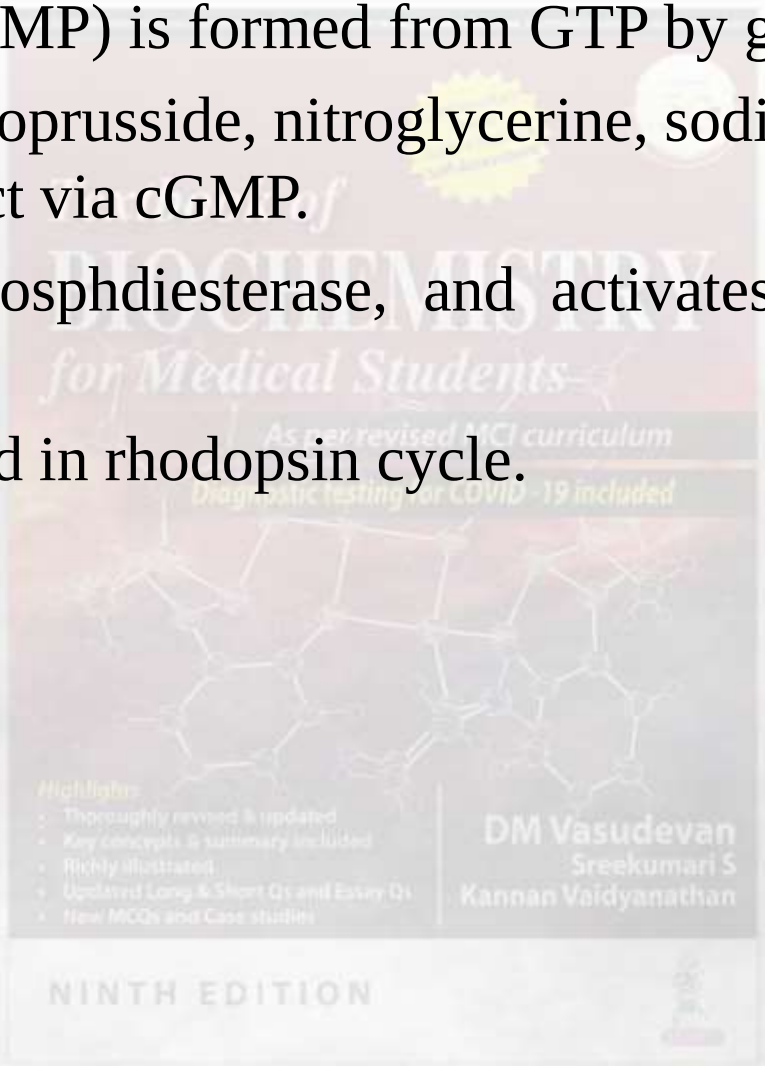
PIP 2 Pathway

- Many hormones act via PIP2 cascade pathway.
- It releases two 2nd messengers IP3 and DAG.
- It is made by an enzyme phospholipase C (PLC).
- Process may involve G proteins.
- IP3 releases calcium, and DAG activates protein kinase C (PKC) which acts on downstream molecules.
- DAG also releases calcium, and there is synergism between DAG and IP3.



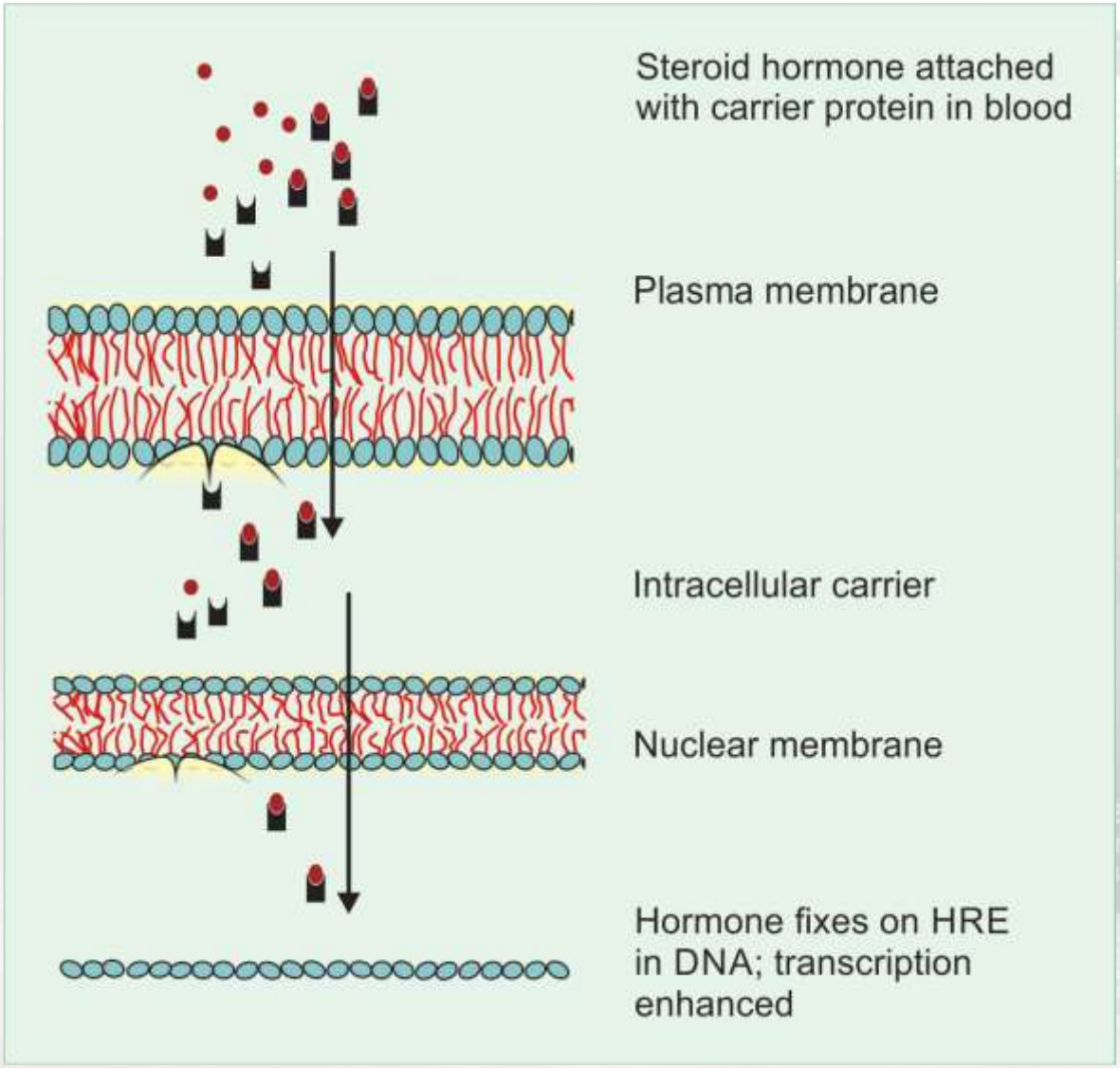
Cyclic GMP

- Cyclic GMP (cGMP) is formed from GTP by guanyl cyclase.
- Many drugs, nitroprusside, nitroglycerine, sodiumnitrite, atrio-peptides, act via cGMP.
- They inhibit phosphdiesterase, and activates cGMP-dependent protein kinases.
- It is also involved in rhodopsin cycle.

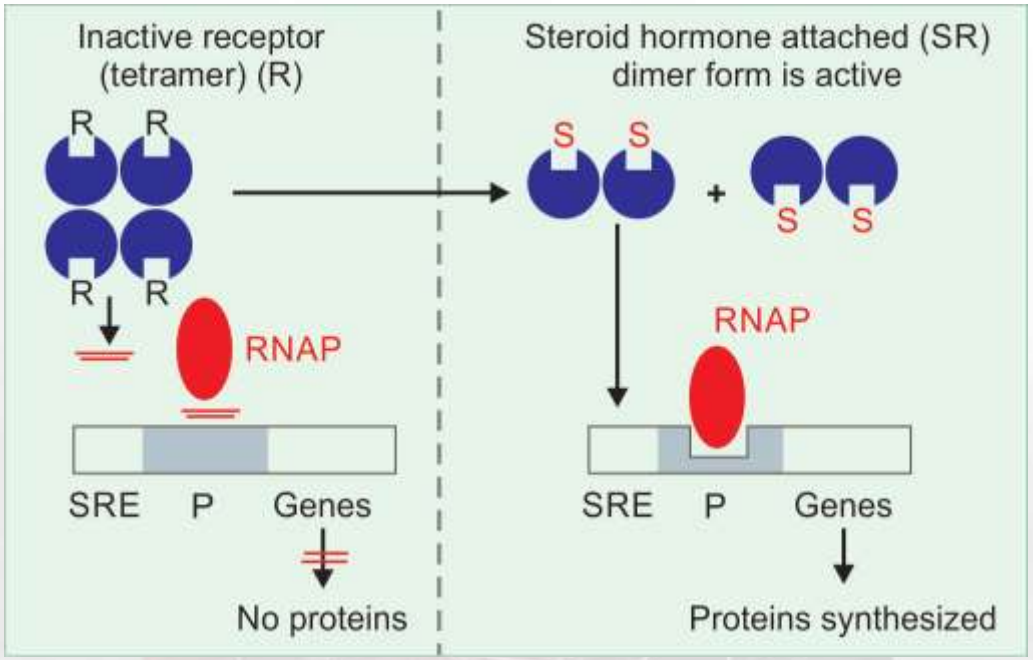


Hormones with Intracellular Receptors

- They act via mediating effect on gene expression, hence takes a longer time to act.
- Main hormones are steroid hormones and thyroid hormones.
- They diffuse through plasma membrane and bind to receptors in cytoplasm.
- Hormone-receptor (HR) complex is translocated to nucleus, and it binds to promoter or regulatory elements of DNA and activates or inactivates genes.
- Hormones bind to specific areas of genes, known as hormone response elements (HRE).
- Steroid hormones have steroid response elements (SRE), which acts as enhancer element, and when stimulated by hormone, increases transcriptional activity.
- mRNA synthesis is increased and metabolic effects are thereby brought about.

