BIOCHEMISTRY

Biochemical Endocrinology
March 31st – April 7th 2022

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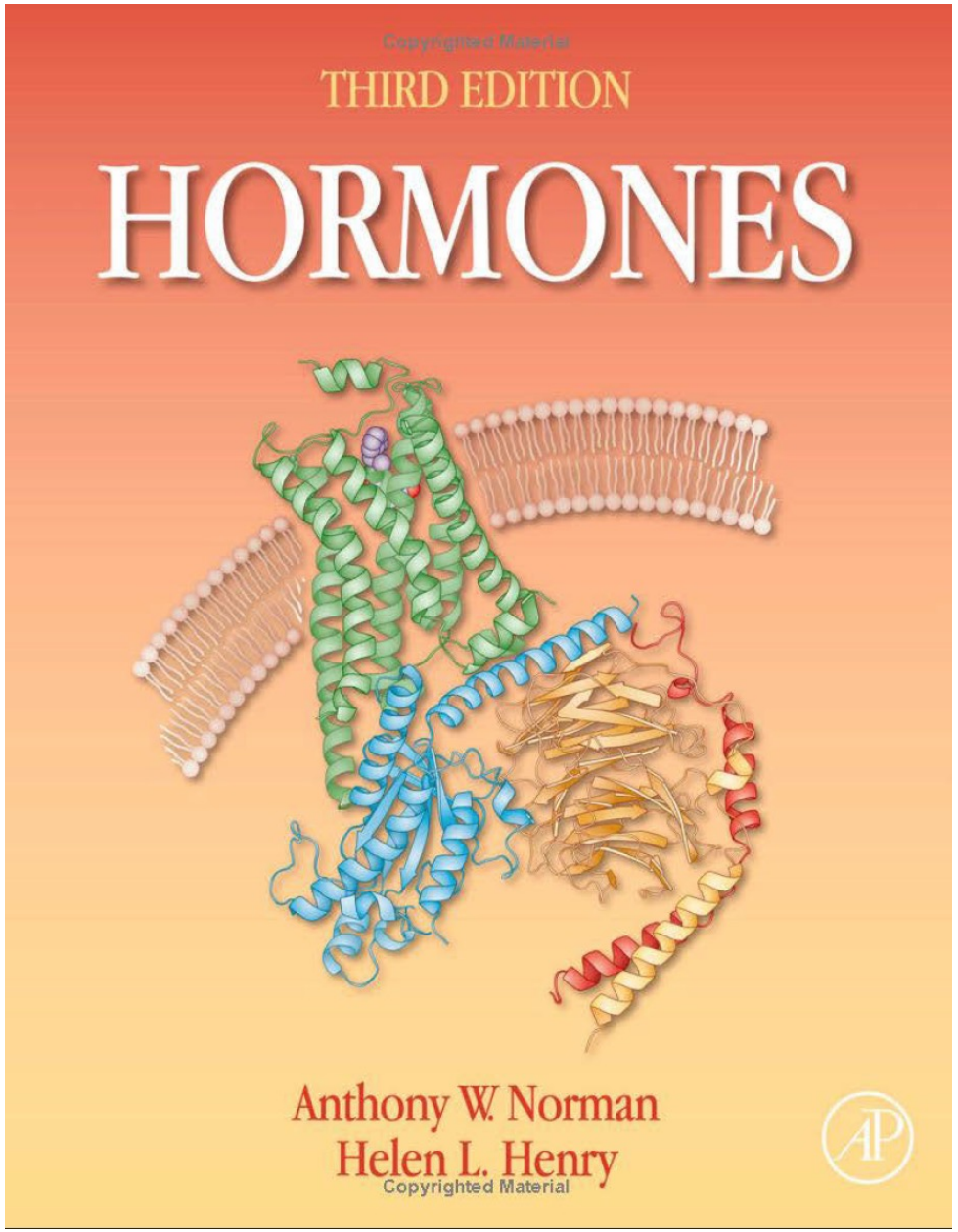
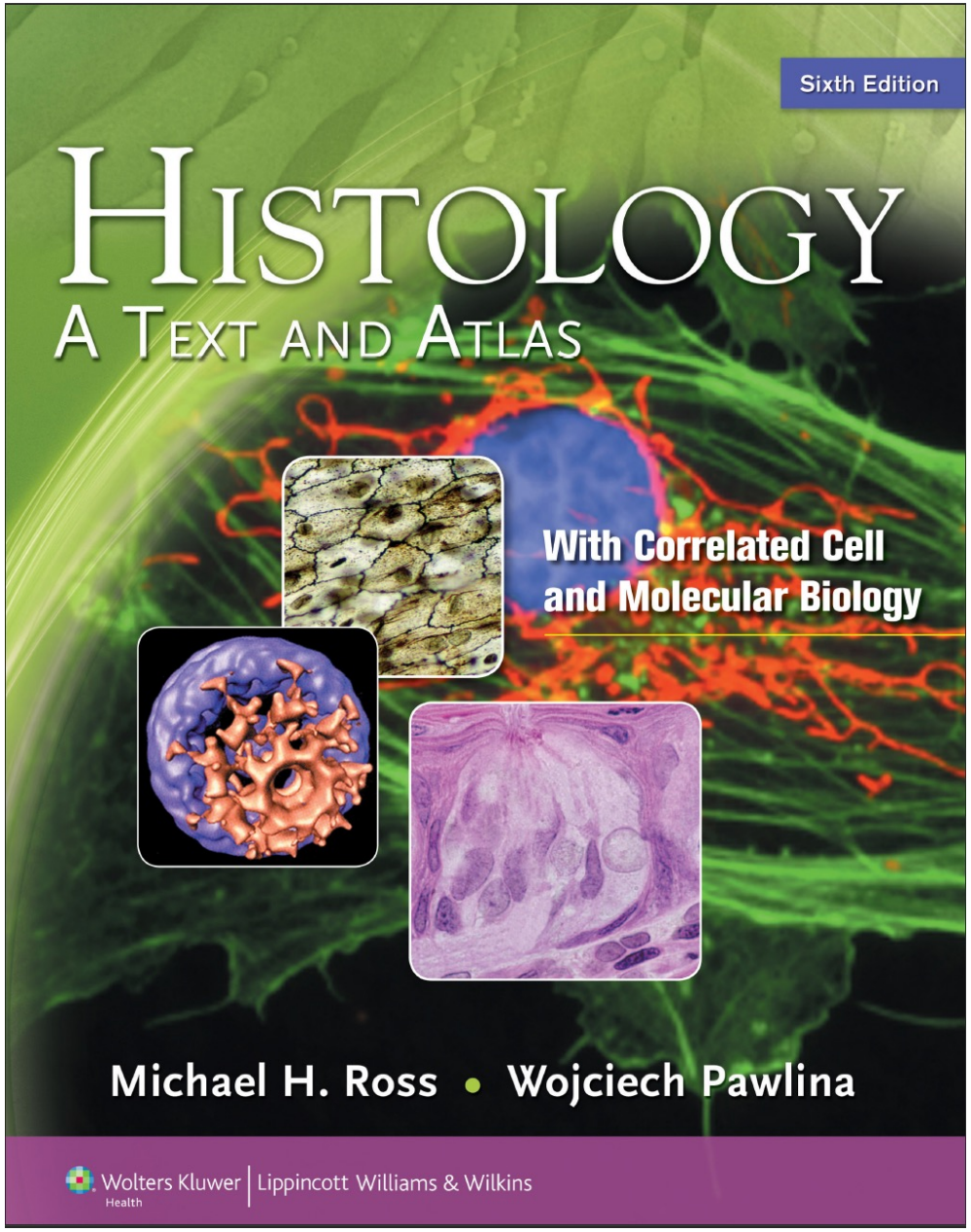
Course Outline

WEEK	TOPIC	LECTURER (S)
WEEK 20 **21-25/02/2022**	**Gene regulation: Structural and transcriptional regulation of gene expression in prokaryotes and eukaryotes repression and induction of transcription of prokaryotic gene, bacterial operon concept, negative vs positive control, other regulatory mechanisms.**	**Dr. Mulinge**
WEEK 21 28-04/03/2022	DNA repair and DNA recombination. Disease/syndromes associated with DNA repair	,,
WEEK 22 07 - 11/03/2022	Molecular virology: Classification and properties of viruses, replication and life cycle of viruses. Interferons, Oncogenes and oncogenic viruses. Viroids and prions. Application –HIV	,,
WEEK23 14 - 18/03/2022	Molecular virology: Classification and properties of viruses, replication and life cycle of viruses. Interferons, Oncogenes and oncogenic viruses. Viroids and prions. Application –HIV	,,
WEEK 24 21 - 25/03/2022	Bacterial Biochemistry: Bacterial cell structure: Cell envelope; Cell cytoplasm; Cellwall and its biosynthesis. Bacterial toxins, virulence and pathogenesis.	,,
WEEK 25 28 - 01/04/2022	Bacterial chemotherapy: Mechanisms of action of antibiotics Bacterial resistance to antimicrobial chemotherapy.	,,
WEEK 26 04 - 08/04/2022	Biochemical endocrinology: Endocrine, paracrine and autocrine mode of secretions. Classification of hormones. Mechanism of hormone action: Signal and signal transduction, Receptors: intracellular and membrane bound receptors. Second messenger role in signal transduction: cAMP, cGMP, lipids, Calcium ions.	,,
WEEK 27 11 - 15/04/2022	Biochemical endocrinology: Synthesis, storage, release, transport, mode of action and degradation of peptide, steroid and prostaglandins derived hormones	,,
12/04/2022	MID 2nd SEMESTER CAT	Dr Mulinge

ENDOCRINOLOGY





ENDOCRINE SYSTEM – an Overview

- ✓ The endocrine system produces various secretions called hormones [Gr. hormaein, to set in motion] that serve as effectors to regulate the activities of various cells, tissues, and organs in the body.
- ✓ Its functions are essential in maintaining homeostasis and coordinating body growth and development and are similar to that of the nervous system: Both communicate information to peripheral cells and organs.
  - ✓ Communication in the nervous system is through transmission of neural impulses along nerve cell processes and the discharge of neurotransmitter.
  - ✓ Communication in the endocrine system is through hormones, which are carried to their destination via connective tissue spaces and the vascular system.

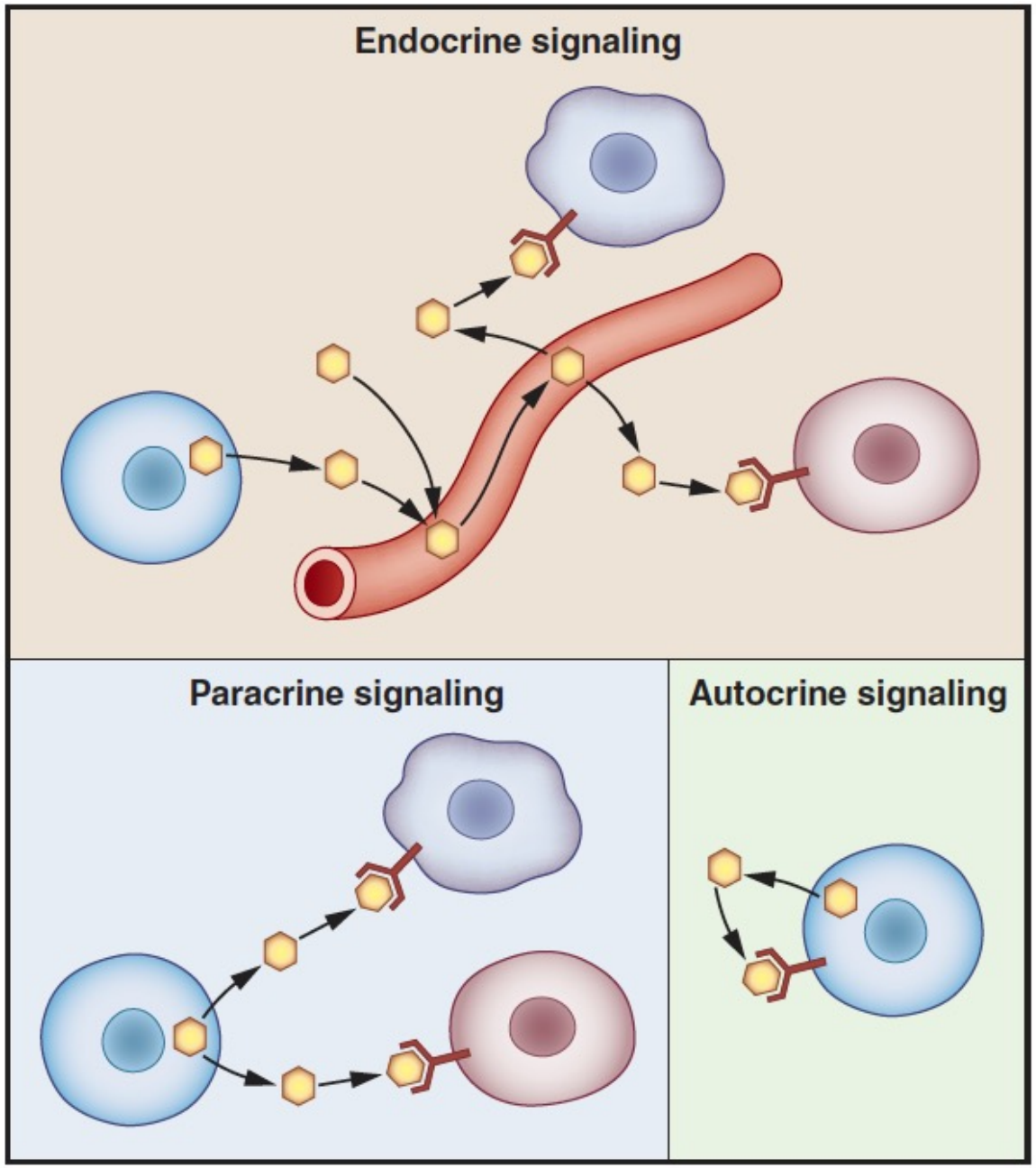
These two systems are functionally interrelated.

- ✓ The endocrine system produces a slower and more prolonged response than the nervous system.
- ✓ Both systems may act simultaneously on the same target cells and tissues, and some nerve cells secrete hormones.

Hormones and their receptors

For years this endocrine control of target tissues became a central part of endocrinology. Recent research shows that a variety of hormones and hormonally active substances are not always discharged into the bloodstream but are released into connective tissue spaces.

- They may act on adjacent cells or diffuse to nearby target cells that express specific receptors for that particular hormone. This type of hormonal action is referred to as paracrine control.
- In addition, some cells express receptors for hormones that they secrete. This type of hormonal action is referred to as autocrine control. These hormones regulate the cell's own activity.

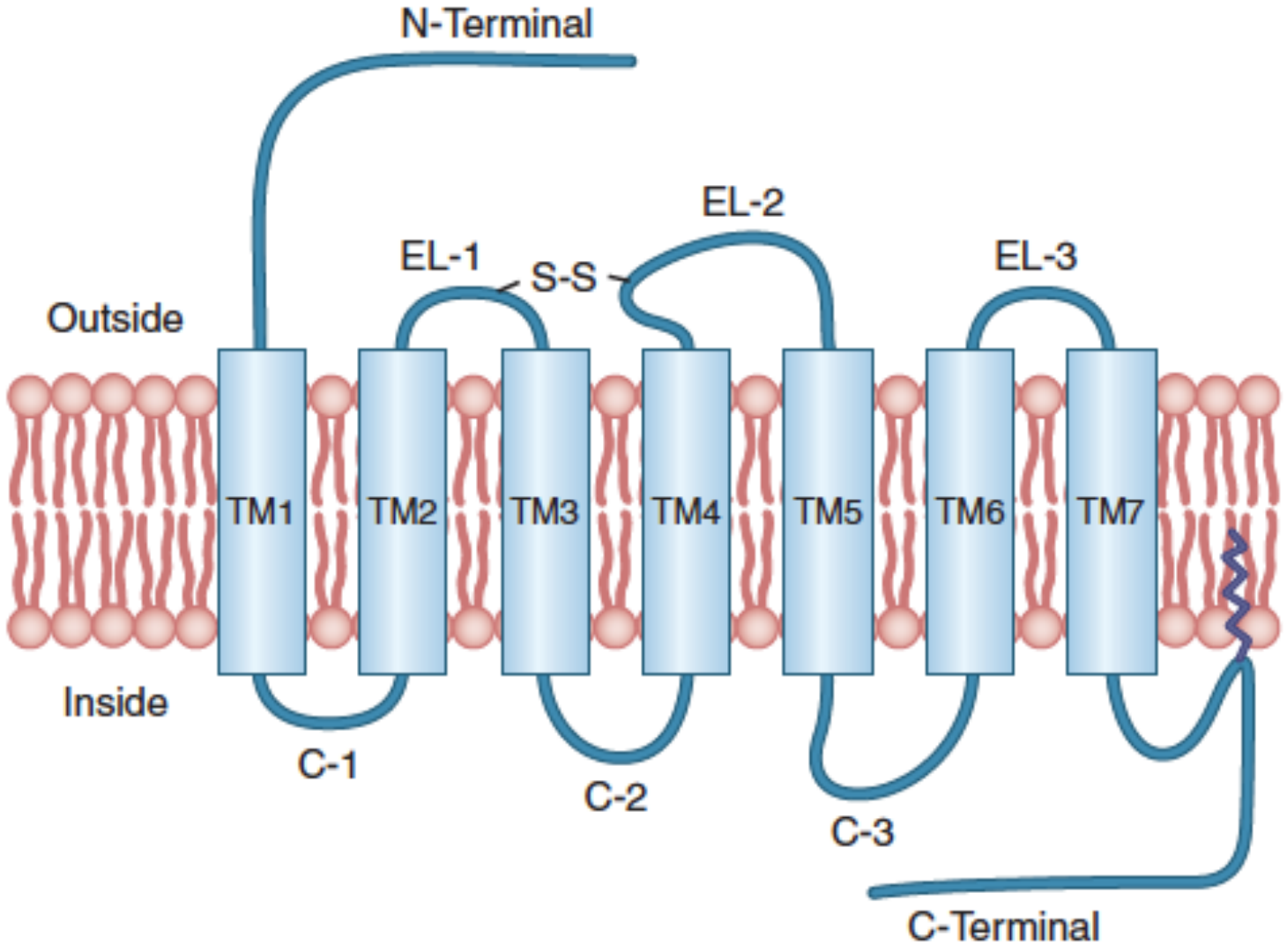


Mechanisms of Hormone action

Hormones interact with receptors that are located either inside the cell or within the cell membrane.

Cells are exposed to many hormones.

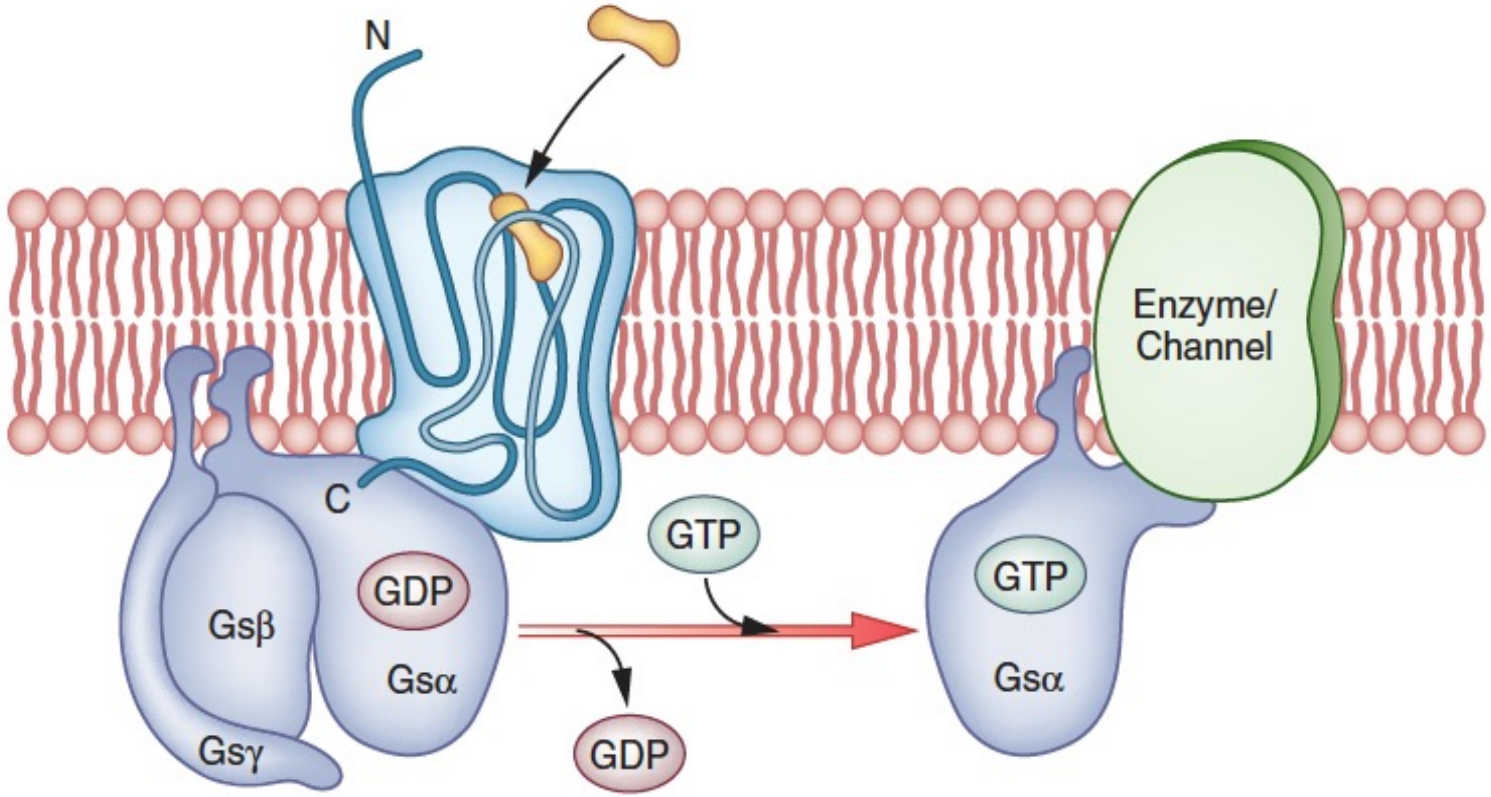
- Whether a given hormone will elicit a response in a particular cell depends on the complement of receptors that the cell contains.



Mechanisms of Hormone action: G-protein coupled receptors

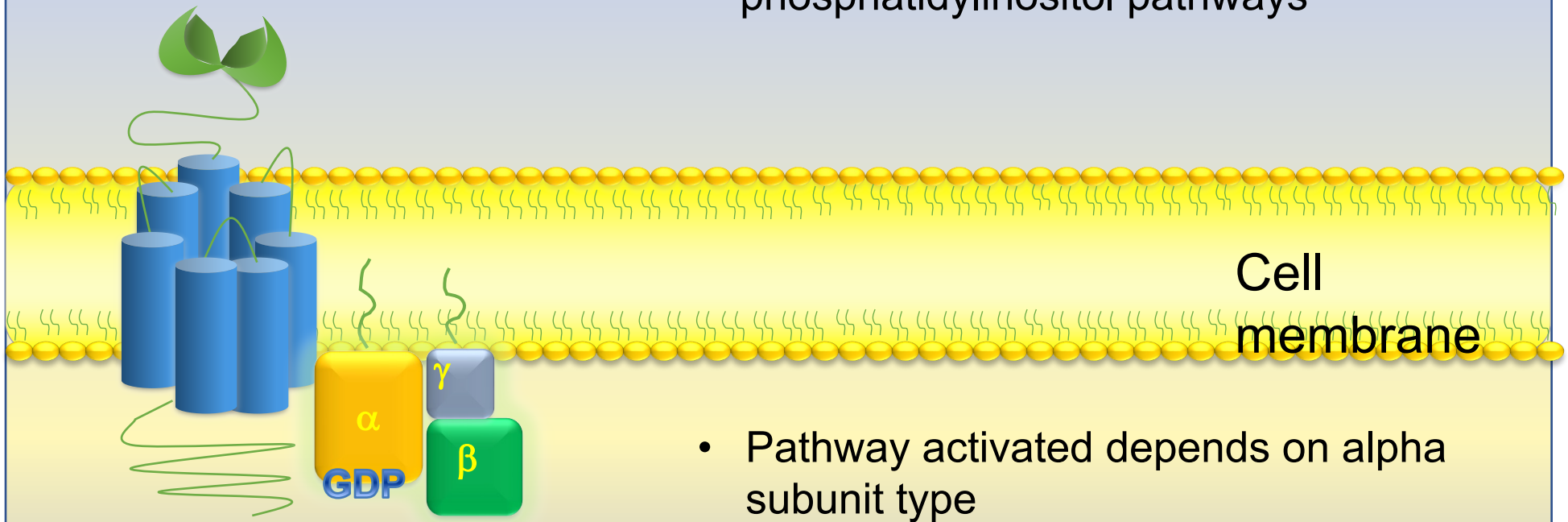
Receptor interaction with G-protein. Inactive G-proteins (left) consist of three subunits in a heterotrimer, α, β, and γ.

- Two of the subunits, α and γ, have lipid moieties binding them to the membrane and GDP is bound to the α-subunit.
- When a ligand binds to the receptor and activates it, GDP is replaced with GTP; the α-subunit dissociates from the trimer and moves through the membrane to a nearby protein, an enzyme or ion channel, for example, and activates it, initiating the biological response



G-protein coupled receptors

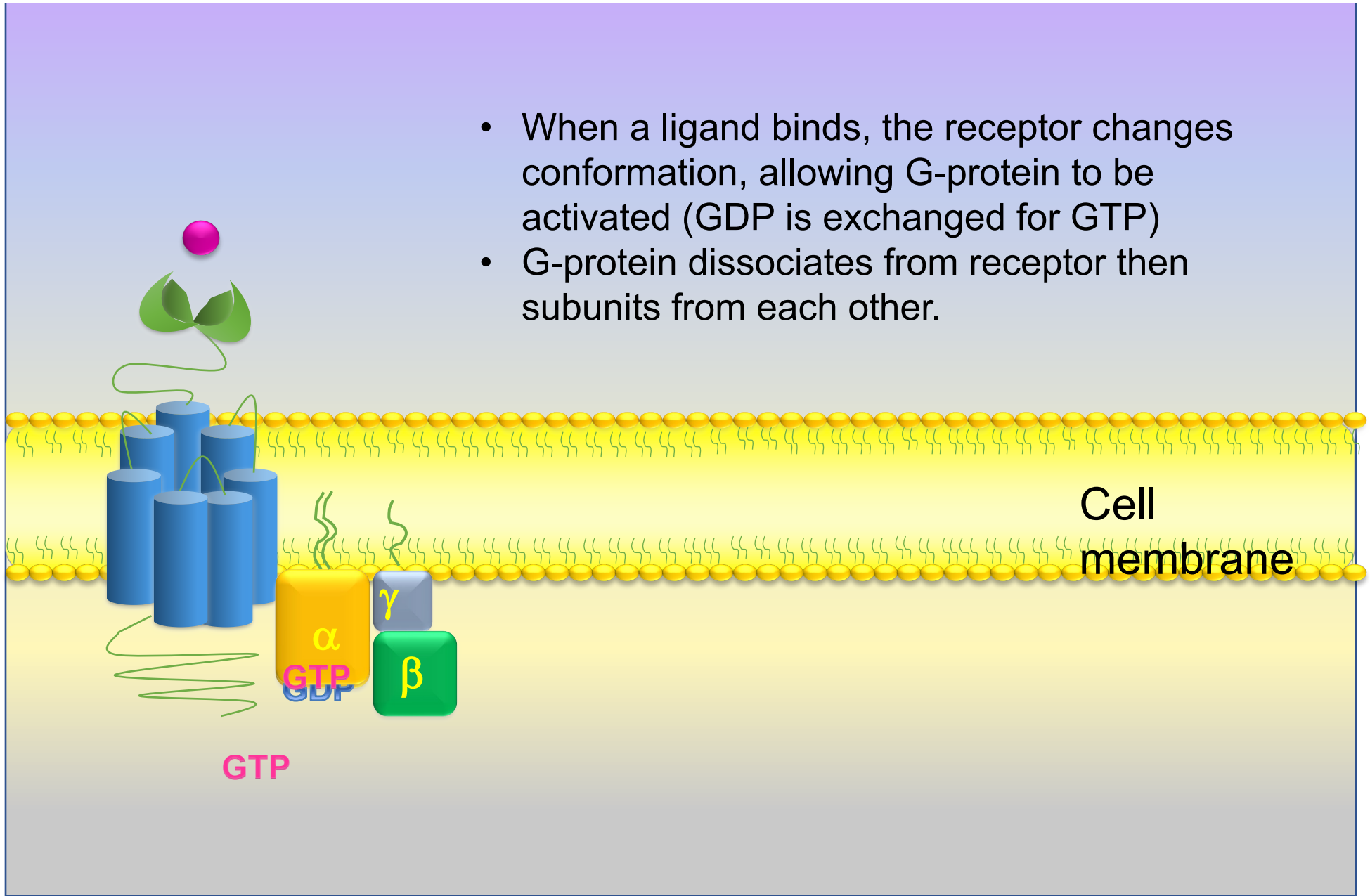
- G-protein composed of one alpha, beta, and gamma subunit
- 2 primary signaling cascades: cAMP or phosphatidylinositol pathways



- Pathway activated depends on alpha subunit type
  - ($G\alpha_s$, $G\alpha_i$, $G\alpha_q$)
  - GDP bound to α when inactive

G-protein coupled receptors

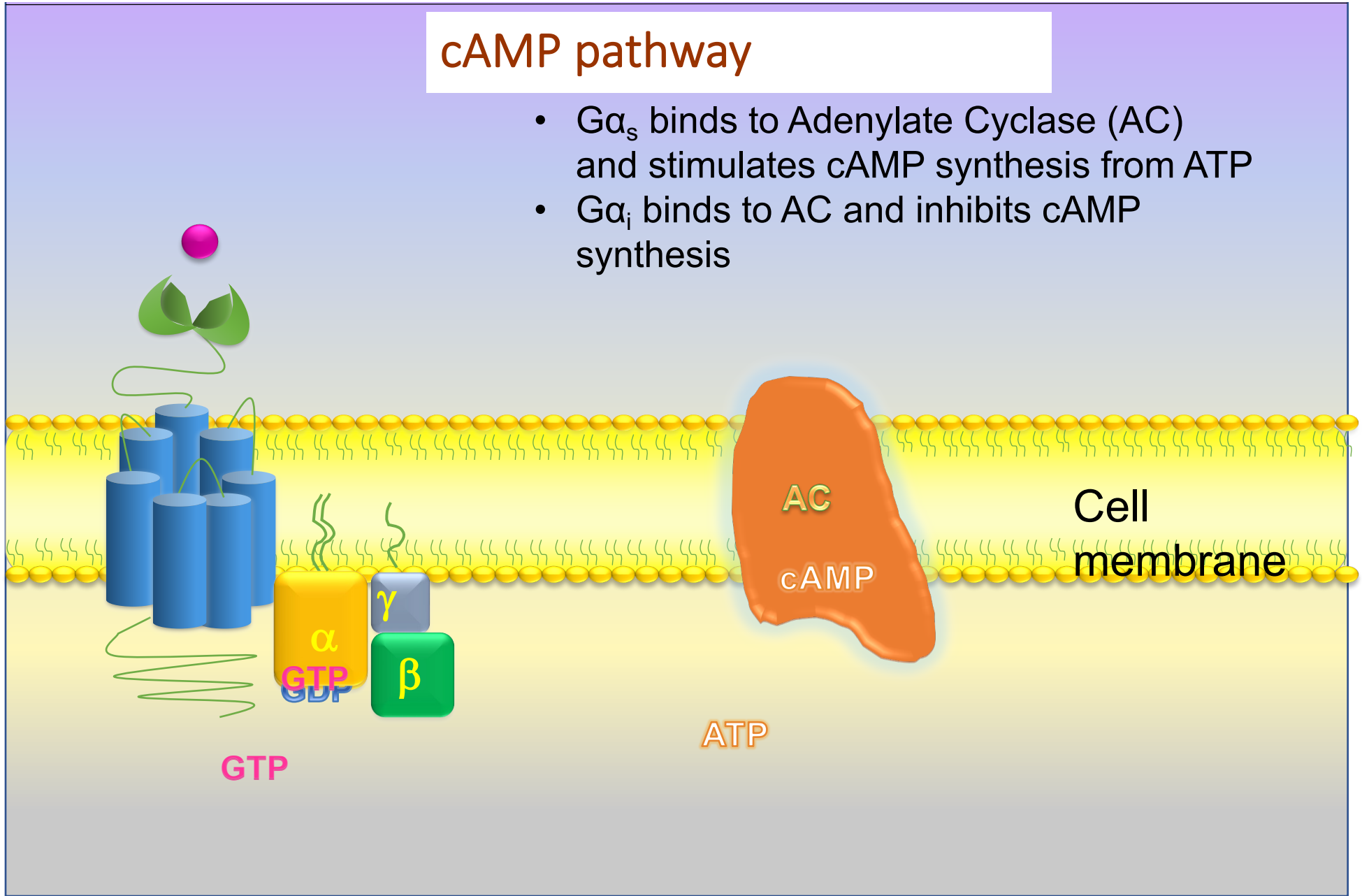
- When a ligand binds, the receptor changes conformation, allowing G-protein to be activated (GDP is exchanged for GTP)
- G-protein dissociates from receptor then subunits from each other.



G-protein coupled receptors

cAMP pathway

- $G\alpha_s$ binds to Adenylate Cyclase (AC) and stimulates cAMP synthesis from ATP
- $G\alpha_i$ binds to AC and inhibits cAMP synthesis



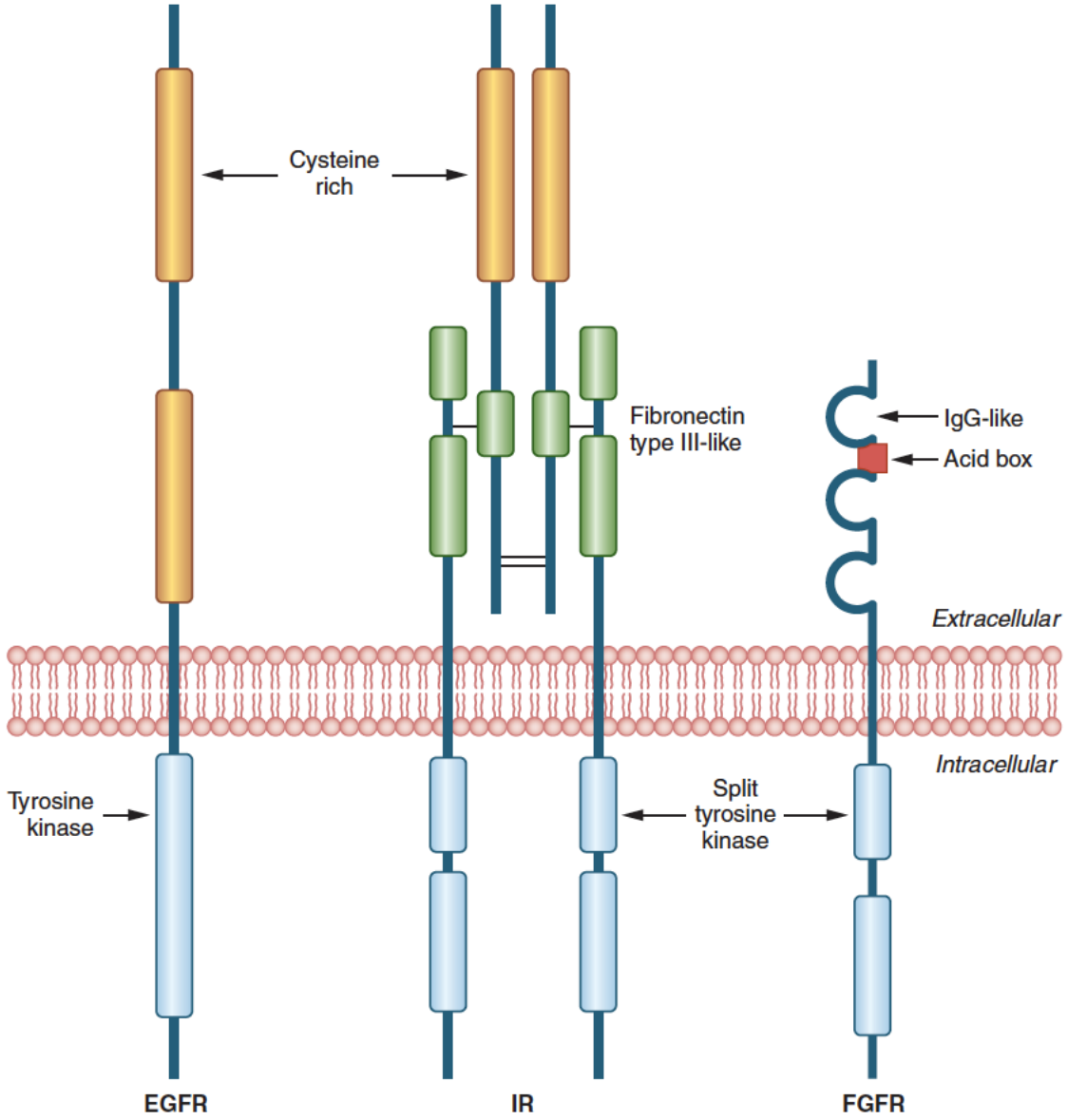
Mechanisms of Hormone action: Receptor Tyrosine Kinases

The structural features of the receptor tyrosine kinases (RTK) are illustrated in three examples:

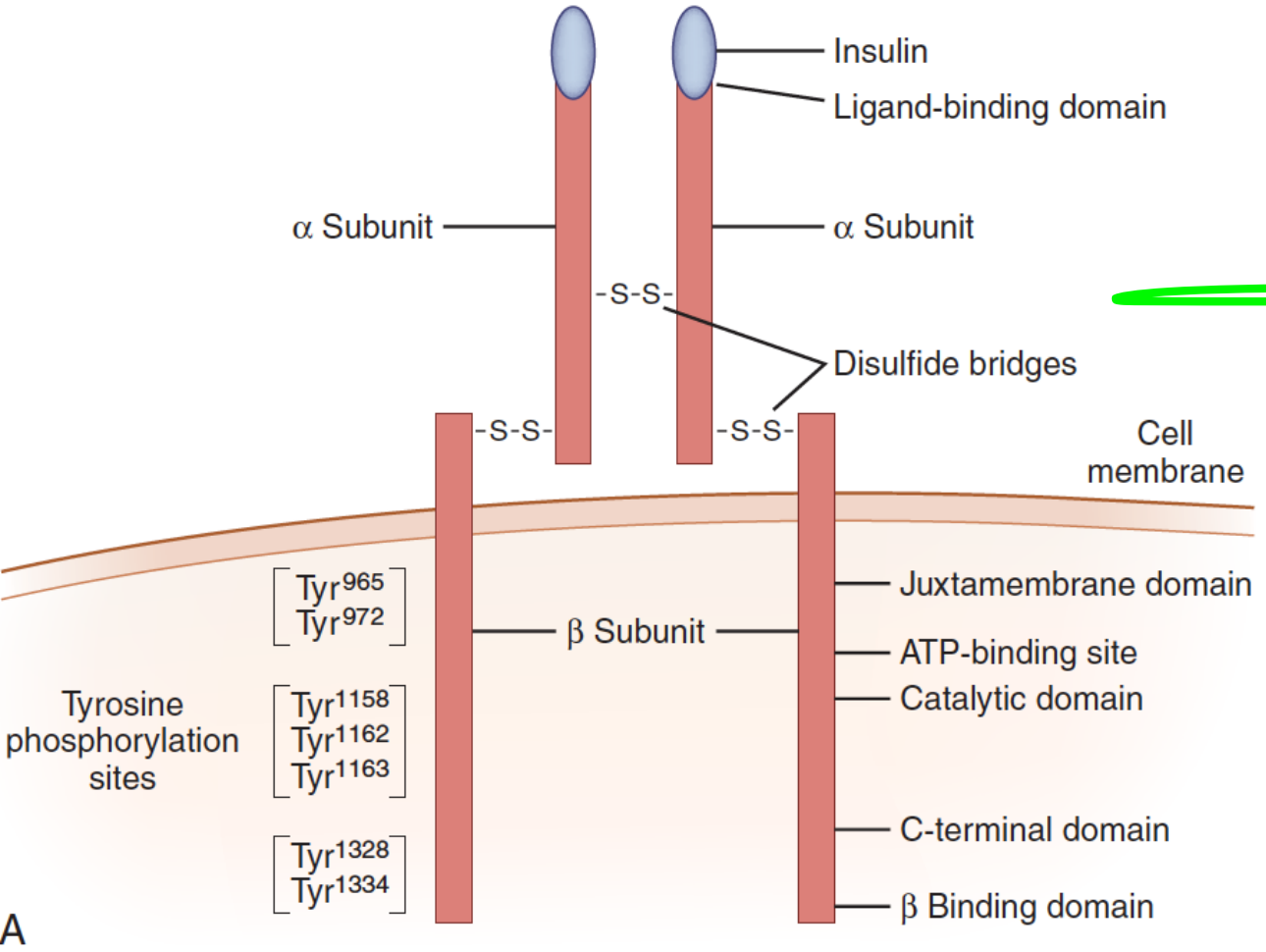
- Epidermal growth factor receptor (EGFR)
- Ins/IGF-1 receptor
- fibroblast growth factor receptor (FGFR)

The RTKs are single membrane spanning proteins with a variable extracellular N-terminal region and a cytoplasmic carboxyl portion that contains the catalytic activity to phosphorylate tyrosines (tyrosine kinase; blue) in itself (autophosphorylation) or in nearby proteins.

- Examples of N-terminal region motifs include cysteine rich sequences (gold), fibronectin type III-like regions (green), a series of IgG (immunogammaglobulin; blue) regions, and the acid box (red).
- Most RTKs are monomers that dimerize upon ligand binding.



RTK receptors: Insulin receptor



Schematic model of the insulin receptor tetramer in the plasma membrane of a target cell.

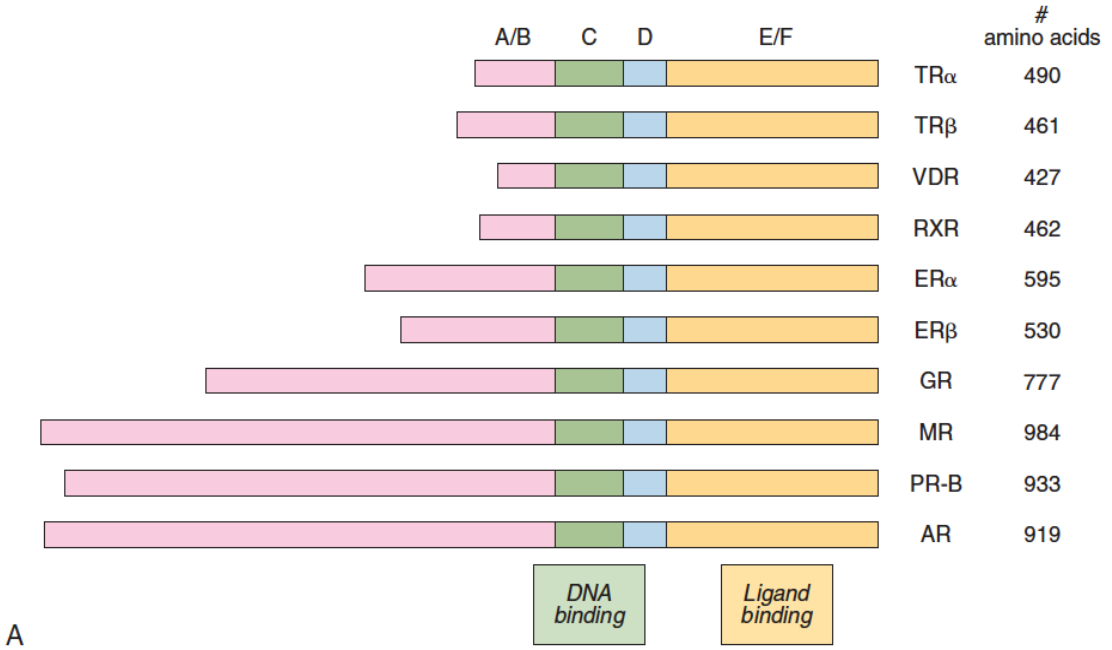
- The two smaller extracellular insulin receptor subunits are stabilized by a disulfide bond.
- The two larger intracellular receptor subunits are each individually stabilized by a disulfide bond with the extracellular smaller insulin receptor subunit.
- The process of insulin signaling begins through the binding of two insulin molecules, one to each of the two α subunits of the receptor.
- This results in a conformational change in the α subunits which is detected by the two intracellular insulin receptor β subunits.

Mechanisms of Hormone action: Nuclear receptor families

The nuclear receptors are a group of ancient evolutionarily related transcription factors. Examples

i. thyroid hormone (TRα and TRβ)
ii. 1,25-dihydroxyvitamin D3 (VDR)
iii. retinoic acid (RXR)
iv. estrogen (ERα and ERβ)
v. cortisol (GR)
vi. aldosterone (MR)
vii. progesterone (PR-B)
viii. testosterone/dihydrotestosterone (AR).

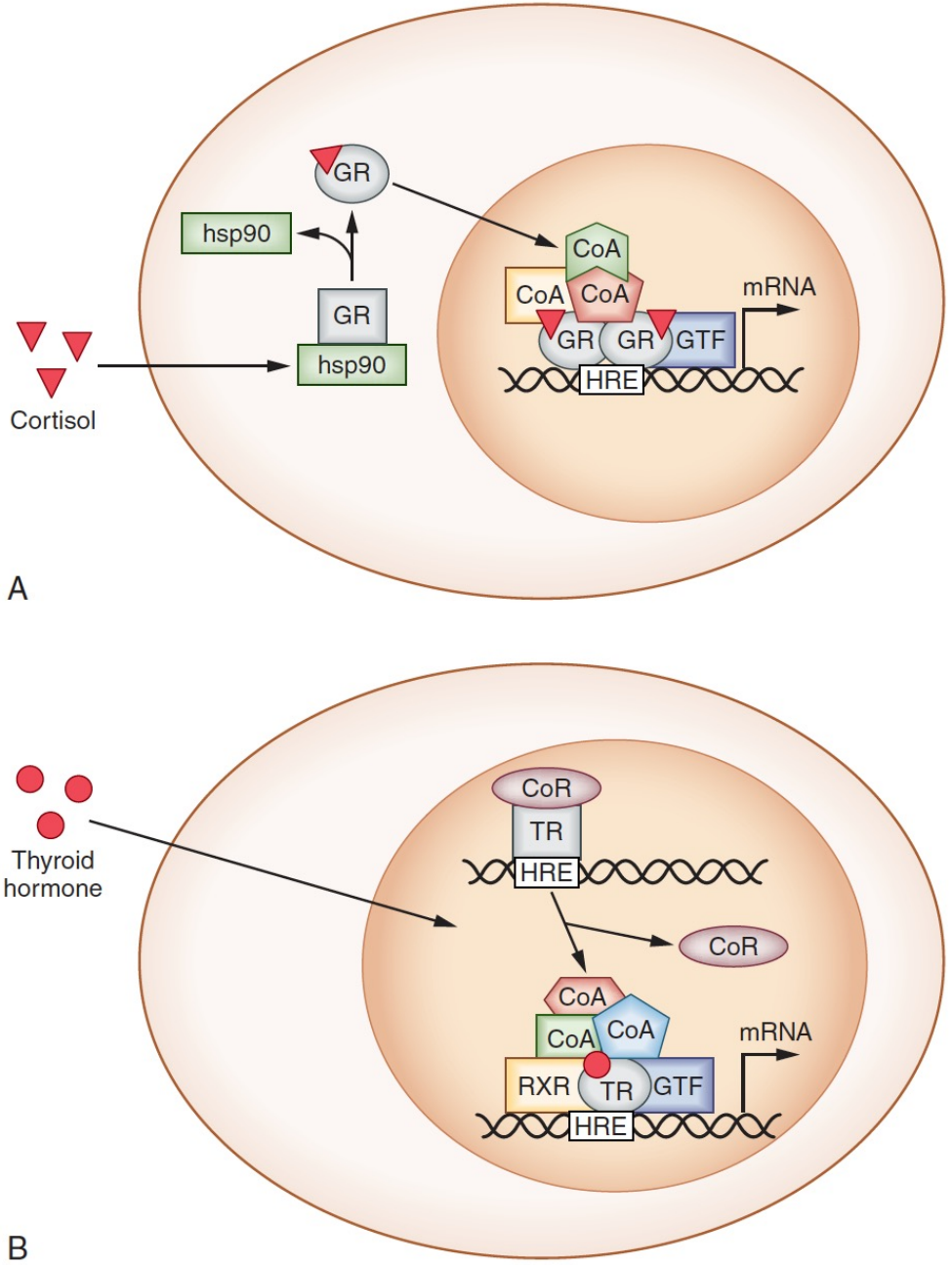
- These receptors share a highly conserved DNA binding domain (C, green) and a short non-conserved region (D, blue), which serve as a hinge between the N-terminal and C-terminal portions of the molecule.
- The difference in size between the receptor proteins is the highly variable N terminal A/B domain (pink).
- Two elements that are necessary for control of gene transcription, termed activation functions, exist, AF-1 in the A/B domain and AF-2 in the E/F domain.



Transcriptional activation by nuclear receptors

- Nuclear receptors for some of the classical steroid hormones are typified in this figure by the glucocorticoid receptor, GR, and its interaction with cortisol (panel A).
  - In the absence of ligand these receptors are in the cytosol complexed with heat shock proteins (green; HSP) that maintain them in an inactive state.
  - Ligand binding causes the HSP to dissociate and the receptor translocates to the nucleus. GR, MR, ER, AR, and PR all form heterodimers prior to DNA binding.

- Nuclear receptors for 1,25(OH)2D3 (VDR) and thyroid hormone (TR) are in the nucleus (panel B) prior to ligand binding and form heterodimers with the retinoic X receptor (RXR).
  - These are usually maintained in an inactive state by forming a complex with a corepressor (purple; CoR), which can bind to DNA and repress its transcription.
  - Ligand binding results in a conformational change that causes the corepressor to dissociate, activating the VDR/RXR heterodimer. The ligand-activated dimer of either type of nuclear receptor (hetero- or homodimer) binds to a specific sequence of DNA, a hormone response element (HRE)
  - A variety of proteins, termed coactivators(CoA), are recruited to the complex to modify chromatin structure and recruit and stabilize the basal transcriptional machinery. This includes the general transcriptional factors (GTF) and DNA-dependent-RNA polymerase.



Mechanisms of Hormone action: Nuclear receptor families

TABLE 1-1 Nuclear Receptors and Involvement in Genomic and/or Rapid Biological Responses

(Steroid receptor) & ligand	# aa Receptor	Steroid nuclear receptors & gene transcription generate genomic responses (GR)	Steroid membrane receptors generates rapid responses (RR)
(Thyroid β) T_3	461	T_3 binding to its nuclear receptor, in target cells stimulates dissociation of co-repressors, recruitment of co-activators, etc. to complete a GR.	T_3 activates PI3kinases and MAP kinase **RR** pathways which can result in glucose uptake, Ca^{2+}-ATPase, Na^+/H^+ antiporter.
(Vitamin D receptor) $1\alpha,25(OH)_2$- vitamin D_3	427	Both intestinal Ca^{2+} absorption & kidney Ca^{2+} reabsorption requires **GR** for production of new calcium binding proteins (CaBP).	**RR** opening of Cl^- channels in osteoblasts & keratinocytes in 20 min; insulin secretion from β-cells, MAP kinase activation in NB4 cells.
(Estrogen receptor α) Estradiol	595	ERα **GR** are required for normal ovarian function.	ERα activates PI3K and then AKt **RR** stimulates nitric oxide NO.
(Estrogen receptor β) Estradiol	530	ERβ **GR** are required for ovulation & pregnancy.	The cell membrane ERβ bound to caveola has been implicated in RR.
(Glucocorticoid receptor) Cortisol	777	Knockout (KO) of the mouse GC receptor is lethal at time of birth.	Cortisol stimulates PI3-kinase/Akt to activate in seconds NO release.
(Mineralocorticoid receptor) Aldosterone	919	MR **KO** mice die of Na^+ and H_2O deprivation.	Aldosterone activates in 3–15 minutes the **RR** of Na^+/H^+ exchange in renal cells.
(Progesterone receptor) Progesterone	933	The progesterone receptor participates in **GR** sexual differentiation determination.	Progesterone stimulates **RR** within seconds to minutes, the acrosome reaction in spermatozoa.
(Androgen receptor) Testosterone	919	**KO** of the AR male mouse causes development of female genitalia.	Activation of MAP kinase then activates the ERK pathway via **RR**.

GR = genomic responses; RR = rapid responses. RR are not dependent on genomic responses. KO = Knock-out renders affected genes inactive.

Classes of hormones

Cells of the endocrine system release more than 100 hormones and hormonally active substances that are chemically divided into three classes of compounds:

1. Steroids
2. Small peptides, polypeptides and proteins
3. Amino acids & arachidonic acid analogs

Steroids, cholesterol-derived compounds, are synthesized and secreted by cells of the ovaries, testes, and adrenal cortex.
These hormones (gonadal and adrenocortical steroids) are released into the bloodstream and transported to target cells with the help of plasma proteins or specialized carrier proteins such as androgen-binding protein. Hormone-binding carrier proteins protect the hormone from degradation during transport to the target tissue. When needed, the hormone is released from the carrier protein to become active.

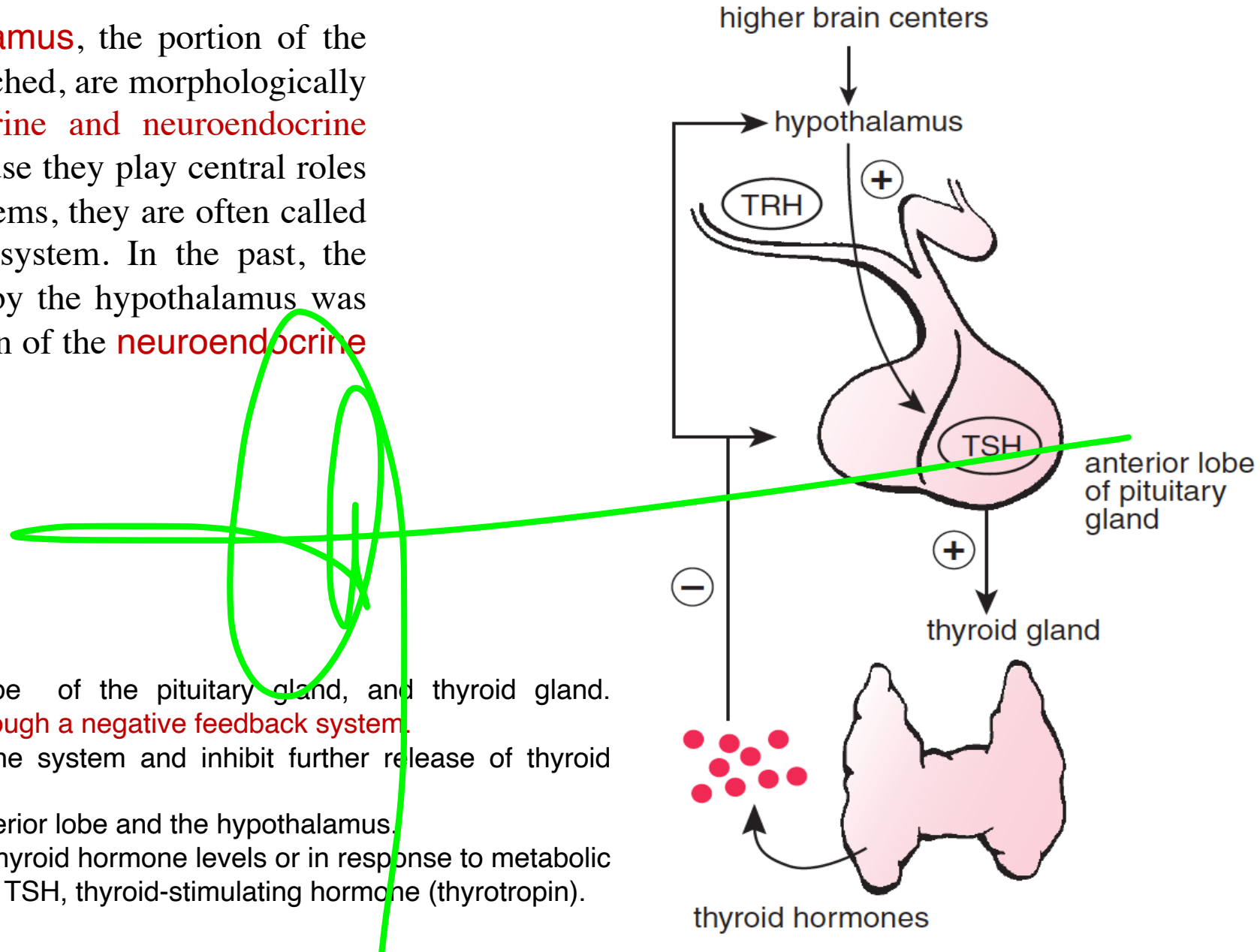
Small peptides, polypeptides, and proteins are synthesized and secreted by cells of the hypothalamus, pituitary gland, thyroid gland, parathyroid gland, pancreas, and scattered enteroendocrine cells of the gastrointestinal tract and respiratory system. This group of hormones (e.g., insulin, glucagon, growth hormone [GH], adrenocorticotropic hormone [ACTH], follicle-stimulating hormone [FSH], luteinizing hormone [LH], antidiuretic hormone [ADH], oxytocin, interleukins, and various growth factors), when released into the circulation, dissolve readily in the blood and generally do not require special transport proteins. However, most if not all polypeptides and proteins have specific carrier proteins (e.g., insulin growth factor–binding protein (IGFBP).

Amino acids and arachidonic acid analogs, and their derivatives, including the catecholamines (norepinephrine and epinephrine–phenylalanine/tyrosine derivatives) and prostaglandins, prostacyclins, and leukotrienes (arachidonic acid derivatives). They are synthesized and secreted by many neurons as well as a variety of cells including cells of the adrenal medulla. Also included in this group of compounds are thyroid hormones, the iodinated derivatives of the amino acid tyrosine that are synthesized and secreted by the thyroid gland. When released into the circulation, catecholamines dissolve readily in the blood, in contrast to thyroid hormones that bind to the prealbumin fraction of serum proteins (transthyretin) and a specialized thyroxin-binding protein.

Hypothalamus & Pituitary gland Hormones

Pituitary Gland & Hypothalamus

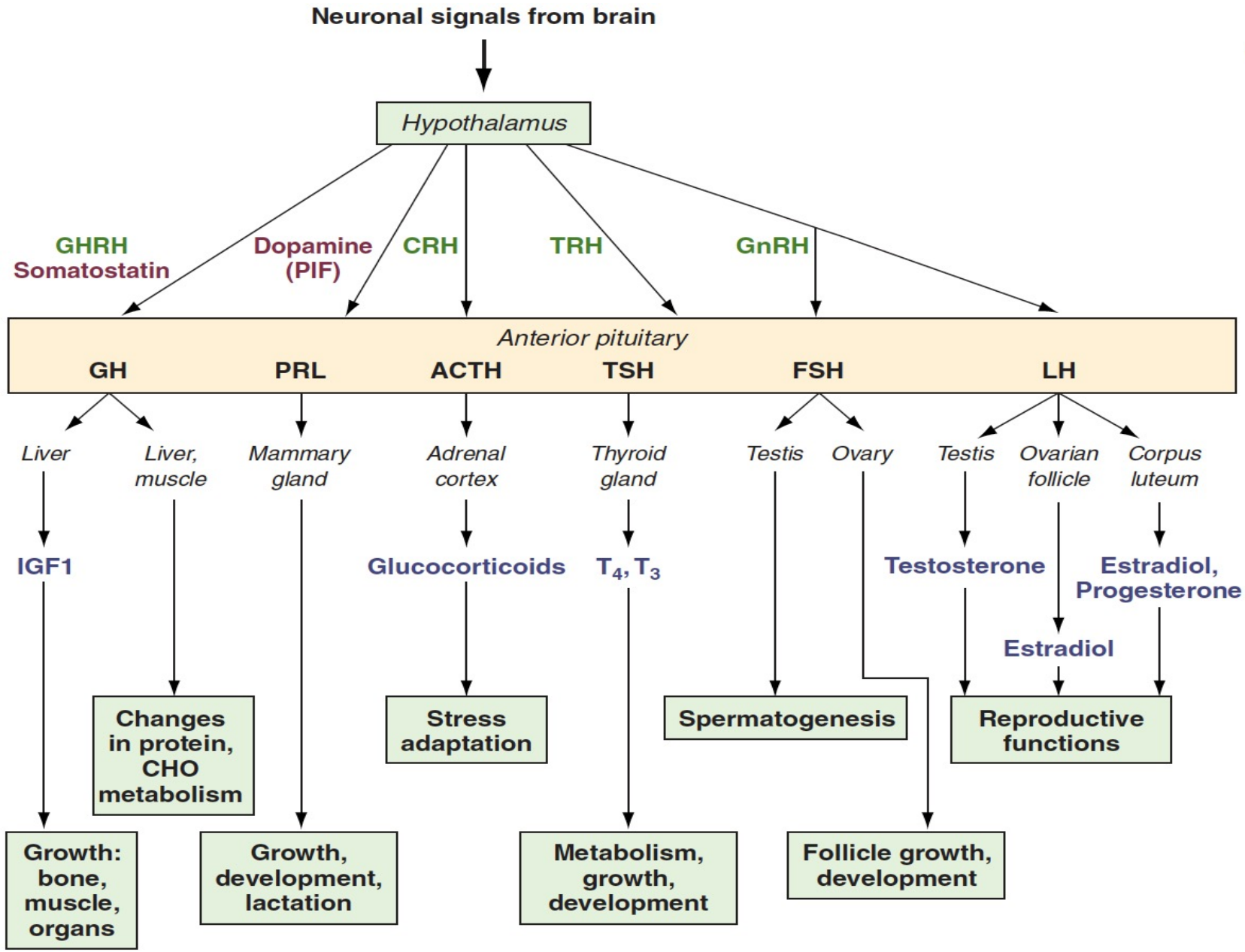
The pituitary gland and the hypothalamus, the portion of the brain to which the pituitary gland is attached, are morphologically and functionally linked in the endocrine and neuroendocrine control of other endocrine glands. Because they play central roles in a number of regulatory feedback systems, they are often called the "master organs" of the endocrine system. In the past, the control of pituitary hormone secretion by the hypothalamus was classically regarded as the major function of the neuroendocrine system.

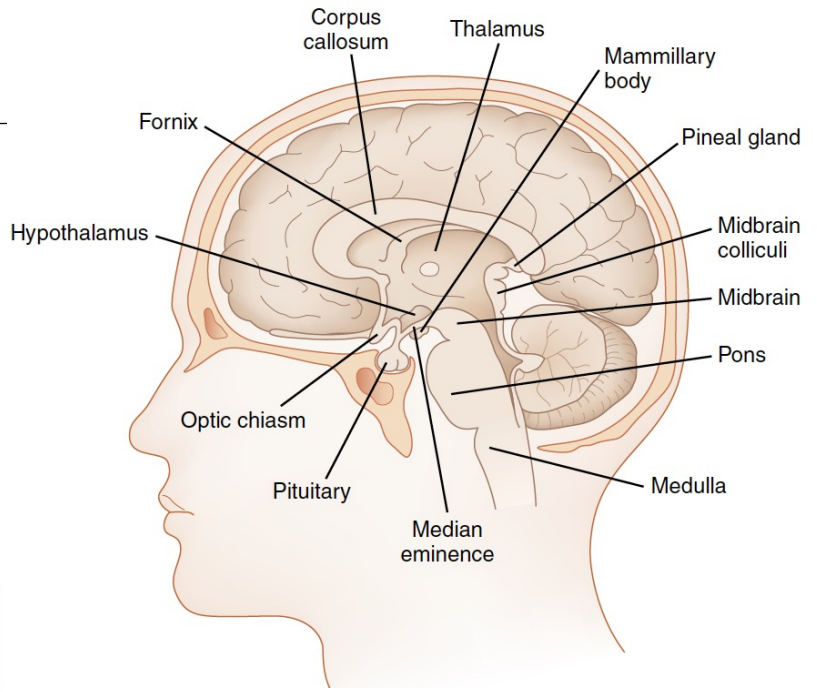


Interaction of the hypothalamus, anterior lobe of the pituitary gland, and thyroid gland. Production of thyroid hormones is regulated through a negative feedback system.

- The thyroid hormone can feed back on the system and inhibit further release of thyroid hormones.
- Such inhibition occurs at the level of the anterior lobe and the hypothalamus.
- The system is activated in response to low thyroid hormone levels or in response to metabolic needs. TRH, thyrotropin-releasing hormone; TSH, thyroid-stimulating hormone (thyrotropin).

Hypothalamus-pituitary hormonal system





The hypothalamus regulates pituitary gland activity. Some of the functions that it regulates include blood pressure, body temperature, fluid and electrolyte balance, body weight, and appetite. The hypothalamus produces numerous neurosecretory products.

A feedback system regulates endocrine function at two levels: hormone production in the pituitary gland and hypothalamic releasing hormone production in the hypothalamus. The predominant hypothalamic releasing hormone (in green) or release-inhibiting factor (red). The main target tissues of the anterior pituitary hormones are indicated, along with the hormones they produce and, in the green boxes, major biological actions.

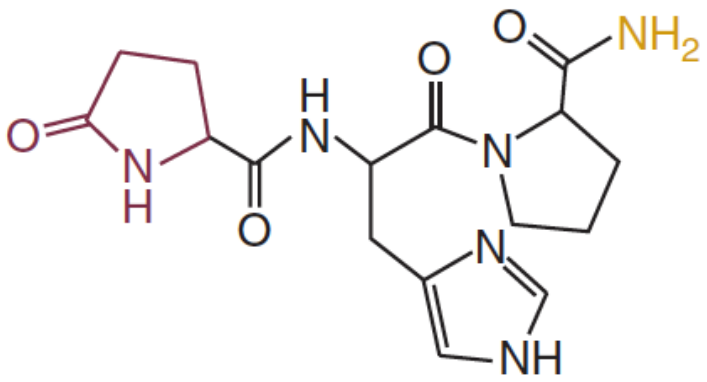
Hypothalamus regulating hormones

Hormone	Composition	Source	Major Functions
Growth hormone–releasing hormone (GHRH)	Two forms in human: polypeptides containing 40 and 44 amino acids	Cell bodies of neurons located in the arcuate nucleus of hypothalamus	Stimulates secretion and gene expression of GH by somatotropes
Somatostatin	Two forms in human: polypeptides containing 14 and 28 amino acids	Cell bodies of neurons located in the periventricular, paraventricular, and arcuate nuclei of the hypothalamus	Inhibits secretion of GH by somatotropes, inhibits insulin secretion by B cells of pancreatic islets
Dopamine	Catecholamine (amino acid derivative)	Cell bodies of neurons located in the arcuate nucleus of hypothalamus	Inhibits secretion of PRL by lactotropes
Corticotropin-releasing hormone (CRH)	Polypeptide containing 41 amino acids	Cell bodies of neurons located in the arcuate, periventricular, and medial paraventricular nuclei of hypothalamus	Stimulates secretion of ACTH by corticotropes; stimulates gene expression for POMC in corticotropes
Gonadotropin-releasing hormone (GnRH)	Polypeptide containing 10 amino acids	Cell bodies of neurons located in the arcuate, ventromedial, dorsal, and paraventricular nuclei of hypothalamus	Stimulates secretion of LH and FSH by gonadotropes
Thyrotropin-releasing hormone (TRH)	Polypeptide containing 3 amino acids	Cell bodies of neurons located by the ventromedial, dorsal, and paraventricular nuclei of hypothalamus	Stimulates secretion and gene expression of TSH by thyrotropes; stimulates synthesis and secretion of PRL

Hormones of the anterior lobe of Pituitary Gland

Hormone	Composition	MW (kDa)	Major Functions
Growth hormone (somatotropin, GH)	Straight-chain protein (191 aa)	21,700	Stimulates liver and other organs to synthesize and secrete insulin-like growth factor I (IGF-I), which in turn stimulates division of progenitor cells located in growth plates and in skeletal muscles, resulting in body growth
Prolactin (PRL)	Straight-chain protein (198 aa)	22,500	Promotes mammary gland development; initiates milk formation; stimulates and maintains secretion of casein, lactalbumin, lipids, and carbohydrates into the milk
Adrenocorticotropic hormone (ACTH)	Small polypeptide (39 aa)	4,000	Maintains structure and stimulates secretion of gluco-corticoids and gonadocorticoids by the zona fasciculata and zona reticularis of the adrenal cortex
Follicle-stimulating hormone (FSH)	2-chain glycoprotein[a] (α, 92 aa; β, 111 aa)	28,000	Stimulates follicular development in the ovary and spermato-genesis in the testis
Luteinizing hormone (LH)	2-chain glycoprotein[a] (α, 92 aa; β, 116 aa)	28,300	Regulates final maturation of ovarian follicle, ovulation, and corpus luteum formation; stimulates steroid secretion by follicle and corpus luteum; in males, essential for maintenance of and androgen secretion by the Leydig (interstitial) cells of the testis
Thyrotropic hormone (TSH)	2-chain glycoprotein[a] (α, 92 aa; β, 112 aa)	28,000	Stimulates growth of thyroid epithelial cells; stimulates production and release of thyroglobulin and thyroid hormones

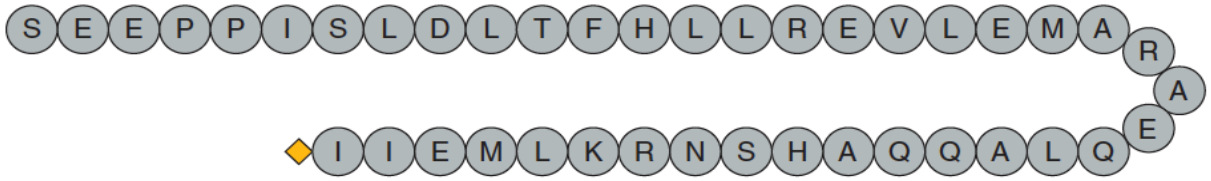
Structure of Hypothalamus regulating hormones



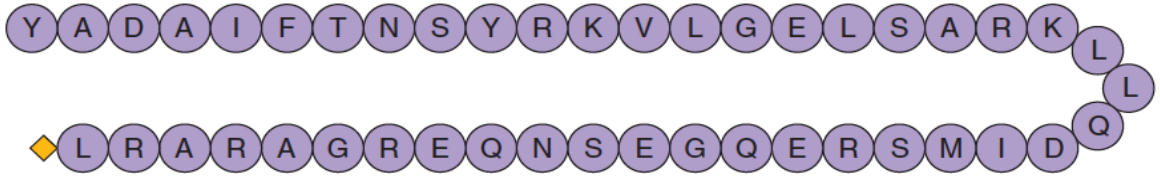
thyrotropin-releasing hormone, TRH.

TRH: Thyrotrophin releasing hormone

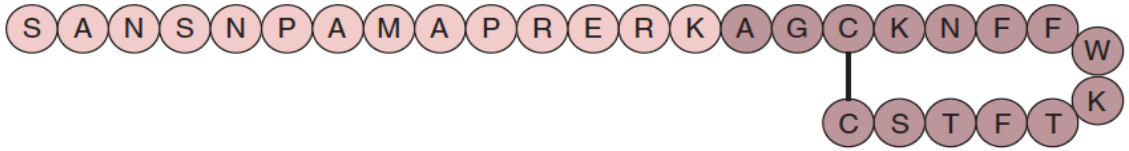
GnRH: Gondaotrophin releasing hormone



CRH: Corticotrophin releasing hormone



GHRH: Growth hormone releasing hormone

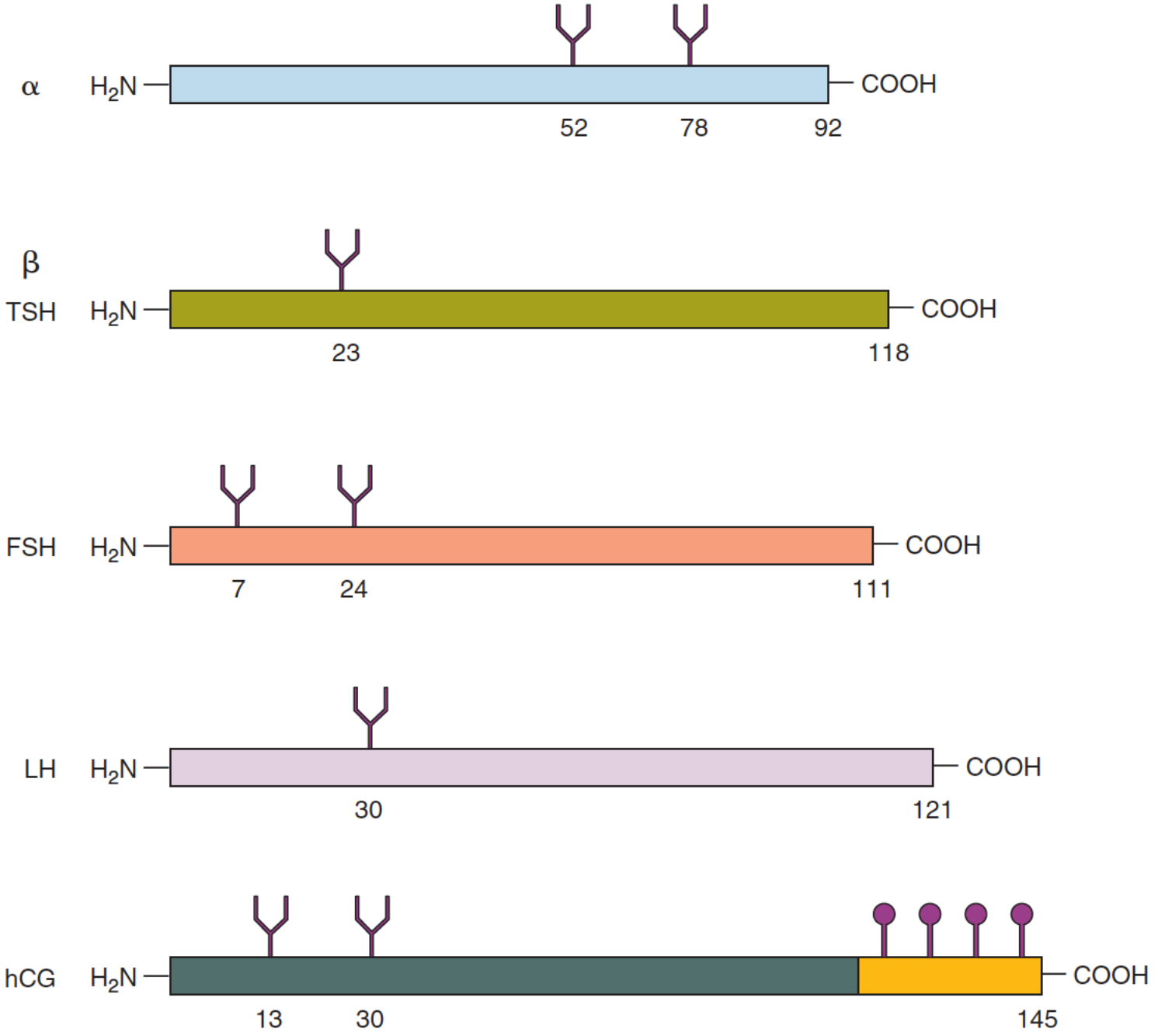


SST: Somatostatin

E = pyroglutamyl

= c-terminal amide: prolinamide (TRH); glycinamide (GnRH); isoleucinamide (CRH); leucinamide (GHRH)

Structure of pituitary hormones

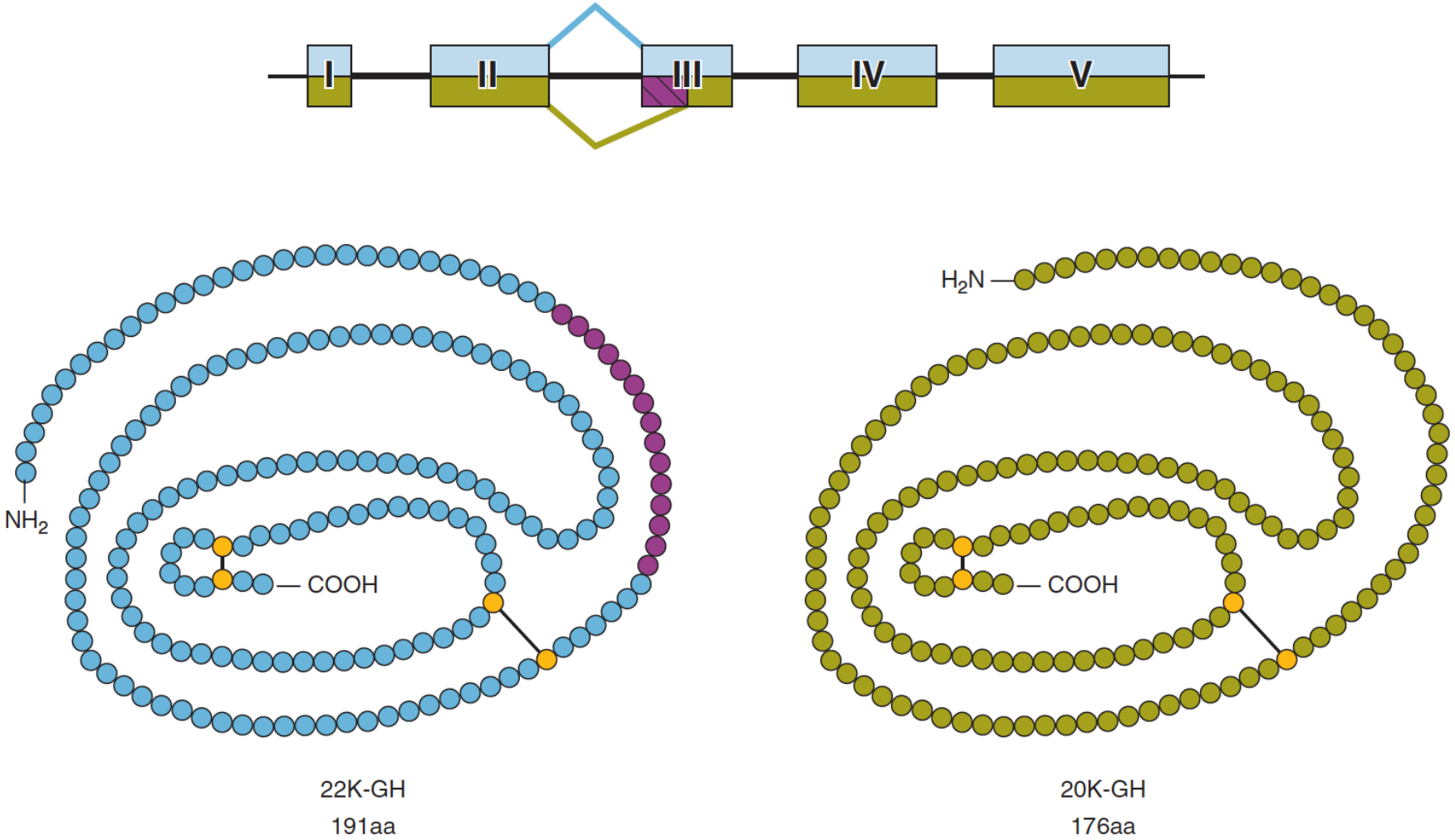


The three pituitary glycoprotein hormones:

1. Thyroid stimulating hormone (TSH)
2. Follicle stimulating hormone (FSH)
3. Luteinizing hormone (LH)
4. Human chorionic gonadotropin (hCG)

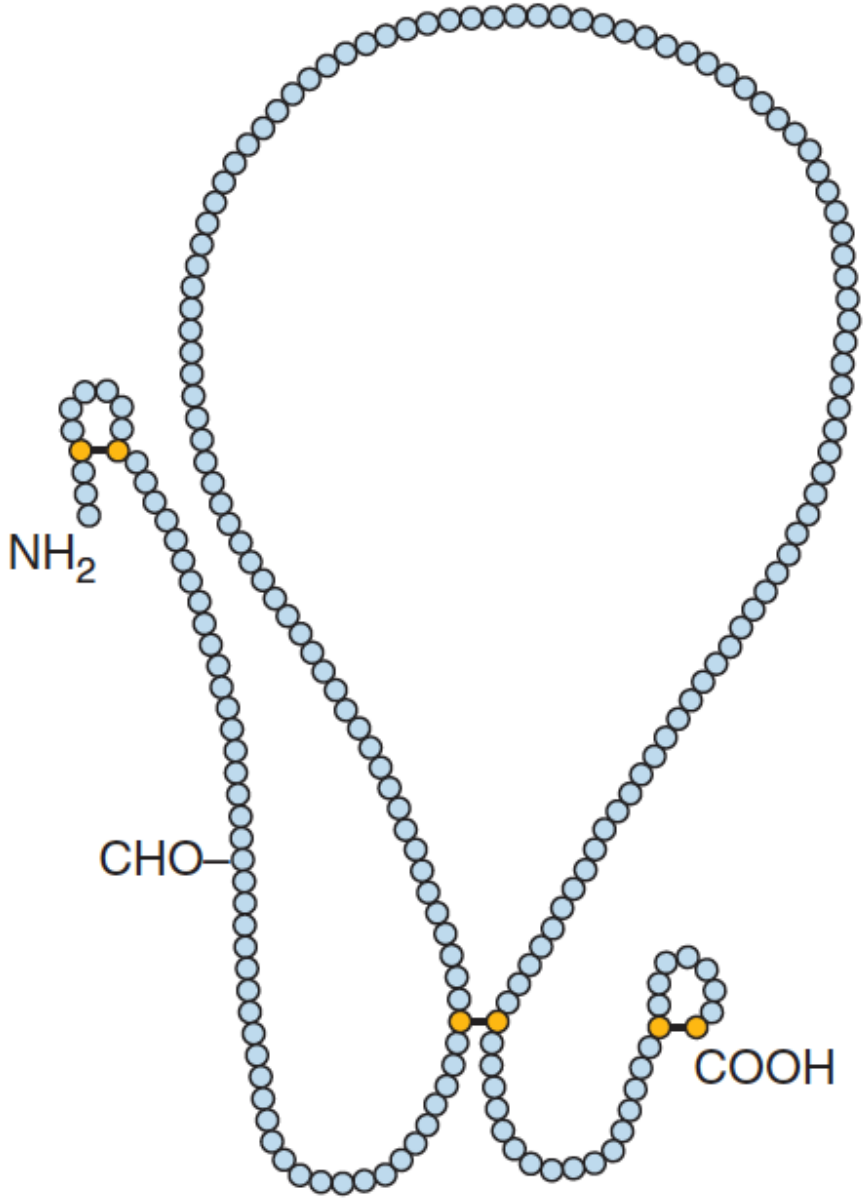
❖ The positions of the N-glycosylated asparagine sites are indicated by the forks for each of the five subunit types; hCG is characterized by a C-terminal extension with O-glycosylated serine sites.