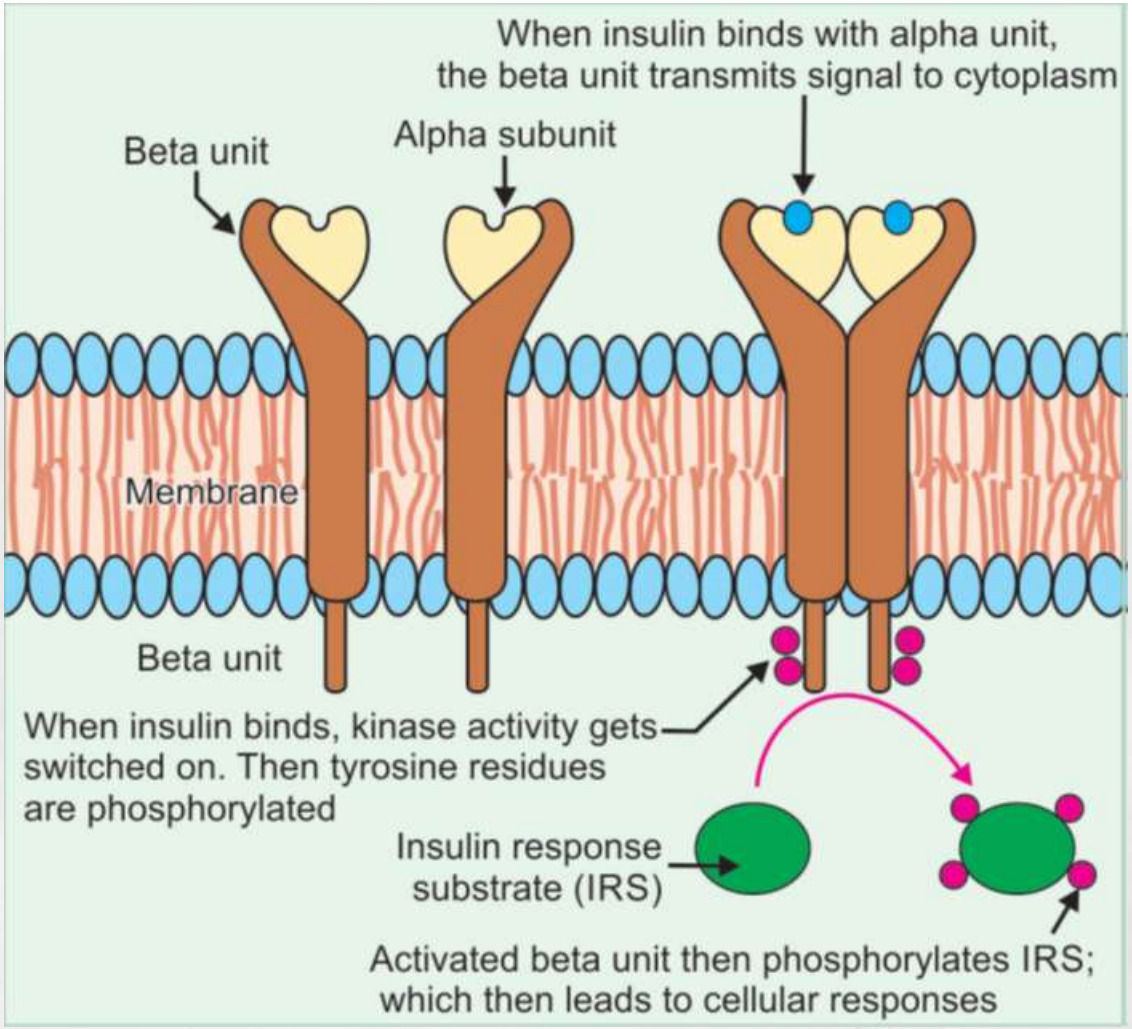


Steroid hormone enters nucleus.



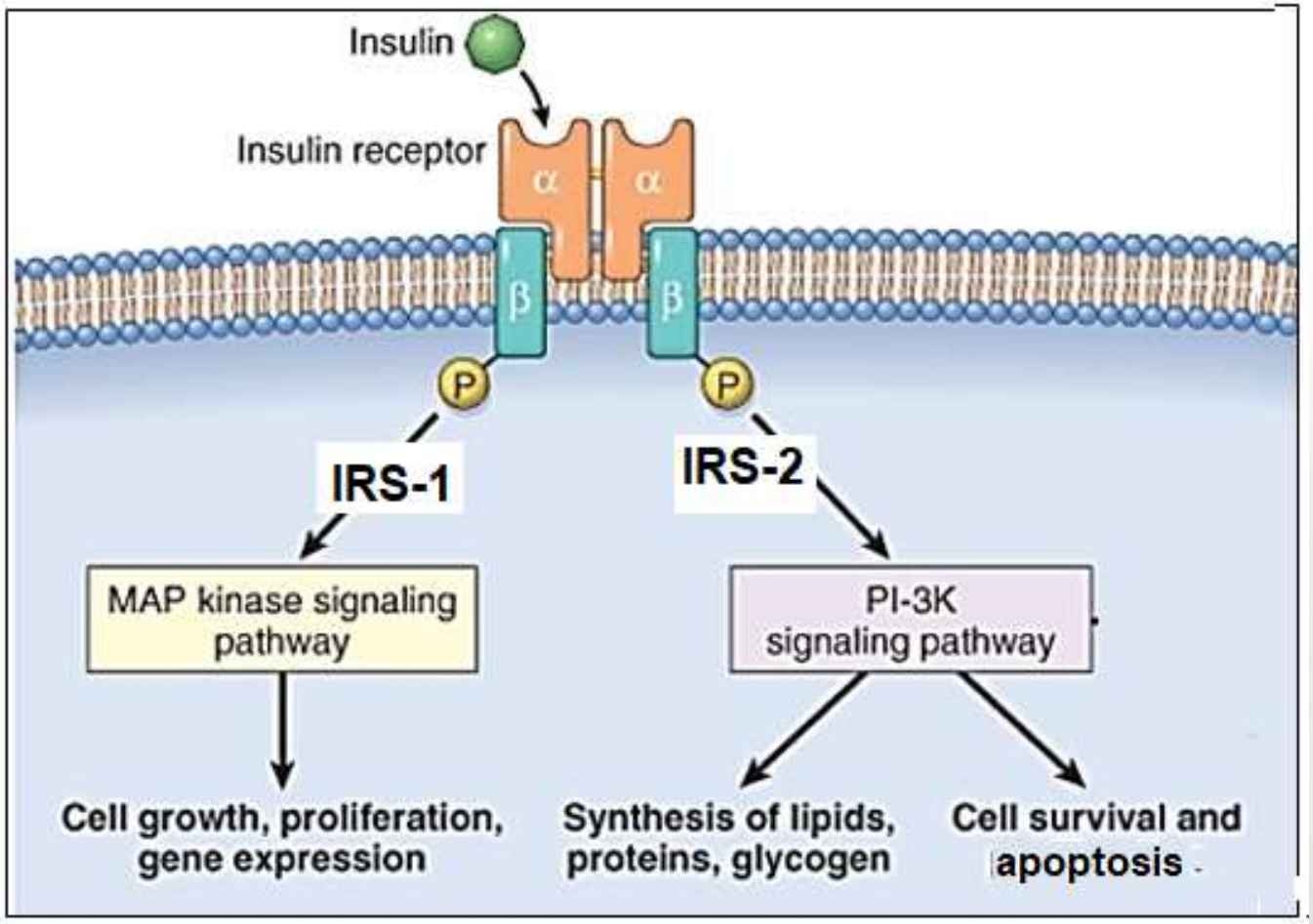
Mechanism of action of steroid hormones. Left side: in normal conditions, promoter site is repressed so that proteins cannot be synthesized; Right side: when steroid receptor complex is binding to the HRE, the P site is open, when the RNAP fixes and transcription starts; thus new protein is synthesized. (S: steroid hormone; R: receptor; SR: steroid receptor complex; SRE: steroid hormone response element in DNA; P: promoter site; RNAP: RNA polymerase.

Insulin Singnaling Pathways



Insulin Receptor.

Insulin Singnaling Pathways



Insulin signaling. IRS bifurcates the insulin response into different pathways.

Key features of signal transduction

1. Membrane receptors transfer information from the environment to the cell's interior; molecules themselves do not enter the cell.
2. A ligand is a molecule produced by secretion from signaling cells. Ligands may be proteins or steroids. The ligand binds in the extracellular domain of the receptor, which brings the cytoplasmic domains of the two receptor subunits into close proximity and activates the signaling.
3. Protein phosphorylation is important for signal transduction, mediated by protein kinases on serine, threonine and tyrosine residues of proteins.
4. Signal is terminated once the action is over – Uncontrolled signal transduction is one reason for the development of cancer. Protein phosphatases are important in signal termination.

Key features of signal transduction

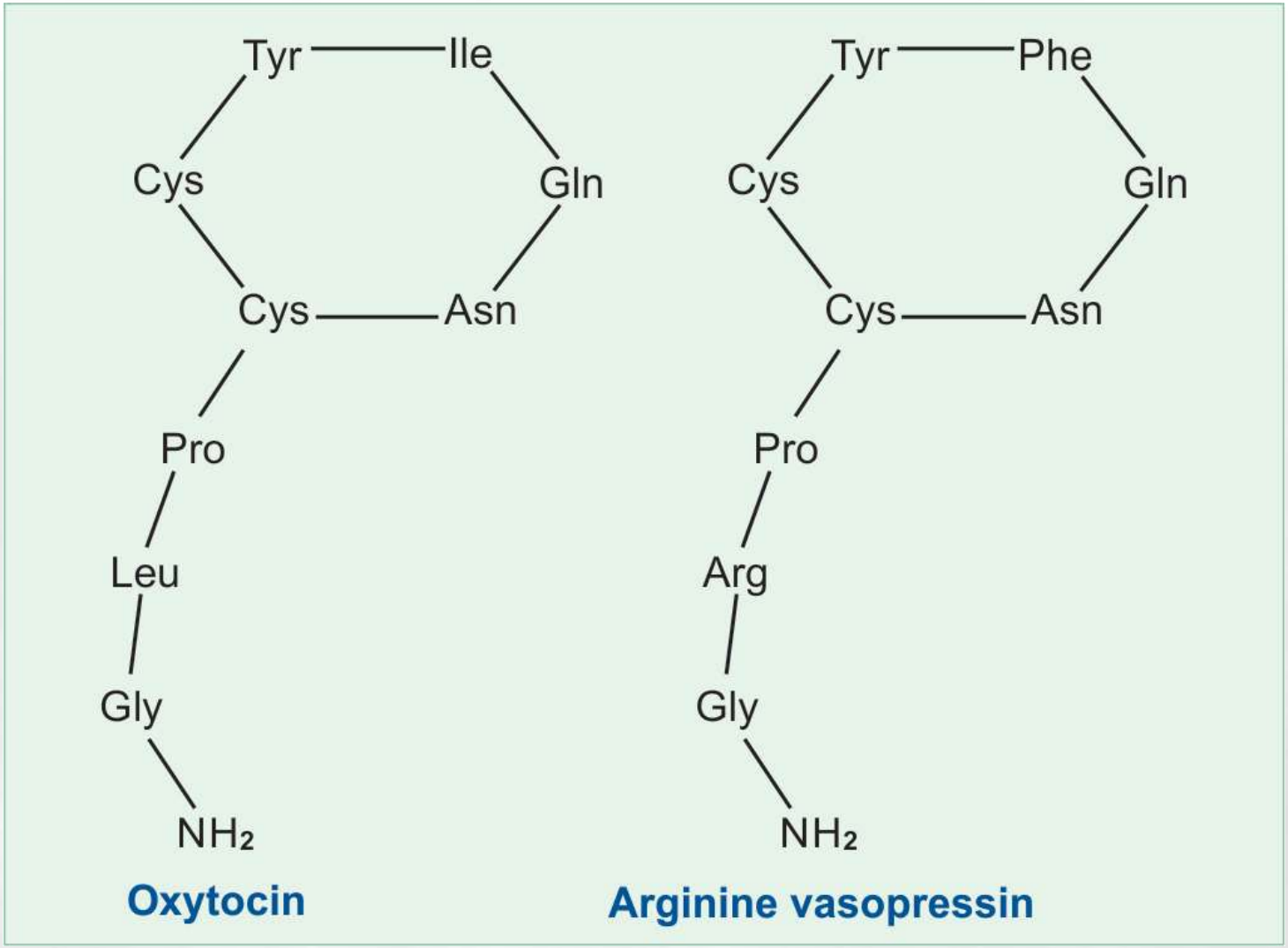
5. Important second messengers are cAMP, cGMP, Ca++, inositol 1,4,5-triphosphate (IP3), diacylglycerol (DAG).
6. Calcium channels may be transiently opened favoring signaling.
7. Second messengers can diffuse inside the cell, to the nucleus as well, to induce changes in gene expression.
8. Further downstream, G proteins activate other target molecules like PKA. Examples are, RTK signaling pathways, Ras/ERK pathways, JAK/STAT pathways and EGFR pathways.
9. Abnormalities in signal transduction lead to various clinical conditions, eg, Cancer is associated with deregulated signaling; in cholera there is excessive signaling; defective rhodopsin signaling leads to night blindness.