Growth Hormone



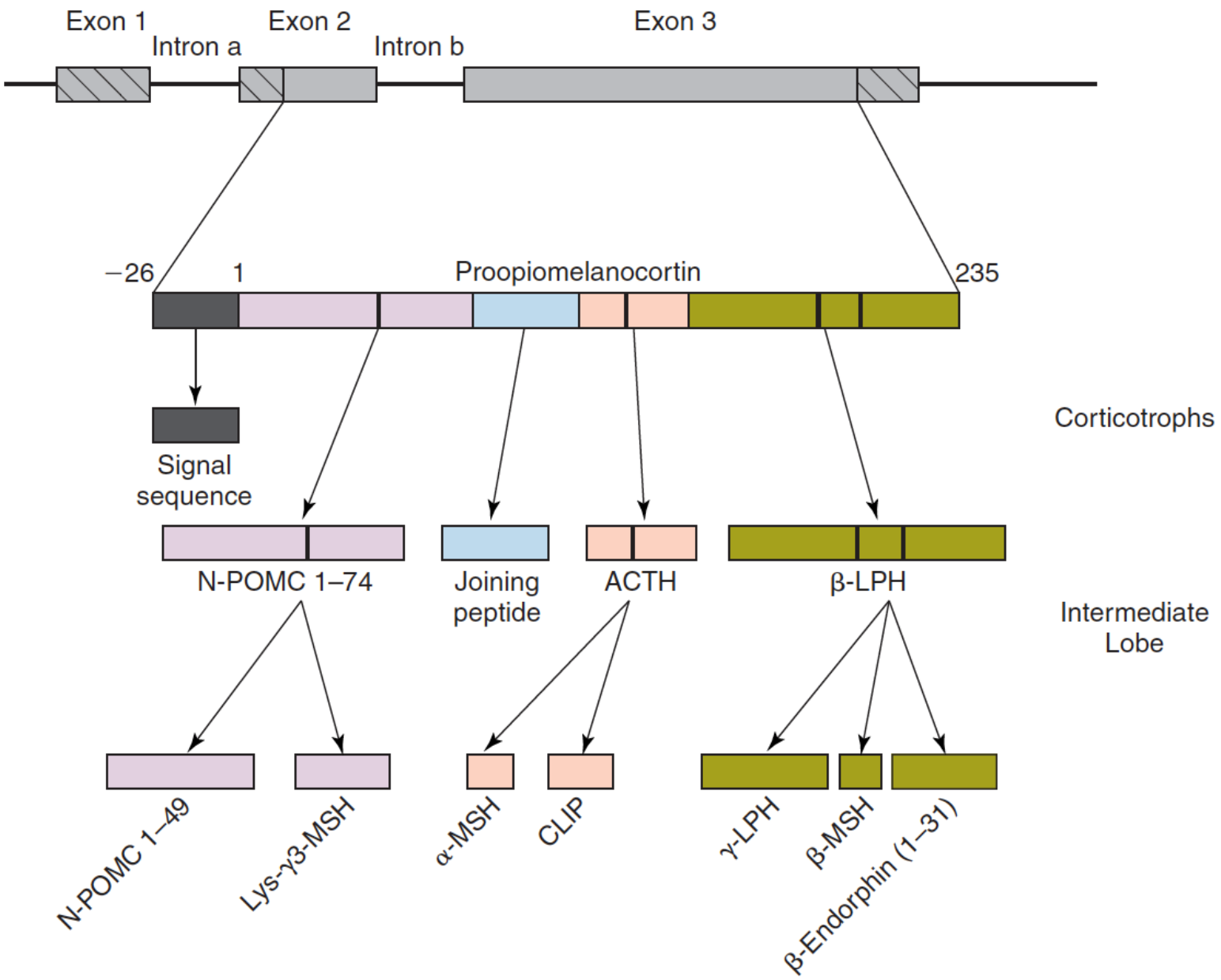
Gene and amino acid sequences of growth hormone (GH). The two main forms of GH are shown. GH- 22k (left), is derived from all five exons whereas in GH- 20k use of an alternative splice site in exon III results in omission of 15 amino acids, which are indicated in pink in GH-22k.

Human prolactin



Amino acid sequence of human prolactin. Prolactin is a single polypeptide of 199 amino acids and 3 internal disulfide bonds as shown.

Proopiomelanocortin (POMC)



The proopiomelanocortin (POMC) gene and its protein products.

- POMC is encoded by portions of the second and third exons of its gene and consists of a signal peptide and several bioactive peptides.
- The protein is processed differently in different cell types.
  - In pituitary corticotrophs the pro-protein is cleaved into ACTH (pink), the main secretory product of these cells, and β-lipotropin (green).
  - In the cells of the intermediate lobe, ACTH and β-lipotropin, along with the N-terminal section, N-POMC 1-74 (light purple), are further processed as shown.

** The vertical lines within the proteins represent the dibasic residues at the cleavage sites.

Hormones of the posterior lobe of Pituitary Gland

Hormone	Composition	Source	Major Functions
Oxytocin	Polypeptide containing 9 amino acids	Cell bodies of neurons located in the supraoptic and paraventricular nuclei of the hypothalamus[a]	Stimulates activity of the contractile cells around the ducts of the mammary glands to eject milk from the glands; stimulates contraction of smooth muscle cells in the pregnant uterus
Antidiuretic hormone (ADH; vasopressin)	Polypeptide containing 9 amino acids; two forms: arginine-ADH (most common in humans) and lysine-ADH	Cell bodies of neurons located in the supraoptic and paraventricular nuclei of the hypothalamus[a]	Decreases urine volume by increasing reabsorption of water by collecting ducts of the kidney; decreases the rate of perspiration in response to dehydration; increases blood pressure by stimulating contractions of smooth muscle cells in the wall of arterioles

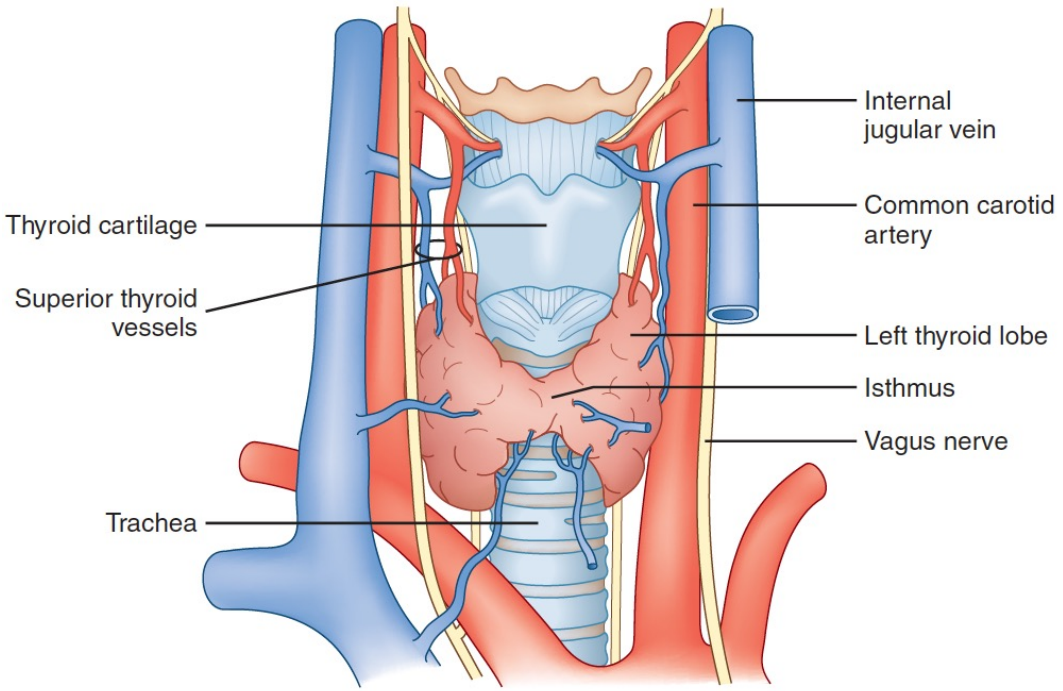
[a] Immunocytochemical studies indicate that oxytocin and ADH are produced by separate sets of neurons within the supraoptic and paraventricular nuclei of the hypothalamus. Biochemical studies have demonstrated that the supraoptic nucleus contains equal amounts of both hormones, whereas the paraventricular nucleus contains more oxytocin than ADH, but less than the amount found in the supraoptic nucleus.

Thyroid Gland and Its Hormones

Thyroid Gland

The thyroid gland is located in the anterior neck region adjacent to the larynx and trachea.

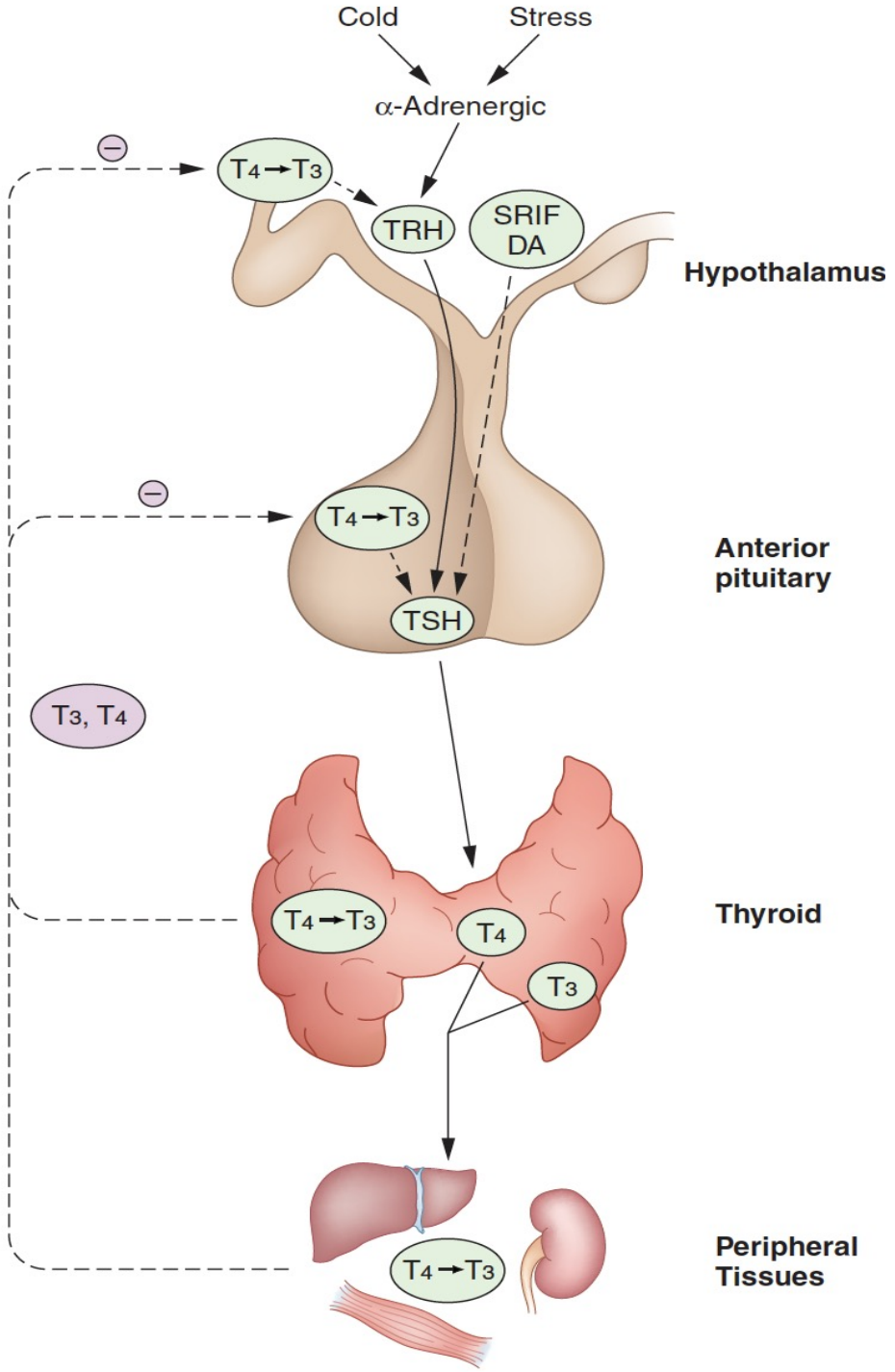
The thyroid gland is a bilobate endocrine gland located in the anterior neck region and consists of two large lateral lobes connected by an isthmus, a thin band of thyroid tissue. The two lobes, each approximately 5 cm in length, 2.5 cm in width, and 20 to 30 g in weight, lie on either side of the larynx and upper trachea. The isthmus crosses anterior to the upper part of the trachea. A pyramidal lobe often extends upward from the isthmus. A thin connective tissue capsule surrounds the gland. It sends trabeculae into the parenchyma that partially outline irregular lobes and lobules. Thyroid follicles constitute the functional units of the gland.



The hypothalamic-pituitary-thyroid axis

Control of thyroid hormone involves stimulation of pituitary TSH (thyroid stimulating hormone) by TRH (thyrotropic releasing hormone) from the hypothalamus.

- Many signals from other areas of the brain, such as cold and stress, influence TRH secretion by the hypothalamus.
- TSH stimulates synthesis and release of T4 (and some T3) from the thyroid gland.
- T4 is deiodinated to T3 (green ovals: T4→T3) in peripheral target tissues as well as in the pituitary and in the hypothalamus.
- The circulating thyroid hormones (purple oval) exert feedback inhibition on TSH secretion in the pituitary and, to a variable degree depending on species, on TRH secretion.
- Somatostatin (SRIF; SST) and dopamine (DA) also influence TSH secretion.
  - Stimulatory and inhibitory effects are represented by solid and dashed lines, respectively.



Hormones of thyroid Gland

Hormone	Composition	Source	Major Functions
Thyroxine (tetraiodothyronine, T4) and triiodothyronine (T_3)[a]	Iodinated tyrosine derivatives	Follicular cells (principal cells)	Regulates tissue basal metabolism (increases rate of carbohydrate use, protein synthesis and degradation, and fat synthesis and degradation); regulates heat production; influences body and tissue growth and development of the nervous system in the fetus and young child[b]; increases absorption of carbohydrates from the intestine
Calcitonin (thyrocalcitonin)	Polypeptide containing 32 amino acids	Parafollicular cells (C cells)	Decreases blood calcium levels by inhibiting bone resorption and stimulating absorption of calcium by the bones

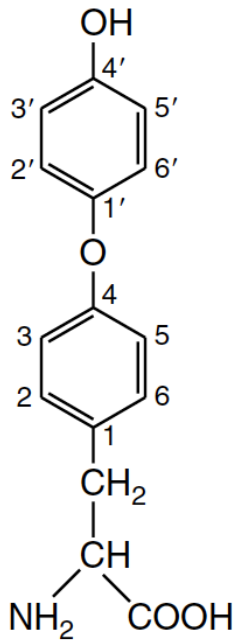
[a]Thyroid gland secretes substantially more T_4 than T_3; however, about 40% of T_4 is peripherally converted to T_3, which acts more rapidly and is a more potent hormone.

[b]Deficiency of T_3 and T_4 during development results in fewer and smaller neurons, defective myelination, and mental retardation.

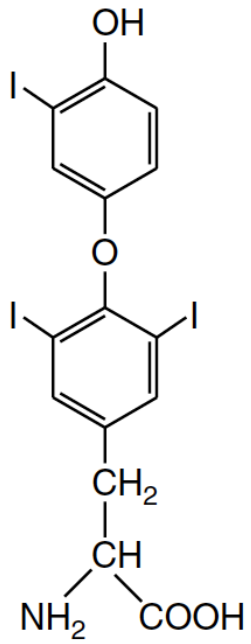
Synthesis and secretion of thyroid hormones

Each epithelial cell of the thyroid follicle, or thyrocyte, is specialized to carry out all the steps required for the synthesis and secretion of T4 and T3. These are

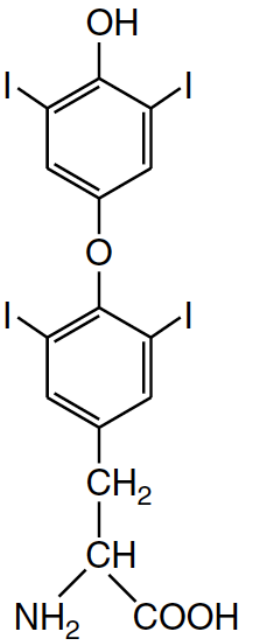
i. Active transport of iodide into the thyroid gland follicular cells;
ii. Oxidation of iodide and iodination of tyrosyl residues within the protein thyroglobulin;
iii. Transfer and coupling of iodotyrosines within thyroglobulin to form T4 and T3;
iv. Storage of thyroglobulin as the colloid in the lumen of the thyroid follicle;
v. Endocytosis of the colloid back into the thyroid epithelial cell;
vi. Proteolysis of thyroglobulin with concomitant release of T4 and T3 as well as free iodotyrosines and iodothyronines;
vii. Secretion of T4 and T3 into the blood;
viii. Deiodination of iodotyrosines within the thyroid follicular cells for reutilization of the liberated iodine.



Thyronine



T_3: 3,5,3′-triiodo-thyronine



T_4 = Thyroxine: 3,5,3′,5′-tetraiodothyronine

Synthesis and secretion of thyroid hormones

Each epithelial cell of the thyroid follicle, or thyrocyte, is specialized to carry out all the steps required for the synthesis and secretion of T4 and T3. These are

- Active transport of iodide into the thyroid gland follicular cells;
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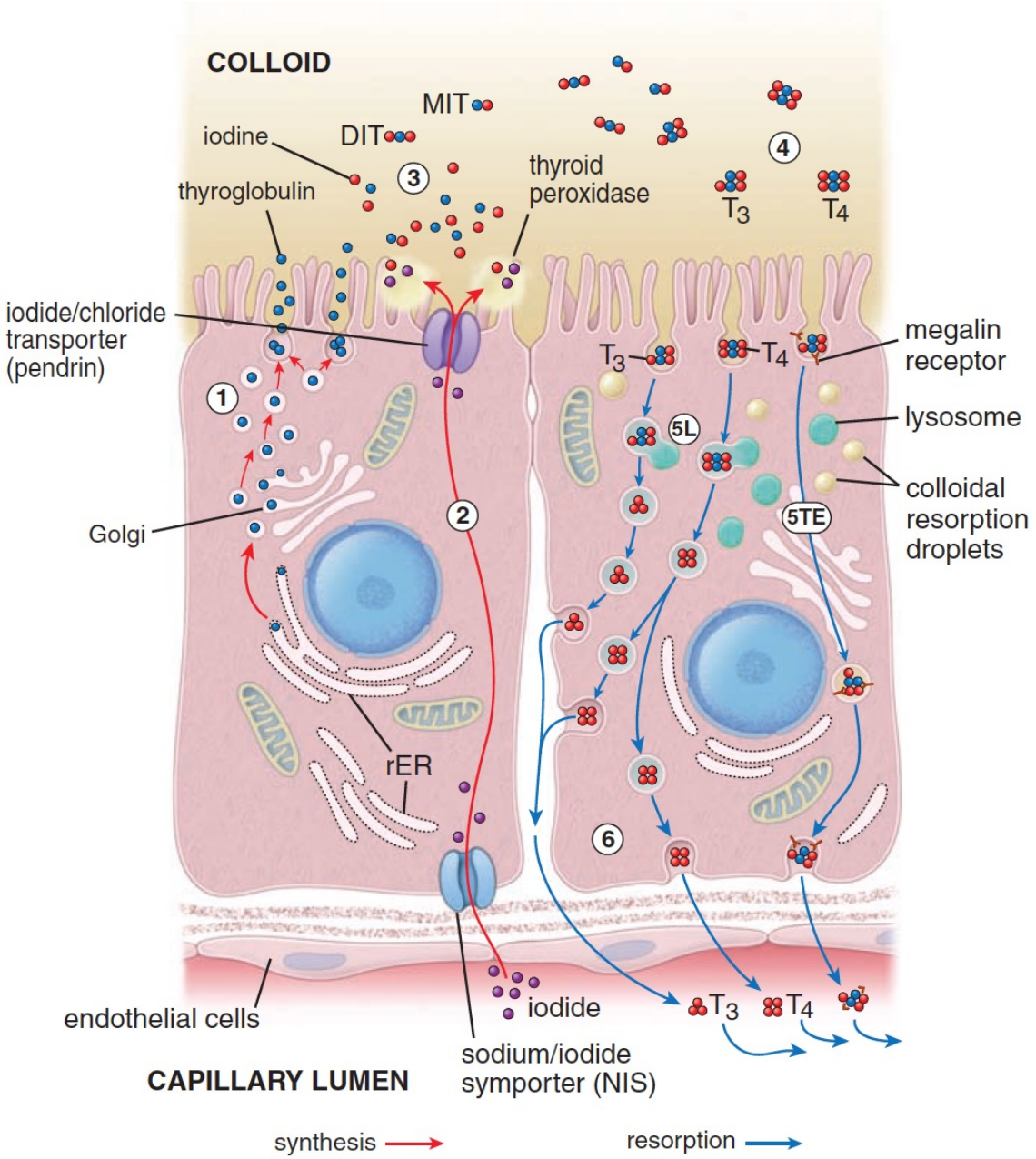
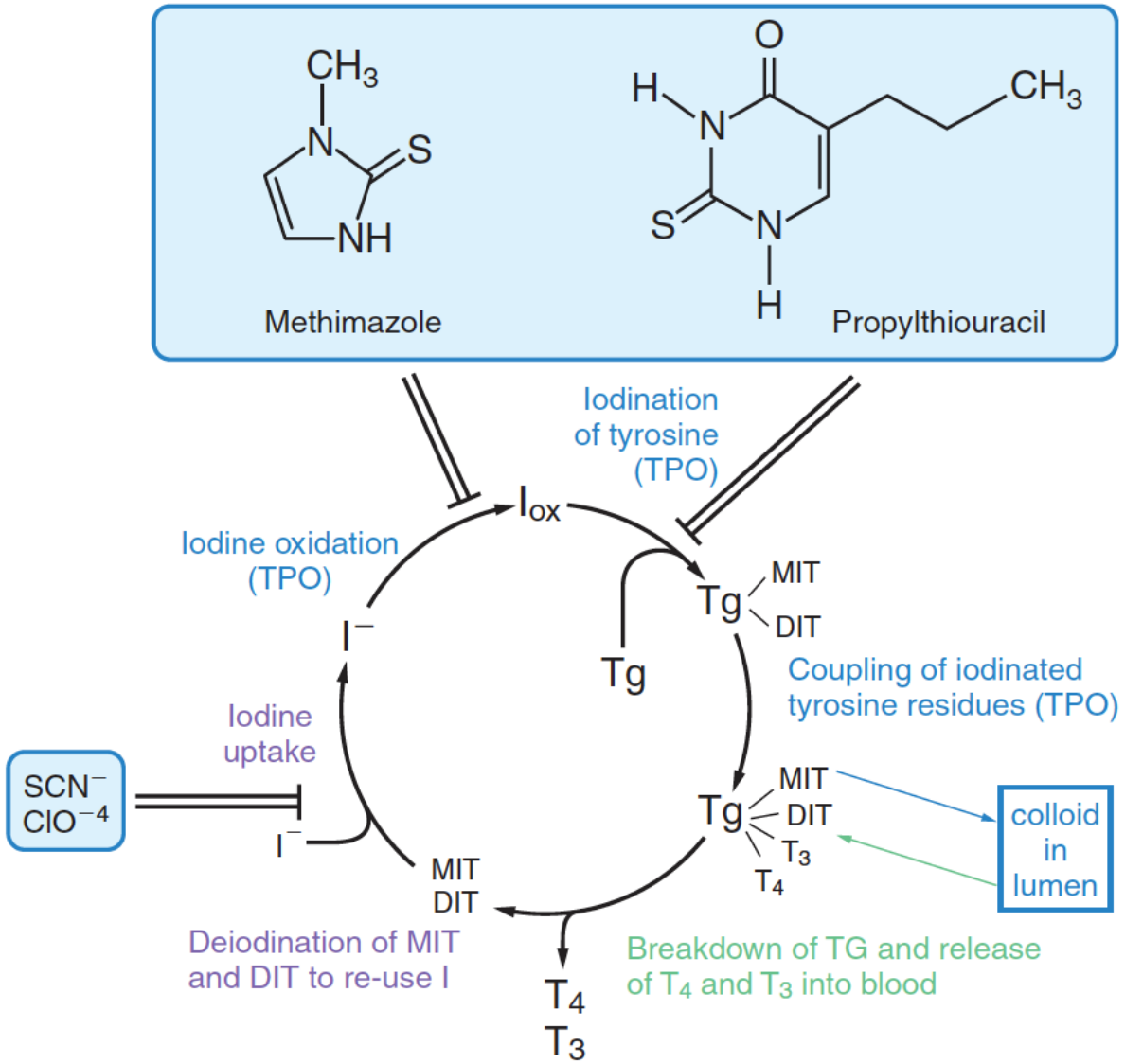
- Storage of thyroglobulin as the colloid in the lumen of the thyroid follicle;
- Endocytosis of the colloid back into the thyroid epithelial cell;
- Proteolysis of thyroglobulin with concomitant release of T4 and T3 as well as free iodotyrosines and iodothyronines;
- Secretion of T4 and T3 into the blood;
- Deiodination of iodotyrosines within the thyroid follicular cells for reutilization of the liberated iodine.



Inhibitors of thyroid hormone synthesis



The steps of thyroid hormone synthesis are shown clockwise, beginning with iodide uptake at about 7 o'clock.
Some common antithyroid agents and their points of interference are shown.
TPO, thyroid peroxidase; Tg, thyroglobulin; MIT, monoiodotyrosine; DIT, diiodotyrosine; SCN− , thiocyanate; ClO−4, perchlorate.

Effects of T_3 on metabolic processes

TABLE 5-5 Effects of T_3 on Metabolic Processes

Process	Effect of T_3	Tissues	Molecular target	Signaling interactions
BMR	↑	heart, liver, muscle, GI, kidney	Na^+/K^+ ATPase	SNS
Adaptive thermogenesis	↑	BAT, WAT	UCP1, D2	SNS, BA
Fatty acid synthesis	↑	liver, WAT	ChREBP FAS, ACC	PPAR-α,-γ, LXR, ChREBP, SNS
Fatty acid oxidation	↑	liver, WAT	CPT	PPAR-α,-γ, LXR, SREBP
Cholesterol synthesis, excretion	↑	liver, intestine	LDL-R, CYP7A1	PPAR-α,-γ, LXR, SREBP
Gluconeogenesis	↑	liver, muscle	PEPCK	glucose, insulin
Insulin secretion: sensitivity	↓	pancreas	GLUT4	SREBP, LXR PPARα

ACC, acetyl CoA-carboxylase; BA, bile acids; BAT, brown adipose tissue; ChREBP, carbohydrate response element binding protein; CPT, carnityl palmityl transferase; CYP7A1, cholesterol 7α-hydroxylase; D2-deiodinase type 2; FAS-fatty acid synthase; GI, gastrointestinal; GLUT-4, glucose transporter, type 4; LDL-R, low density lipoprotein receptor; LXR-liver X receptor; PEPCK, phosphoenolpyruvate carboxykinase; PPARα, PPARγ, peroxisome proliferator-activated receptor α or γ; SNS, sympathetic nervous system; SREBP, sterol response element binding protein; UCP-1, uncoupling protein type 1; WAT, white adipose tissue.

Clinical manifestations of disturbed thyroid function

System	Hyperthyroid	Hypothyroid
Cardiovascular Heart rate	↑: tachycardia	↓
Gastrointestinal Appetite	↑	↓
Intestinal peristalsis	↑	↓
Weight	↑	(↑)
Skeletal Muscle	Wasting: weakness	Slow contraction, relaxation: stiffness
Nervous System	↑: hyperkinesia, irritability, insomnia, emotional lability	↓: slow reflexes, memory loss, lethargy
Skin	Warm, moist	Cool, dry, myxedema
Basal Metabolic Rate	↑	↓

TABLE 5-7 Causes of Hypothyroidism

Dietary iodine insufficiency
Loss of functional thyroid tissue Hashimoto's disease (chronic autoimmune thyroiditis) Treatment with radioactive iodine Thyroidectomy
Diminished TSH secretion Low hypothalamic TRH secretion Defect in TSH secretion from pituitary thyrotrophs
Inherited defects in thyroid hormone synthesis Na^+/I^- symporter Thyroglobulin Thyroid peroxidase Pendrin
Peripheral resistance to thyroid hormone Defect in thyroid hormone receptor (TR)

FOLDER 21.4 Clinical Correlation: Abnormal Thyroid Function

The most common symptom of thyroid disease is a **goiter**, the enlargement of the thyroid gland. It may indicate either hypothyroidism or hyperthyroidism.

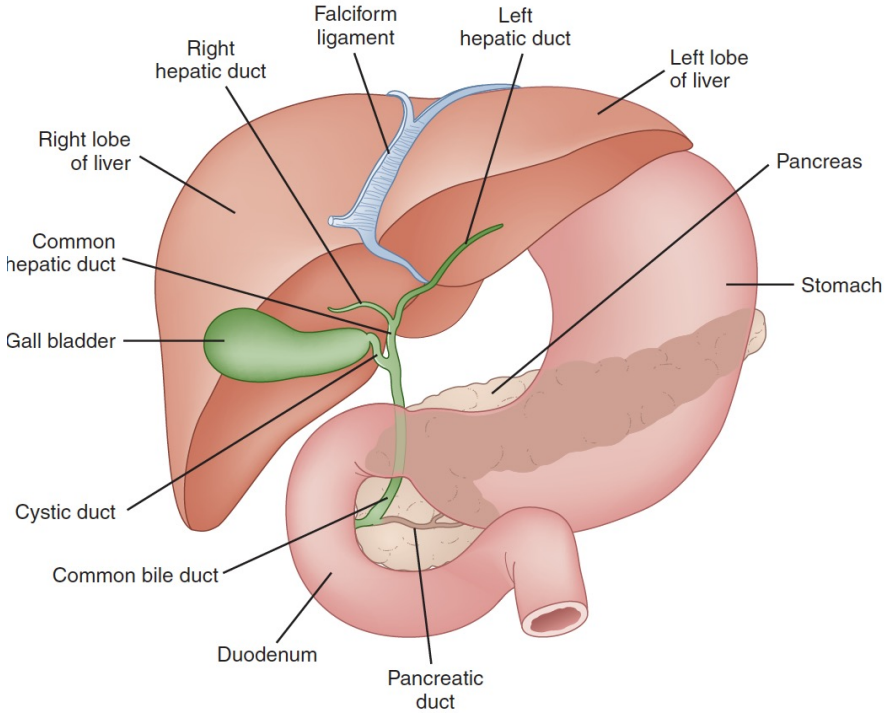
Hypothyroidism can be caused by insufficient dietary iodine **(iodine-deficiency goiter, endemic goiter)** or by one of several inherited autoimmune diseases, such as **autoimmune thyroiditis (Hashimoto's thyroiditis)**. Autoimmune thyroiditis is characterized by the presence of abnormal autoimmunoglobulins directed against thyroglobulin (TgAb), thyroid peroxidase (TPOAb), and the TSH receptor (TSHAb). The results are thyroid cell apoptosis and follicular destruction. The low levels of circulating thyroid hormone stimulate release of excessive amounts of TSH, which cause hypertrophy of the thyroid through synthesis of more thyroglobulin. Adult **hypothyroidism**, formerly called myxedema (due to the puffy appearance of the skin) is characterized by mental and physical sluggishness. The edema that occurs in the severe stages of hypothyroidism is caused by the accumulation of large amounts of hyaluronan in the extracellular matrix of the connective tissue of the dermis.

In **hyperthyroidism (toxic goiter or Graves' disease)**, excessive amounts of thyroid hormones are released into the circulation. Individuals with Graves' disease have detectable levels of autoantibodies. These abnormal immunoglobulins (IgG) bind to the TSH receptors on the follicular cells and stimulate adenylate cyclase activity. As a result, increased levels of cAMP in follicular cells lead to continuous stimulation of the cells and increased thyroid hormone secretion. Because of negative feedback, the levels of TSH in the circulation are usually normal. However, under such stimulation the thyroid gland undergoes hypertrophy, and the thyroid hormone is secreted at abnormally high rates, causing increased metabolism. Most of the clinical futures are associated with increased metabolic rate and increased sympathetic nerve activities. These include weight loss, excessive sweating, tachycardia, and nervousness. Noticeable features include protrusion of the eyeballs and retraction of the eyelids, resulting from increased sympathetic activity and increased deposition of extracellular matrix in the adipose tissue located behind the eyeball (Fig. F21.4.1a). The thyroid gland is enlarged. Microscopic features include the presence of columnar follicular cells lining the thyroid follicles. Because of the high utilization of colloid, the follicle tends to be depleted in the areas of contact with the apical surface of follicular cells (Fig. F21.4.1b). The treatment for Graves' disease is either surgical to remove the thyroid gland or radiotherapy by ingestion of radioactive iodine (^{131}I), which destroys most active follicular cells.

Pancreatic Hormones

Pancreas

The pancreas is an elongate gland described as having a head, body, and tail. The head is an expanded portion that lies in the C-shaped curve of the duodenum. It is joined to the duodenum by connective tissue. The centrally located body of the pancreas crosses the midline of the human body, and the tail extends toward the hilum of the spleen.
The pancreatic duct (of Wirsung) extends through the length of the gland and empties into the duodenum at the hepatopancreatic ampulla (of Vater), through which the common bile duct from the liver and gallbladder also enters the duodenum.
The hepatopancreatic sphincter (of Oddi) surrounds the ampulla and not only regulates the flow of bile and pancreatic juice into the duodenum but also prevents reflux of intestinal contents into the pancreatic duct. In some individuals, an accessory pancreatic duct (of Santorini) is present, a vestige of the pancreas's origin from two embryonic endodermal primordia that evaginate from the foregut.



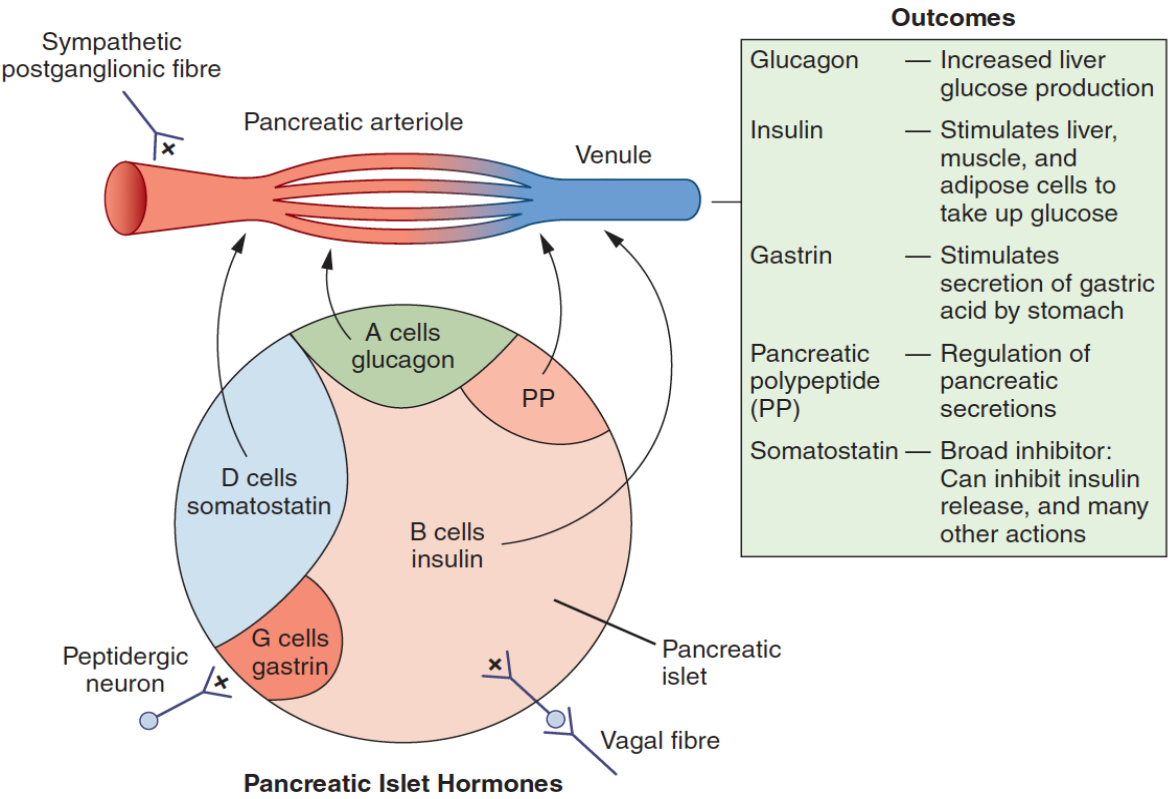
The pancreas is an exocrine and endocrine gland.
Unlike the liver, in which the exocrine and secretory (endocrine) functions reside in the same cell, the dual functions of the pancreas are relegated to two structurally distinct components.

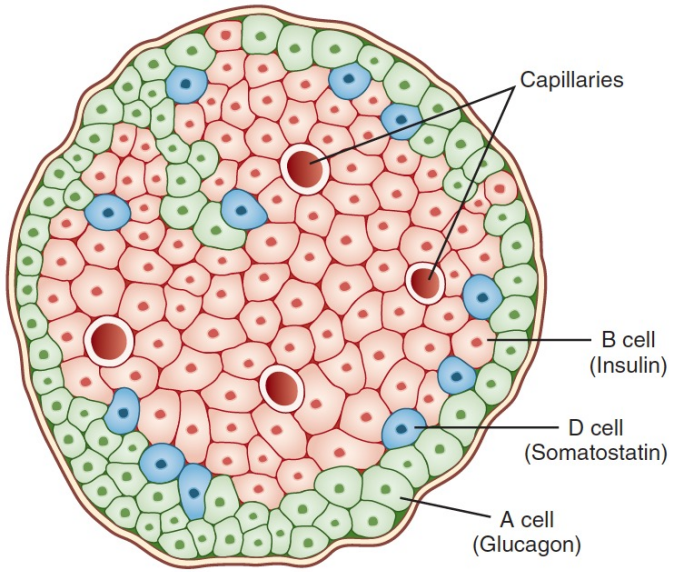
- The exocrine component synthesizes and secretes enzymes into the duodenum that are essential for digestion in the intestine.
- The endocrine component synthesizes and secretes the hormones insulin and glucagon into the blood. These hormones regulate glucose, lipid, and protein metabolism in the body.

The exocrine pancreas is found throughout the organ; within the exocrine pancreas, distinct cell masses called islets of Langerhans are dispersed and constitute the endocrine pancreas.

Pancreatic hormones

Pancreatic cell of origin[a]	Hormone	No. of amino acid residues	Function(s)
β (B)	Insulin	51	Reduction of blood glucose
α (A)	Glucagon	29	Elevation of blood glucose
β cells	Amylin[b]	37	Slows gastric emptying and promotes satiety
Δ (D)	Somatostatin	14	Inhibits secretion of insulin, glucagon, and PP
(F)	Pancreatic polypeptide (PP)	36	Stimulates secretion of gastric acid (HCl) by the parietal cells of the stomach
(G)	Gastrins[c]	34, 17 & 14	Induces secretion of HCl by parietal cells adjacent to the antrum of the stomach





Schematic diagram of a human pancreatic islet with respect to the relative proportion of cells.

Pancreatic hormones: Insulin & Glucagon

Insulin,

- Insulin the major hormone secreted by the islet tissue, decreases blood glucose levels.
- Insulin is the most abundant endocrine secretion.
- Its principal effects are on the liver, skeletal muscle, and adipose tissue. Insulin has multiple individual actions in each of these tissues. In general, insulin stimulates:
  i. uptake of glucose from the circulation. Specific cell membrane glucose transporters are involved in this process.
  ii. storage of glucose by activation of glycogen synthase and subsequent glycogen synthesis.
  iii. phosphorylation and use of glucose by promoting its glycolysis within cells.
    - Absence or inadequate amounts of insulin lead to elevated blood glucose levels and the presence of glucose in the urine, a condition known as diabetes mellitus.
- Insulin stimulates glycerol synthesis and inhibits lipase activity in adipose cells.
- Circulating insulin also increases the amount of amino acids taken up by cells (which may involve cotransport with glucose) and inhibits protein catabolism.

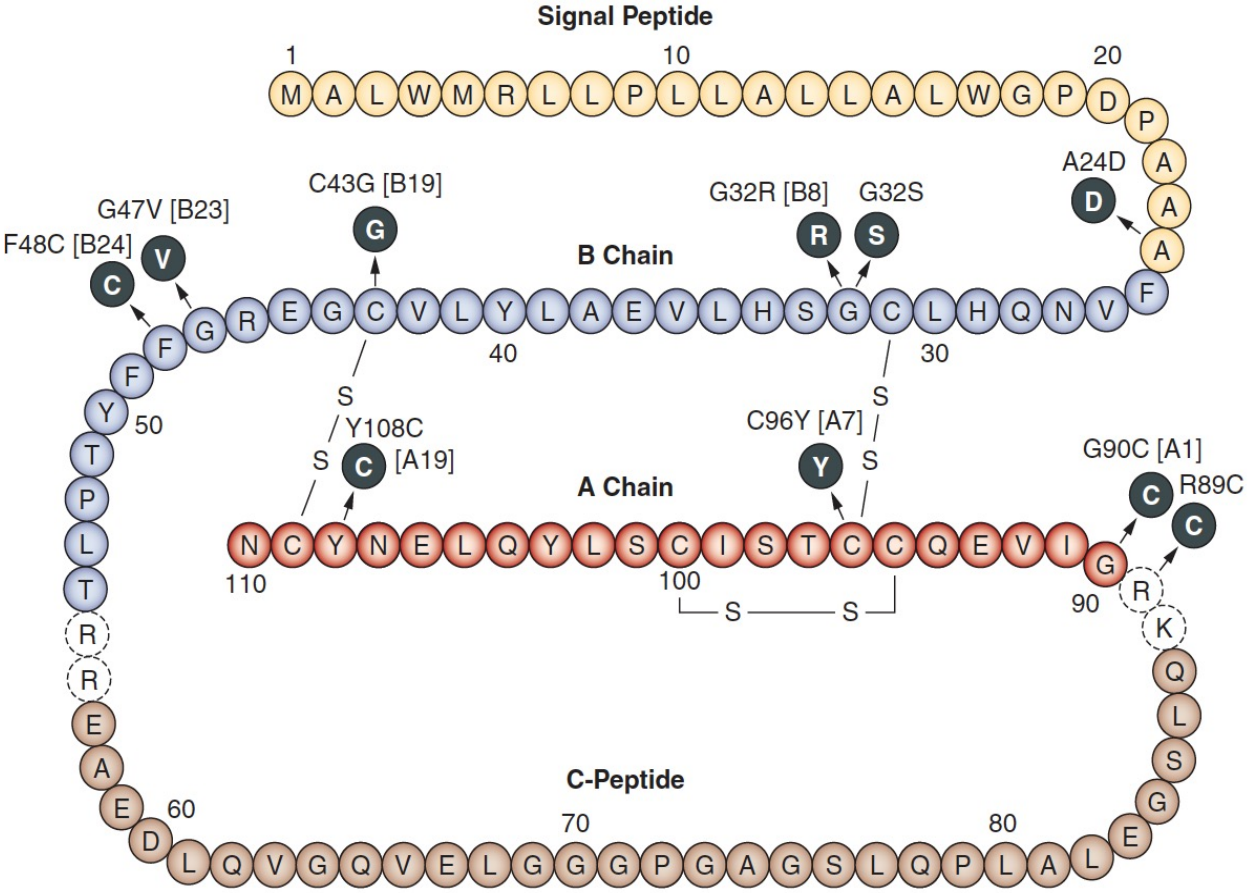
Glucagon

- **Glucagon** secreted in amounts second only to insulin, increases blood glucose levels.
  - The actions of glucagon are essentially reciprocal to those of insulin.
    i. Glucagon stimulates release of glucose into the bloodstream and stimulates gluconeogenesis (synthesis of glucose from metabolites of amino acids) and glycogenolysis (breakdown of glycogen) in the liver.
    ii. Glucagon also stimulates proteolysis to promote gluconeogenesis, mobilizes fats from adipose cells, and stimulates hepatic lipase.

Factors contributing to glucose homeostasis

Factors resulting in a reduction in blood glucose level	Factors resulting in an elevation in blood glucose level
Insulin	Glucagon actions in the liver to stimulate glycogenolysis Epinephrine stimulation of glycogenolysis
Glucose uptake by peripheral tissues	Cortisol stimulation of gluconeogenesis
Glucosuria	Insulin antagonists; growth hormone; cortisol
Exercise	Dietary intake of carbohydrates and proteins; mobilization from storage sites (glycogenolysis)
Stimulation of glucagon catabolism	Stimulation of insulin catabolism

Structure of Insulin



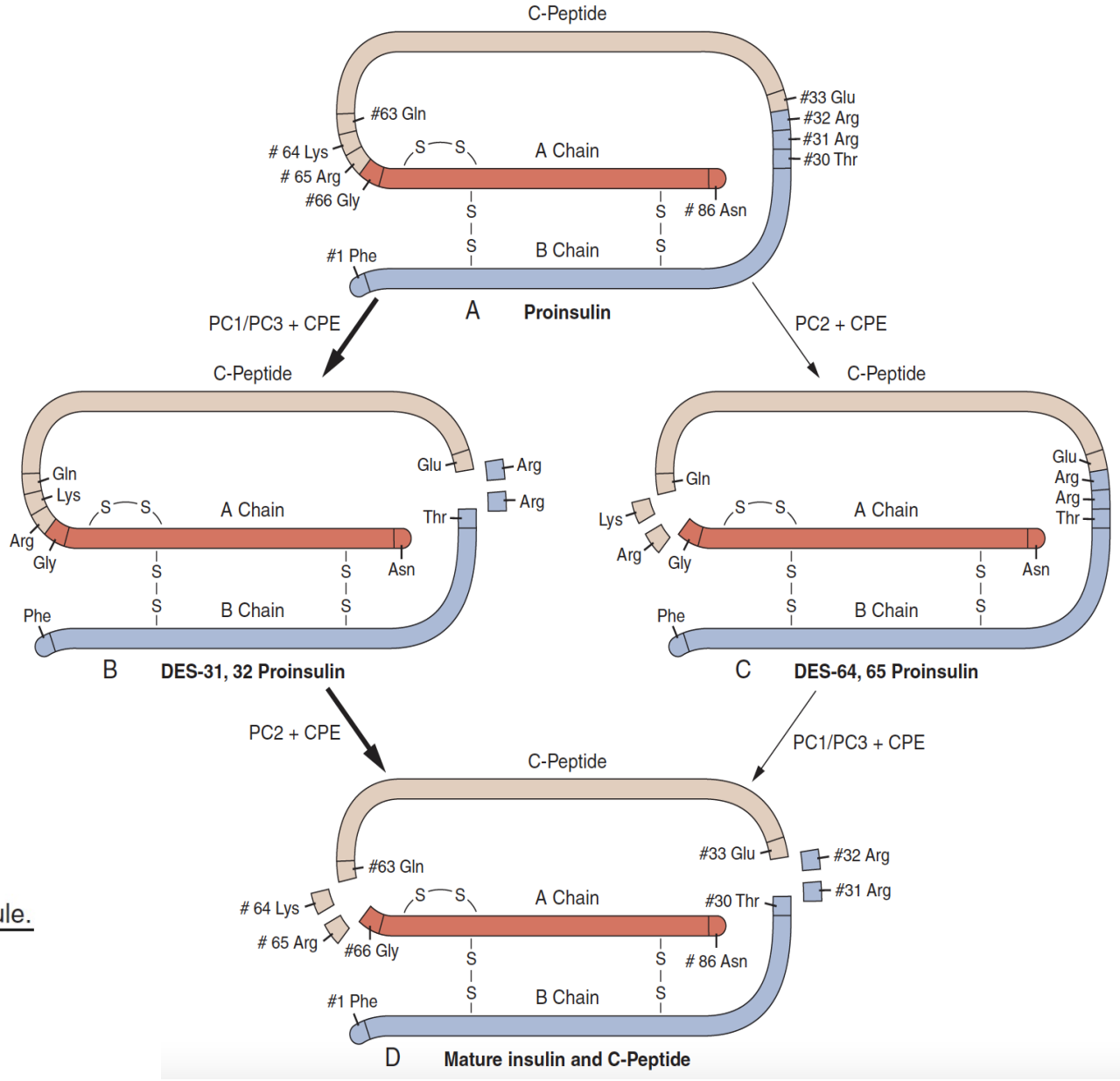
Amino acid sequence and structure of insulin and human preproinsulin.

- The preproinsulin has 110 amino acids.
- Dashed circles around either an R or K indicate sites of peptidase cleavage that result in generation of the mature insulin that is comprised by two separate peptides:
  - the A chain with 21 and the B chain with 30 amino acids. A third C peptide with 21 amino acids served as a linker between the A and B chains.
- The solid black circles represent mutations which result in a disruption of the formation of disulfide-bond formation and/or the proinsulin's normal folding; these mutations can lead to the **onset of neonatal diabetes**.
- There are also other single amino acid changes that lead to a variety of other insulin-dependent disorders (hyperinsulinemia, hyperproinsulinemia, mature onset diabetes of the young [MODY], and Type 1b diabetes) that have clinical consequences.

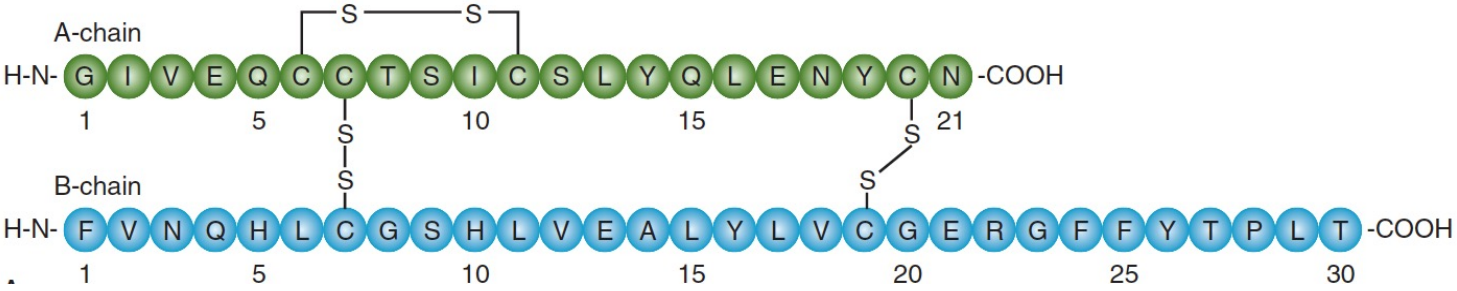
Maturation of Insulin

Steps of proteolytic cleavage of preproinsulin to generate both a mature insulin and a separate C-peptide.

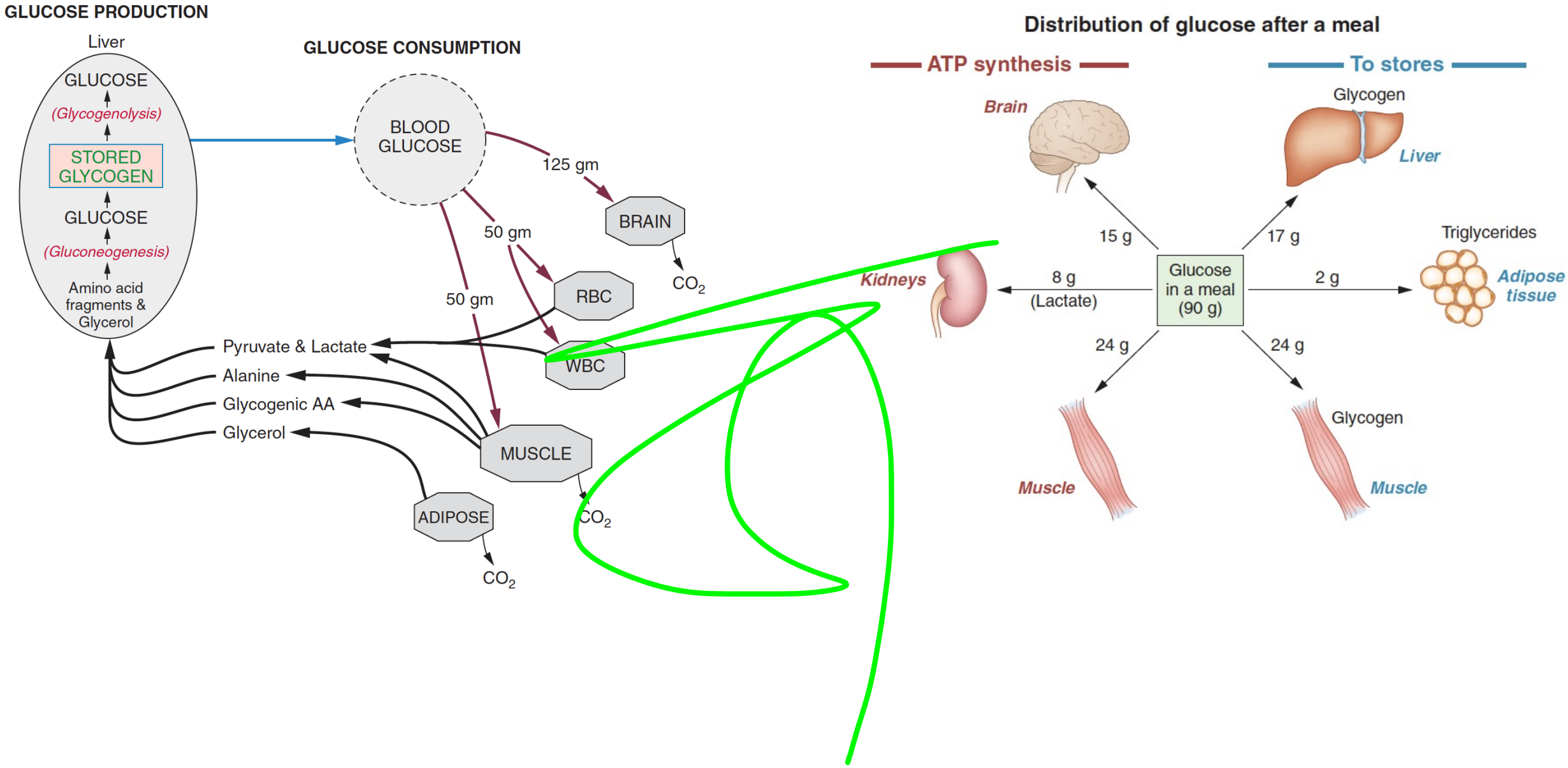
Processing of proinsulin by specific endopeptidases, PC1/PC3 + CPE (left side) and PC2 + PCE (right side) which ultimately generates in (panel D) a mature insulin (a red A chain linked to a blue B chain by two disulfide bonds) and a separate brown C-peptide).



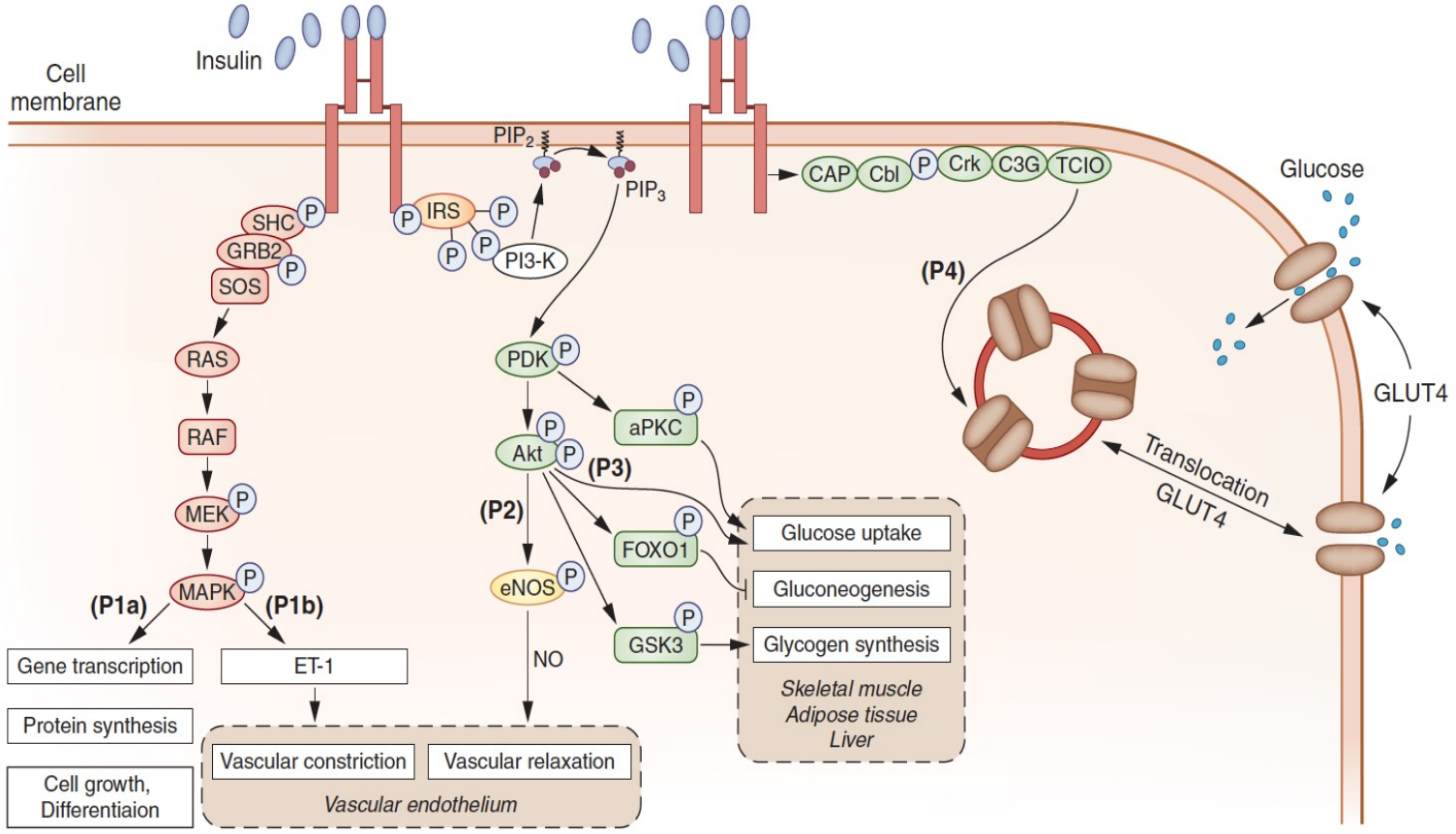
Primary structure of insulin: Amino acid sequence of the A-chain and B-chain of one insulin molecule.



Glucose metabolism



Insulin signalling



SHC, *Src homology 2 domain containing transforming protein 1;* ***GRB2,*** *growth factor receptor-bound protein;* ***SOS,*** *son of seven less;* ***RAS,*** *rat sarcoma oncogene; RAF; MEK, mitogen-activated protein kinase kinase; and* ***MAPK,*** *mitogen-activated protein kinase.* ***eNOS*** *endothelial nitrogen oxide synthase which secretes the hormone nitric oxide (NO)* ***PI3-K,*** *phosphatidylinositide-dependent protein kinase-1;* ***PDK,*** *a constitutive membrane threonine kinase;* ***Akt,*** *protein kinase B;* ***aPKC,*** *a typical protein kinase;* ***FOXO1,*** *forkhead box-containing protein O; and* ***GSK3,*** *glycogen synthase kinase—3.* ***CAP,*** *Cbl-associated protein;* ***Cbl,*** *Cas-Br-M (murine) ecotropic retroviral transforming sequence;* ***Crk,*** *CT-10 factor;* ***C3G,*** *guanine nucleotide exchange factor* ***C3G;*** *and TCIO, small GTP binding protein TCIO.*

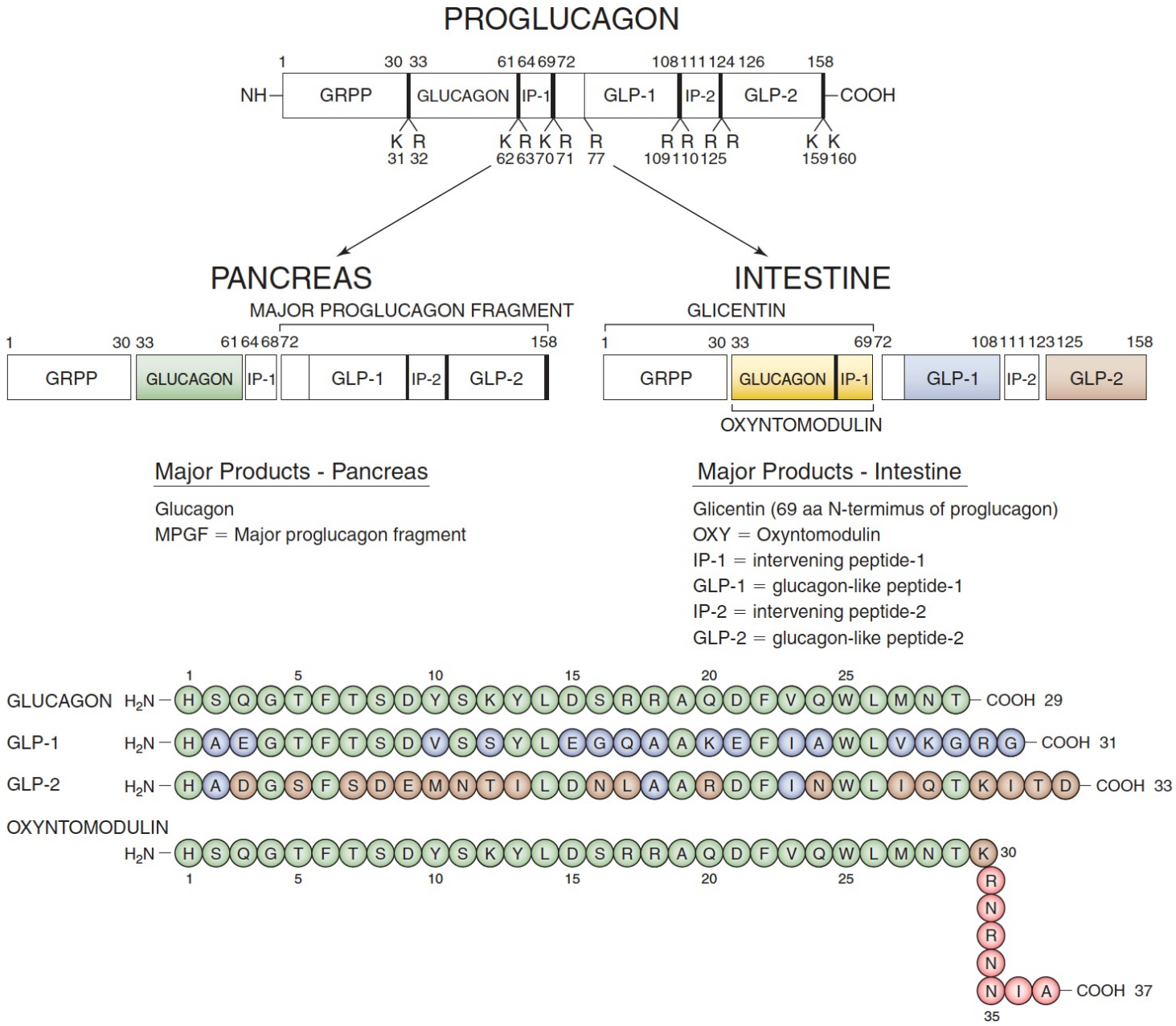
- Summary of the insulin receptor's stimulation of signal transduction and exocytosis of the GLUT4 glucose transporter.
- The activated β subunits of the insulin receptor continue delivery of the signal transduction message so that one or more of the tyrosine kinases on the β subunit becomes activated.
- Then, in this composite cell, the activated tyrosine kinase will activate one of five signal transduction pathways designated (P1a, P1b, P2, P3, or P4).
- The ultimate biological outcome of each of the five pathways can range from one of the following 5 processes:
  i. (P1a) activation of gene transcription, and protein synthesis that can lead to cell growth and/or cell differentiation via the MAPK pathway;
  ii. (P1b) vascular constriction of the endothelium via MAPK stimulating blood pressure;
  iii. (P3) vascular relaxation of the endothelium via PI3-K and Akt stimulating the hormone production of nitric oxide (NO) which causes vascular relaxation;
  iv. (P2) glucose uptake, activation of gluconeogenesis or glycogen synthesis in liver, skeletal muscle, and adipose tissues by stimulating PKC, FOX1 and GSK3; and
  v. (P4) CAP stimulating translocation of GLUT4 to the cell membrane thereby increasing uptake of glucose into the host cell.

Glucose Transporters

Protein	# of amino acids	Km (mM)[a]	Tissue & cell locations	Proposed functions
GLUT1	492	3–7	Ubiquitous distribution in cells	Basal glucose uptake
GLUT2	524	17	Liver, β-cells, kidney, small intestine	High capacity, low affinity
GLUT3	496	1.4	Brain & nerve cells	Neuronal transport
GLUT4	509	6.6	Muscle, fat, heart	Insulin regulated transport in muscle & fat
GLUT5	501	NA[b]	Intestine, kidney, testis	Transport of fructose
GLUT6	507	NA[b]	Spleen, leukocytes, brain	NA[b]
GLUT7	524	0.3	Small intestine, colon, testis	Transport of fructose
GLUT8	477	2	Testis, brain, muscle adipocytes, blastocyst	Fuel supply to spermatozoa Insulin-response transport in blastocyst
GLUT9	540	NA	Liver, kidney	Transport of fructose
GLUT10	541	0.3	Liver, pancreas	NA[b]
GLUT11	496	NA	Heart, muscle	Muscle specific fructose transporter
GLUT12	629	NA	Heart, prostate, mammary gland	NA[b]

[a]Relative net influx of glucose or 2-deoxyglucose
[b]Not available
Data was abstracted from F. Q. Zhao and A. F. Keating, Functional properties and genomics of glucose transporters, Current Genomics, *2007, 8:113–128. Class I GLUTs (1–4) are glucose transporters; Class II GLUTs (5, 7, 9, & 11) are fructose transporters, and Class III GLUTs (6, 8, 10 &12) are structurally atypical members of the GLUTs family and are not well described.*

Glucagon and Glucagon like peptides Biosynthesis and secretion

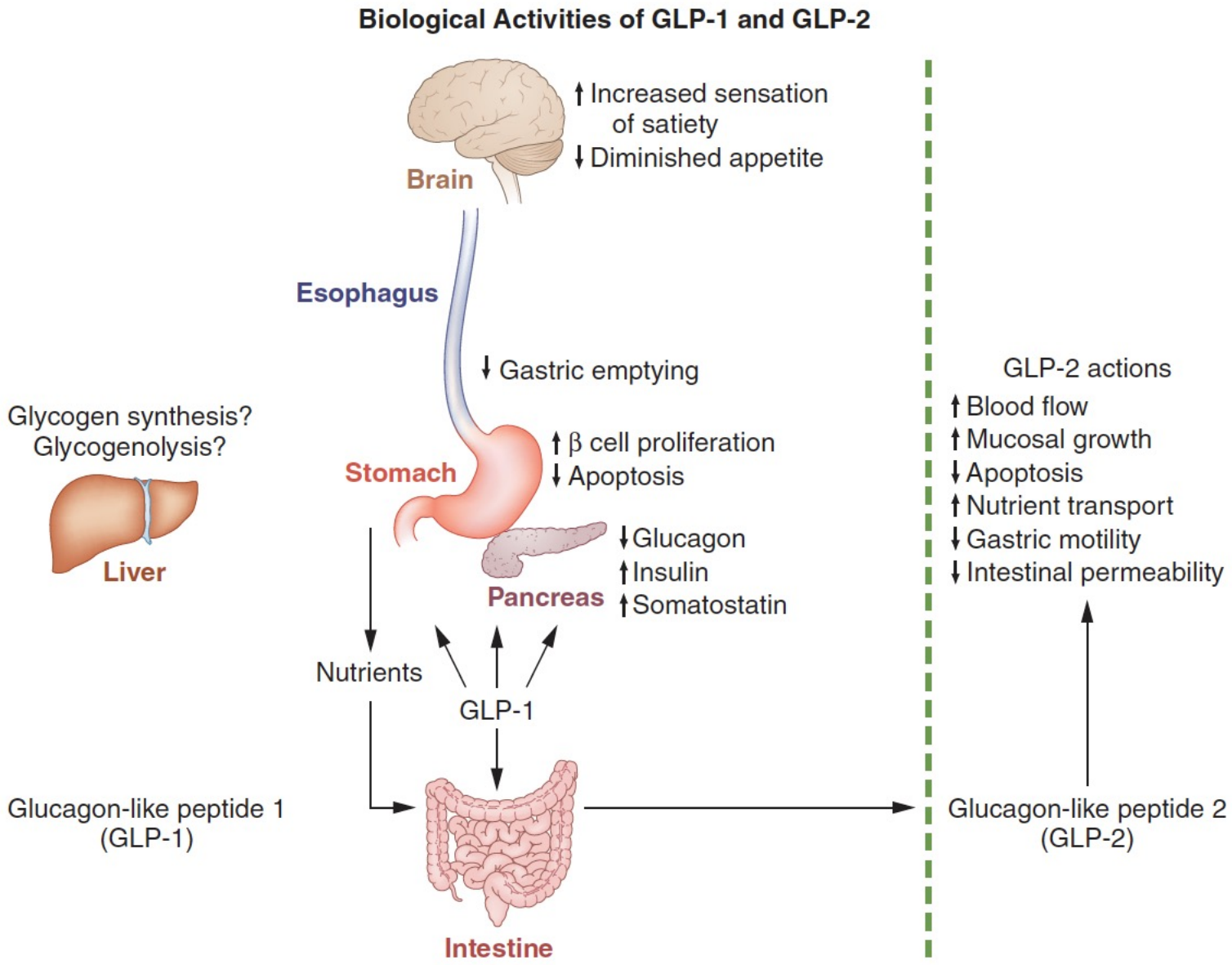


Schematic diagram of the proglucagon domain organization in the pancreas and intestine and secretion products from the pancreas (glucagon) and small intestine (GLP-1, GLP-2, and oxyntomodulin peptides).

- In the pancreas, proglucagon is processed to secrete intact full-length glucagon (29 amino acids). The "major" proglucagon fragment (amino acid residues 72–158) has no known biological functions.
- In contrast, in the intestine, proglucagon is designed to secrete:
  i. oxyntomodulin, a 37 amino acid peptide that contains the 29 amino acid sequence of glucagon followed by an 8 amino acid carboxy-terminal,
  ii. glucagon-like peptide-1 (GLP-1),
  iii. glucagon-like-peptide-2 (GLP-2).

- There is also some information suggesting that the intestinal oxyntomodulin displays weak affinity for the glucagon receptor and may mimic glucagon actions in the pancreas and liver.

Functions of Glucagon like peptides

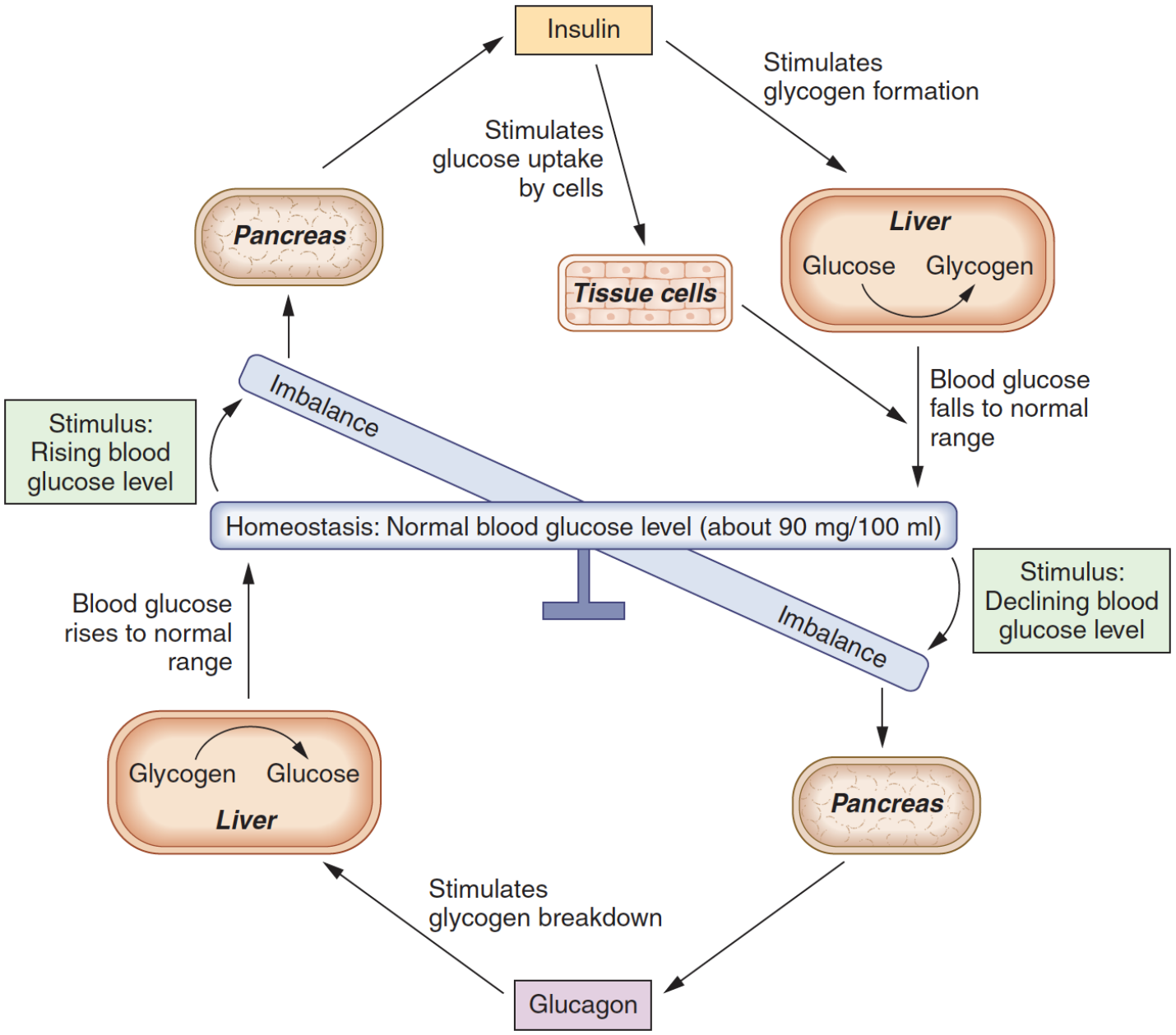


Biological actions of the glucagon-like peptides include:

i. intestine (secretion of GLP-1),
ii. pancreas (reduction in glucagon secretion and an increase in glucose-dependent secretion of insulin and somatostatin),
iii. stomach (reduction in gastric emptying),
iv. Brain (sensations of satiety and decreased appetite)

The biological actions of GLP-2 are tabulated in the right panel. The source of GLP-1 and GLP-2 is illustrated

Regulation of blood glucose by insulin and Glucagon



Comparison of the relative contributions of insulin and glucagon to the maintenance of normal blood glucose levels in a human.

- The figure shows the consequences of blood glucose levels deviating from the normal level of about **90 mg/100 mL of blood.**
- The upper half of the figure focuses on the scenario of a "rising" blood glucose level, whereas the lower half of the figure focuses on a scenario of a "declining" blood glucose level.
- Modest **elevation of glucose levels stimulates the pancreas to secrete insulin** which in liver and muscle will stimulate storage of the excess glucose and the metabolic energy that it represents
- In contrast, a modest fall in blood glucose levels (bottom half of the figure) stimulates the pancreas to secrete glycogen which stimulates glycogen breakdown to glucose only by the liver.

***** Muscle does not have a glucagon receptor.

Calcium regulating Hormones

Vitamin D

Parathyroid Hormone

Calcitonin and

Fibroblast Growth Factor 23

Calcium and Phosphorus homeostasis

The principal organs of the body involved in the maintenance of calcium and phosphate homeostasis are:

- Intestine
- bone
- kidney.

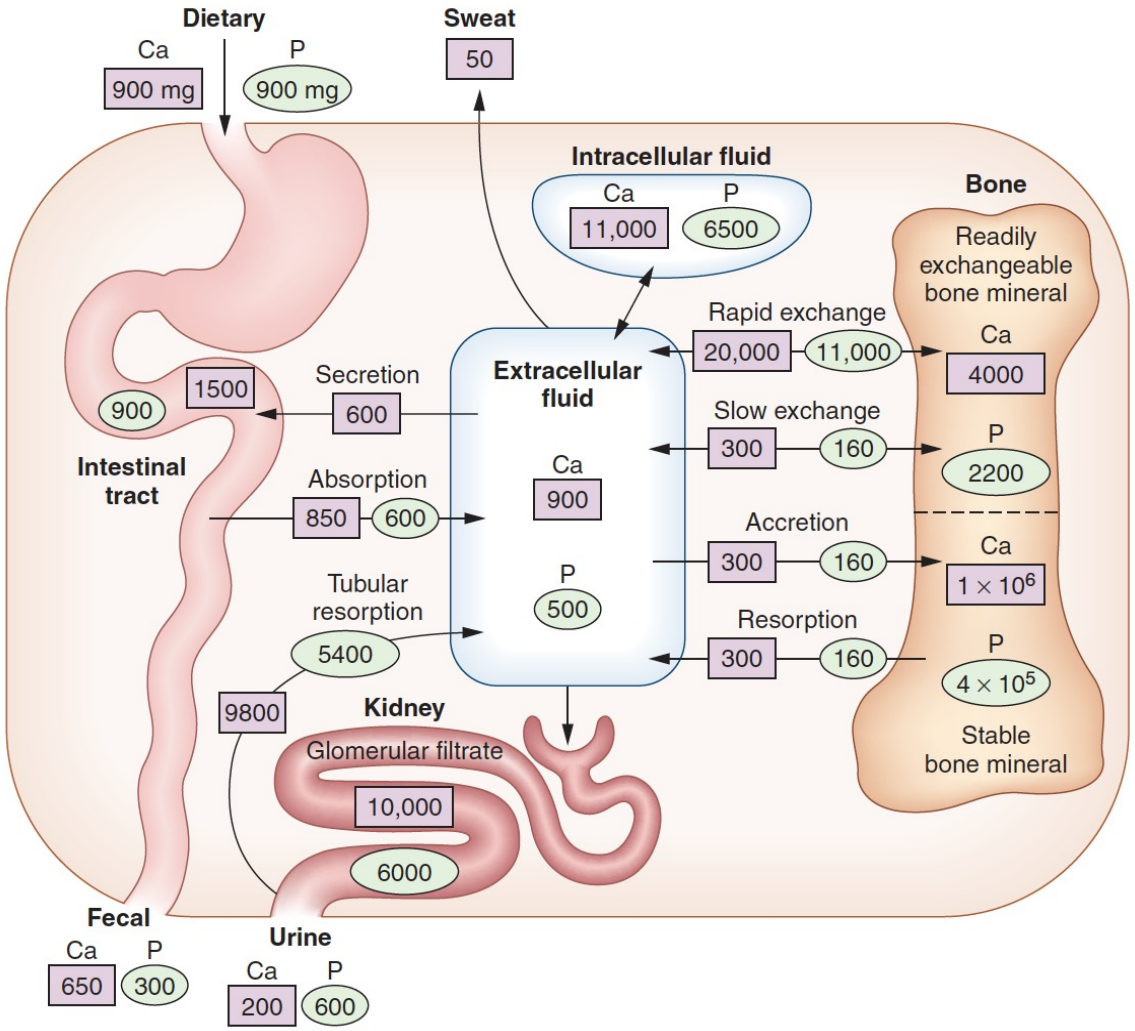
- It is here that the four calcium-regulating hormones PTH, CT, 1,25$(OH)_2$D3, and FGF23 (a phosphate-regulating hormone) initiate an integrated set of biological responses that results in maintenance of calcium and phosphorus homeostasis.
- The steroid hormone 1α,25$(OH)_2$D3 is the primary stimulator of the intestinal absorption of both Ca2+ and H2PO4−. The calcium uptake process is regulated according to the needs of the animal.
- Once the absorbed Ca2+ and H2PO4−/HPO42− from the intestine arrives in the plasma, a delicate hormonally mediated balancing of the concentrations of Ca2+ and H2PO4−/HPO42− occurs in both the skeleton, between bone accretion and bone mobilization, and in the kidney tubules, between urinary excretion and urinary reabsorption.

TABLE 9-1 Biological Calcium and Phosphorus

Calcium	Phosphorus
Body content	Body content
70-kg man has 1000 g of Ca^{2+}	70-kg man has 700 g of P
Utilization	Utilization
Structural: bone has 98% of body Ca^{2+}	Structural: bone has 90% of body P_i
Plasma [Ca^{2+}] is 8.5–10.5 mg/100 mL or 2.12–2.62 mM) Cell division Cell adhesion Protein secretion Plasma membrane integrity Nerve pulse transmission Muscle contraction	Plasma [P_i] is 2.5–4.5 mg/100 ml (0.81–1.45 mM) Intermediary metabolism (phosphorylated intermediates) Genetic information DNA RNA (mRNA) Phospholipids
Blood coagulation Glycogen metabolism Enzyme cofactors (amylase, lipases, ATPases) Eggshell (birds)	Enzyme–protein components (phosphohistidine, phosphoserine) Membrane structure
Daily requirements (70-kg man) Dietary intake: 600–1600[a] Fecal excretion: 300–600[a] Urinary excretion: 100–300[a,b] Sweat: 100–200[a,b]	Daily requirements (70-kg man) Dietary intake: 600–2000[a] Fecal excretion: 200–600[a,b] Urinary excretion: 400–1400[a,b]

[a]Values in milligrams per day for an adult.
[b]Based on the indicated level of dietary intake.

Calcium and Phosphorus Metabolism



Schematic model of Metabolic balance calcium and phosphorus metabolism in an adult man having a calcium intake of 900 mg/day and a phosphorus intake of 900 mg/day.

- Calcium and phosphorus (as phosphate) are both absorbed into the body primarily in the duodenum and jejunum regions of the intestine.
- In addition to the ~900 mg/day calcium ingested from the diet (for this example) ~600 mg is added to the intestinal contents by pancreatic and intestinal secretions. Of the ~1500 mg of total calcium present in the lumen of the intestine, ~850 mg is absorbed by the intestinal epithelial cells and transported to the blood compartment, leaving the remaining ~650 mg to be excreted in the feces.
- After the newly absorbed Ca2+ has entered the extracellular pool, it is in constant exchange with the Ca2+ already present in the extracellular and intracellular fluid compartments of the body and in certain compartments of the bone and the kidney's glomerular filtrate. The glomerulus of the kidney filters ~10,000 mg of Ca2+ per day, but the renal tubular reabsorption of this ion is so efficient that only ~200 mg of Ca2+ appears in the urine.
- In the event of hypercalcemia, the urinary excretion of Ca2+ rises in a compensatory fashion; however, it rarely exceeds a value of 400–600 mg/day.
- The renal tubular reabsorption of Ca2+ is stimulated by the separate actions of PTH and $1\alpha,25(OH)_2D3$ in the distal nephron of the kidney. Also, depending on the ambient temperature, an additional 50–200 mg of Ca2+ may be lost per day through the skin via sweating.
- Absorption of phosphate is interrelated in a complex fashion with the presence of Ca2+ and can be stimulated by a low-calcium diet and also by $1\alpha,25(OH)_2D3$.
- Phosphate in the body is also partitioned among three major pools: the kidney ultrafiltrate, the readily exchangeable fraction of bone, and the intracellular compartments in the various soft tissues.
- The major excretory route for phosphate is through the kidney. The handling of phosphate by the kidney is determined by the rates of glomerular filtration, tubular reabsorption, and possibly tubular secretion.
- Every day the kidney glomerulus filters some 6000–10,000 mg of phosphorus. A normal 70 kg person, given a diet containing 900 mg of phosphorus, excretes ~600 mg/day in the urine.

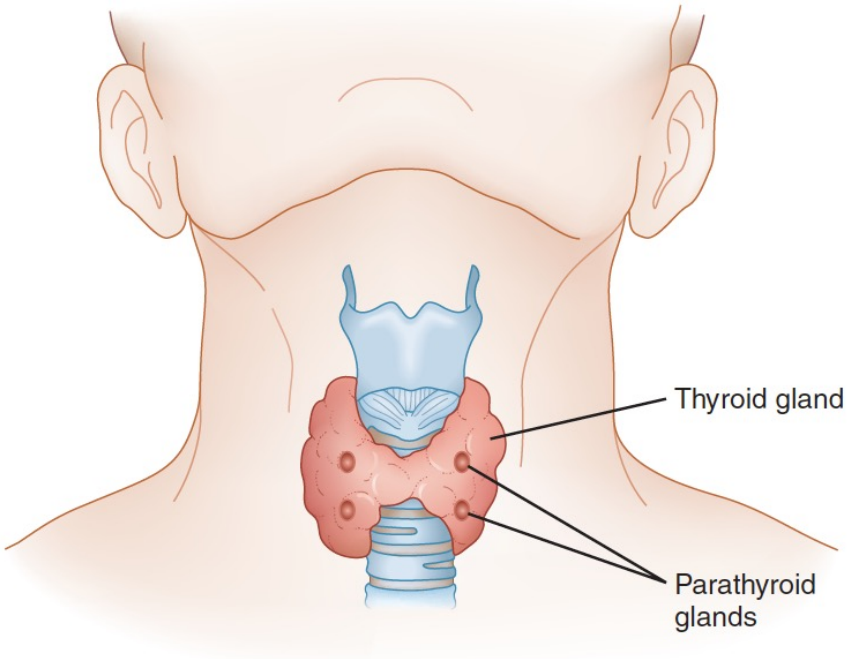
Hormones of parathyroid Gland

The parathyroid glands are small endocrine glands closely associated with the thyroid. They are ovoid, a few millimeters in diameter, and arranged in two pairs, constituting the superior and inferior parathyroid glands. They are usually located in the connective tissue on the posterior surface of the lateral lobes of the thyroid gland. However, the number and location may vary. In 2% to 10% of individuals, additional glands are associated with the thymus.

Structurally, each parathyroid gland is surrounded by a thin connective tissue capsule that separates it from the thyroid. Septa extend from the capsule into the gland to divide it into poorly defined lobules and to separate the densely packed cords of cells.