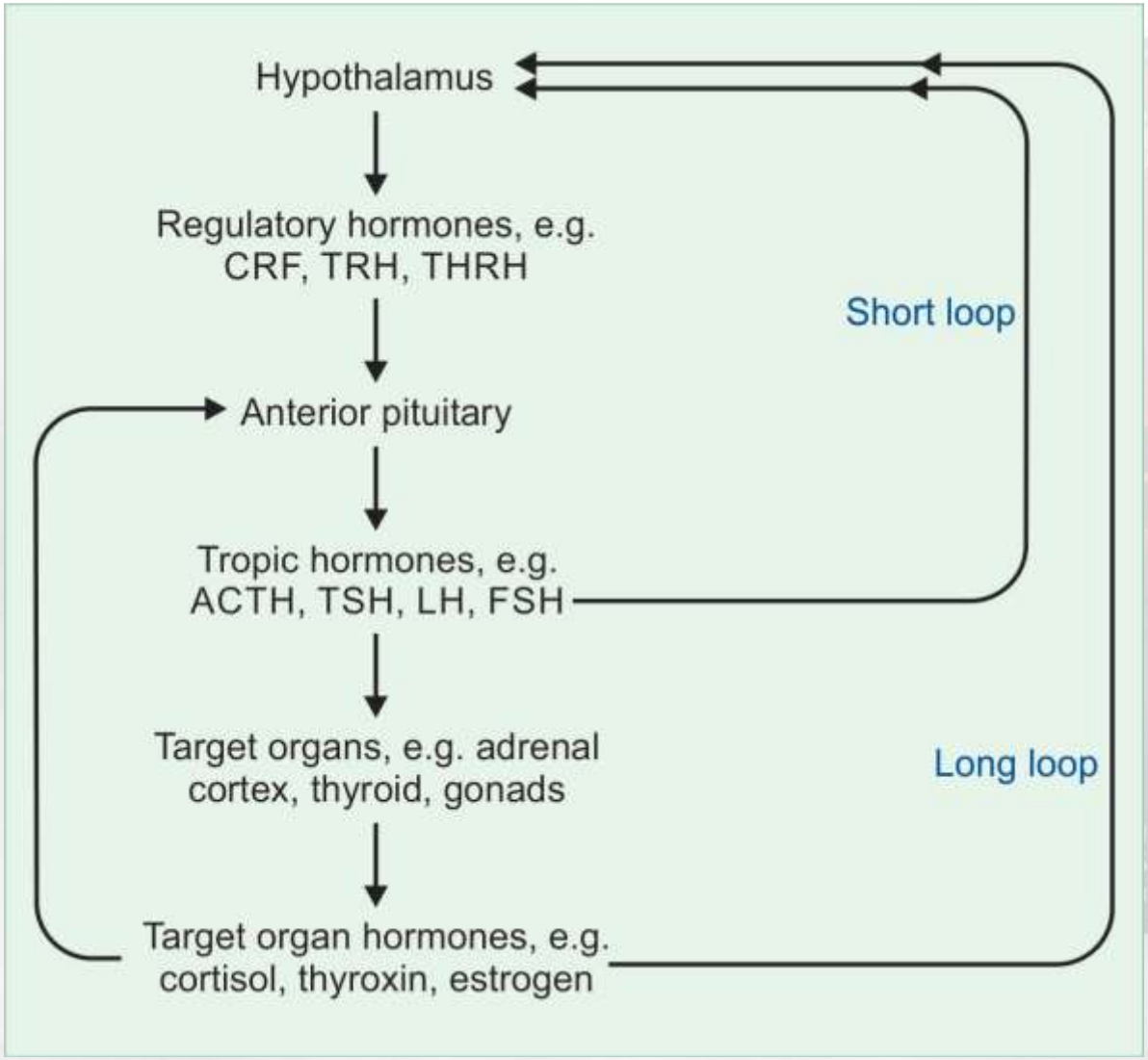
Hypothalamic and Pituitary Hormones

- Hypothalamus produces –
  - ➢ Hypothalamic neurpeptides
    - ✓ Antidiuretic hormone (ADH) or arginine vasopressin (AVP) – Prevents diuresis and reduces urine output.
    - ✓ Oxytocin
  - ➢ Hypothalamic releasing factors
    - ✓ TRH (thyrotropin releasing hormone), GnRH (gonadotropin releasing hormone), GHRH (growth hormone releasing hormone, CRF (corticotropin releasing factor), somatostatin, PIF (prolactin inhibitory factor) etc.

Hypothalamic Neuropeptides

- **ADH** acts on distal convoluted tubules of kidneys, producing water re-absorption.
- ADH is regulated by osmolality of blood; increase in osmolality increases ADH.
- Deficiency leads to diabetes insipidus.
- Excess secretion of ADH leads to SIADH (syndrome of inappropriate secretion of ADH).
- **Oxytocin** causes release of milk from breast.


Tyr
Ile
Cys
Gln
Cys
Asn
Pro
Leu
Gly
NH2
Oxytocin
Tyr
Phe
Cys
Gln
Cys
Asn
Pro
Arg
Gly
NH2
Arginine vasopressin



Long and short loops of feedback.

Hypothalamic releasing factor	Biological actions
TRH	Induces secretion of TSH, PRL; neuro-modulator
GnRH	Releases LH, FSH; induces spermatogenesis, ovulation and testosterone
GHRH	Stimulates growth hormone secretion
CRF	Release of ACTH; inhibited by cortisol
Somatostatin	Inhibits GH, TSH; inhibits gut hormones, pancreatic and gastric secretion
PIF	Inhibits prolactin release

Anterior Pituitary Hormones

- Following hormones are secreted by anterior pituitary –
  - Growth hormone (GH)
  - Adrenocorticotropic hormone (ACTH)
  - Luteinizing hormone (LH)
  - Follicle stimulating hormone (FSH)
  - Thyroid stimulating hormone (TSH)
  - Melanocyte stimulating hormone (alpha MSH)
  - Prolactin (PRL), beta endorphins
  - beta lipotropic hormone (bLPG)

Growth hormone (Somatotropin)

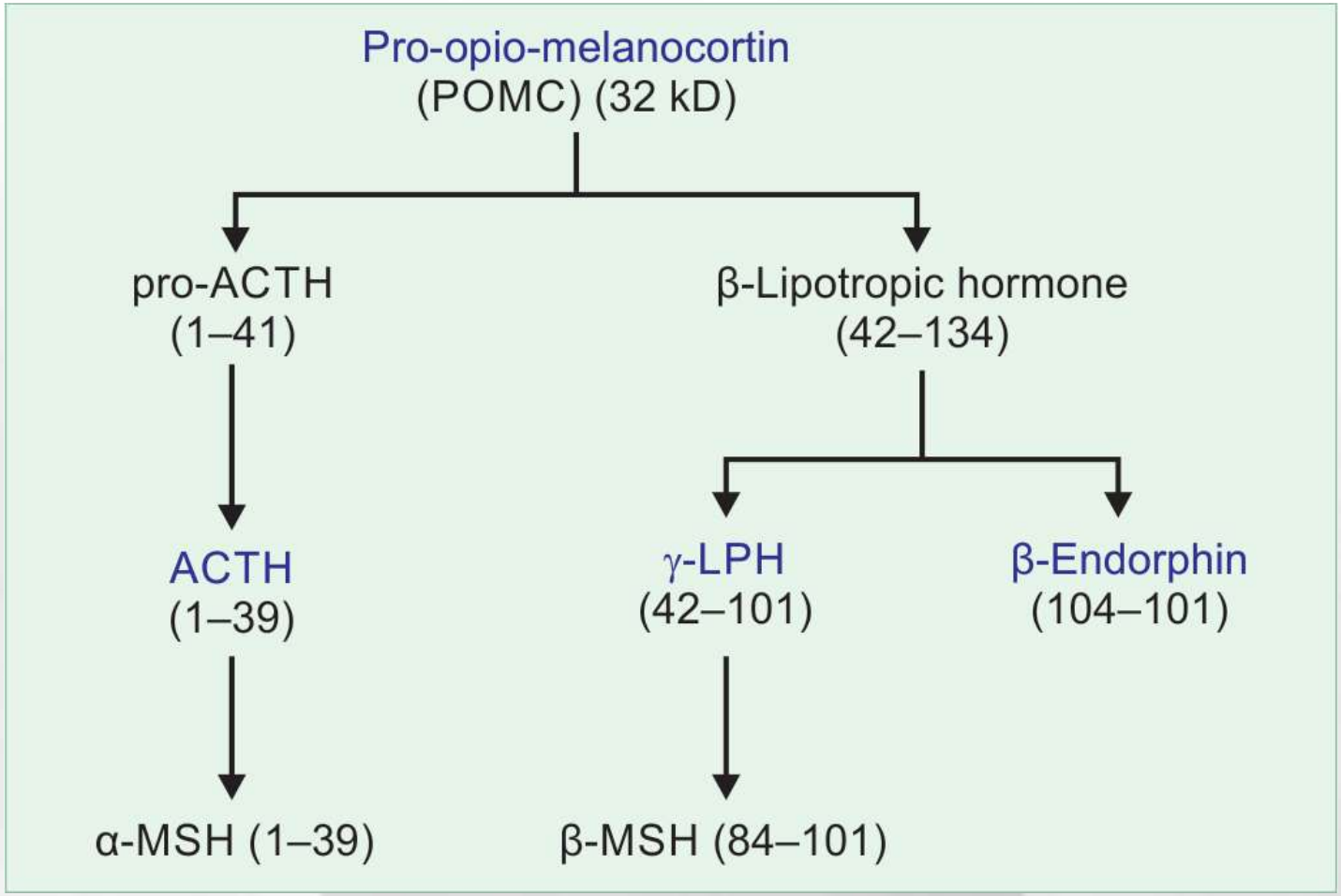
- Secreted by somatotropic cells of anterior pituitary.
- Regulated by balance between GHRH and GHIH (somatostatin).
- Hypoglycemia stimulates and hyperglycemia suppresses GH secretion.
- Effects are partially mediated by IGF-1.
- Excess GH leads to gigantism in children and acromegaly in adults.
- Deficiency leads to pituitary dwarfism in children.

ACTH

- Secreted as pro-opio-melanocortin (POMC), cleaved to about 30 different endorphins and diff hormones (αMSH, γLPH, βMSH, ACTH).
- ACTH binds to specific receptors on adrenal and activates adenylate cyclase raising cAMP.
- ACTH is released in a pulsatile manner, with a diurnal rhythm.
- Excess leads to Cushing's syndrome and deficiency is part of panhypopituitarism.

Endorphins and Glycoprotein Hormones

- Small peptides formed from POMC have endogenous morphine-like or opiate-like activity.
- Glycoprotein hormones of pituitary are TSH, FSH and LH.
- TSH increases secretion of thyroid hormones.
- TSH is stimulated by TRH and levels of thyroid hormones.
- High TSH is seen in primary hypothyroidism.
- Deficiency as part of panhypopituitarism.

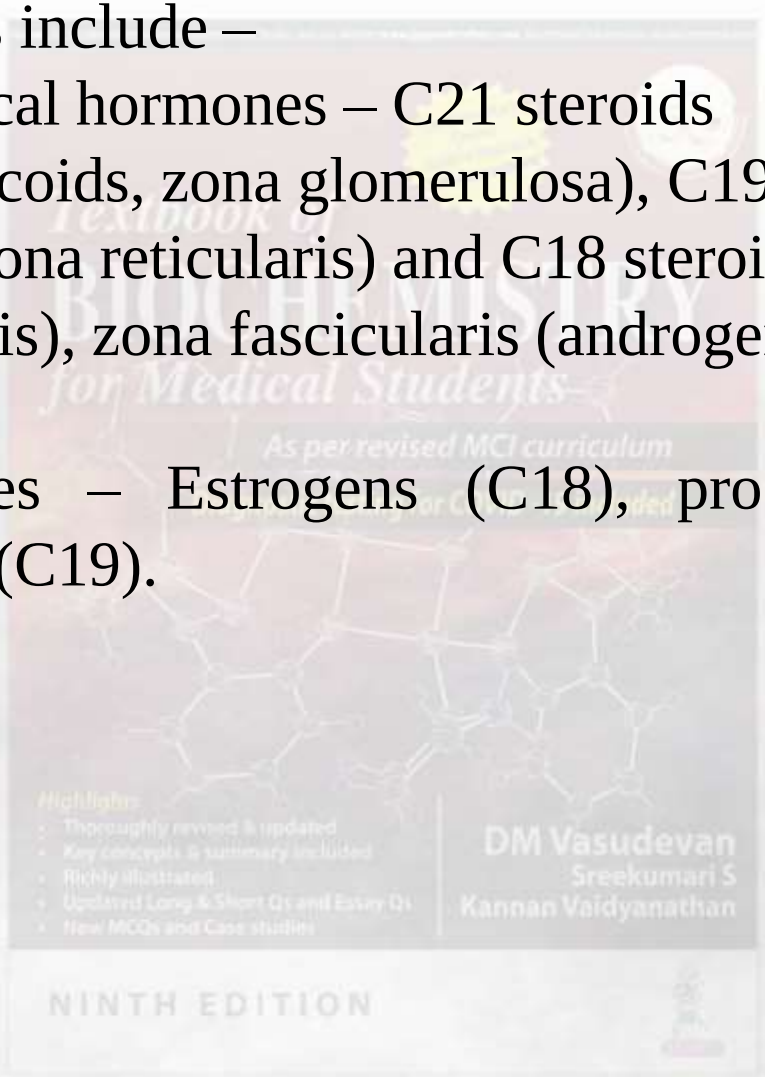


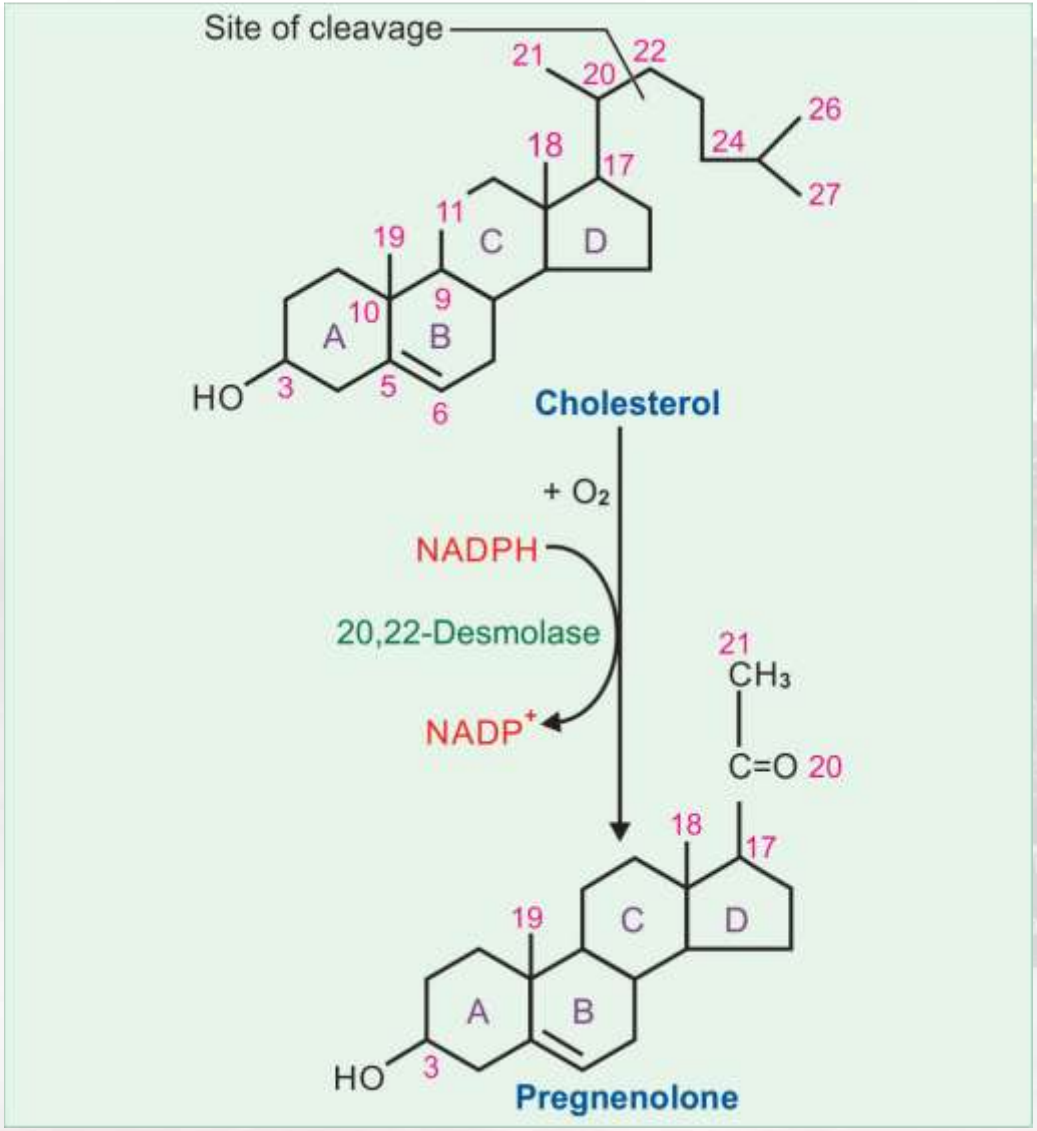
Cleavage of pro-opio-melanocortin (POMC). The numbers denote the amino acid sequence.

- Gonadotropins (LH, FSH) are secreted by pituitary.
- Placenta secretes hCG (human chorionic goandotropin).
- FSH stimulates growth of ovarian follicles in female and spermatogenesis in male.
- Testosterone (male) and progesterone (female) are increased by FH.
- FSH and LH regulated by GnRH.
- Abnormalities of gonadotropin secretion can lead to failure to achieve menarche/puberty (pre-pubertal deficiency), infertility, ovarian / testicular failure, amenorrhea / impotence, loss of libido (post-pubertal deficiency) whereas excess secretion can lead to precocious puberty.
- Hyperprolactinemia leads to infertility in female.

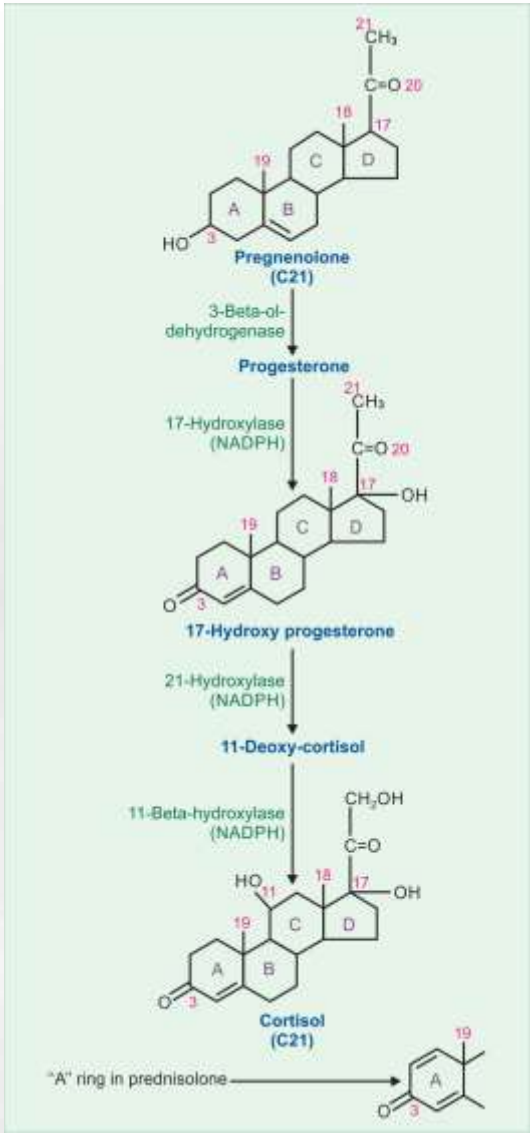
Steroid Hormones

- Steroid hormones include –
  - Adrenal cortical hormones – C21 steroids (mneralocorticoids, zona glomerulosa), C19 steroids (androgens, zona reticularis) and C18 steroids (estrogens, zona reticularis), zona fascicularis (androgens and estrogens, partially)
  - Sex hormones – Estrogens (C18), progesterones (C21), testosterones (C19).