The connective tissue is more evident in the adult, with the development of fat cells that increase with age and ultimately constitute as much as 60% to 70% of the glandular mass.

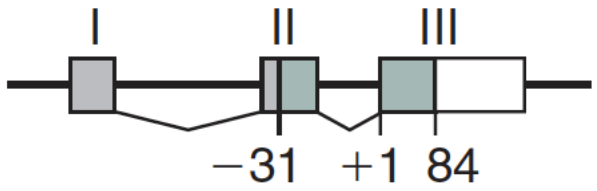
The glands receive their blood supply from the inferior thyroid arteries or from anastomoses between the superior and inferior thyroid arteries. Typical of endocrine glands, rich networks of fenestrated blood capillaries and lymphatic capillaries surround the parenchyma of the parathyroids.

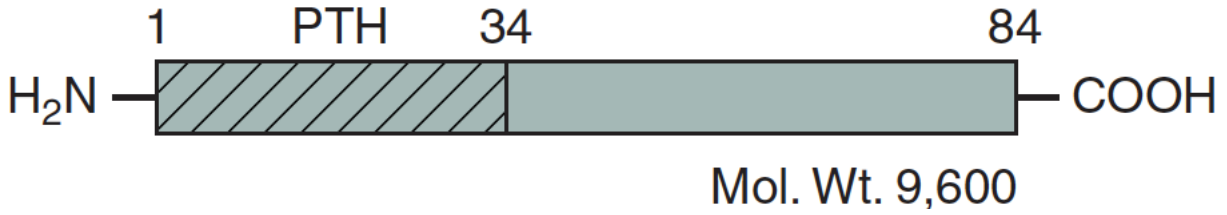


Hormones of parathyroid Gland

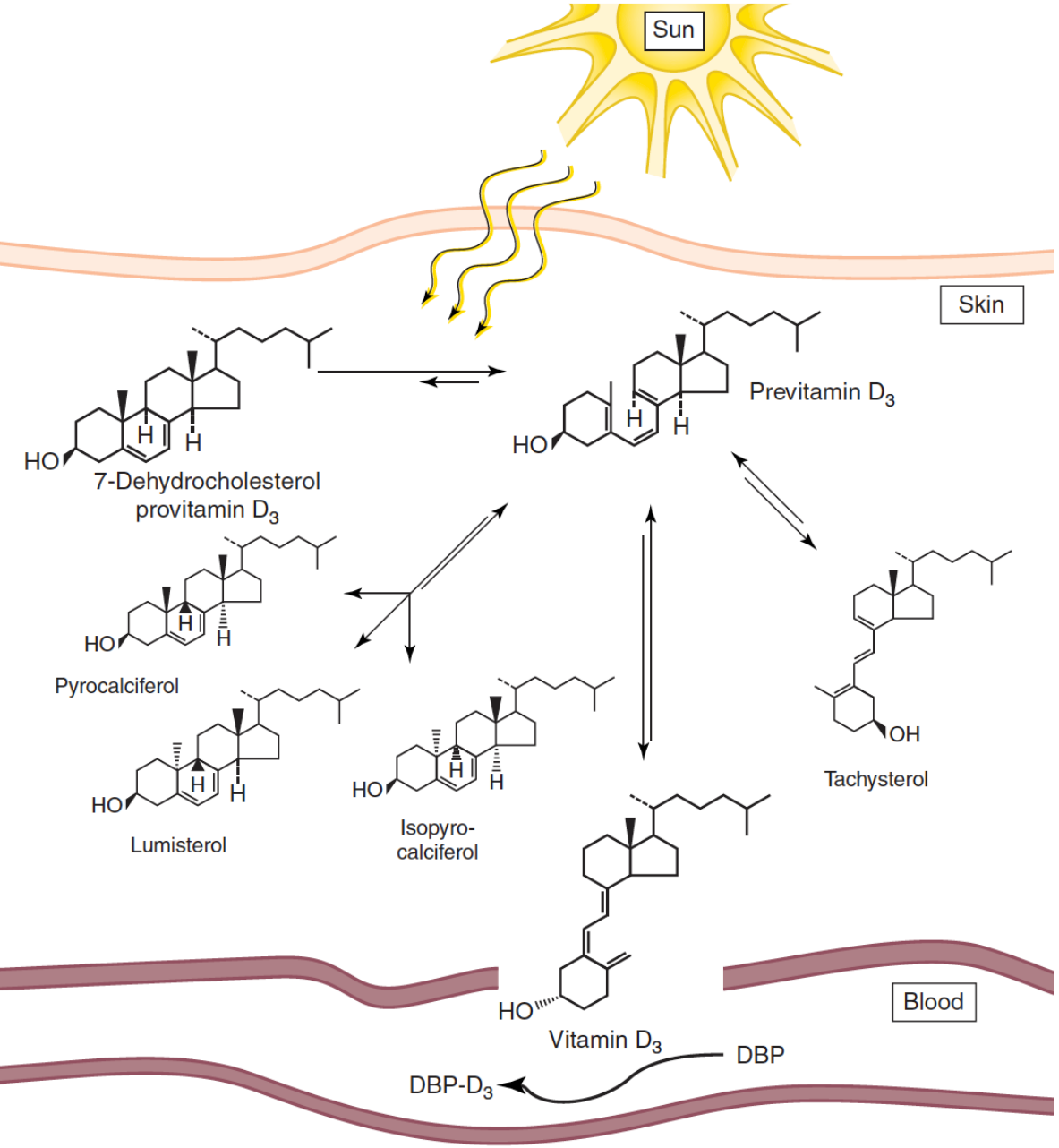
Hormone	Composition	Source	Major Functions
Parathyroid hormone (PTH)	Polypeptide containing 84 amino acids	Principal (chief cells)[a]	Increases blood calcium level in three ways: (1) promotes calcium release from bone (acting on osteoblasts via RANK-RANKL signaling system, it increases the relative number of osteoclasts); (2) acts on the kidney to stimulate calcium reabsorption by the distal tubule while inhibiting phosphate reabsorption in the proximal tubule; and (3) increases formation of hormonally active 1,25-dihydroxycholecalciferol (1,25-(OH)2 vitamin D_3) in the kidney, which promotes tubular reabsorption of calcium.

[a]Some evidence suggests that oxyphil cells, which first appear in the parathyroid gland at about 4 to 7 years of age and increase in number after puberty, may also produce PTH.





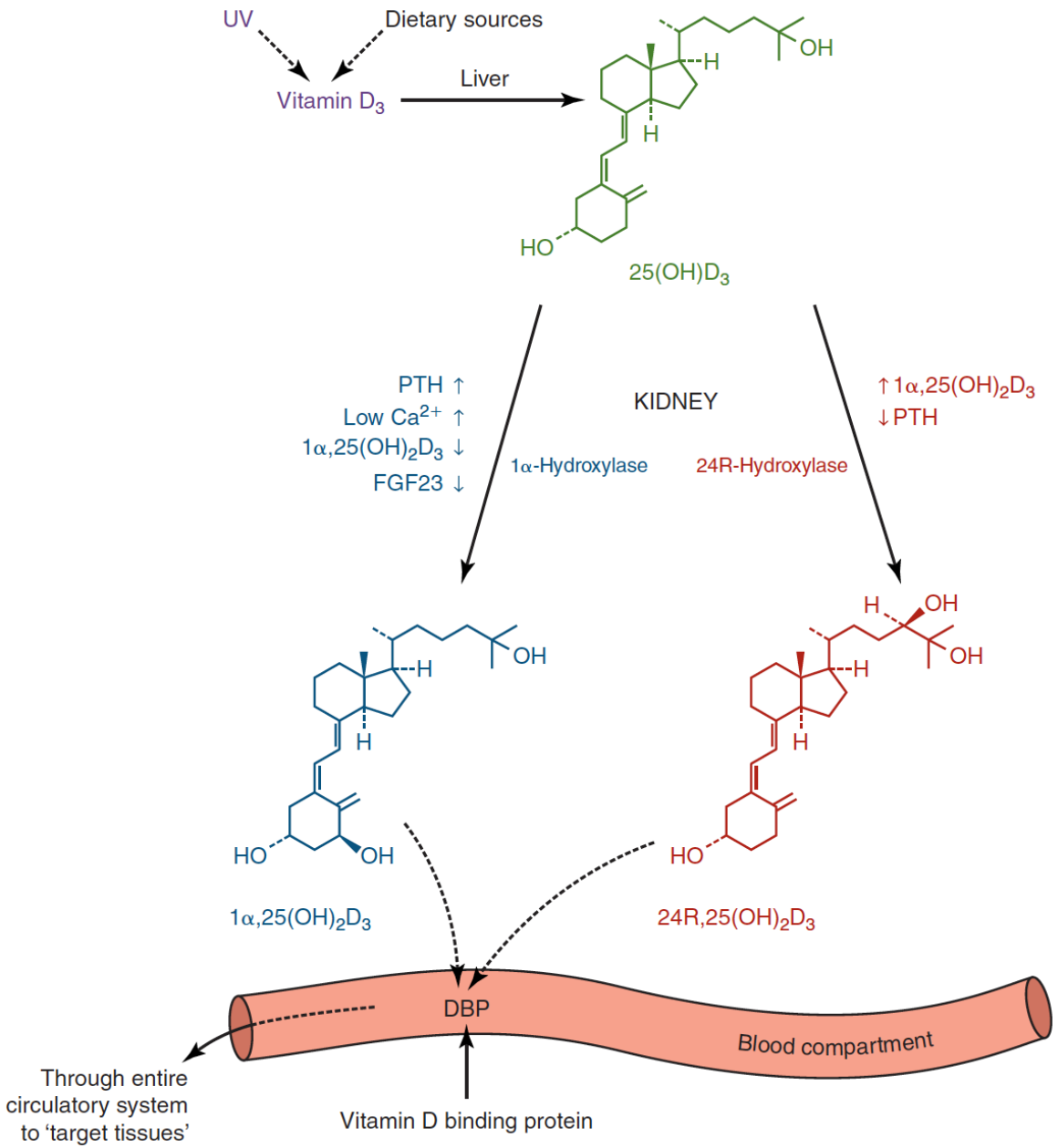
Vitamin D production from sun



Photochemical pathway of production of vitamin D3 (cholecalciferol) from 7-dehydrocholesterol.

- The starting point is the irradiation of a provitamin D, which contains the mandatory Δ5,7-conjugated double bonds; in the skin this is 7-dehydrocholesterol.
- After absorption of a quantum of light from sunlight (UV-B), the activated molecule can return to the ground state and generate at least six distinct products.
- The four steroids that do not have a broken 9, 10-carbon bond (provitamin D, lumisterol, pyrocalciferol, and isopyrocalciferol) represent the four diastereomers with either an *α*- or a *β*-orientation of the methyl group on carbon-10 and the hydrogen on carbon-9.
- The three secosteroid products, vitamin D3, previtamin D3 and tachysterol3, each have differing positions of the three conjugated double bonds. In the skin the principal product is previtamin D3, which then undergoes a 1,7-sigmatropic hydrogen transfer from C-19 to C-9, yielding the final vitamin D3.
- Vitamin D3 can be drawn as either a 6-*s*-*trans* representation (this figure) or a 6-*s*-*cis* representation depending upon the state of rotation about the 6,7-single bond.
- The resulting vitamin D3, which is formed in the skin, is removed by binding to the plasma transport protein, the vitamin D-binding protein (DBP), present in the capillary bed of the dermis.
- The DBP-D3 then enters the general circulatory system. The same overall mechanism applies to the commercial irradiation of ergosterol to yield vitamin D2.

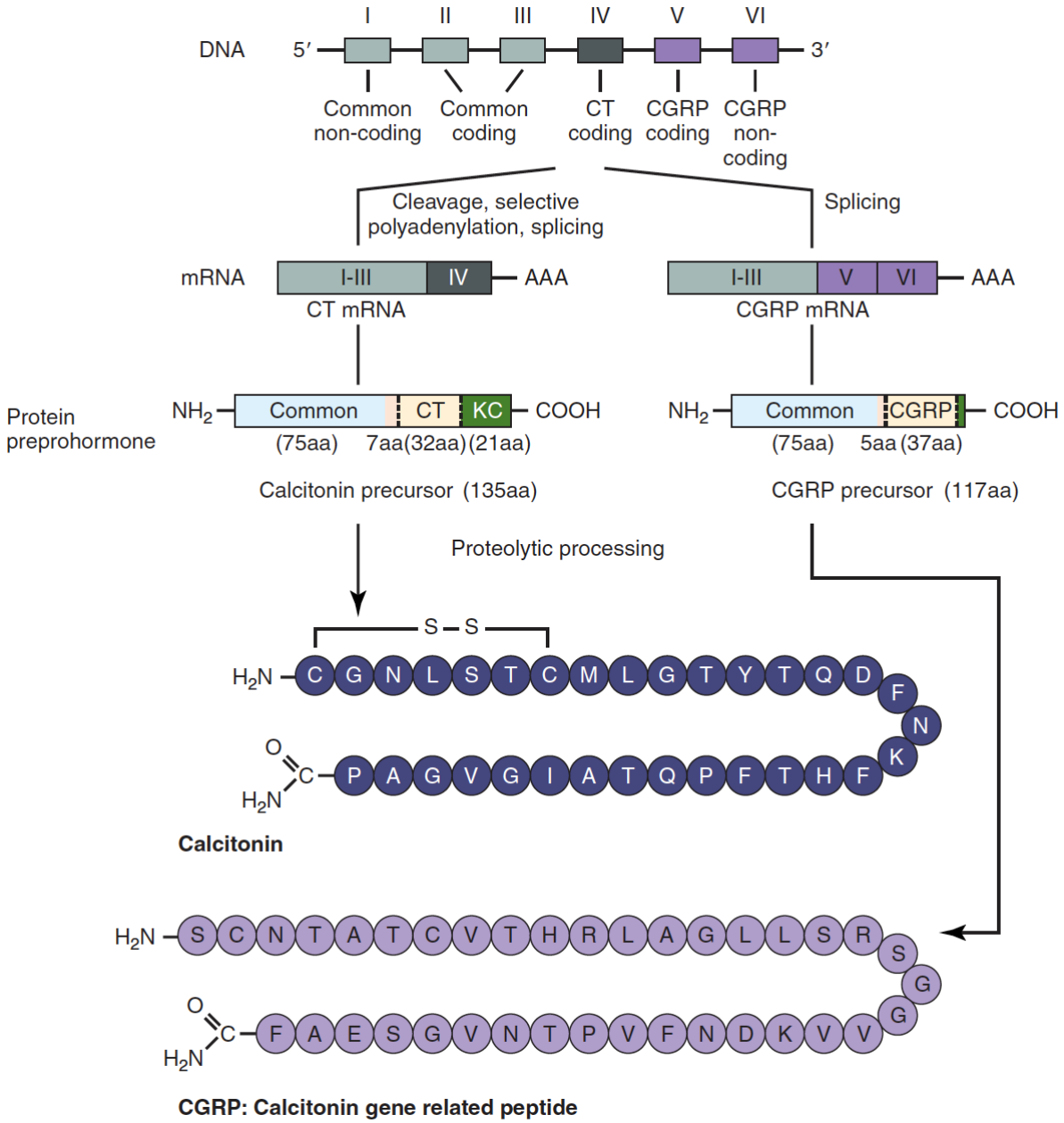
Vitamin D metabolism



- The secosteroid vitamin D3 itself is biologically inert and does not stimulate or mediate any biological responses.
- Vitamin D3 produced photochemically in the skin or obtained dietarily is 25-hydroxylated in the liver to generate 25(OH)D3 and then further metabolized in the kidney.
- Thus vitamin D3 is a precursor to three key daughter metabolites. Accordingly, there are three key enzymes involved in conversion of vitamin D3 into 25(OH)D_3, 1α,25(OH)$_2D_3$, or 24R,25(OH)$_2D_3$. They include the following:
  i. vitamin D3-25-hydroxylase (a liver mitochondrial CYP27A1);
  ii. 25(OH)D_3-1α-hydroxylase (the proximal kidney tubule mitochondrial CYP27B1); and
  iii. 25(OH)D_3-24R-hydroxylase (the proximal kidney tubule mitochondrial CYP24).

  *** The liver 25-hydoyxlase is not subject to physiological regulation. Thus, the amount of 25(OH)D3 produced is dependent upon the substrate concentration of vitamin D3 present. In contrast, both the kidney 1α-hydroxylase and the 24R-hydroxylase are highly regulated.
- As shown in the figure, the activity of the 1α-hydroxylase is increased by PTH, and low serum Ca2+ and decreased by FGF-23 and the circulating concentration of 1α,25(OH)2D3.
- Both the kidney-produced 1α,25(OH)$_2D_3$ and 24R,25(OH)$_2D_3$ as well as the liver-produced 25(OH)D3 move to the circulatory system where they bind to the vitamin D binding protein (DBP) for transport throughout the circulatory system.
- Target tissues for 1α,25(OH)2D3 are defined by the presence of the VDR.

Structure of Calcitonin

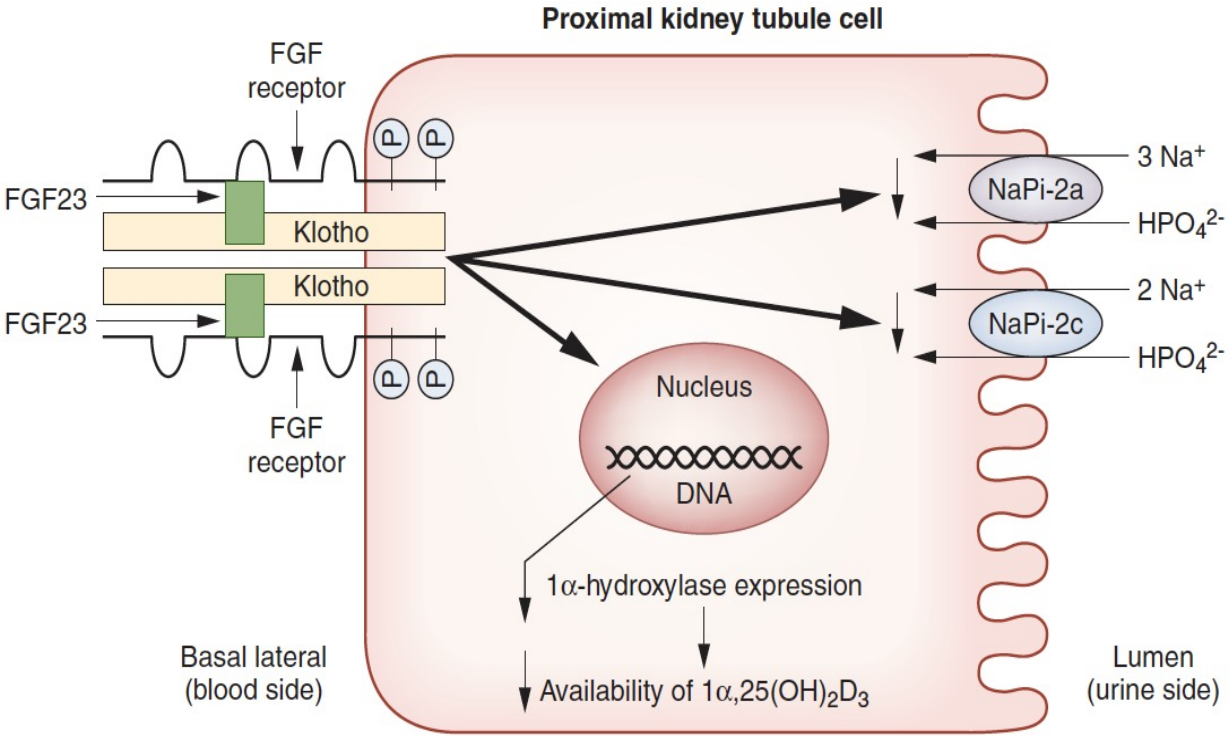


- Model for the production of calcitonin (**CT**) and calcitonin gene-related peptide (**CGRP**) via the alternative RNA processing pathways utilized in the expression of the calcitonin gene.
- The calcitonin gene supports the production of CT in the thyroid and of CGRP in the hypothalamus.
- Mature CT, which has 32 amino acid residues, and mature CGRP, which has 37 amino acid residues, are derived from different precursor proteins.
- However, these two precursor proteins have an identical "common region" of 75 amino acid residues, which is derived from the C1 and C2 exons of the gene.

Fibroblast Growth Factor 23

- Fibroblast Growth Factor 23 (FGF23) was proven in 2004 to be an essential regulator of phosphate homeostasis.
- FGF23 is one of at least 22 known proteins that comprise the family of fibroblast growth factors.
- This family of proteins displays amino acid sequence and structural similarities. The molecular weight of FGF23 is ~31 kDa and it has 251 amino acids; its amino acid sequence of residues 25 to 176 are very similar to the other members of the FGF family of proteins.
- **FGF23 is principally secreted by bone osteocytes/osteoblasts** but smaller amounts are present in the brain, muscle, heart, thymus, and spleen.
- FGF23 generates its biological responses through binding to its cognate plasma membrane spanning receptor
- FGF23 also requires the presence of both a protein cofactor known as klotho (1024 amino acids; 122 kDa) and the FGF23 receptor to create a functional trimeric complex. Both the C-termini of klotho and the phosphorylated FGF23 receptor span the plasma membrane as a hetero-dimer which generates an as yet unknown signal transduction second messenger(s).
- In the proximal renal tubule cells the FGF23 receptor generated messengers result in two separate responses.
  - One is an impairment of two classes of Na+-dependent phosphate transporters (NaPi-2a and NaPi-2c) which results in a reduction in renal tubular phosphate reabsorption.
  - The second response works in the cell nucleus to reduce the expression of 25(OH)D3-1α-hydroxylase leading to a reduction in the production of 1α,25(OH)2D3 and lowering of 1α,25(OH)2D3 plasma levels.

Schematic of binding of FGF23 to its receptor on proximal kidney cell



- Schematic of binding of Fibroblast Growth Factor 23 (FGF23) to its receptor in a proximal kidney cell, resulting in the reduction of gene expression of two sodium and phosphate transporters and also the 25(OH)D3-1α-hydroxylase.
- The FGF23 receptor requires the presence of a protein cofactor known as klotho to generate its signal transduction signals.
- Generation of biological responses by FGF23 requires the interaction on the surface of the proximal (basal lateral) side of the kidney cell of FGF23 binding to a Klotho-FGF receptor dimeric complex creating formation of a trimeric complex.
- This trimeric complex then activates phosphorylation of the FGF receptor and activation of the intracellular signal activating the ERK kinase pathway.
- This then leads to the reduction of gene expression of the NaPi-2a and NaPi-2c electrogenic phosphate transporters and also the expression of the 25(OH)D3-1α-hydroxylase.

Integrated Actions of 1α,25(OH)2D3, PTH, Calcitonin, and FGF23 on Bone Remodeling and Calcium Homeostasis

- **Bone is a metabolically active organ**, undergoing throughout life a continual turnover and remodeling process involving bone resorption followed by accretion.
- The balance between the rates of bone resorption by osteoclasts and bone formation by osteoblasts will determine, both at a local level or globally (the entire skeleton), whether there is a negative, neutral, or positive calcium balance.
- The biological activities of bone cells are subject to the actions of a multitude of hormones, cytokines, and other physiological regulators

Stimulators of bone resorption	Inhibitors of bone resorption
PTH	Calcitonin
PTHrP	
$1\alpha,25(OH)_2D_3$	Glucocorticoids
Prostaglandins	Estrogens
PGE_2	Androgens
Interleukin-1 (IL-1)	Insulin-like growth factor
Tumor Necrosis Factors	TGF-1
TNF-α	Fluoride (F^-)
TNF-β	
Thyroxine	
Retinol	
Growth factors	
EGF (epidermal growth factor)	

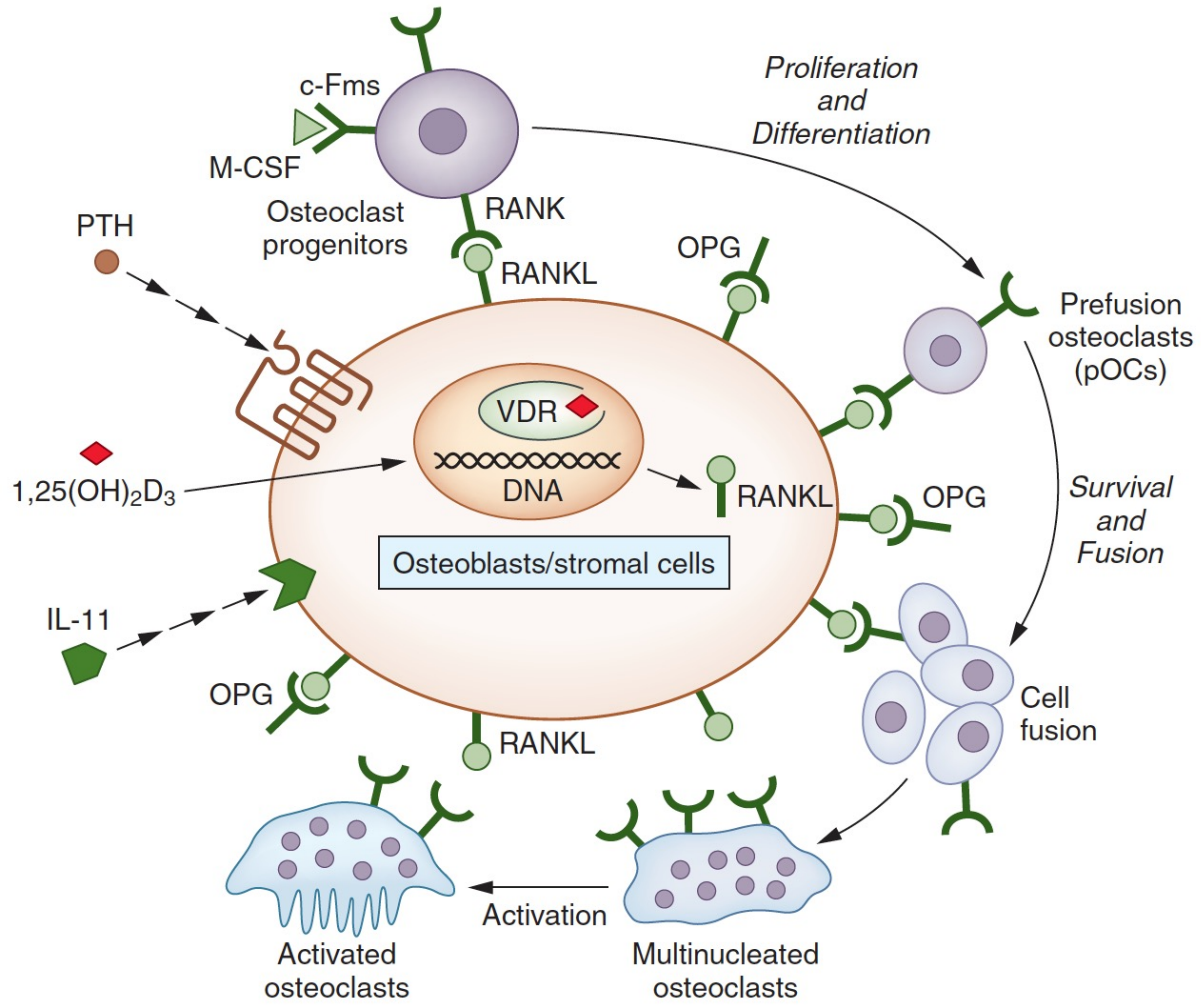
Integrated Actions of 1α,25(OH)2D3, PTH, Calcitonin, and FGF23 on Bone Remodeling and Calcium Homeostasis

TABLE 9-4 Physiological Effects of Calcitonin, Parathyroid Hormone, and Vitamin D (Metabolites) Related to Mineral Metabolism[a]

	Calcitonin	Parathyroid hormone	$1\alpha,25(OH)_2D_3$
Intestinal			
Calcium absorption	–	↑ (indirect)	↑
Phosphate absorption		–	↑
Renal			
Phosphate excretion	↑	↑	↓
Calcium excretion	↑	↓	
Adenyl cyclase activity	↑	↑	–
Skeletal			
Calcium mobilization	↓	↑	↑
Mineralization of bone matrix	–	–	↑
Plasma Levels			
Calcium	↓	↑	↑
Phosphate	↓	↓	↑

The important role of bone as a central organ in calcium and phosphorus metabolism, acting both as a source of and a reservoir for these two ions, is discussed in the text. It is apparent that bone remodeling processes may contribute to both short- and long-term events necessary for calcium and phosphorus homeostasis. The relative actions of bone formation and resorption are known to be modulated by various endocrine regulators during times of skeletal growth and lactation and in birds during the process of egg laying. Also, it is not surprising that bone is involved in a wide variety of disease states that reflect perturbations in calcium and phosphorus homeostasis.

Osteoclastogenesis



- Osteoclast progenitor cells are derived from a monocytes/macrophage lineage.
- They enter into a differentiation pathway starting with stimulation by M-CSF (monocyte/macrophage-colony stimulating factor) that binds to its cell surface receptor, c-Fms.
- This results in the appearance of the cell surface receptor, **RANK** (the receptor activator of NF-κB ligand) on several cell types including osteoclast progenitors, prefusion osteoclasts, multinucleated osteoclasts, and fully activated and functional osteoclasts.
- **RANKL**, which is present on the cell surface of osteoblasts/stromal cells, is the ligand for RANK.
- The binding of RANKL to RANK results in communication between the osteoblast (which possesses PTH, IL-11 and 1α,25(OH)2D3 receptors) with the progenitor osteoclasts, prefusion osteoclasts, multinucleated osteoclasts and functional activated osteoclasts.
- **OPG** is a decoy soluble receptor for RANKL produced by osteoblasts that acts as a decoy receptor for RANKL and thereby inhibits osteoclastogenesis and osteoclast activation by binding to RANKL.
- Interleukin-11 (**IL-11**) is a 23 kDa protein that participates in osteoclast progenitor proliferation and differentiation into prefusion osteoclasts.
- **VDR** is the receptor for 1α,25(OH)2D3 that is present in osteoblasts, but not osteoclasts.

Clinical correlation: Osteoporosis

FOLDER 8.2 Clinical Correlation: Osteoporosis

Osteoporosis, which literally means porous bone, is the most commonly occurring bone disease characterized by progressive loss of normal bone density accompanied by the deterioration of its microarchitecture. It is caused by an imbalance between osteoclast-mediated bone resorption and osteoblast-mediated bone deposition, resulting in decreased bone mass, enhanced bone fragility, and increased risk of fracture. In healthy individuals, osteoclast activity is primarily regulated by PTH and to a lesser degree by IL-1 and TNF. In addition, differentiation of osteoclast precursors is under the influence of M-CSF and IL-6. Female hormones known as *estrogens* (especially estradiol) inhibit formation of these cytokines, therefore limiting the activity of osteoclasts. In postmenopausal women in whom estrogen levels are reduced, secretion of these cytokines is increased, resulting in enhanced activity of osteoclasts leading to intensified bone resorption. Osteoporosis is a disease that affects an estimated 75 million people in the United States, Europe, and Japan, including one-third of postmenopausal women and most of the elderly population. It results in more than 1.3 million fractures annually in the United States

There are three general types of osteoporosis.

1. **Type I primary osteoporosis** occurs in postmenopausal women. Since this type appears at an earlier stage of life than type II, its long-term effect is usually more severe than osteoporosis that develops in the later years of life.
2. **Type II primary osteoporosis** occurs in elderly individuals in their seventh or eighth decade of life and is the leading cause of serious morbidity and functional loss in this age group.
3. **Secondary osteoporosis** develops as a result of drug therapy (i.e., corticosteroids) or disease processes that may affect bone remodeling, including malnutrition, prolonged immobilization, weightlessness (i.e., with space travel), and metabolic bone diseases (i.e., hyperparathyroidism, metastatic cancers).

Osteoporotic bone has normal histologic structure; however, there is less tissue mass (Fig. F8.2.1). This results in weakened bones that are more prone to fractures following even minor trauma. Femoral head and neck fractures (commonly known as *hip fractures*), wrist fractures, and compressed vertebrae fractures are common injuries that frequently disable and confine an elderly person to a wheelchair. Individuals suffering from fractures are at greater risk for death, not directly from the fracture, but from the complications of hospitalization because of immobilization and increased risk of pneumonia, pulmonary thrombosis, and embolism.

Traditional treatment of individuals with osteoporosis includes an improved diet with vitamin D and calcium supplementation and moderate exercise to help slow further bone loss. In addition to diet and exercise, pharmacologic therapy directed toward slowing down bone resorption is employed.

Until recently, the treatment of choice in postmenopausal women with osteoporosis was **hormone replacement therapy** with estrogen and progesterone. Estrogen is known to retard bone resorption, thereby diminishing bone loss. The results of the Women's Health Initiative have shown that hormone replacement therapy can indeed reduce the risk of fractures; however, it causes greater risk of adverse cardiovascular diseases as

- In healthy individuals, osteoclast activity is primarily regulated by PTH and to a lesser degree by IL-1 and TNF. In addition, differentiation of osteoclast precursors is under the influence of M-CSF and IL-6.
- Female hormones known as estrogens (especially estradiol) inhibit formation of these cytokines, therefore limiting the activity of osteoclasts.
- In postmenopausal women in whom estrogen levels are reduced, secretion of these cytokines is increased, resulting in enhanced activity of osteoclasts leading to intensified bone resorption.
- The treatment of choice in postmenopausal women with osteoporosis was hormone replacement therapy with estrogen and progesterone but can cause cardiovascular diseases as well as increased risk for breast cancer.
- Selective estrogen receptor modulators (SERMs), such as raloxifene, is slowly replacing estrogen therapy.

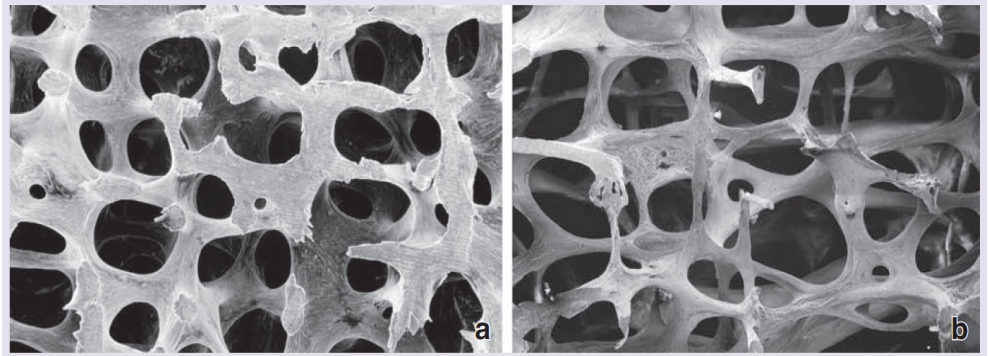
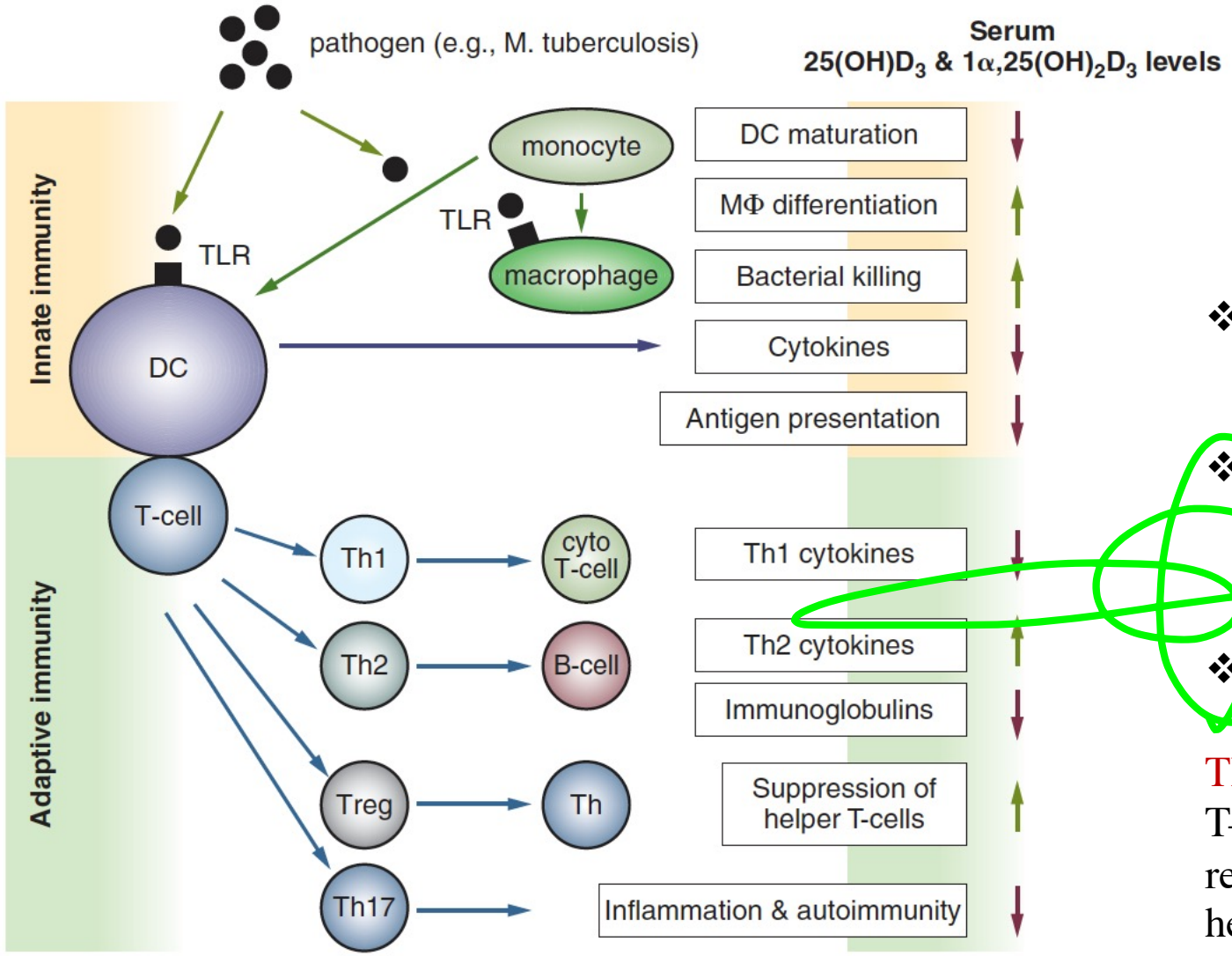


FIGURE F8.2.1 • **Scanning electron micrograph of trabecular bone. a.** This image shows section from the trabecular bone obtained from a vertebral body of a healthy individual. **b.** This specimen was obtained from a vertebral body of elderly women showing extensive signs of osteoporosis. Compare the pattern of trabecular architecture in osteoporosis with normal vertebral bone. (Courtesy of Dr. Alan Boyd).

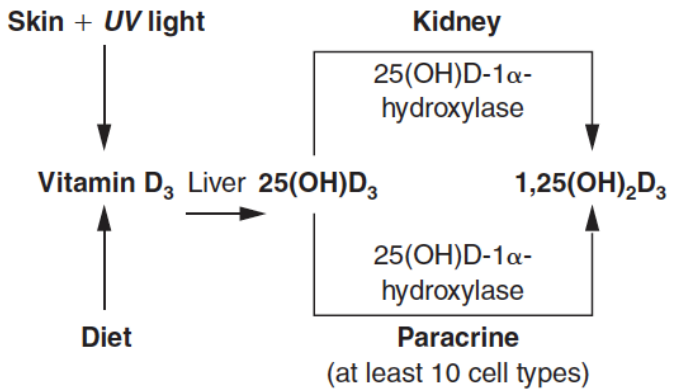
innate and adaptive immune systems: The consequences of the presence of 1α,25(OH)2D3.



- The top ➔ innate immune system in a dendritic cell (DC), and bottom ➔illustrates the complexity of the adaptive immune system in a T-cell.
- The right-hand column (white boxes) illustrates the biological responses that are stimulated or repressed (green and red arrows) by the actions of 1α,25(OH)2D3 that is produced from 25(OH)D3.
- The presence of infective pathogens are shown by brown circles.

TLR, toll-like receptor (black box); DC, dendritic cell; T-cell, T lymphocytes, Mø, macrophage, Treg, regulatory T cell; cyto T-cell, cytotoxic T-cell; Th1, T helper cells.