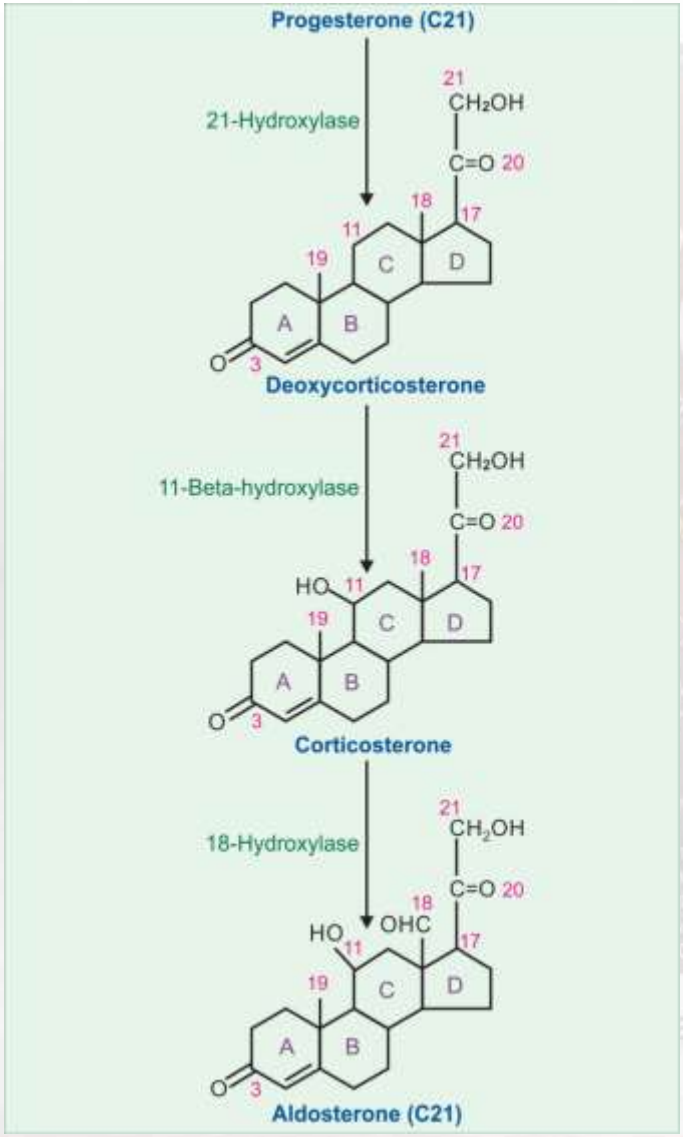




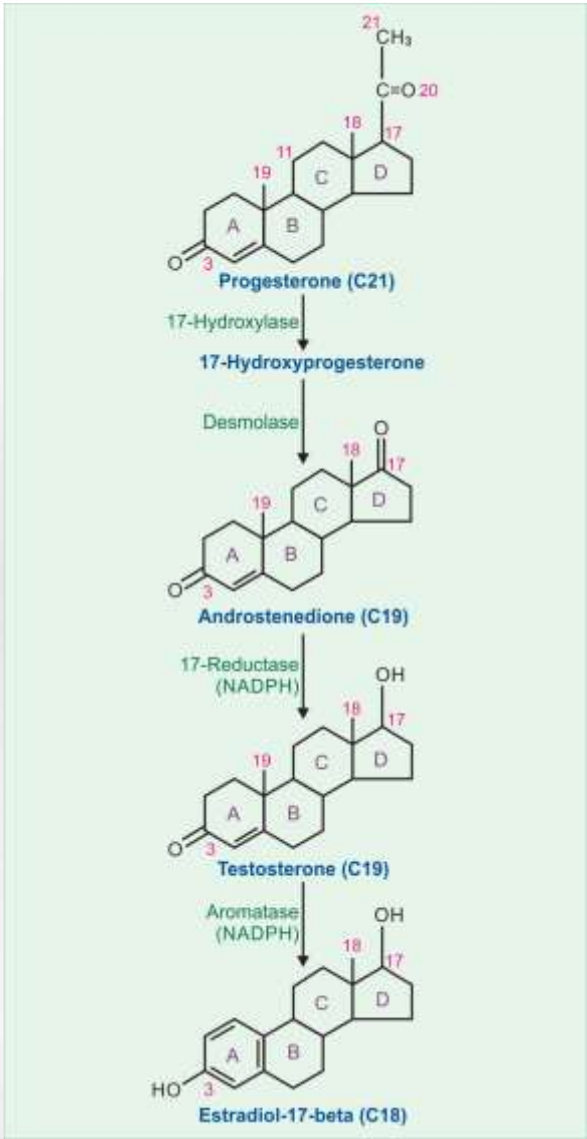
Synthesis of pregnenolone.



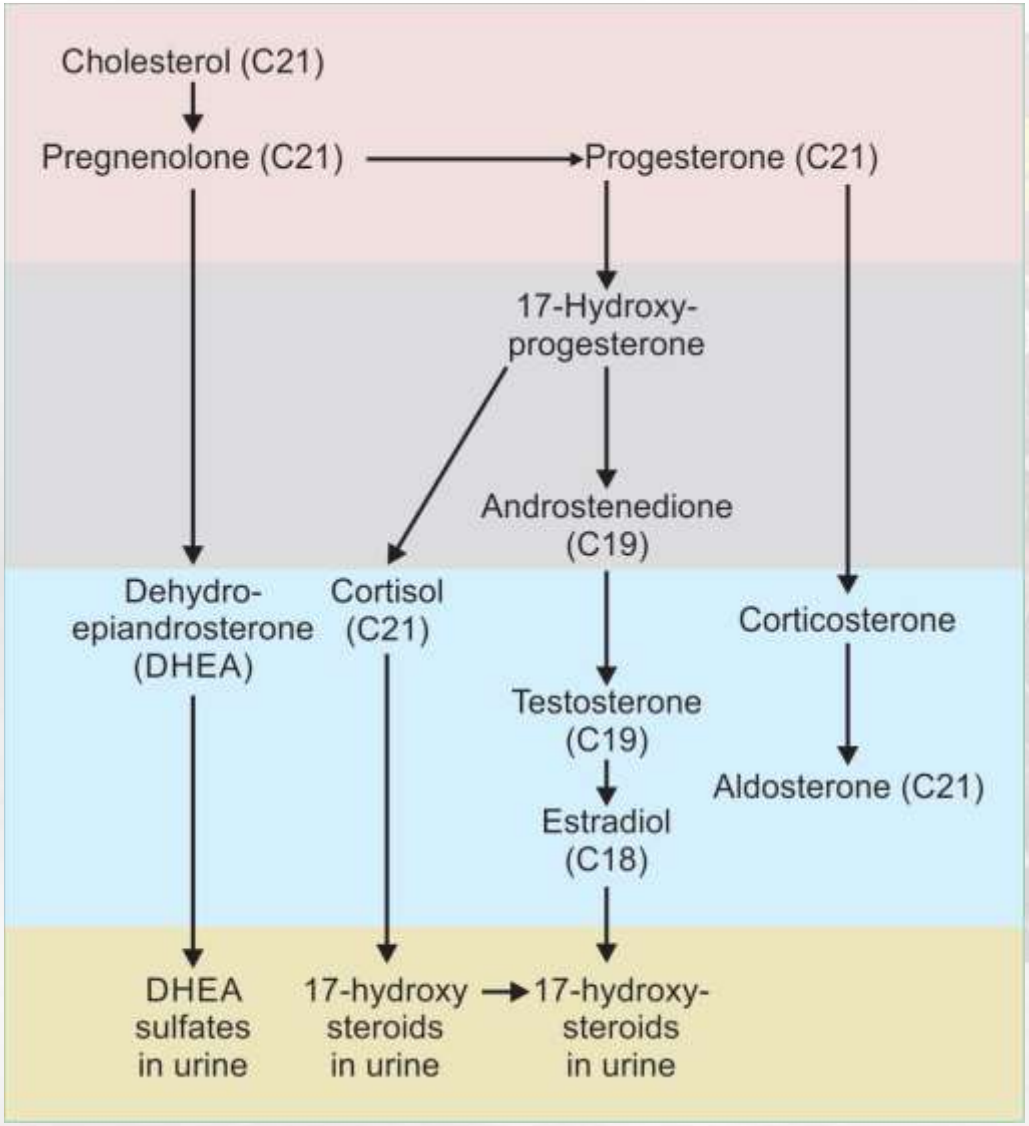
Cortisol synthesis.



Synthesis of mineralocorticoids.



Synthesis of sex hormones.



Summary of major pathways for production of glucocorticoids, mineralocorticoids and sex steroids. Precursors are shown in the red box; intermediaries in the gray box; hormones in the blue box; excretory products in the brown box.

- Urinary steroids – Also known as 17 keto-steroids and 17 hydroxy steroids, are derived from both adrenal steroids and androgens from gonads.
- The term 17 ketogenic steroids include all compounds with keto or hydroxy groups at 17^{th} position.
- Glucocorticoids have effects on carbohydrate, lipid and protein metabolism as well as effects on fluid and electrolyte metabolism, cardio-vascular, bone and calcium, connective tissues, immune systems and secretory actions.
- Major adrenal glucocorticoids are cortisol, cortisone and corticosterone.
- Under the control of ACTH.

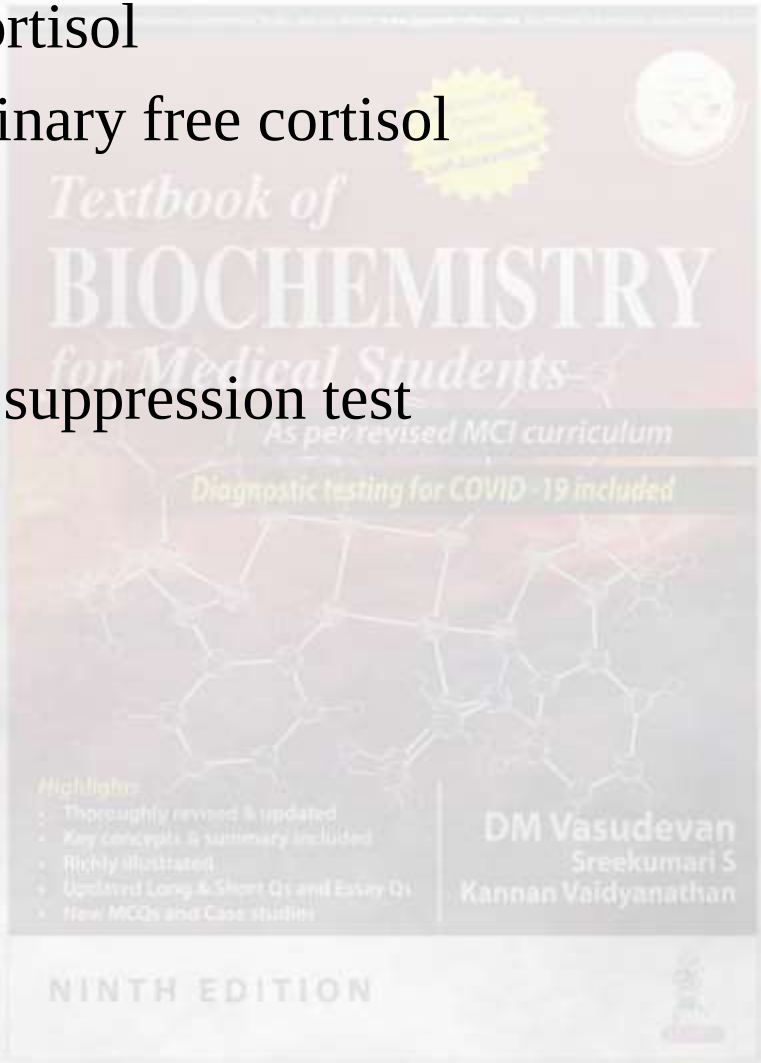
Effects of Glucocorticoids

System	Effect
Carbohydrates	Activity of transaminases and gluconeogenic enzymes (PC, PEPCK, F-1,6-BPase and GPase) are stimulated, increasing gluconeogenesis. Glycolytic enzymes (GK, PFK and PK) are suppressed. Decreased glucose uptake by peripheral tissues. All of them lead to hyperglycemia.
Lipids	Increase lipid mobilisation; facilitate lipolytic hormones leading to hyperlipidemia.
Proteins and nucleic acids	Catabolism of proteins and nucleic acids increased. Increase urea production.
Fluid and electrolytes	Promotes water excretion by increase in GFR and inhibition of ADH secretion.

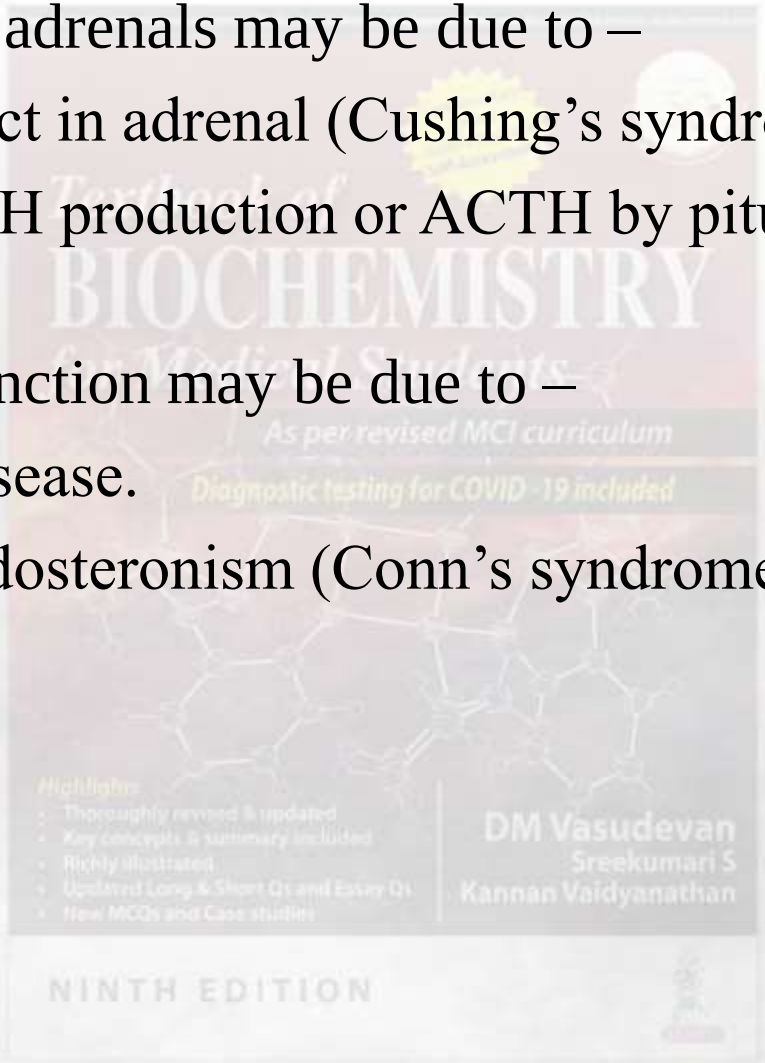
System	Effect
Secretory action	Stimulates secretion of gastric acid. Induces acid peptic disease.
Connective tissue	Impaired collagen formation. Poor wound healing.
Immune system	Immunosuppressant. Lysis of lymphocytes. Antiinflammatory and antiallergic.

Assessment of Glucocorticoid Function

1. Basal level of cortisol
2. Estimation of urinary free cortisol
3. Plasma ACTH
4. Urinary steroids
5. Dexamethasone suppression test
6. Stimulation test
7. Metyrapone test
8. CRH test.



- Hyperactivity of adrenals may be due to –
  - Primary defect in adrenal (Cushing's syndrome)
  - Ectopic ACTH production or ACTH by pituitary (Cushing's disease)
- Adrenal hypo-function may be due to –
  - Addison's disease.
- Primary hyperaldosteronism (Conn's syndrome) – Aldosterone secreting tumor.



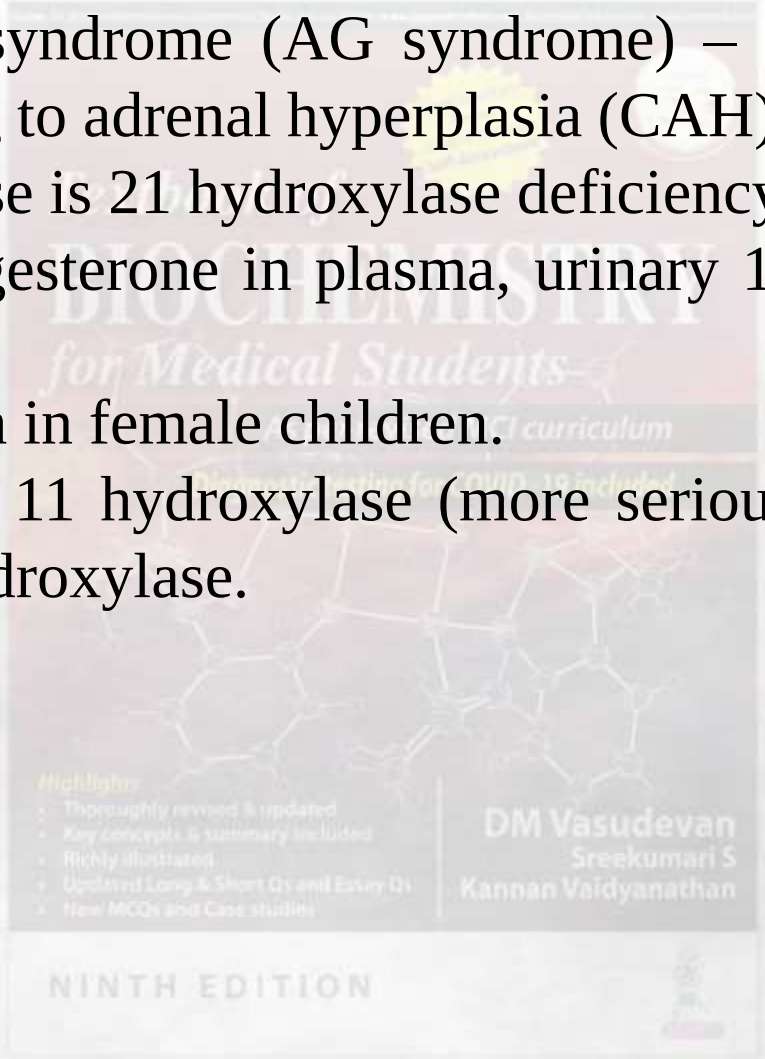
Findings in Adrenal Hyperfunction

Cause	Plasma cortisol	Urinary free cortisol	Plasma ACTH
Adrenal adenoma	Increased; diurnal rhythm is lost	Increased	**Decreased**
Adrenal carcinoma	Increased; diurnal rhythm is lost	Increased	**Decreased**
Pituitary adenoma	Increased; no diurnal rhythm	Increased	**Increased**
Ectopic ACTH production	**Increased; no diurnal rhythm**	**Increased**	**Increased**

Laboratory Findings in Adrenal Hypofunction

Cause of adrenal insuffi-ciency	Plas-ma cor-tisol	Urinary free cortisol	Plas-ma ACTH	ACTH stimulation	CRH stimulation	Na^+ & K^+ in blood
Primary	Low	Low	Elevated	No effect	No effect	**Na^+↓; K^+↑**
Secondary	Low	Low	Low	Normal/ exaggerated	No effect	**Na^+↓; K+↑**
Tertiary	**Low**	**Low**	**Low**	**Normal/ exaggerated**	**Exaggerated**	**Na^+↓; K+↑**

- Adreno-genital syndrome (AG syndrome) – Continuous ACTH secretion leading to adrenal hyperplasia (CAH).
- Commonest cause is 21 hydroxylase deficiency.
- 17 hydroxy progesterone in plasma, urinary 17 keto steroids are elevated.
- Hirsutism is seen in female children.
- Variants include 11 hydroxylase (more serious), 17 hydroxylase and rarely 18 hydroxylase.



Laboratory Findings in Adrenogenital (AG) Syndrome and Related Diseases

	17-hydroxy progesterone	Testo-sterone	DHEAS	LH	FSH
AG syndrome	↑↑	↑	↑	N or ¯	N or ¯
Simple hirsutism	N	slight ↑	slight ↑	N	N
Adrenal tumor	N	N or slight ↑	↑↑	N or ¯	N or ¯
Ovarian tumor	N	↑↑	N	N or ¯	N or ¯

DHEAS = dehydroepiandrosterone sulfate; N = normal.

Effects of Mineralocorticoids:

System	Effects
Sodium balance	Reabsorption of sodium from renal tubules
Potassium balance	Excretion of potassium in exchange for sodium at renal tubules
Water balance	Retention of sodium leads to water retention
ECF pH	Potassium loss leads to metabolic alkalosis

Aldosterone in Blood:

Increased levels are seen in primary aldosteronism such as Conn's syndrome (aldosterone secreting adenoma) and in bilateral adrenal hyperplasia.
Secondary aldosteronism is seen in the cases of abuse of diuretics, cardiac failure, cirrhosis of the liver with ascites, pregnancy, and chronic obstructive airway disease.

Decreased levels of aldosterone in the blood are seen in Addison's disease, renin deficiency, excess deoxycortisone secretion, and acute alcoholic intoxication.

Sex Hormones

- **Ovarian hormones** are C18 estogens, C19 androgens and C21 progesterone.
- Estogen antagonists (tamoxifen) are useful in breast cancer, because breast cancer in pre-menopausal women is estrogen dependent.
- **Testicular hormones** – Testosterone (human) and androstenedione (animals).
- Dihydrotestosterone (DHT) is responsible for male pattern of baldness.