Contributions of Vitamin D endocrine system to good Health



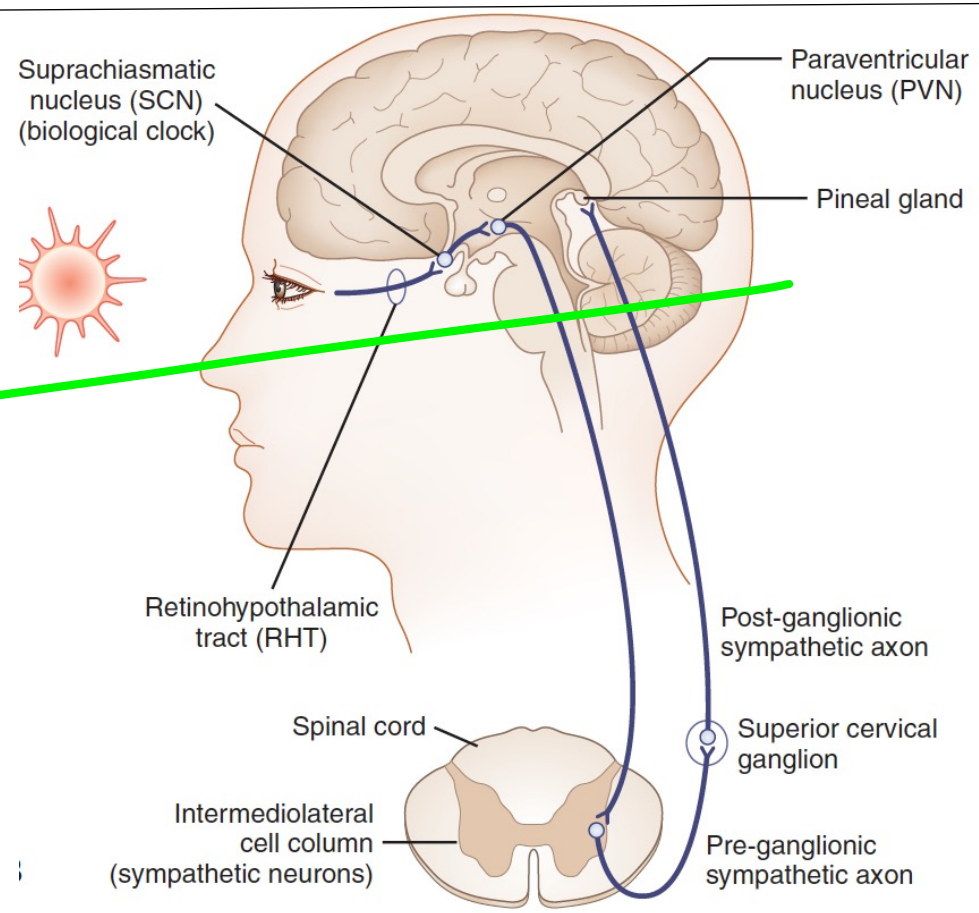
Serum	25(OH)D	Nutritional descriptor
ng/ml	nmoles/L	
< 5	< 12	Severe D deficiency
< 10	< 25	Vit. D deficiency
10–20	25–50	Vit. D insufficiency
40–70	100–150	Vit. D sufficiency
> 150	> 300	Risk for toxicity

Physiological systems	Biological responses	Vitamin D deficiency associated diseases
All cells	Cell cycle regulation Cell proliferation inhibition	Cancer Prostate, breast, colon cancer (prevention) Leukemia(s) (treatment)
Calcium homeostasis	Intestinal calcium absorption & bone remodeling	Rickets, osteomalacia, osteoporosis
Immune system Innate Adaptive	Stimulate synthesis of antimicrobial peptides Dendritic and T-cell function	Increased prevalence of infection e.g., tuberculosis Increased autoimmune diseases; e.g., type-I diabetes, multiple sclerosis, inflammatory bowel disease, psoriasis
Pancreas β cells	Facilitate insulin secretion	Impaired glucose tolerance and type II diabetes
Heart & cardiovascular	Renin-angiotensin regulation, coagulation, fibrinolysis, heart muscle function	High renin hypertension, increased cardiovascular risk factor, increased thrombogenesis
Muscle	Promote normal skeletal muscle development; improve muscle strength	Muscle myopathy; increased falls
Brain	*In progress* Brain has VDR & 1α-hydroxylase	Vitamin D deficiency *in utero* alters adult behavior in rodents

Pineal Gland Hormones

Hormones of Pineal Gland

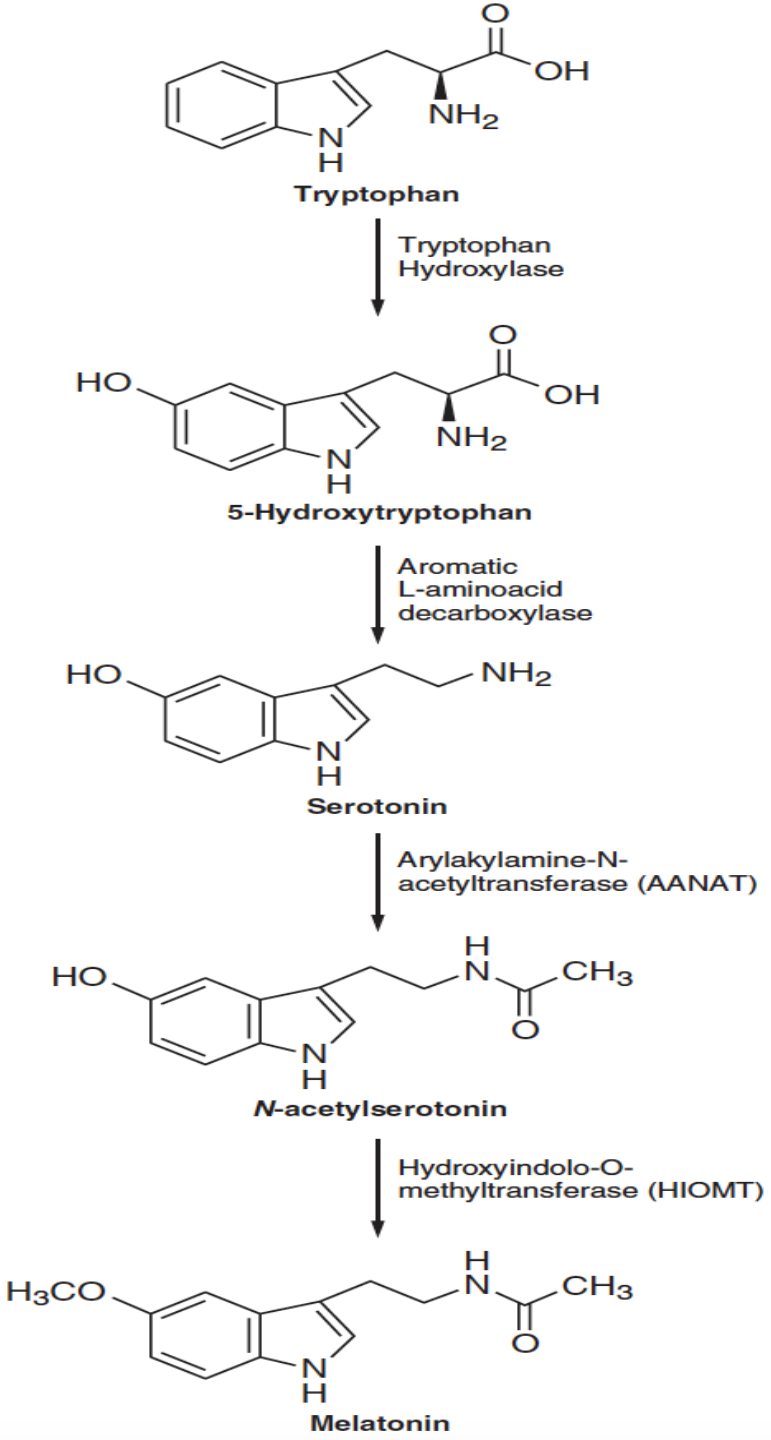
The pineal gland (pineal body, epiphysis cerebri) is an endocrine or neuroendocrine gland that regulates daily body rhythm. It develops from neuroectoderm of the posterior portion of the roof of the diencephalon and remains attached to the brain by a short stalk. In humans, it is located at the posterior wall of the third ventricle near the center of the brain. The pineal gland is a flattened, pine cone–shaped structure, hence its name. It measures 5 to 8 mm high and 3 to 5 mm in diameter and weighs between 100 and 200 mg.



Hormones of Pineal Gland

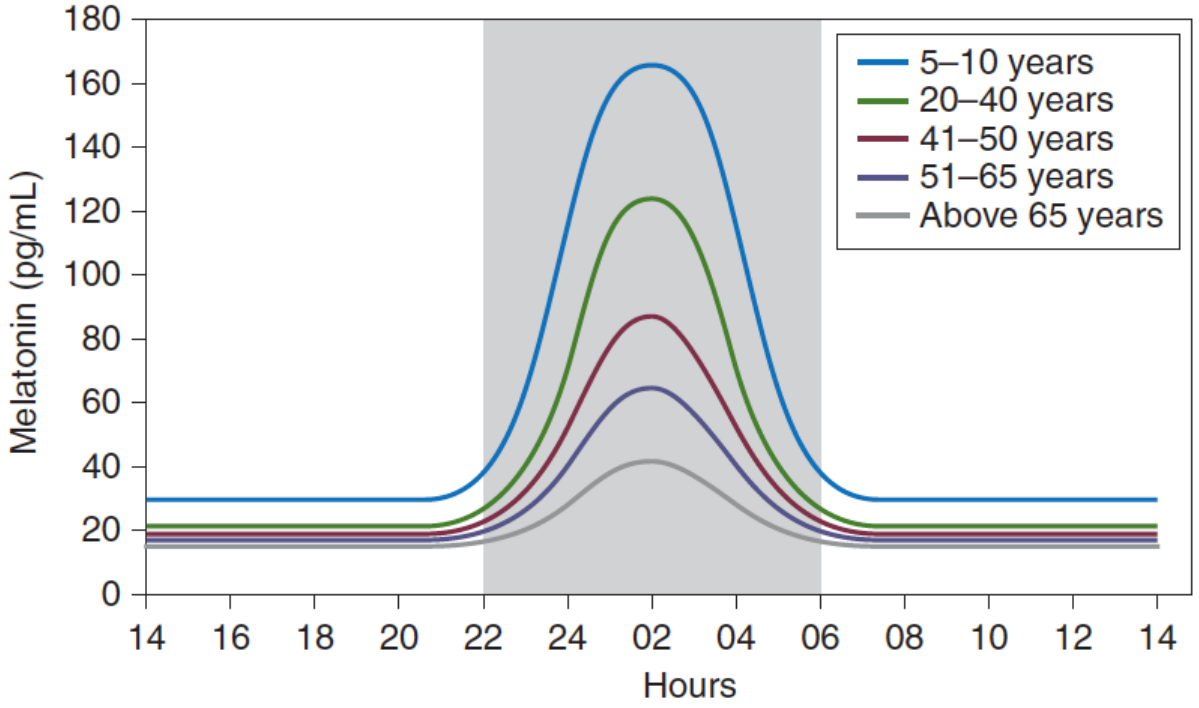
Hormone	Composition	Source	Major Functions
Melatonin	Indolamine (*N*-acetyl-5-methoxytryptamine)	Pinealocytes	Regulates daily body rhythms and day/night cycle (circadian rhythms); inhibits secretion of GnRH and regulates steroidogenic activity of the gonads particularly as related to the menstrual cycle; in animals, influences seasonal sexual activity

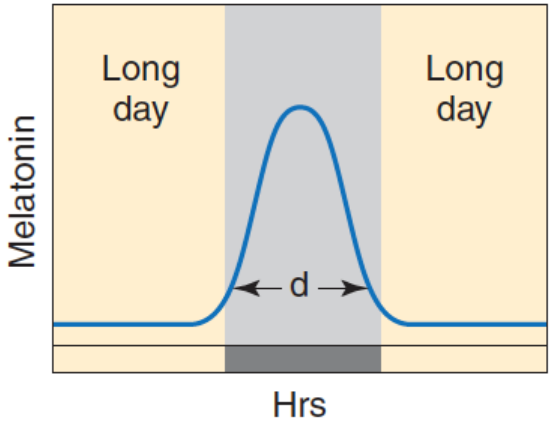
Melatonin Biosynthetic Pathway

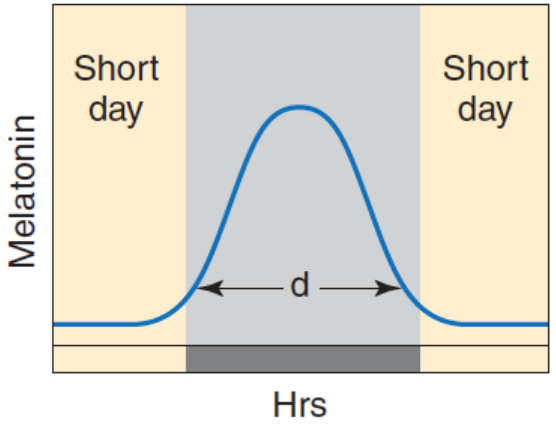


Pathway of melatonin biosynthesis. The modifications of tryptophan that take place in melatonin biosynthesis in the pinealocyte are shown.
The step that is regulated by the dark–light cycle is the conversion of serotonin to N-acetyl serotonin, catalyzed by arylakylamine-N-acetyl transferase.

Patterns of melatonin secretion by Pineal Gland



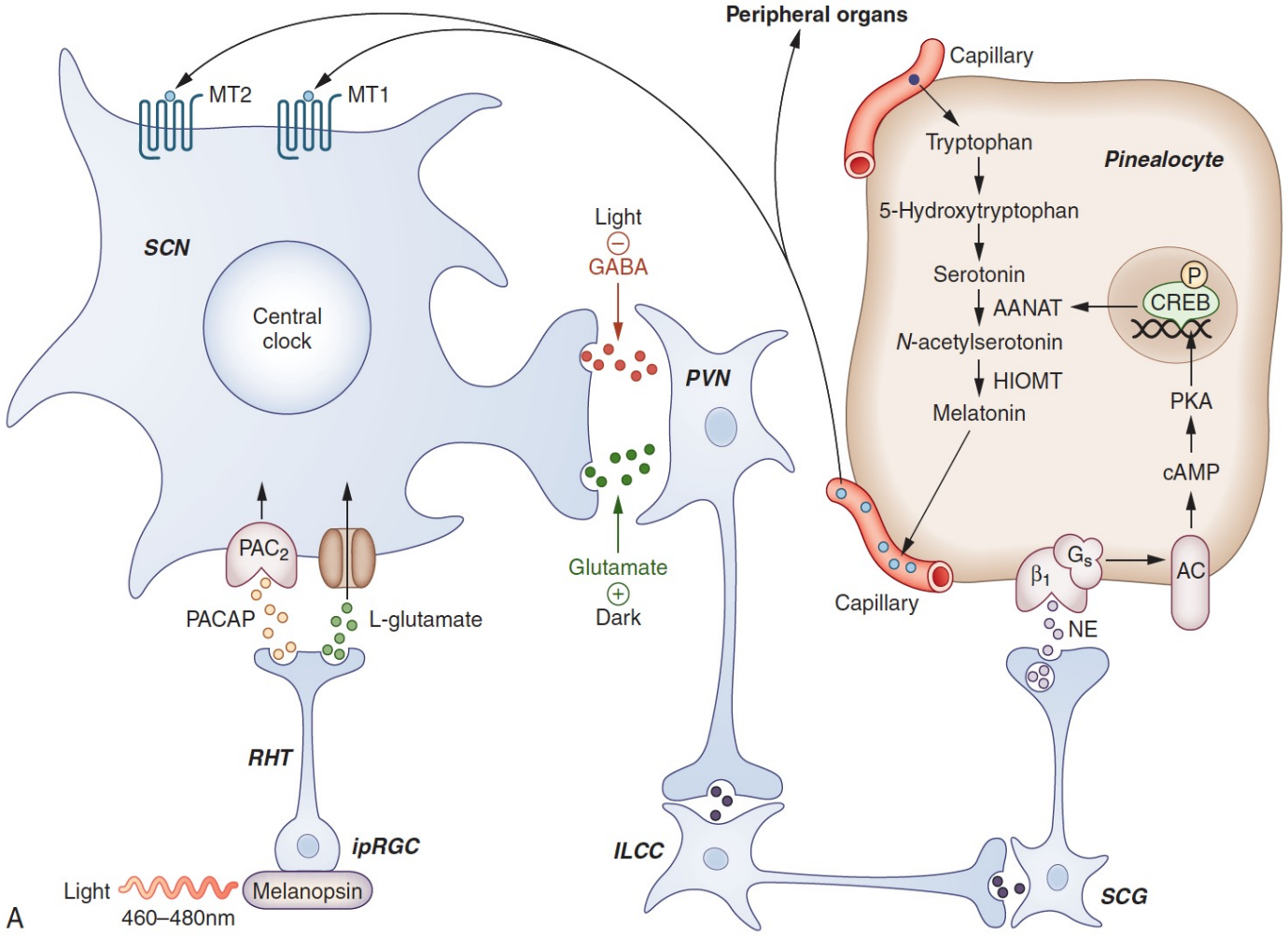




- **TOP:** The pineal conveys information about the light–dark cycle of the current day because melatonin is secreted only during darkness. Serum levels of melatonin rise several-fold to a peak in the midpoint of the dark cycle. Peak melatonin levels are seen during childhood and decrease progressively during adulthood and aging.

- **BOTTOM:** The pineal gland also conveys seasonal information by varying with the length of days. As the areas under these two curves indicate, the shorter the day, the more melatonin is produced and the longer it is present in the bloodstream.

Regulation of melatonin synthesis



- Light interacts with an intrinsically photosensitive retinal ganglion cell (ipRGC), the axon of which passes along the retinal-hypothalamic tract (RHT) and terminates on a neuron of the suprachiasmatic nucleus (SCN).
- The SCN neuron releases γ-amino-butyric acid (GABA; red) which inhibits the firing of the neuron of the paraventricular cell (PVN) of the hypothalamus.
- In the **absence of light this cell releases glutamate** which stimulates the firing of the PVN neuron so that the signal continues through the intermediolateral cell column (ILCC) neuron to the neurons of the superior cervical ganglion (SCG).
- These neurons release norepinephrine (NE) which interacts with its β-adrenergic receptor to stimulate intracellular cyclic AMP levels, leading to increased synthesis and translation of mRNA encoding N-acetyltransferase (AANAT) required for the conversion of serotonin to N-acetylserotonin.
- Melatonin is released into capillaries and carried to peripheral organs to transmit information about the light/dark cycle and to the SCN to contribute to the entrainment of the 24-hour central clock to the light dark cycle.

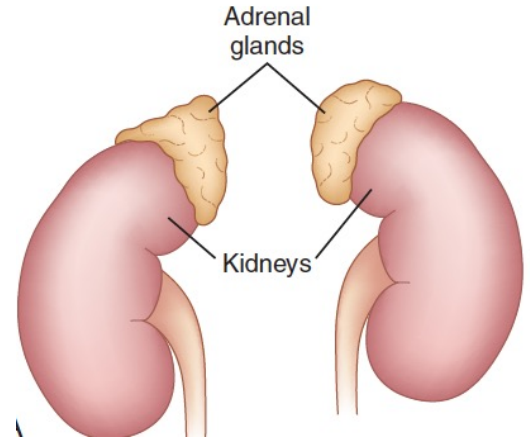
Sleep and Jet lag

- The clearest and most important role of melatonin in the human is the one it plays in influencing, in partnership with the retina and the SCN, circadian rhythms throughout the body.
- In the SCN, where the central clock in the SCN has an autonomous period of slightly longer than 24 hours, the feedback effect of melatonin on SCN firing helps maintain entrainment of the central clock to the external light/dark cycle.
- It is now known that many peripheral cells have their own internal oscillators and melatonin is important in helping to synchronize many of these with the light/dark cycle.
- In humans, who are characteristically active by day and at rest during the night, manifestations of disruption of the normal circadian rhythm occur when an individual travels through several time zones, a condition known as "jet lag."
- Fatigue, sleep problems, and reduced performance are common symptoms of jet lag.
- People who alternate between day and night shifts of work and are, therefore, exposed to light of 480 nm at night, also experience these symptoms.
- After the initial disturbance (travel or shift change), it can take several days for endogenous rhythms and environmental cues to become synchronized again.
- Exogenous melatonin can be effective in accelerating the phase shift if given at the appropriate time prior to bedtime at the destination.

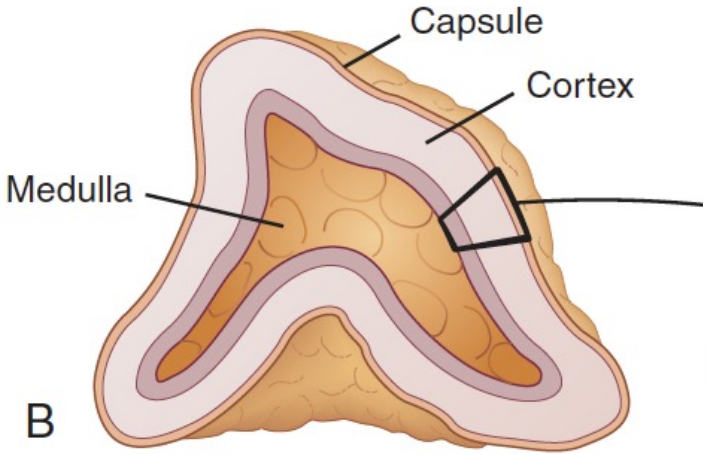
Hormones of Adrenal Gland

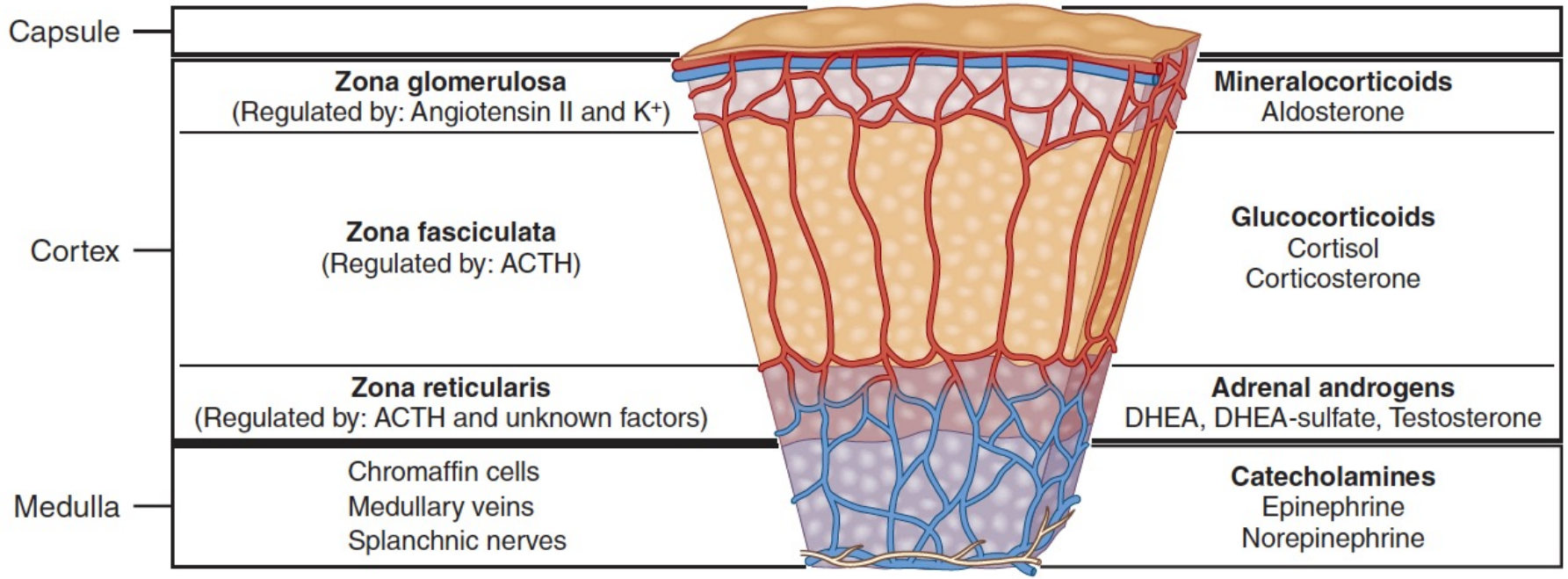
Adrenal Gland

- The adrenal (suprarenal) glands secrete both **steroid hormones and catecholamines**. They have a flattened triangular shape and are embedded in the perirenal fat at the superior poles of the kidneys.



- The adrenal glands are covered with a thick connective tissue capsule from which trabeculae extend into the parenchyma, carrying blood vessels and nerves. The secretory parenchymal tissue is organized into two distinct regions
  - The cortex is the steroid-secreting portion. It lies beneath the capsule and constitutes nearly 90% of the gland by weight.
  - The medulla is the catecholamine-secreting portion. It lies deep to the cortex and forms the center of the gland.



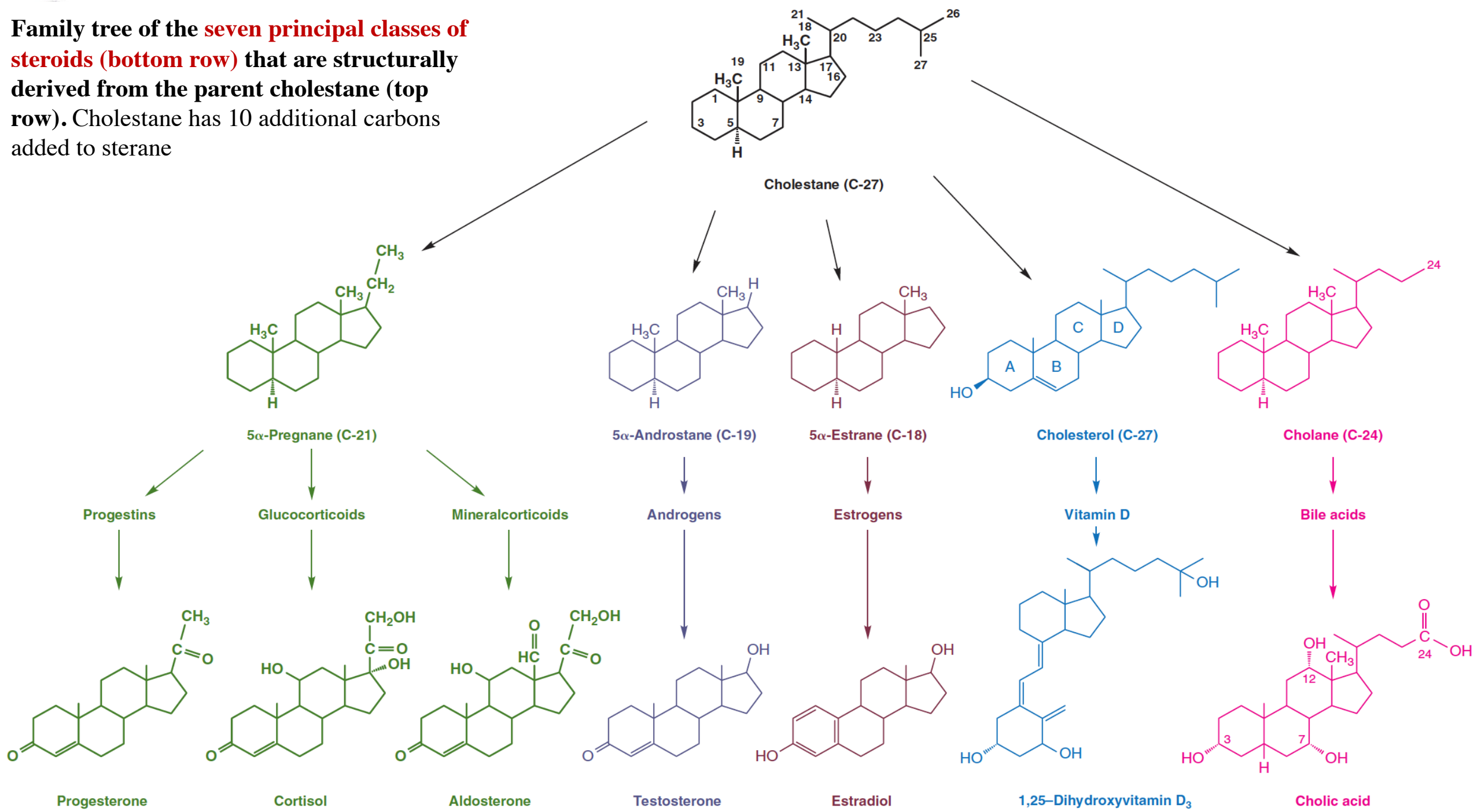


Hormones of Adrenal Gland ➔ Adrenal cortex

TABLE 21.9 Hormones of the Adrenal Glands

Hormone	Composition	Source	Major Functions
Adrenal cortex			
Mineralocorticoids (95% of mineralocorticoid activity in aldosterone)	Steriod hormones (cholesterol derivatives)	Parenchymal cells of the zona glomerulosa	Aid in controlling electrolyte homeostasis (act on distal tubule of kidney to increase sodium reabsorption and decrease potassium reabsorption); function in maintaining the osmotic balance in the urine and in preventing serum acidosis
Glucocorticoids (corticosterone, and cortisol; 95% of glucocorticoid activity in cortisol)	Steriod hormones (cholesterol derivatives)	Parenchymal cells of the zona fasciculata (and to a lesser extent of the zona reticularis)	Promote normal metabolism, particularly carbohydrate metabolism (increase rate of amino acid transport to live, promote removal of protein from skeletal muscle and its transport to liver, reduce rate of glucose metabolism by cells and stimulate glycogen synthesis by liver, stimulate mobilization of fats from storage deposits for energy use); provide resistance to stress; suppress inflammatory response and some allergic reactions
Gonadocorticoids (dehydroepiandrosterone [DHEA] is a major sex steroid produced in both men and women)	Steriod hormones (cholesterol derivatives)	Parenchymal cells of the zona reticularis (and to a lesser extent of the zona fasciculata)	Induce weak masculinizing effect; at normal serum levels usually their function is insignificant

Family tree of the seven principal classes of steroids (bottom row) that are structurally derived from the parent cholestane (top row). Cholestane has 10 additional carbons added to sterane



Classes of steroids

TABLE 2-1 Classes of Steroids

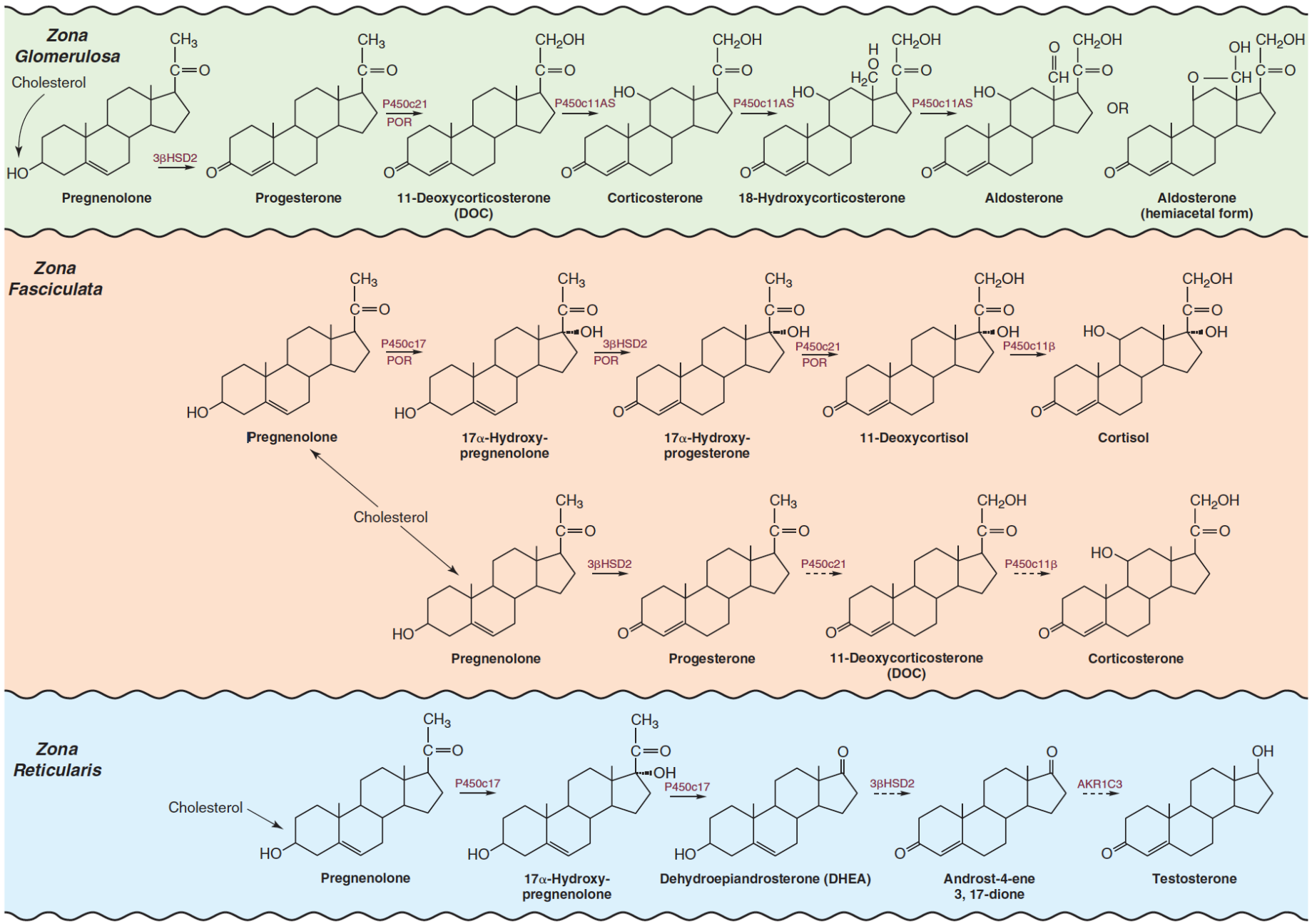
Steroid class	Principal active steroid in humans[a]	Number of carbon atoms	Parent ring structure[a]
Estrogens	Estradiol	18	Estrane
Androgens	Testosterone	19	Androstane
Progestins	Progesterone	21	Pregnane
Glucocorticoids	Cortisol	21	Pregnane
Mineralocorticoids	Aldosterone	21	Pregnane
Vitamin D steroids	1,25-Dihydroxyvitamin D_3	27	Cholestane
Bile acids	Cholic acid	24	Cholane

[a]The parent ring steroid structures and active steroid hormone are given in Figure 2-2.

Adrenal cortex pathway for production of 3 classes of steroid hormones

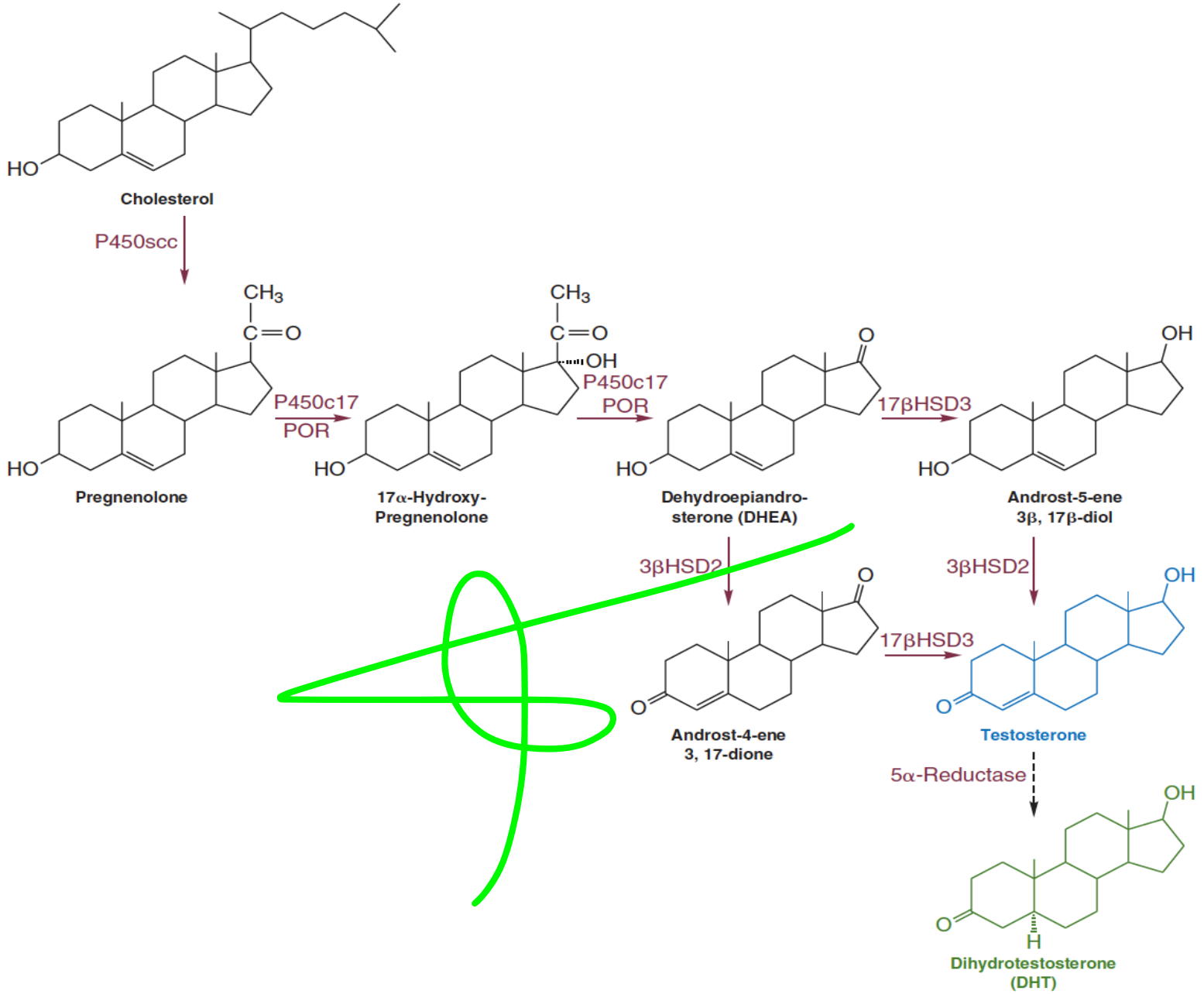
Cholesterol and the presence of the cholesterol side chain cleavage enzyme are the starting point of separate steroid hormone(s) biosynthesis for the three classes.

- ***zona glomerulosa*** (mineralocorticoids) produces aldosterone. A structural hallmark of aldosterone is the presence of both a C-11 hydroxyl and a C-18 aldehyde. The C-18 aldehyde can form either a five member hemiacetal ring, which uses the C-11 hydroxyl group or a six member hemiacetal ring, which uses the C-21 hydroxyl group. These are reminiscent of carbohydrate chemistry.
- ***zona fasciculata*** **(glucocorticoids)** produces both cortisol and corticosterone.
- ***zona reticularis*** produces limited amounts (represented by the dashed arrow) of the androgens, dehydroepiandrosterone (DHEA), androst-4-ene-3,17-dione and testosterone.



Pathways of androgen biosynthesis in testicular Leydig cells

- Cholesterol is the starting point for production of the principal androgen, testosterone (shown in blue color).
- The conversion of cholesterol to DHEA is in a manner similar to that of the adrenal cortex zona reticularis.
- The conversion of testosterone to the more potent dihydrotestosterone (DHT; shown in green color; also see black dashed arrow) by the 5α-reductase occurs in androgen target glands such as the prostate, epididymis, seminal vesicles, and certain regions of the brain.



Hormonal regulation of spermatogenesis

Normal function of testis is dependent upon hormones acting through endocrine and paracrine pathways. The endocrine function of the testis resides primarily in the Leydig cell population that synthesizes and secretes the principal circulating androgen, **testosterone**. Nearly all of the testosterone is produced by the testis; less than 5% is produced by the adrenal glands. It is estimated in humans that the total Leydig cell population produces about 7 mg of testosterone per day. As testosterone leaves the Leydig cells, it passes into blood and lymphatic capillaries and across the peritubular tissue to reach the seminiferous epithelium.

High local levels of testosterone within the testis (estimated to be as much as 200 times the circulating levels) are necessary for the proliferation and differentiation of spermatogenic cells. This high testicular level of testosterone can be significantly decreased by negative feedback from exogenous testosterone. Intensive research in this area is being directed into development of a prototype of testosterone-based contraceptive drugs for men. In early clinical studies, these drugs have been shown to cause a significant decrease in the testicular testosterone concentration and inhibition of spermatogenesis. Recovery of spermatogenesis occurs after discontinuation of contraceptive use. However, in some individuals, this type of contraceptive is not efficacious and does not cause spermatogenic suppression.

Peripheral testosterone levels have the following effects:

- Differentiation of the central nervous system (CNS) and the genital apparatus and genital excurrent duct system
- Growth and maintenance of secondary sexual characteristics (such as the beard, male distribution of pubic hair, and low-pitched voice)
- Growth and maintenance of the accessory sex glands (seminal vesicles and prostate and bulbourethral glands), genital excurrent duct system, and the external genitalia (mainly byproducts of testosterone conversion to DHT)
- Anabolic and general metabolic processes, including skeletal growth, skeletal muscle growth, distribution of subcutaneous fat, and kidney function
- Behavior, including libido

The steroidogenic and spermatogenic activities of the testis are regulated by hormonal interaction among the hypothalamus, anterior lobe of the pituitary gland, and gonadal cells (i.e., Sertoli, spermatogenic, and Leydig cells). The anterior lobe of the pituitary gland produces three hormones involved in this process: luteinizing hormone (LH), which in the male is sometimes referred to as interstitial cell–stimulating hormone (ICSH); follicle-stimulating hormone (FSH); and prolactin (PRL). In response to LH release by the pituitary, Leydig cells produce increasing amounts of testosterone. PRL acts in combination with LH to increase the steroidogenic activity of Leydig cells. Because FSH and testosterone receptors are found in Sertoli cells, these cells are the primary regulators of spermatogenesis.