Abnormalities in Sex Hormones

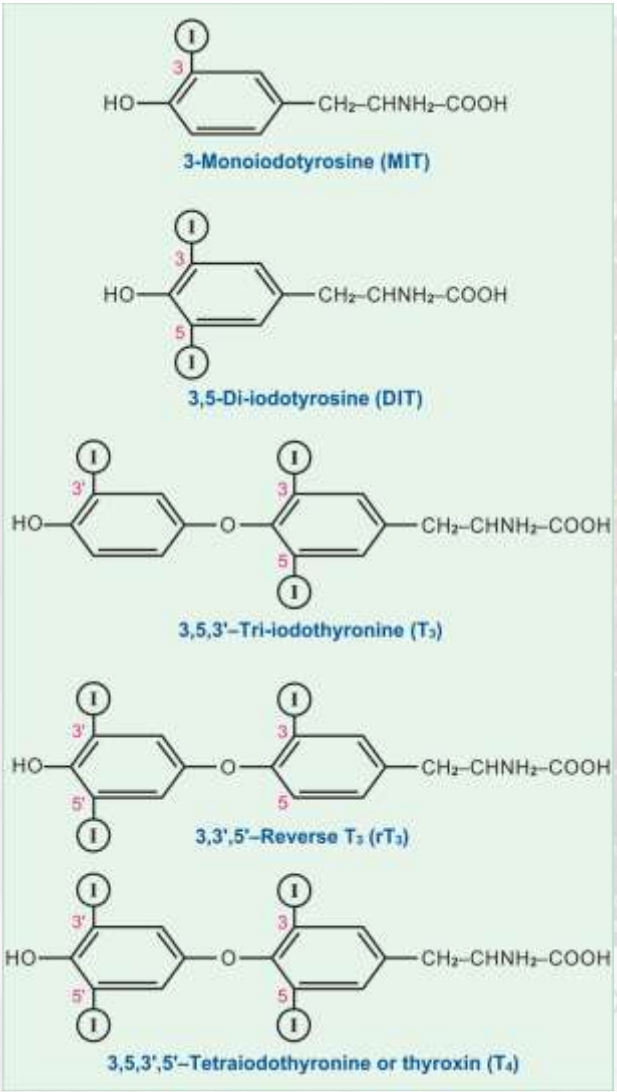
Disease	Laboratory findings
Primary testicular dysfunction	Low testosterone, high LH
Secondary testicular dysfunction	Hypopituitarism with low testosterone and LH levels
Delayed puberty	Deficiency of pituitary or gonadal hormones
Precocious puberty	Premature secretion of gonadotropins
Primary ovarain failure	Low estrogen, high LH, FSH
Virilization	High androgen, low estradiol, normal LH, FSH

Summary of Steroid Hormones.

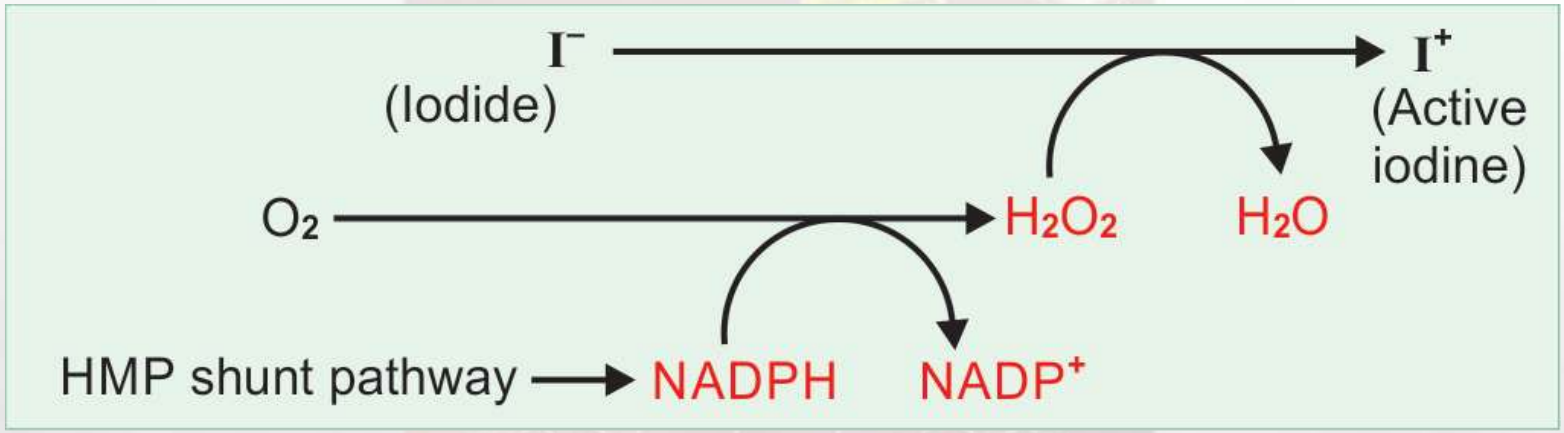
Hormone	Tissue of origin	Function
Estrogen (Estradiol)	Ovary	Maturation and function of female secondary sex organs
Estrogens	Placenta	Maintenance of pregnancy
Progestins (Progesterone)	Ovary	Implantation of ovum and maintenance of pregnancy
Progestins	Placenta	Mimic the action of progesterone
Androgens (Testosterone)	Testes	Maturation and function of male secondary sex organs
Glucocorticoids (Cortisol and corticosterone)	Adrenal cortex	Diverse effects on inflammation and protein synthesis
Mineralocorticoids (Aldosterone)	Adrenal cortex	Maintenance of salt balance

Thyroid Hormones

- Main hormones secreted by thyroid are T3 (tri-iodo thyronine) and T4 (tetra iodo thyronine, thyroxine).
- Necessary for proper functioning of all cells and for all biological processes.
- Hormones are derived from tyrosine by iodination.
- Thyroid hormone secretion is stimulated by pituitary thyrotropic hormone.
- TSH binds to receptors on thyroid cells and stimulates all steps in production and secretion of hormone.



Thyroid hormones and precursors



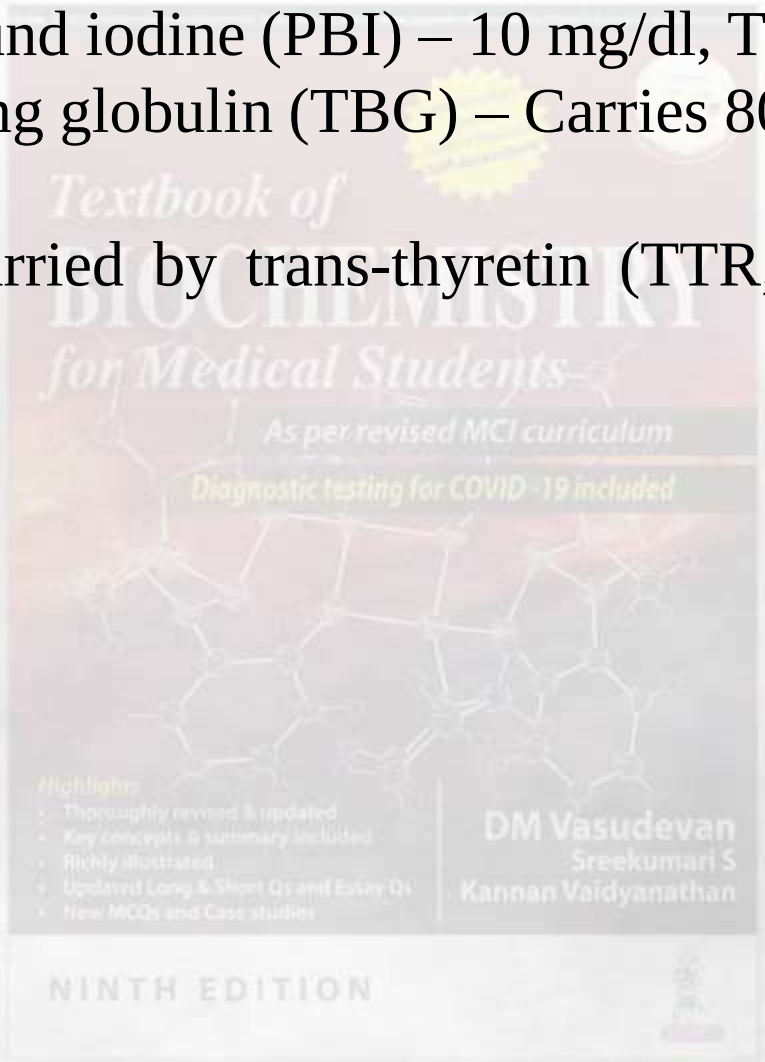
Step 2 of thyroxine synthesis.

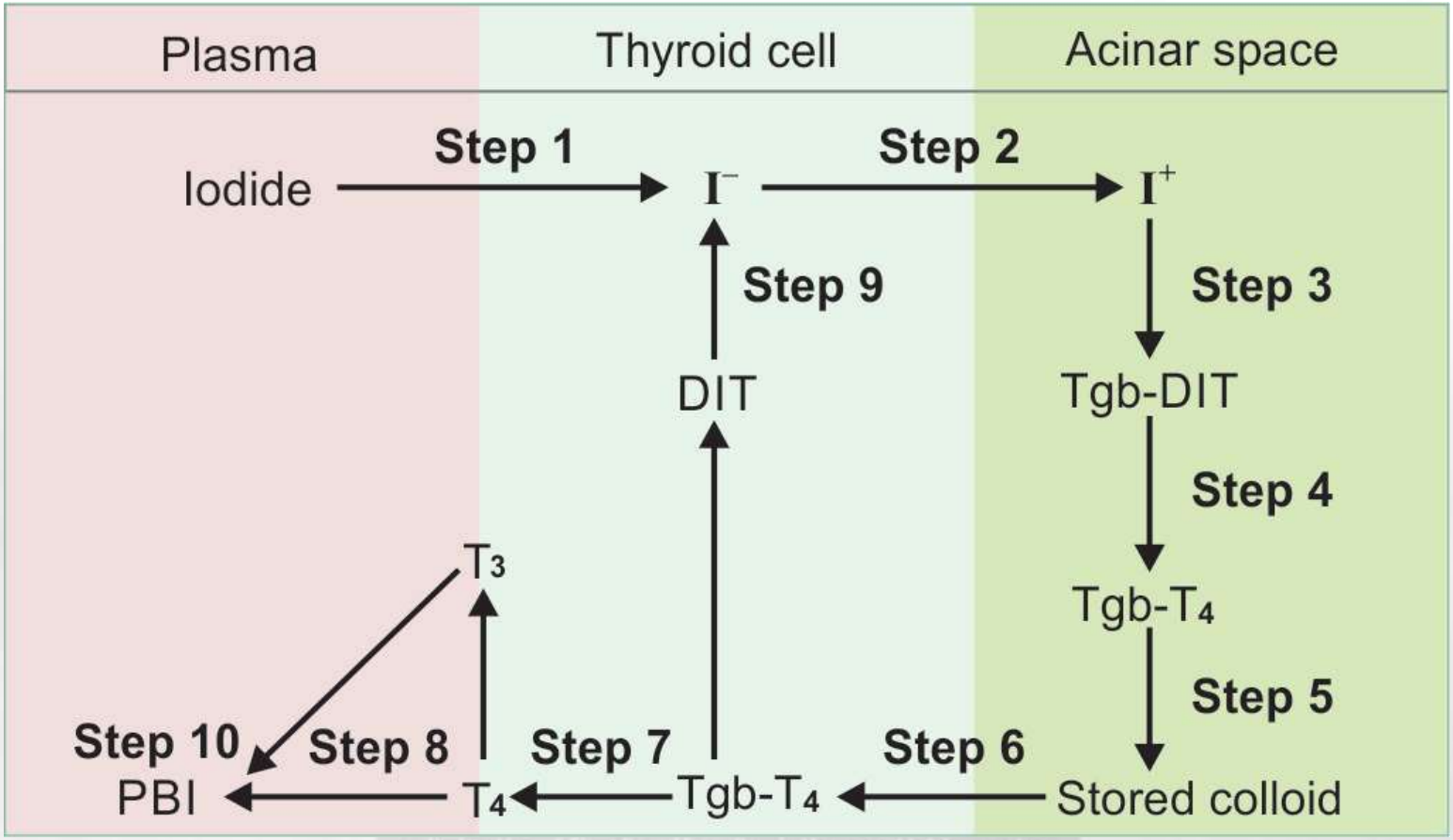
- Synthesis and secretion of thyroxine involves the following steps –
  - **Step 1** – Uptake of iodine (Uptake and concentration of iodine by thyroid). Inhibited by thiocyanate and perchlorate.
  - **Step 2** – Oxidation of iodine. Iodide oxidized to active iodine, catalyzed by thyroperoxidase. Stimulated by TSH and inhibited by anti-thyroid drugs (thiourea, thiouracil, methimazole).
  - **Step 3** – Iodination – Thyroglobulin (Tgb) is iodinated. Mono-iodo and di-iodo tyrosine (MIT, DIT) are produced.
  - **Step 4** – Coupling, T3 and T4 are formed. T3 is commonly formed by de-iodination of T4.

- **Step 5** – Storage. Stored Tg contains 8 T4 residues per molecule. Stored as colloid in thyroid.
- **Step 6** – Utilization – Tg is taken back when needed by pinocytosis.
- **Step 7** – Hydrolysis – T4 is liberated by hydrolysis by specific proteases. Enhanced by TSH. Depressed by iodide. KI is used as adjuvant in hyperthyroidism.
- **Step 8** – Release – Reverse T3 (rT3) is produced by de-iodination at 5' position.
- **Step 9** – Salvage of iodine. Re-utilization of MIT and DIT. Deiodinase defect is a genetic disorder. Iodine deficiency manifests and MIT and DIT are excreted in urine.

Transport of Thyroid Hormones

- Total protein bound iodine (PBI) – 10 mg/dl, T$ is 8 mg/dl.
- Thyroxine binding globulin (TBG) – Carries 80% T4 and 60% T3.
- Remaining is carried by trans-thyretin (TTR, pre-albumin) and albumin.





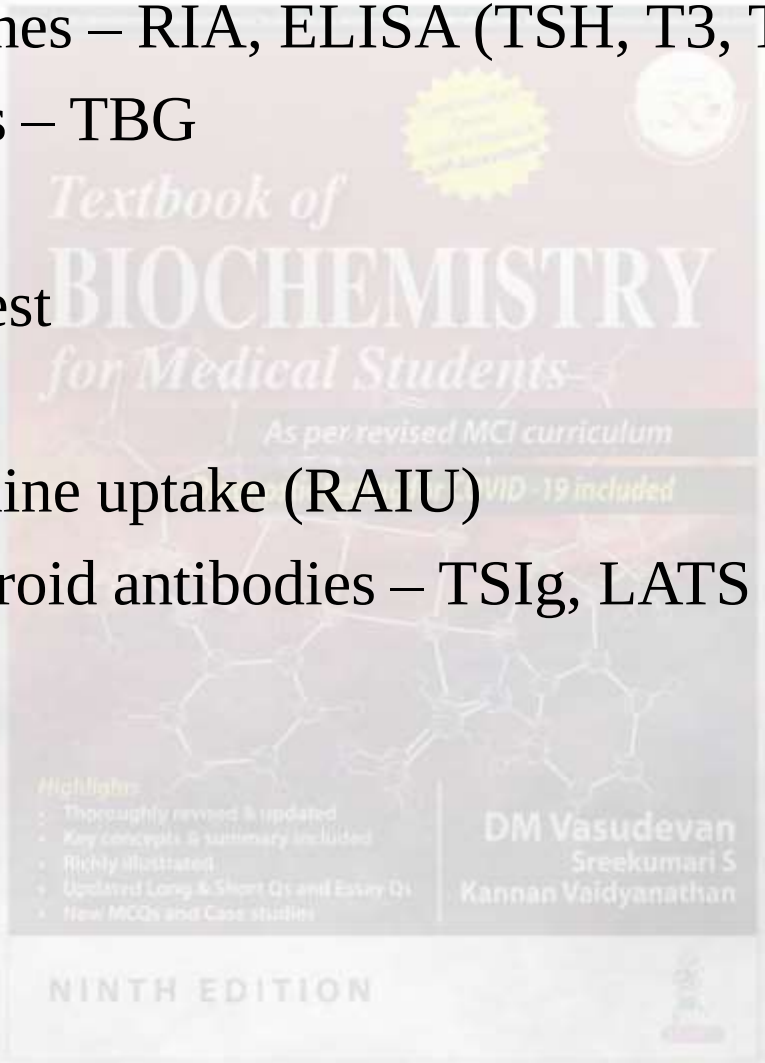
Metabolism of thyroid hormones.

Metabolic Effects of Thyroid Hormones

- Calorigenic effect (thermogenesis) – 1 mg / 1000 Cal. Uncoupling of oxidative phosphorylation. In large quantities, swells mitochondria.
- Increases BMR
- Increases cellular metabolism – RNA synthesis, increase in protein synthesis.
- High levels – Protein catabolism, negative N2 balance, loss of weight.
- Gluconeogenesis, CHO oxidation – Increased.
- Fat metabolism, cholesterol degradation – Increased.
- Differentiation of fibroblasts and osteoblasts.

Assessment of Thyroid Function

1. Assay of hormones – RIA, ELISA (TSH, T3, T4, fT3, rT3 etc)
2. Binding proteins – TBG
3. Plasma TSH
4. TRH response test
5. Cholesterol
6. Radio-active iodine uptake (RAIU)
7. Detection of thyroid antibodies – TSIg, LATS



Abnormalities in Thyroid Function

- Hyperthyroidism (Thyrotoxicosis) – Sustained high levels of thyroid hormones.
- Increased rate of metabolism, weight loss, tachycardia, fine tremors, sweating, diarrhea, emotional disturbances, anxiety, sensitivity to heat.
- Causes – Increase in binding protein, increased affinity of binding protein, effects of auto-antibodies, TSH secreting tumors, receptor defects, 5'-deiodinase deficiency.
- Causes - Graves' disease, toxic goitre, excess intake of thyroid hormones, rarely TSH secreting tumors.
- Hypothyroidism – Due to low circulating levels of thyroid hormones.
- Commonly due to primary thyroid disease (auto-immune) in adults leading to myxedema.

- Lethargy, tolerance to heat, cold intolerance, slow heart rate, weight gain, dry coarse skin, mental dullness, physical slowness.
- In children, mental and physical retardation – Cretinism.
- Maternal hypothyroidism may produce cretinism.
- Hypothyroidism may result from treatment of hyperthyroidism using anti-thyroid drugs or radioactive iodine.
- Replacement is successful.
- Secondary hypothyroidism – Pituitary or hypothalamic causes.
- Euthyroid goitre – can result from iodine deficiency, raised TSH stimulates hyperplasia, hormone levels are sometimes normal.

Laboratory Findings in Hyperthyroidism

Condition	Plasma total T3, T4	Plasma TSH	Response to TRH
Graves' disease	Increased	Decreased	Nil
Toxic goitre	Increase	Decrease	Nil
T3 toxicosis	T3 increase, T4 normal	Decrease	Sluggish
Excess intake of thyroxine	Increase	Decrease	Sluggish

Laboratory Findings in Hypothyroidism

Condition	T3, T4 in blood	TSH in blood	Response to TRH
Primary hypothyroidism	Decreased	Increased	Exaggerated response
Secondary hypothyroidism	Decreased	Decreased	No response

Antithyroid antibodies

Anti thyroperoxidase antibodies (Anti TPO) formerly called antimicrosomal antibodies are sensitive markers of **Hashimoto's thyroiditis.**

In **Grave's disease**, thyroid stimulating immunoglobulin (TSIg), previously known as long acting thyroid stimulator (LATS) is seen in the circulation. TSH receptor is a target for both blocking (antiTSHRB)and stimulating (AntiTSHRS) antibodies. Stimulating antibodies are seen in Graves (TSIg) and blocking in hypothyroidism.

Important Peptide Hormones of Gastro Intestinal Tract

Name	Site of Origin	Structure	Function
Cholecysto-kinin (CCK)	Cells of duodenum, jejunum	33 amino acids	Stimulates gallbladder contraction and bile flow, increases secretion of digestive enzymes from pancreas
Enkephalins	CNS, stomach, duodenum, gallbladder	Pentapeptides (2 forms, met-enkephalin and Leu-enkephalin	They bind to opiate receptors, opiate-like actions
Gastrin	Gastric antrum, duodenum	17 amino acids	Stimulates acid and pepsin secretion, also stimulates pancreatic secretions

Name	Site of Origin	Structure	Function
Ghrelin	Stomach and hypothalamus	28 amino acids; acylated on Ser3 with n-octanoic acid	Increases appetite, stimulates NPY release, energy homeostasis, gastric secretion and emptying, insulin secretion
Glucagon	Alpha cells of pancreas	29 amino acids	Increases lipid mobilisation; glycogenolysis
Glucagon-like peptide (GLP-1)	L cells in ileum and colon	Two forms: 31 amino acids, GLP-1 (7-37)	Potentiates glucose-dependent insulin secretion, inhibits glucagon secretion, inhibits gastric emptying

Name	Site of Origin	Structure	Function
Secretin	S cells of duodenum, jejunum	27 amino acids	Stimulates pancreatic bicarbonate secretion so that gastric HCl is maintained. It also inhibits gastric secretion
Somato-statin (SS)	Delta cells of pancreas, gut and hypothalamus	14 amino acids variety by hypothalamus; 28 amino acids by GIT	Inhibits release of numerous gut peptides, e.g. CCK, gastrin, secretin, motilin, GIP; insulin and glucagon
Vasoactive intestinal peptide (VIP)	Pancreas, hypothalamus	28 amino acids	Relaxes smooth muscles of GI, stimulates pancreatic bicarbonate; inhibits acid and pepsin secretion; neuro-transmitter

Signal Molecules

Hormones regulating food intake - Hunger and Satiety signals	**Ghrelin – Hunger signal**	**Glucagon like peptide (GLP)**	**GIP-insulinotropic peptide**	**Somatostatin**	**Neuropeptide Y**
Hormones regulating digestion	Gastrin group-Gastrin, Cholecysto-kinin (CCK)	Secretin group Secretin, VIP, Glucagon, GLP1, GLP2, GIP	Pancreatic polypeptide group PP, Neuropeptide Y	Guanylin	Serotonin
Adipose tissue derived hormones Adipo-kines	Leptin	Adiponectin	Resistin		

Growth factors	**Cytokines**	**Lympho-kines Interferons**	**Erythro-poetin (EPO) Thromboetin Thrombo-modulin**	**EGFR, FGF, GCSF, GMCSF, MCSF, PDGF**	**HGF, VEGF, IGF,**
Enzymes involved in signal transduction	ERK/ MAP/ ERK pathway	Glycogen synthase kinase 3 (GSK3, Janus kinase (JNK)	MAP kinase MAPKK APK P38MAPK	P70S6Kinase	PARP TNFR
Specialised proteins	Adhesion molecules Cadherin, selectin, VCAM	Receptors cKit, HGFR, Her-2, IGFR,	p53, HMGB, HIF, PIGF, MIP, MMPs, MCP1	Osteocalcein, Osteonectin, Osteopontin, osteo-prolegen	Protein C, rantes, Rb protein, Tau