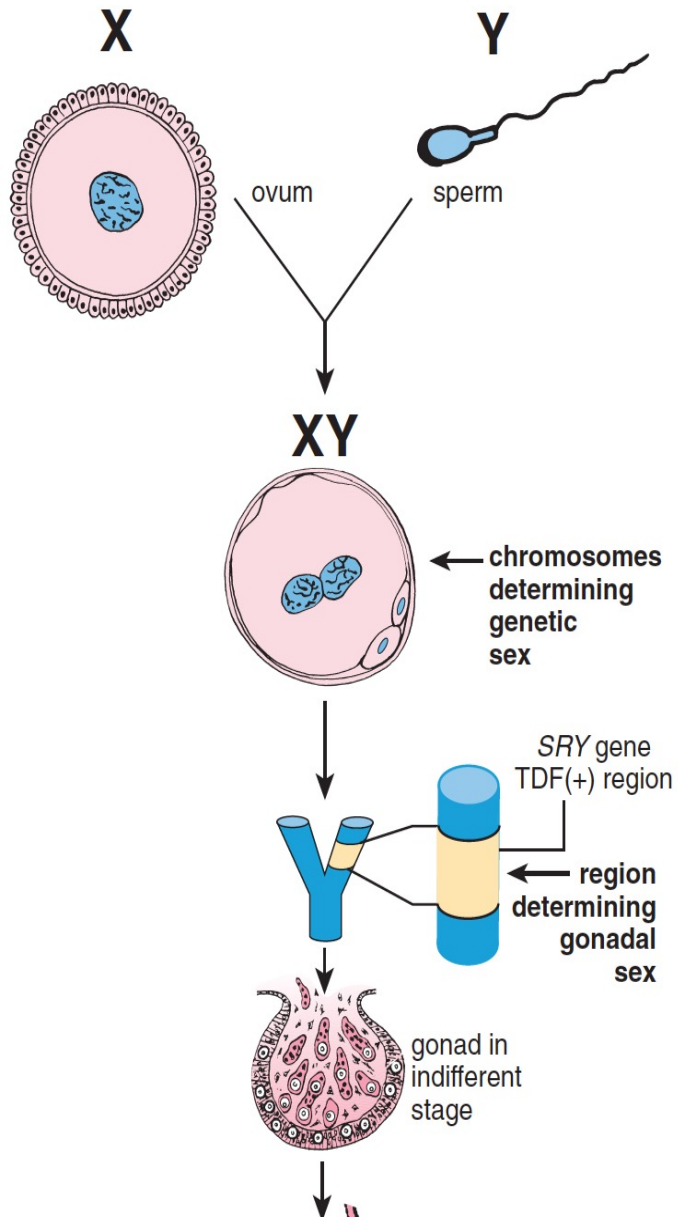
Clinical correlation: Factors affecting spermatogenesis

Spermatogenic cells are very sensitive to noxious agents. Degenerative changes, such as apoptosis, premature sloughing of cells, or formation of multinucleated giant cells, are readily apparent after exposure to such agents. Factors that negatively affect spermatogenesis include these:

- **Dietary deficiencies**. Reduced dietary intake is known to impair spermatogenesis. Vitamins, coenzymes, and microelements such as vitamin A, B_{12}, C, E, β-carotenes, zinc, and selenium have been shown to affect sperm formation.
- **Environmental/lifestyle factors**. A recent study conducted in Denmark compared the sperm count in two groups of young men from rural and urban populations. A higher median sperm count (24%) was found in the men from the rural group compared with those from the urban group.
- **Developmental disorders**. Cryptorchidism, hypospadias, and factors such as low birth weight have been found to be important risk factors for testicular cancer associated with reduced semen quality and reduced fertility.
- **Systemic diseases or local infections**. Infections involving the testis (orchitis) may have an effect on spermatogenesis. Systemic diseases that can impair spermatogenesis include fever, kidney diseases, HIV and other viral infections, and metabolic disorders.
- **Elevated testicular temperature**. A sedentary lifestyle may impair the ability to maintain the lower temperature of the testis in the scrotum. A higher than average scrotal temperature has been linked to failure of spermatogenesis.
- **Steroid hormones and related medications**. Exposure to synthetic estrogen (diethylstilbestrol) and other sex steroids can exert negative feedback on FSH secretion, resulting in decreased spermatogenesis. Prenatal exposure to estrogens can potentially inhibit fetal gonadotropin secretion and inhibit Sertoli cell proliferation.
- **Toxic agents**. Mutagenic agents, antimetabolites, and some pesticides, e.g., dibromochloropropane (DBCP), can drastically affect spermatogenesis and production of normal sperm. DBCP is a nematocide pesticide that is still used in some developing countries. It has been shown to cause a major decrease in sperm count and infertility after human exposure. Other agents that may affect fertility include chemicals in plastics (e.g., phthalates), pesticides (e.g., DDT), products of combustion (e.g., dioxins), polychlorinated biphenyls (PCBs), and others. Most of these chemicals possess very weak estrogen properties and may affect fertility. Direct toxicity to the spermatogonia is linked to changes in sperm quality.
- **Ionizing radiation and alkylating agents**. Nitrogen mustard gas and procarbazine have been found to have toxic effects on spermatogonia. ***Electromagnetic*** and ***microwave radiation*** also affect sperm count and motility.

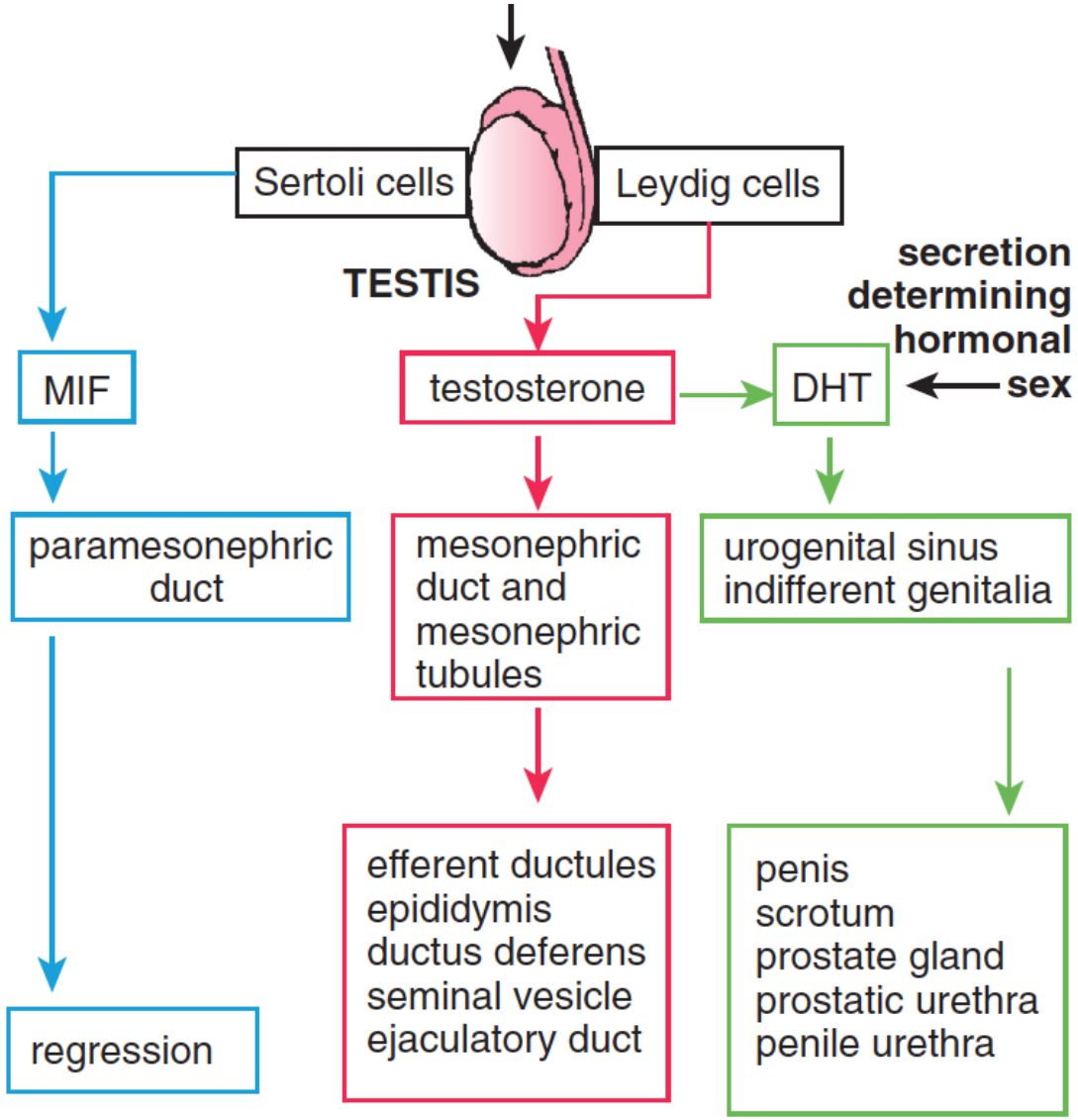
Proliferating cells are particularly sensitive to mutagenic agents and the absence of essential metabolites. Therefore, nondividing Sertoli cells, Leydig cells, and reserve stem cells, which demonstrate low mitotic activity, are much less vulnerable than actively dividing, differentiating spermatogenic cells.

male sex development and hormonal influence on reproductive organs.

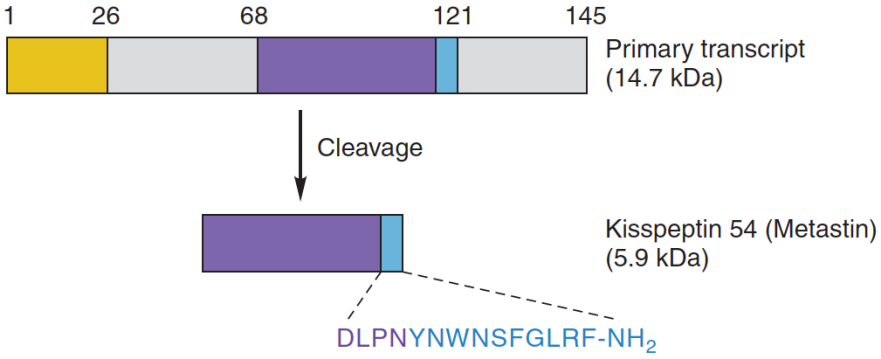


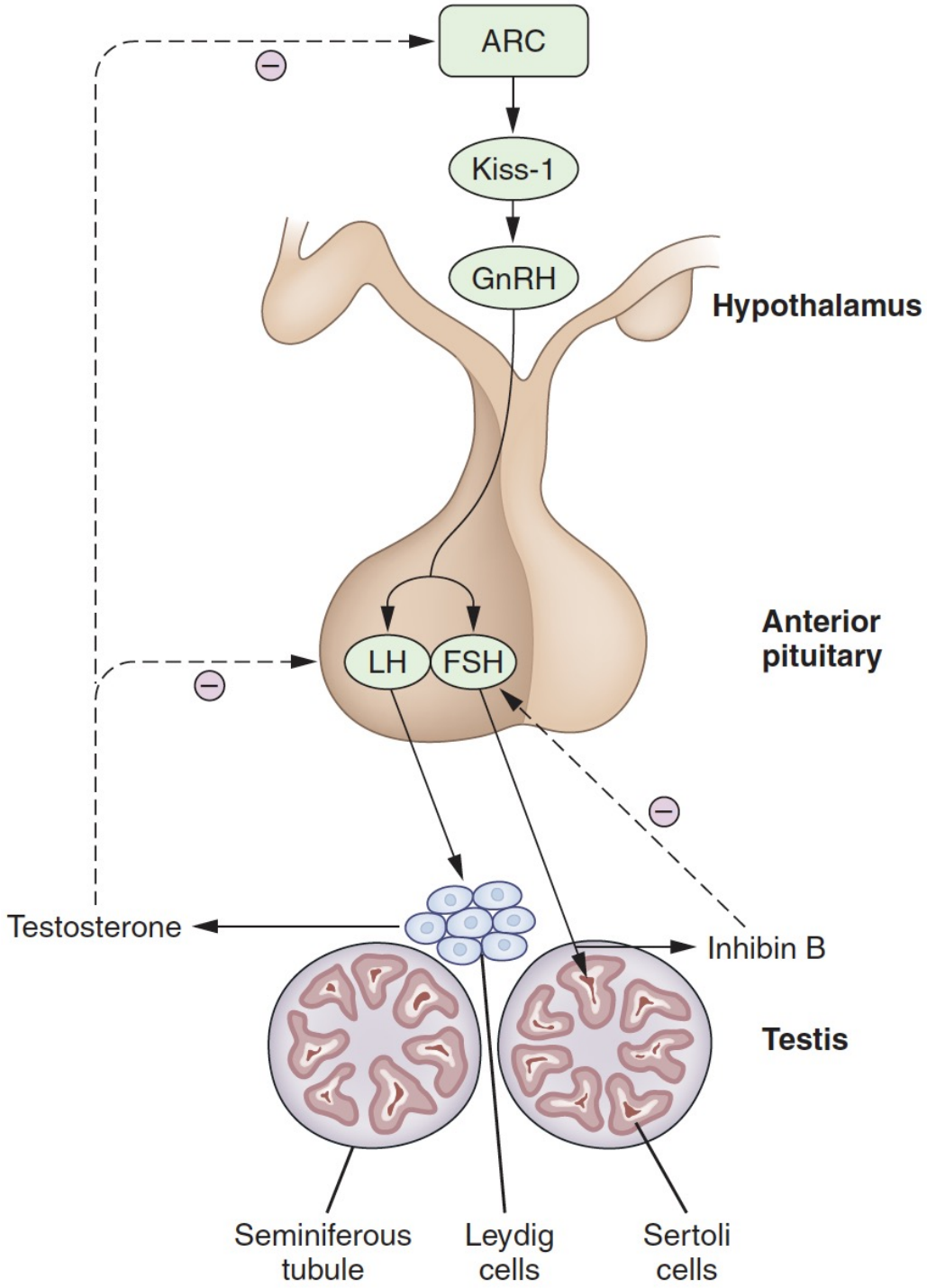
This diagram illustrates three levels on which the sex of the developing embryo is determined.

- The genetic sex is determined at the time of fertilization;
- gonadal sex is determined by activation of the SRY gene located on the short arm of chromosome Y;
- hormonal sex is determined by a hormone secreted by the developing gonad.
- The diagram shows the influence of Müllerianinhibiting factor (MIF), testosterone, and dihydrotestosterone (DHT) on the developing structures.



hormonal regulation of male reproductive function



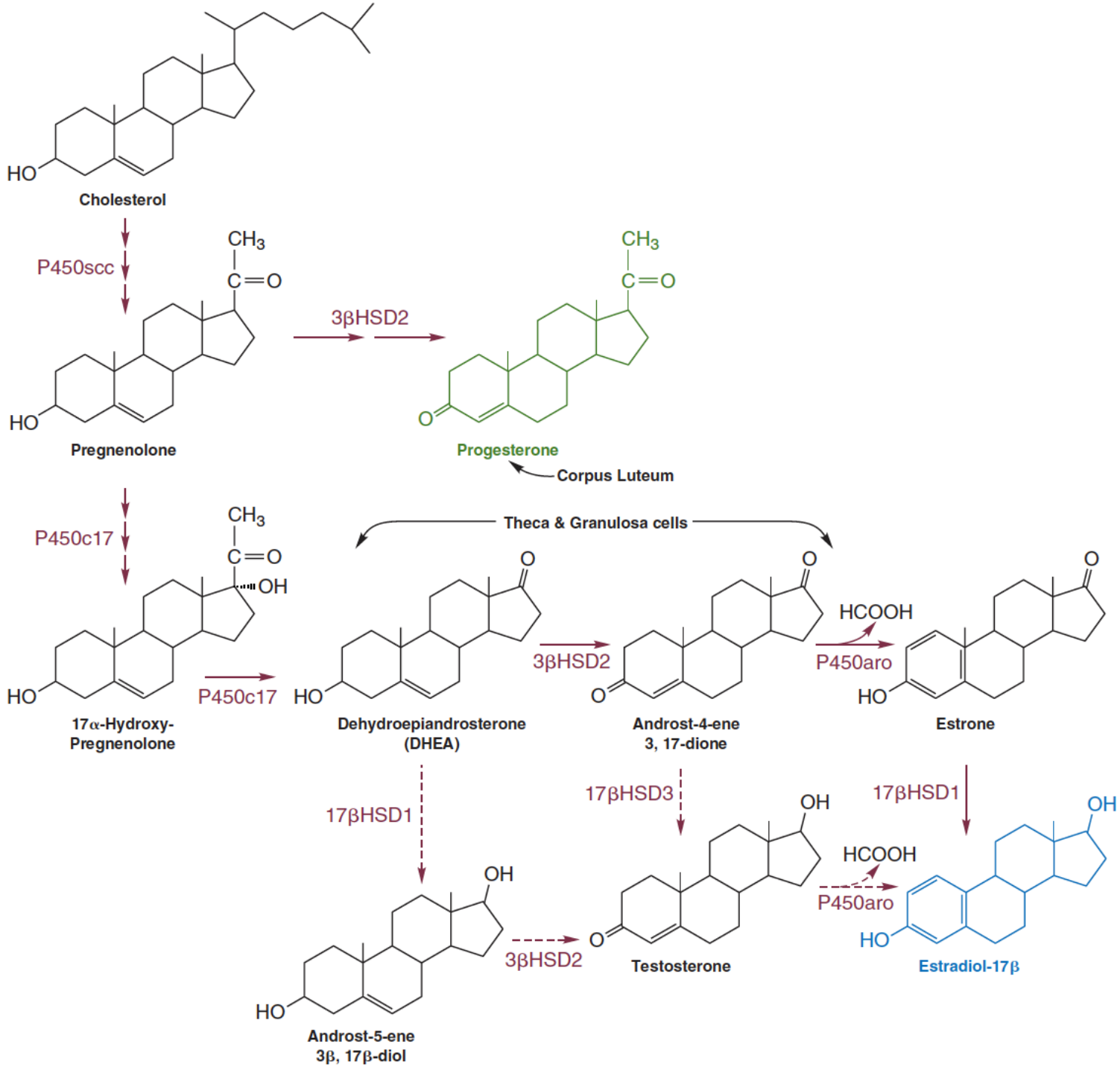


The Hypothalamic-Pituitary-Testis Axis.

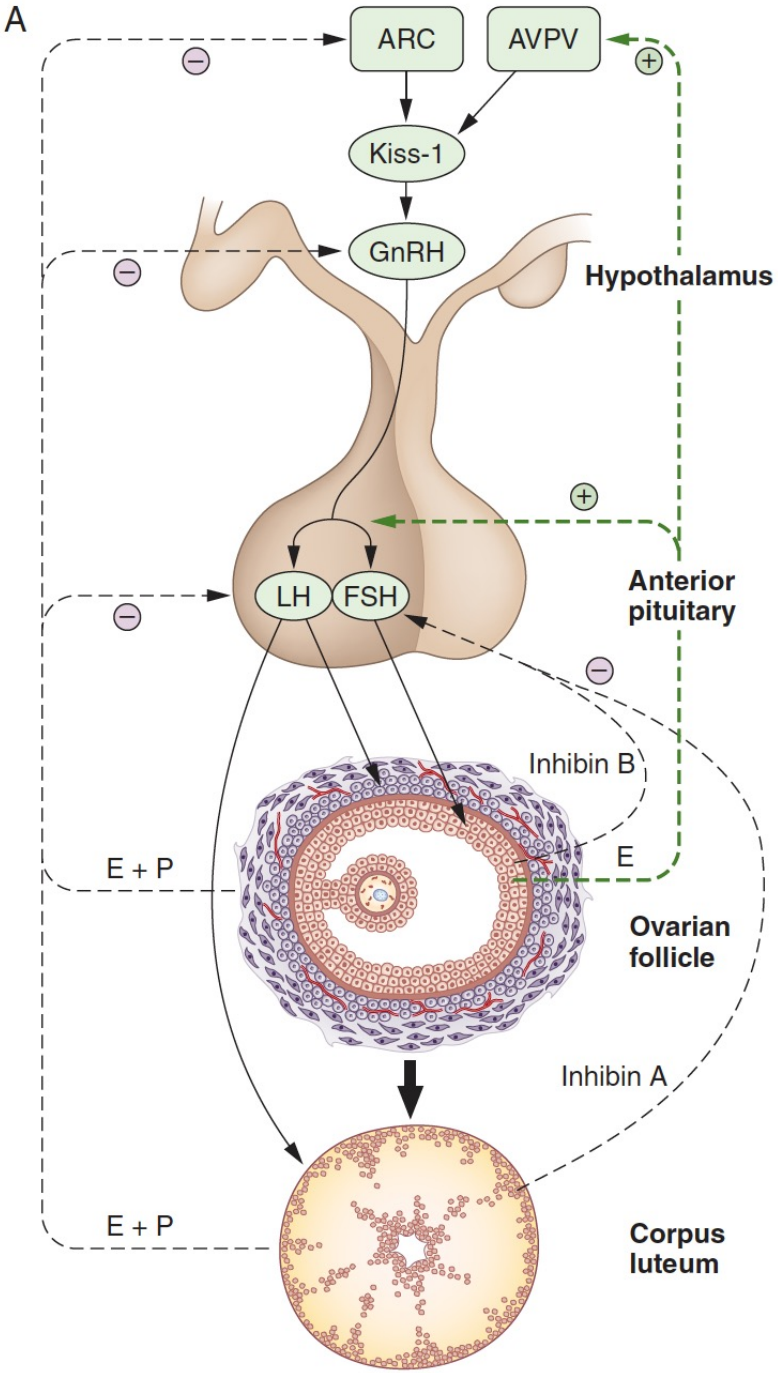
- Gonadotrophin releasing hormone (GnRH) is released from hypothalamic neurons in the median eminence and stimulates gonadotrophs to release luteinizing hormone (LH) and follicle stimulating hormone (FSH).
- GnRH secretion is stimulated by kisspeptin (Kiss-1) from neurons of the arcuate nucleus (ARC).
- Leydig cells in the testis respond to LH stimulation by secreting testosterone. Sertoli cells, the target of FSH, secrete inhibin B.
- Testosterone exerts negative feedback at the pituitary, the hypothalamus, and on kisspeptide neurons.
- Inhibin B inhibits the secretion of FSH at the pituitary.

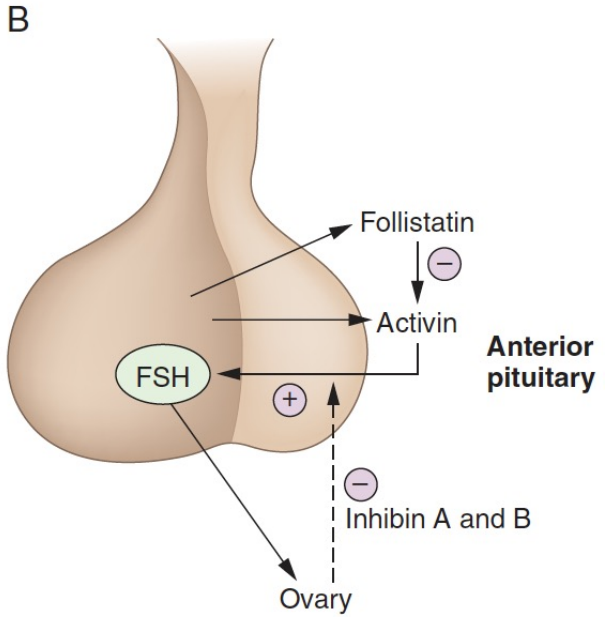
Pathways of production of progesterone and oestradiol

- **Pathway of the production of progesterone by the corpus luteum and estradiol by the theca and granulosa cells.**
- Cholesterol is the starting point for the production of both progesterone (shown in green color) and estradiol (shown in blue color).
- There are two pathways from dehydroepiandrosterone (DHEA) to estradiol-17. The major pathway is via androst-4-ene-3, 17dione and estrone.
- The second pathway via androste-5-ene-3β, 17β-diol and testosterone is only a minor pathway (see three magenta dashed lines).



hormonal regulation of female reproductive function





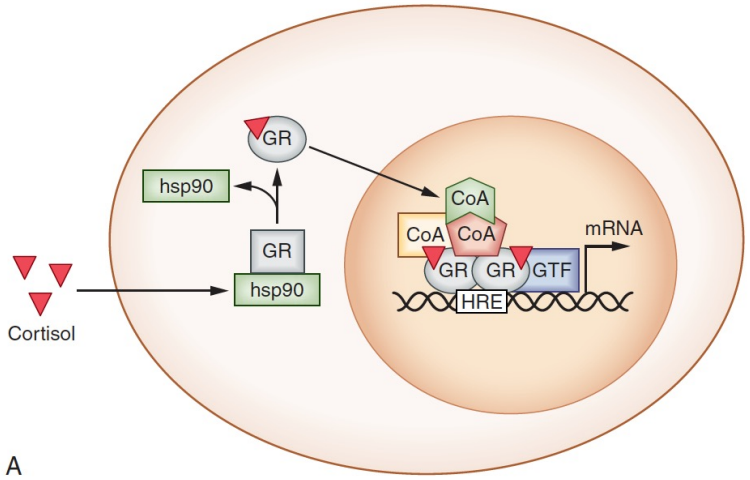
FSH secretion is under local control by activin which stimulates its secretion and follistatin which binds to and blocks the effect of activin. As shown in part A, ovarian inhibins inhibit FSH secretion by blocking activin binding to its receptor.

- Under the influence of Kiss1 peptide from the arcuate nucleus (ARC) or the anteroventral periventricular nucleus (AVPV), hypothalamic neurons in the median eminence release GnRH in a pulsatile fashion.
- GnRH stimulates pituitary gonadotrophs to release luteinizing hormone (LH) and follicle stimulating hormone (FSH).
- Prior to ovulation, the target cells for LH are the thecal cells of the follicle and those of FSH are the granulosa cells. These two components of the follicle collaborate to synthesize estrogen.
- After ovulation (the luteal phase of the cycle) LH stimulates the production of progesterone and estrogen by the corpus luteum.
  - These steroids exert negative feedback inhibition on LH and FSH release at the level of the pituitary and on GnRH secretion, primarily at the arcuate nucleus by inhibiting Kiss-1 secretion.
- Just prior to ovulation, estrogen has a positive (green dashed line) feedback effect on GnRH secretion, through Kiss-1 secretion by the AVPV and at the pituitary.
- Inhibin B, secreted by the follicle and inhibin A, secreted by the corpus luteum, exert negative feedback on FSH secretion by the pituitary.

Glucocorticoids and Stress

Communication of the brain cortex, via the hippocampus, hypothalamus, and the pituitary, with the zona fasciculata of the adrenal glands to produce ACTH

- The **glucocorticoids (cortisol and corticosterone)** which move through the circulatory system of the body bind to their nuclear receptor protein in target cells, which produces a wide variety of biological responses.
- Here GC (glucocorticoids) generate a collective negative feedback in the brain's cortex, hippocampus, hypothalamus, and pituitary.
- Also the consequences of an individual's exposure to stress (hemorrhage, pain, infections, emotions, or cold, etc.) stimulate the production of ACTH.
- Adrenocorticotropic hormone (ACTH), also known as corticotropin (CRH), is a polypeptide tropic hormone that is secreted by the anterior pituitary gland, which travels through the circulatory system to the adrenal gland's cortex *zona fasciculata* region.



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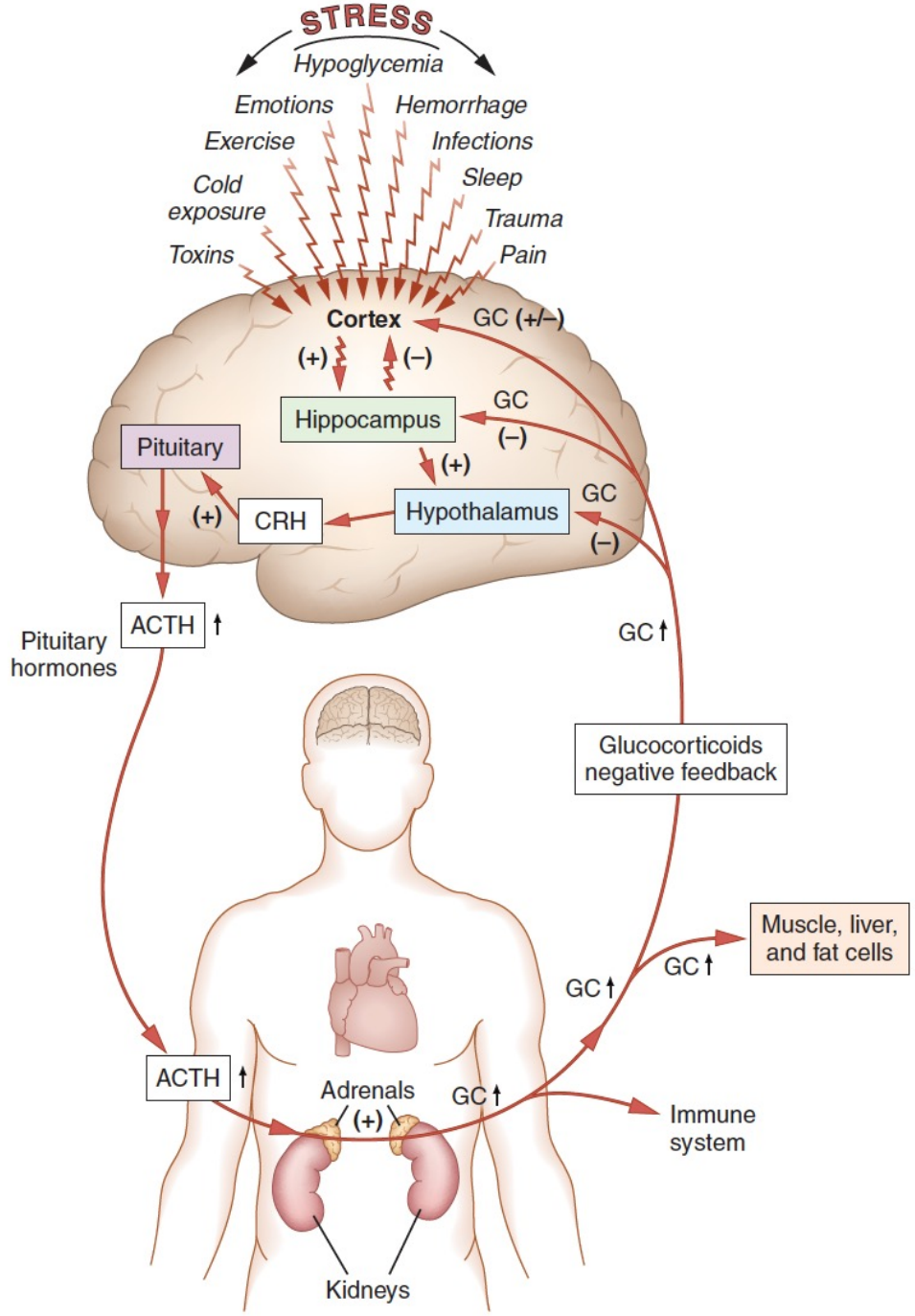


GC = Glucocorticoids

Biological effects of cortisol

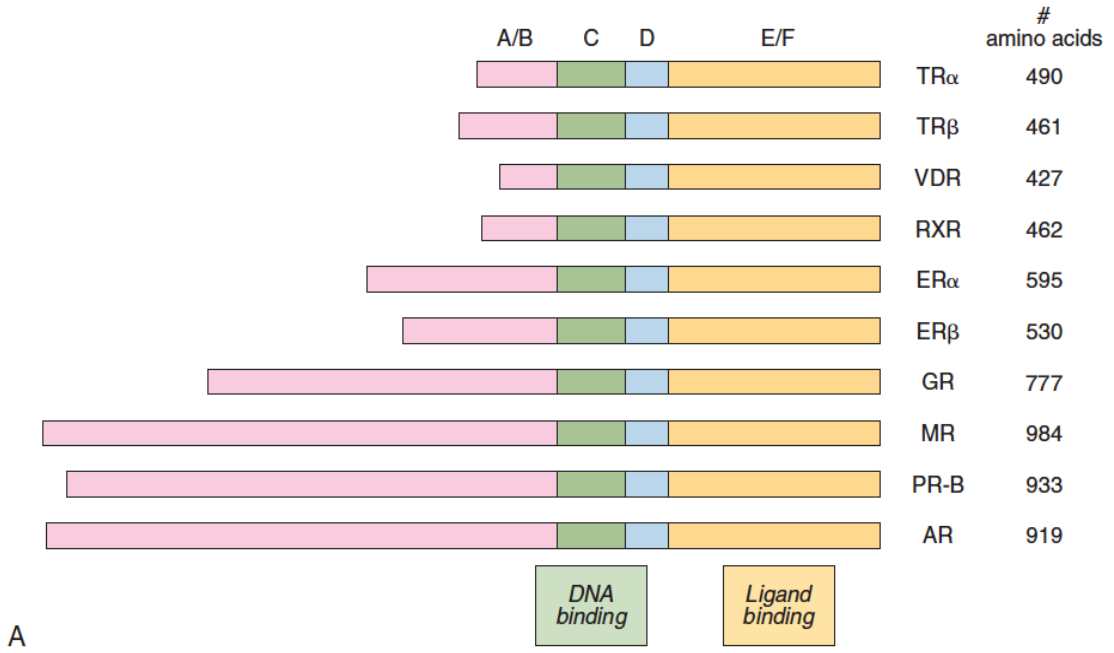
Focus point	Outcome
Hepatic Cells	Stimulate gluconeogenesis Storage of glycogen
Muscle cells	Protein breakdown to amino acids for export to the liver
Adipose (fat) cells	Lipolysis >> free fatty acids for export to the liver
Immune system	Suppressive effects (apoptosis)
Anti-inflammatory actions	IL-6 reduction
Response to stress	Adrenal hypertropy

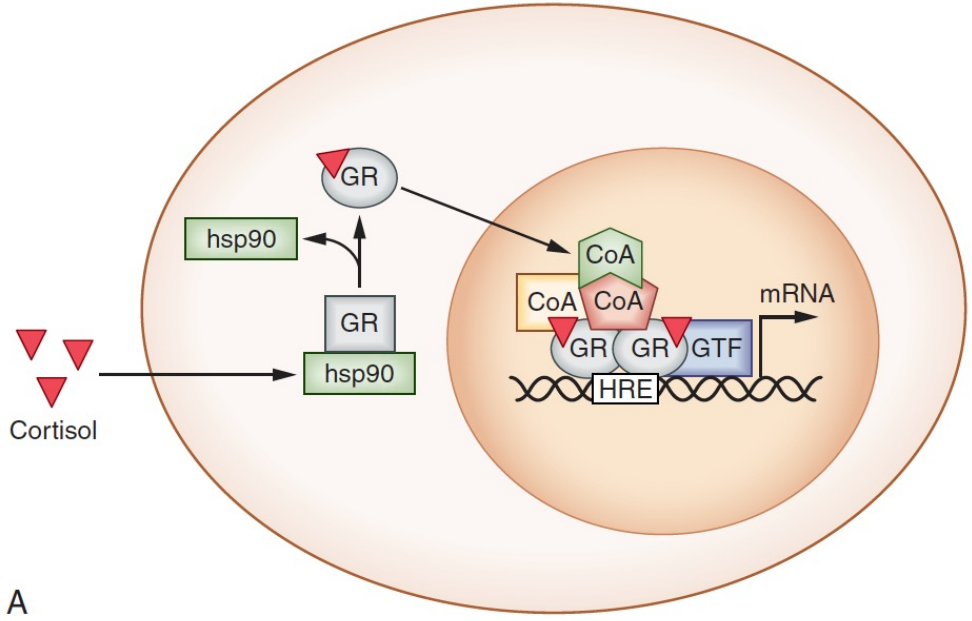
Glucocorticoids are so named because the steroid hormone influences the polymerization of glucose into the form of glucose macromolecules termed glycogen. This **glycogen is an insurance policy that can be utilized on a minute-to-minute basis when the breakdown of glycogen is necessary to enable escape or survive the "fight or flight" or provide "nervous energy."**

Epinephrine is the primary hormonal signal that instantly activates the release of glucose molecules from the stored glycogen.

Many other hormones are involved in stress, including glucagon, growth hormone, prolactin, β-endorphin, vasopressin, angiotensin II, and prostaglandins.

Glucocorticoid receptor





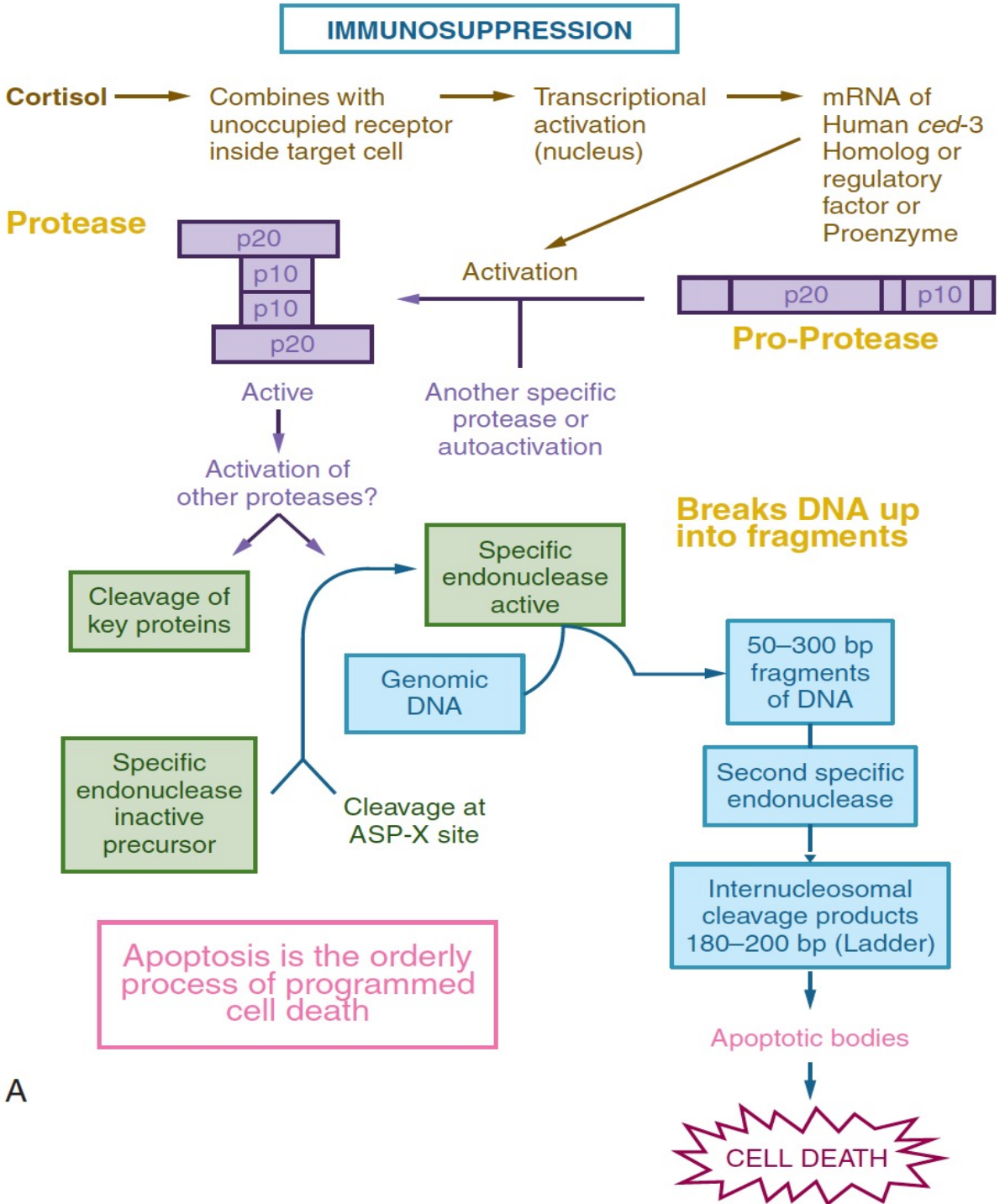
- Nuclear receptors for some of the classical steroid hormones are typified in this figure by the glucocorticoid receptor, GR, and its interaction with cortisol (panel A).
  - In the absence of ligand these receptors are in the cytosol complexed with heat shock proteins (green; HSP) that maintain them in an inactive state.
  - Ligand binding causes the HSP to dissociate and the receptor translocates to the nucleus. GR, MR, ER, AR, and PR all form heterodimers prior to DNA binding.

Chronic stress and Immunosuppression

Cortisol can also be a potent inhibitor of the immune system.

Scheme for the induction of apoptosis in B or T immune cells by glucocorticoids binding to nuclear receptors and inducing gene transcription.

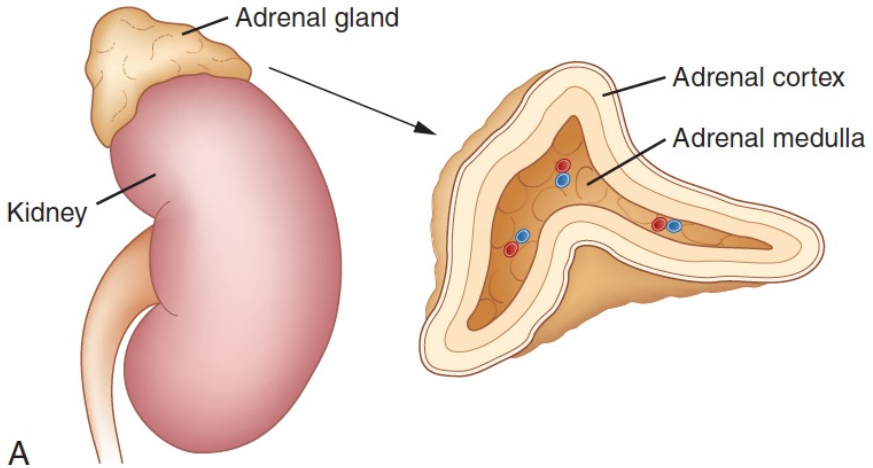
- The nuclease becomes selectively activated by a specific protease cleavage, producing a functional protease that can translocate to the nucleus and attack genomic DNA.
- This generates a family of DNA fragments of 50–300 base pairs.
- The DNA library of fragments based on size will indicate the extent of destruction of the cells' DNA, which results in the cell's death, known as apoptosis.
- The smaller the DNA fragments are, the greater is the onset of death.
- The dead apoptotic cells are quickly recognized by macrophages and removed so that an inflammatory process is not generated.



Hormones of Adrenal Gland➔ Adrenal medulla

Adrenal medulla			
Norepinephrine and epinephrine (in human, 80% epinephrine)	Catecholamines (amino acid derivatives)	Chromaffin cells	Sympathomimetic (produce effects similar to those induced by the sympathetic division of the autonomic nervous system)[a]; increase heart rate, increase blood pressure, reduce blood flow to viscera and skin; stimulate conversion of glycogen to glucose; increase sweating; induce dilation of bronchioles; increase rate of respiration; decrease digestion; decrease enzyme production by digestive system glands; decrease urine production

[a]The catecholamines influence the activity of glandular epithelium, cardiac muscle, and smooth muscle located in the walls of blood vessels and viscera.

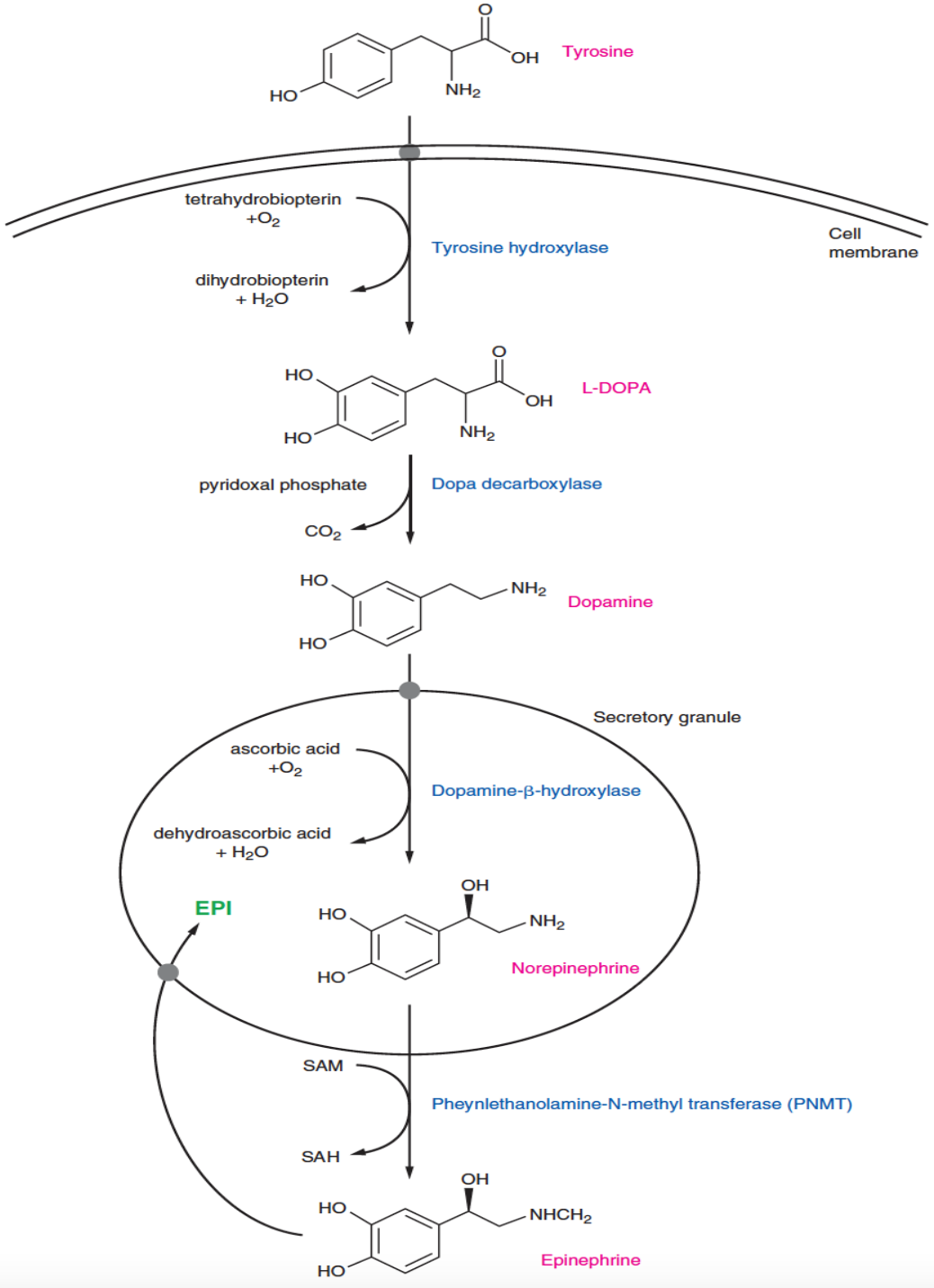


Biosynthesis of catecholamines:

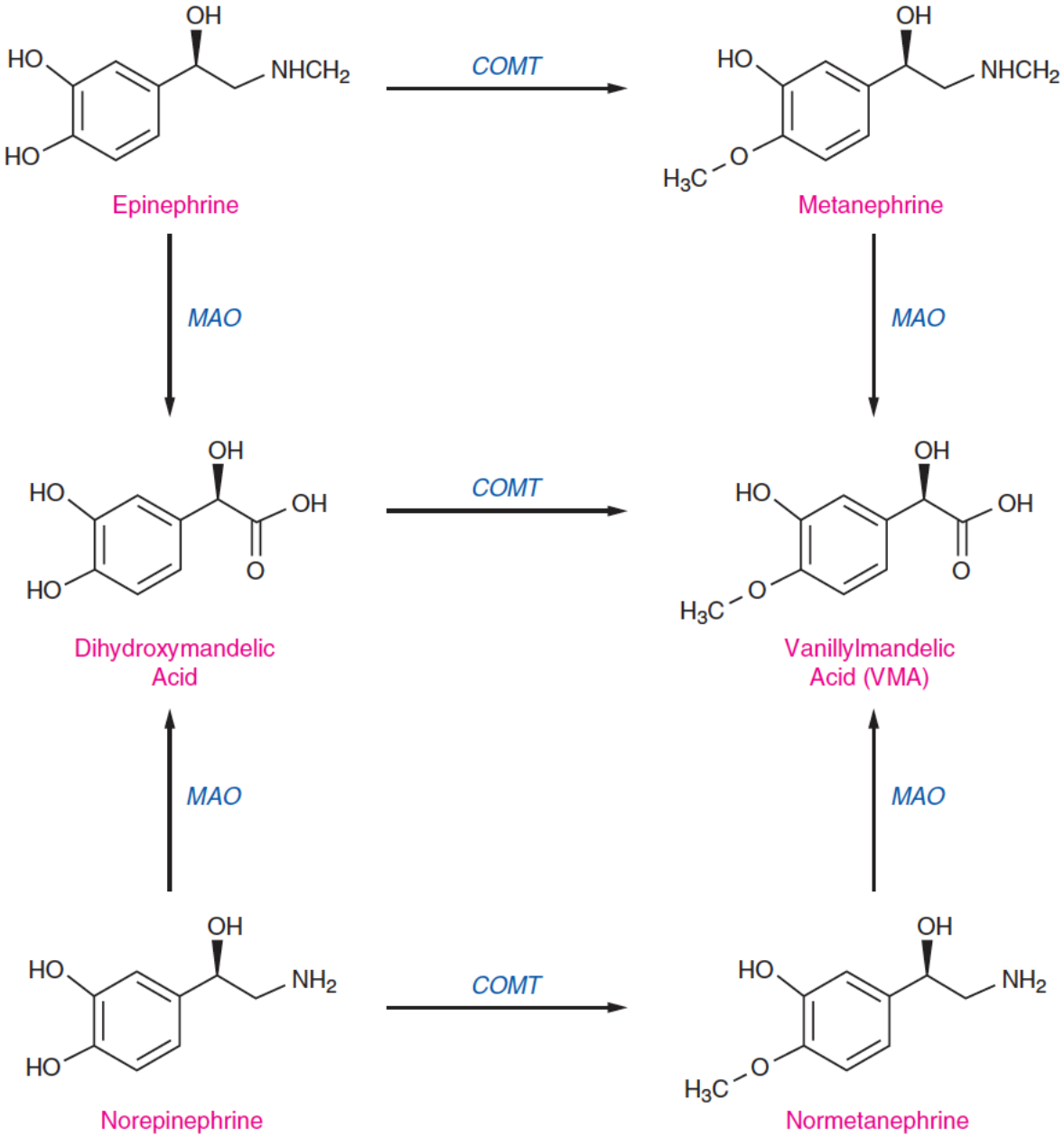
Epinephrine

Epinephrine synthesis in the adrenal medulla.

- The pathway begins with the active uptake of tyrosine from the blood (closed circle, top of figure).
- Followed by its hydroxylation by tyrosine hydroxylase to L-DOPA. This is the first and rate-limiting step of the pathway.
- Dihydroxyphenylalanine (L-DOPA) is decarboxylated by DOPA decarboxylase (also known as aromatic L-amino acid decarboxylase) to form **dopamine**,
- Dopamine is then transported into the secretory granule (closed circle, middle of figure) for **conversion to norepinephrine by dopamine-β-hydroxylase**.
- In the final step, which in the sympatho-medullary system is particular to the adrenal medulla, norepinephrine returns to the cytoplasm for methylation by phenylethanolamine-N-methyl transferase (PNMT) using the methyl group from S-adenosylmethionine (SAM) and generating S-adenosylhomocysteine (SAH).
- The resulting final product, epinephrine, is taken back up into the secretory granule through the vesicular monoamine transporter (closed circle, bottom of figure).



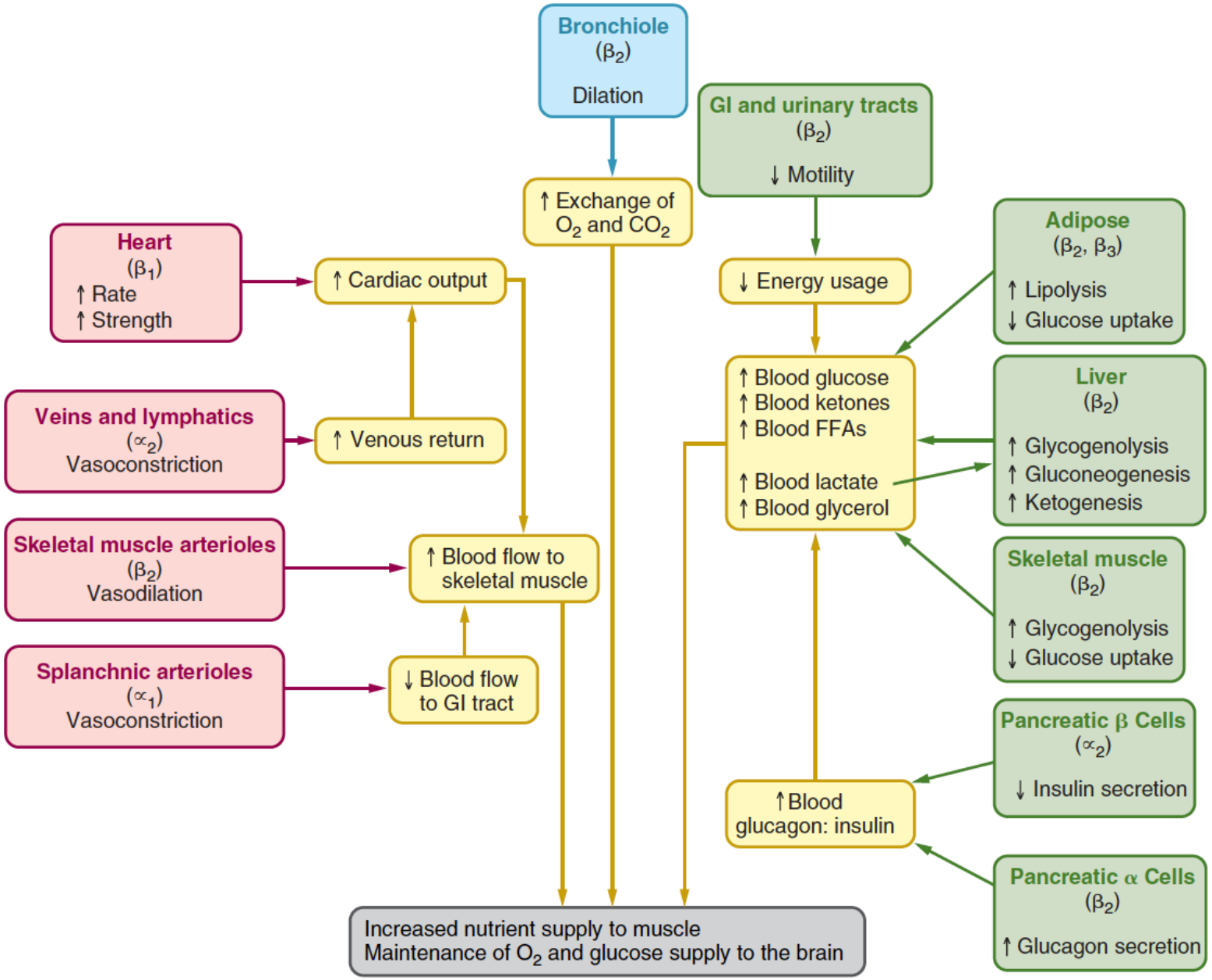
Catabolism of circulating epinephrine and norepinephrine



Catabolism of circulating epinephrine and norepinephrine.

- Epinephrine and norepinephrine are inactivated in the liver, through the action of one or both of two enzymes, monamine oxidase (MAO) and catechol-O-methyltransferase (COMT).
- The latter uses S-adenosyl methionine as the methyl group donor.
- The metabolites shown on the right are excreted in the urine as glucuronide or sulfate conjugates.

Catecholamine-mediated responses to acute stress



Three types of responses are shown:

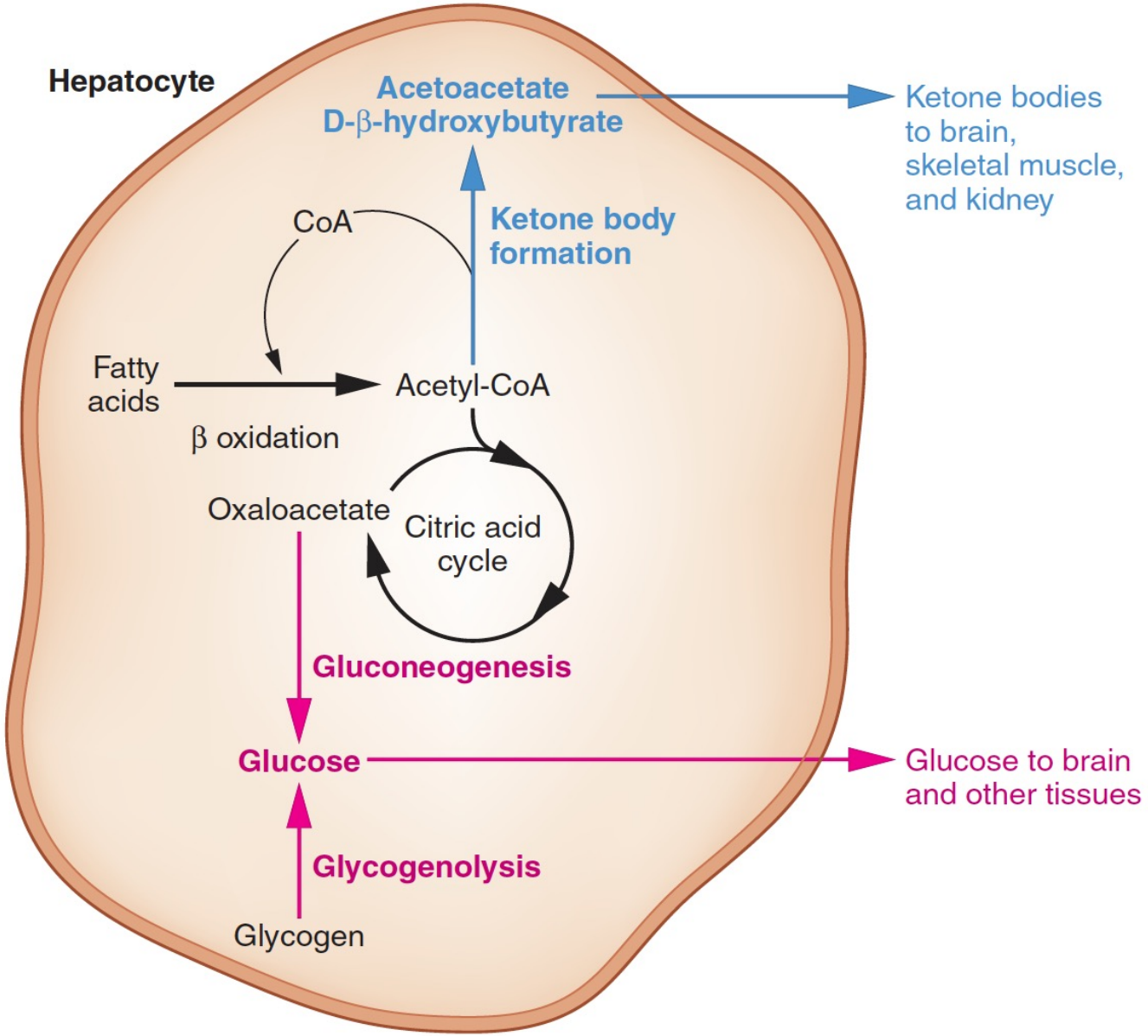
i. On the left (pink) are effects of epinephrine on the heart and vasculature which allow increased blood flow to skeletal muscles and decreased flow to the GI tract.

ii. In the center (blue) is bronchodilation to allow increased gas exchange, thus maintaining the flow of oxygen to the muscles and brain.

iii. On the right (green) are the metabolic responses which increase the supply of fuel to the muscles and brain.

****** In each box, the primary adrenergic receptor responsible for the actions is indicated.**

Epinephrine and liver metabolism



Epinephrine and liver metabolism.

- When the hepatocyte is stimulated by epinephrine, the output of glucose is increased by increased glycogen breakdown and gluconeogenesis (pink pathways).
- Increased free fatty acids, from lipolysis adipose tissue, are available for β-oxidation, resulting in increased ketone bodies, acetoacetate and D-β-hydroxybutyrate (blue pathway).
- Both the increased glucose and ketone bodies are released into the circulation to maintain the fuel supply to the brain and other tissues.

Eicosanoids

Eicosanoids

Eicosanoids are a class of molecules derived from 20-carbon ("eicosa" is Greek for 20) polyunsaturated fatty acids, most frequently arachidonic acid.

The eicosanoids include:

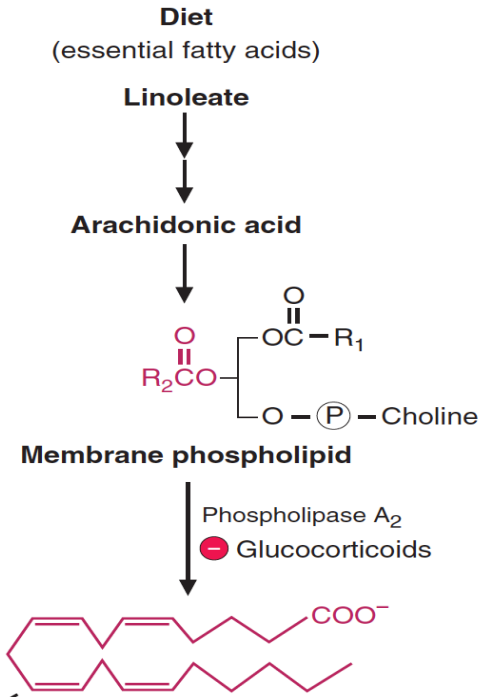
i. **prostaglandins (PG),**
ii. **thromboxanes (TX),**
iii. **leukotrienes (LT), and**
iv. **lipoxins (LX).**

These molecules almost always act on the cells that produce them or on neighboring cells, i.e., over short distances and time periods, and therefore can be classified as autocrine/paracrine hormones.

They are widely distributed in the cells and tissues of the body and, have wide-ranging biological actions.

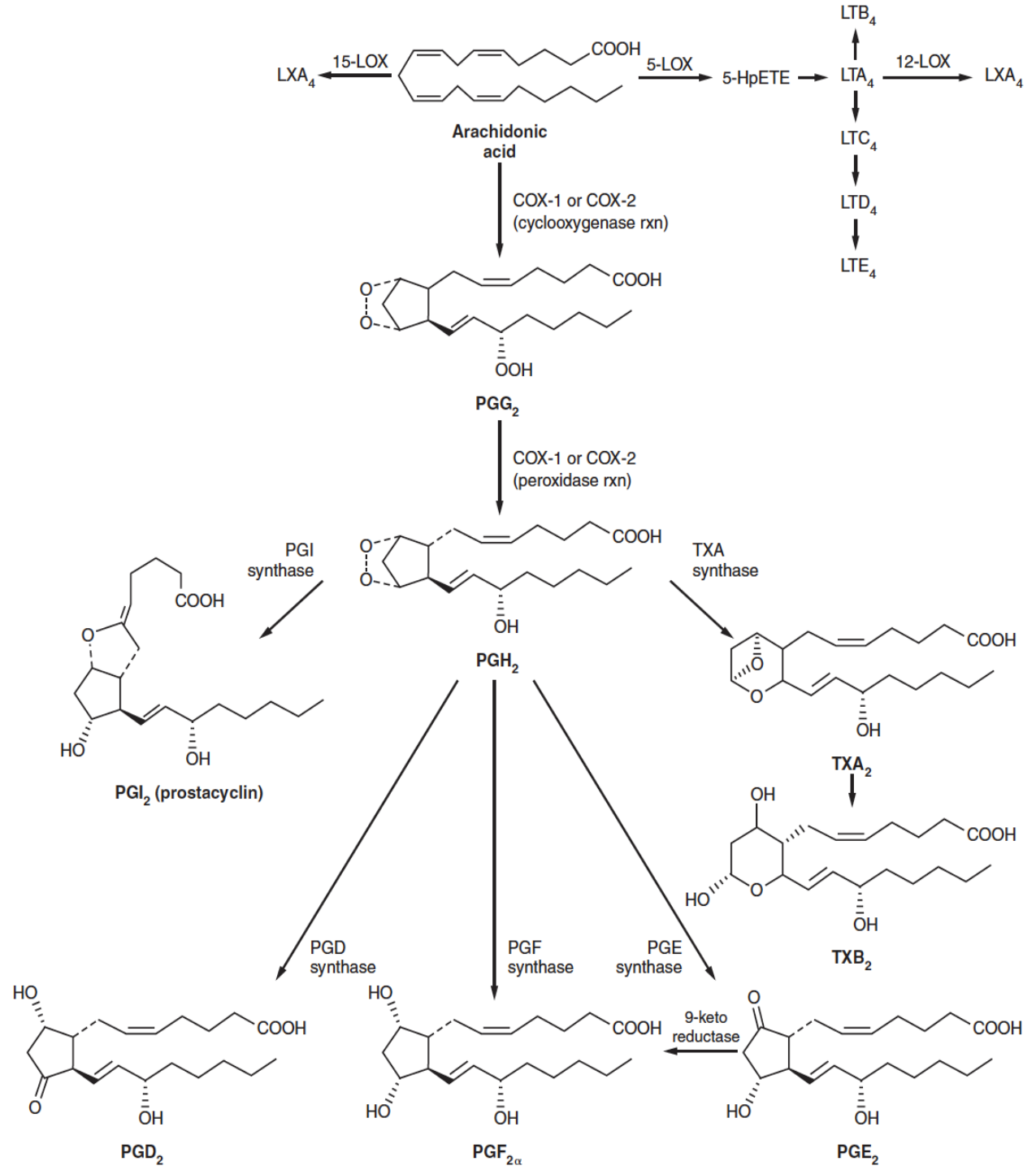
Tissue	Eicosanoid	Action
Hypothalamus-pituitary axis	PGE_1, PGE_2	Hormone secretion
Ovary	PGE_2 $PGF_{2\alpha}$	Ovulation Luteolysis
Uterus	PGI_2 PGE_2, $PGF_{2\alpha}$	Implantation ↑Contraction
Kidney	PGH_2, PGE_1, PGI_2	↑Blood flow, ↑Filtration
Stomach	PGE_2, PGI_2	↓Gastric acid secretion
Intestine	PGE_1, $PGF_{2\alpha}$	↑Motility Nausea, diarrhea
Bronchi	PGE_2, PGI_2 $PGF_{2\alpha}$, TXA_2, LTC_4, LTD_4	Bronchodilation Bronchoconstriction
Platelets	TXA_2 PGE_1, PGI_2	↑Aggregation ↓Aggregation
Blood vessels	PGI_2 $PGF_{2\alpha}$, TXA_2, LTC_4, LTD_4	Vasodilation

Synthesis of Eicosanoids

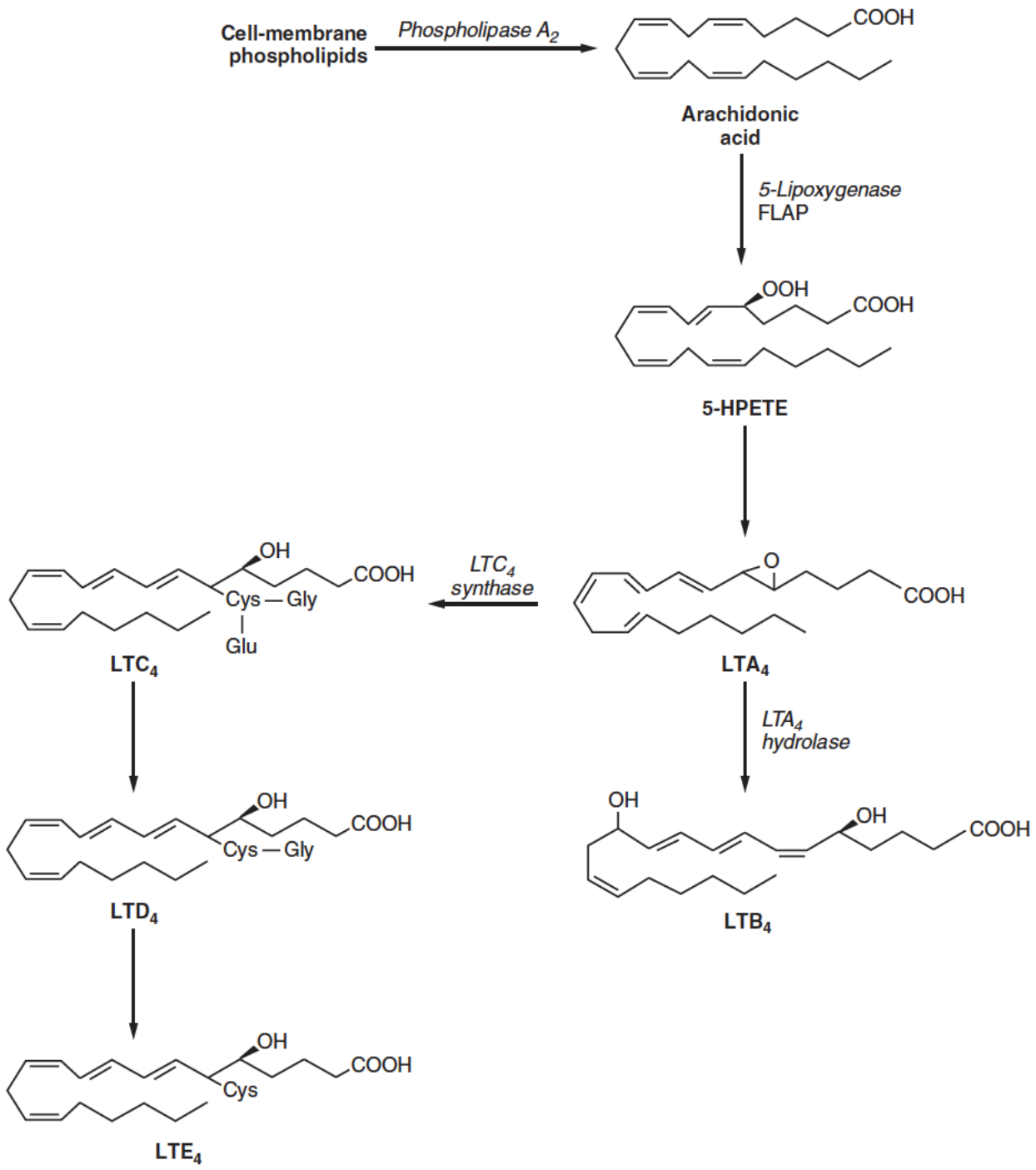


Pathway of the biosynthesis of the main prostanoids from the most abundant substrate, arachidonic acid

- The 5-lipoxygenase (5-LOX) pathway leads to the leukotrienes (LT) through HpETE (hydroxyperoxytetraenoic acid).
- The action of 12-lipoxygenase on LTA4 leads to lipoxin A4. Arachidonic acid can also be converted directly to LXA4 through the 15-lipoxygenase pathway.
- The cyclooxygenase (COX-1 and COX-2) pathway gives rise, through the COX product PGH2, to the prostanoids, prostaglandins, and thromboxanes. Each biologically active prostanoid is produced from PGH2 by a specific synthase. The synthase(s) expressed by a given cell determine which prostanoid(s) the cell will make.



Leukotriene Biosynthesis



Leukotriene biosynthesis. The pathway from arachidonic acid through 5-lipoxygenase (5-LO) is shown.

- 5-LO requires a membrane protein, FLAP (5-lipoxygenase activating protein) for the two reactions it catalyzes to form leukotriene A4 (LTA4), which is converted to leukotriene B4 (LTB4) through the removal of a water molecule by LTA4 hydrolase.
- LTC4 arises from the addition of glutathione to carbon-6 by LTC4 synthase.
- The sequential removal of glutamate and glycine leads to the active leukotrienes D4 and E4.
- These three LTs are referred to as the cysteinal leukotrienes or cys-LTs.

Eicosanoid metabolism

Prostaglandins, prostacyclins, and thromboxanes

1. Polyunsaturated fatty acids containing 20 carbons and three to five double bonds (e.g., arachidonic acid) are usually esterified to position 2 of the glycerol moiety of phospholipids in cell membranes. These fatty acids require essential fatty acids such as dietary linoleic acid (18:2, Δ9,12) for their synthesis.
2. The polyunsaturated fatty acid is cleaved from the membrane phospholipid by phospholipase A2, which is inhibited by the steroidal anti-inflammatory agents.
3. Oxygen is added and a 5-carbon ring is formed by a cyclooxygenase that produces the initial prostaglandin, which is converted to other classes of prostaglandins and to the thromboxanes.

a. The prostaglandins have a multitude of effects that differ from one tissue to another and include inflammation, pain, fever, and aspects of reproduction. These compounds are known as autocoids because they exert their effects primarily in the tissue in which they are produced.

b. Certain prostacyclins (PGI2), produced by vascular endothelial cells, inhibit platelet aggregation, whereas certain thromboxanes (TXA2) promote platelet aggregation.

4. Inactivation of the prostaglandins occurs when the molecule is oxidized from the carboxyl and ω-methyl ends to form dicarboxylic acids that are excreted in the urine.

Leukotrienes

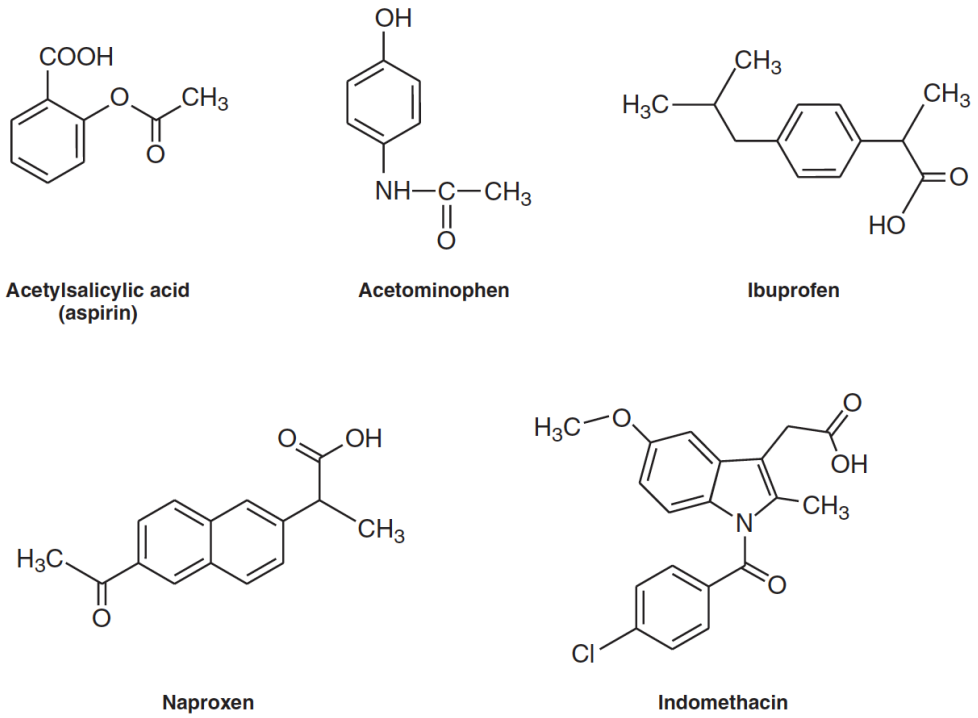
Arachidonic acid, derived from membrane phospholipids, is the major precursor for the synthesis of the leukotrienes.

1. In the first step, oxygen is added by lipoxygenases, and a family of linear molecules, hydroperoxyeicosatetraenoic acids (HPETEs), is formed.
2. A series of compounds, comprising the family of leukotrienes, is produced from these HPETEs. The leukotrienes are involved in allergic reactions. Leukotrienes also contribute to the symptoms of asthma by acting as bronchoconstricting agents, narrowing the airway, and making it more difficult to breathe.

Cyclooxygenase inhibitors

CLINICAL CORRELATES

Nonsteroidal anti-inflammatory drugs (NSAIDs), such as aspirin and ibuprofen, inhibit the cyclooxygenase involved in prostaglandin synthesis. These drugs reduce pain, inflammation, and fever associated with the action of the prostaglandins. Aspirin irreversibly acetylates the enzyme in platelets, inhibiting thromboxane (TXA_2) formation, thus reducing platelet aggregation for the life span of the platelet. Because platelets turn over rapidly, the daily ingestion of small doses of aspirin is often recommended to inhibit platelet aggregation (thrombus formation) that, in conjunction with atherosclerotic plaques, often precipitates heart attacks. There are two forms of cyclooxygenase, **COX1 and COX2**. Aspirin and many nonsteroidal anti-inflammatory drugs affect both, but **COX2-specific drugs**, such as celecoxib, are reversible inhibitors that only affect COX2, the enzyme induced during inflammatory events.



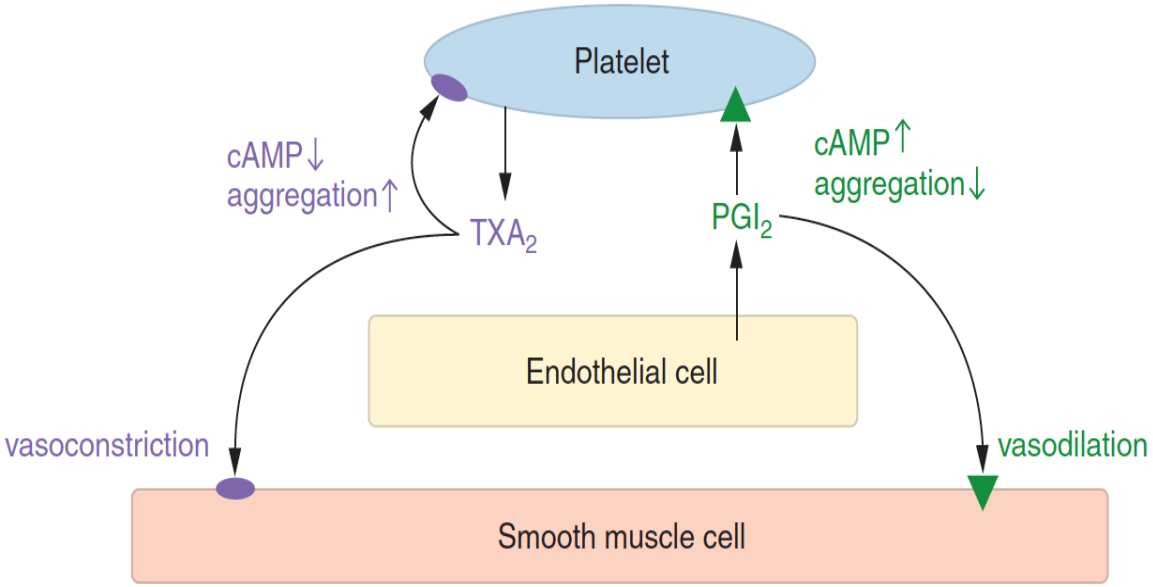
Cyclooxygenase inhibitors. The structures of some commonly used nonspecific nonsteroidal anti-inflammatory drugs (NSAIDS) are shown These compounds inhibit both COX-1 and COX-2

Prostacyclin and Thromboxane in the Vasculature

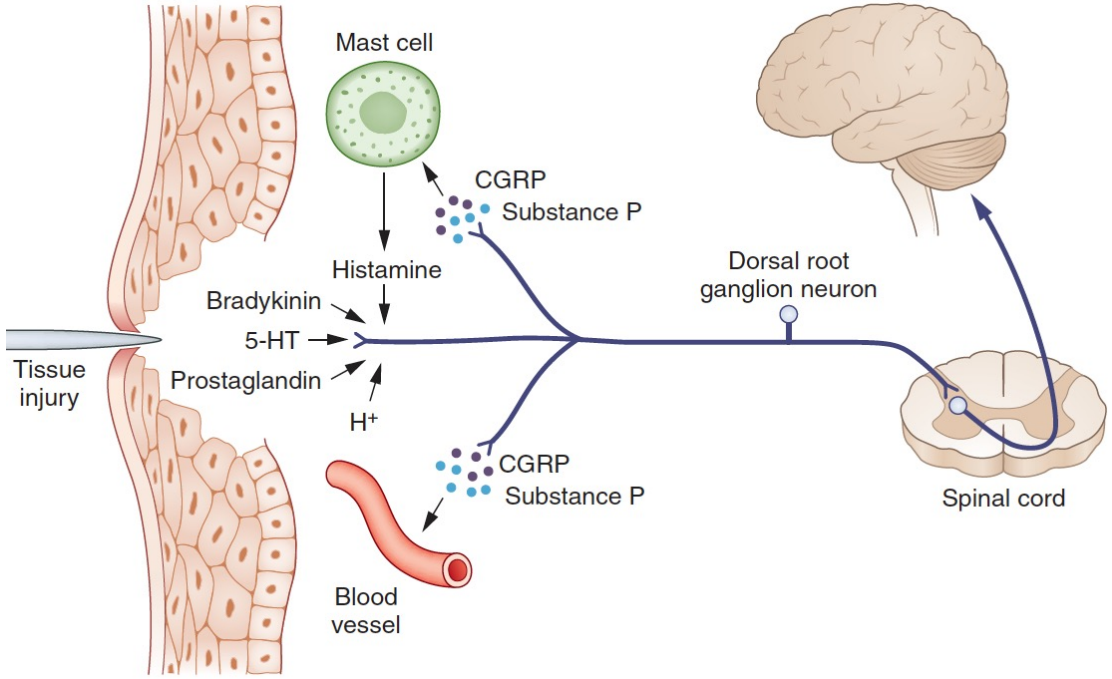
- Platelets are enucleated cell fragments formed from bone marrow megakaryocytes. They retain many cytoplasmic components including mitochondria, granules containing platelet-specific proteins, coagulation factors, and the enzymes (phospholipase A2, COX-1, and thromboxane synthase) to produce TXA2.
- When an injury to the vasculature occurs, platelets are activated through the detection of exposed collagen in the wall of the vasculature. A rise in intracellular Ca2+ in the platelets leads to the activation of phospholipase A2 and cyclooxygenase.
- The resulting TXA2 is released and acts on the platelets to promote aggregation through interaction with its receptor, TP, and the reduction in intracellular cAMP levels.
- TXA2 also acts on nearby smooth muscle cells of the vasculature, constricting them to prevent blood loss. A platelet plug is formed at the site of the injury, setting the stage for clot formation.
- Under normal conditions, that is when no injury to the vasculature is detected, prostacyclin, PGI2, is produced by COX-2 and PGI synthase and released by the endothelial cells lining the vasculature. PGI2 acts on platelets through its receptor, IP, and increased cyclic AMP production to inhibit aggregation. PGI2 also promotes vasodilation of the smooth muscle cells.

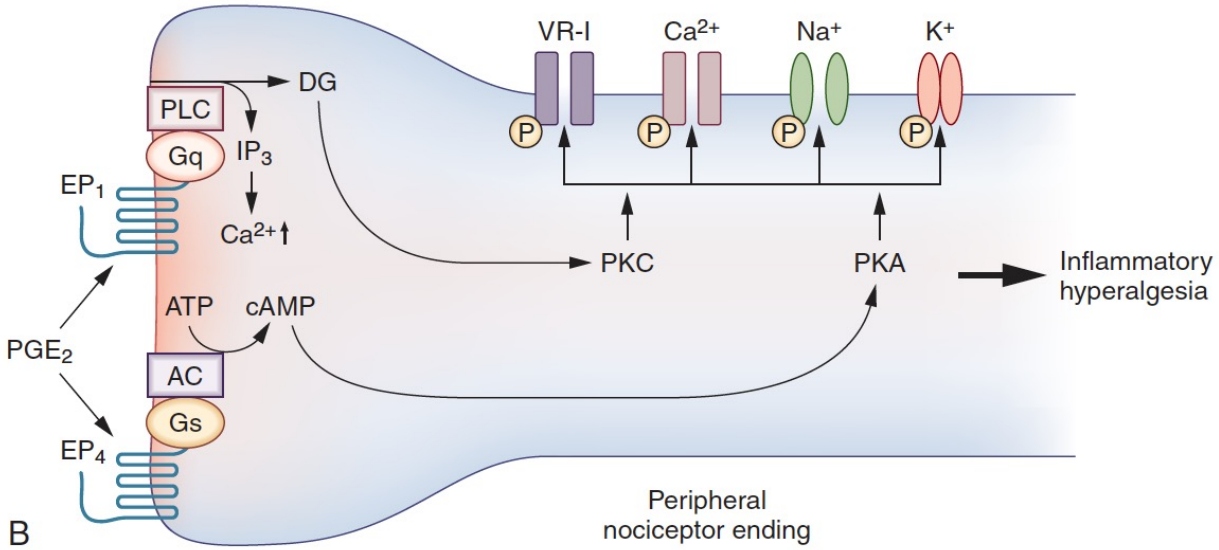
********Thus, balance between the actions of TXA2 and PGI2 in the blood vessels is critical in maintaining vascular homeostasis.

- **Since platelets contain COX-1 and endothelial cells contain COX-2, inhibitors selective for the latter enzyme upset the balance between the two prostanoids and can therefore lead to serious cardiovascular side effects**



Prostaglandins and Pain Perception





- When a **tissue injury** occurs, cells at the site release several substances including bradykinin, serotonin, and prostaglandins, **primarily PGE2**, into the acidic environment of the inflammation.
- All of these act on the terminus of the nociceptor, the afferent neuron, whose cell body lies in the dorsal root ganglion, that will carry the pain signal through the afferent fibers in ascending tracts in the spinal cord to pain perception centers in the brain.
- At the same time the efferent function of the nociceptor engages, releasing the neurotransmitters substance P and CGRP (calcitonin gene related peptide) leading to activation of nearby nonneuronal cells, which contribute other molecules, such as **histamine**, to the inflammatory milieu

Inside the nerve terminal,

- PGE2 acting through either EP1 or EP4 (depending on the tissue and species under study) activates protein kinase C (PKC) or cyclic AMP-dependent protein kinase (PKA), respectively.
- Phosphorylation leads to the opening of Ca2+ and Na+ channels, including the vanilloid receptor, VR-1 (a mono- and divalent cation channel), and the closing of K+ channels.
- Collectively these events lead to membrane depolarization and transmission of the neural signal to the brain.

Prostaglandins in reproduction

1. Ovulation

- The cascade of cellular events that follows the midcycle surge of LH and leads to release of the ovum shares several characteristics with the process of inflammation.
- Thus it is not surprising that induced COX-2 in granulosa, rather than the constituitively expressed COX-1 in the thecal cells, is the critical enzyme for the prostaglandin pathway in ovulation.
- In nonhuman primates it has been shown that PGE2 is specifically involved in the regulation of plasminogen activator-mediated proteolysis required for follicule rupture.

2. Luteolysis

- In nonprimate mammals, such as rodents and domesticated species, the regression of the corpus luteum (luteolysis) at the end of a nonfertilization reproductive cycle, is brought about by PGF2α produced by the uterus.
- In primates including humans, the corpus luteum can undergo regression in the absence of the uterus although PGF2α is synthesized by the human corpus luteum and FP receptors are found there.
- While this and other evidence suggests that locally produced PGF2α may participate in primate luteolysis, further studies are required to have a definitive answer on this point.

3. Cervical Ripening

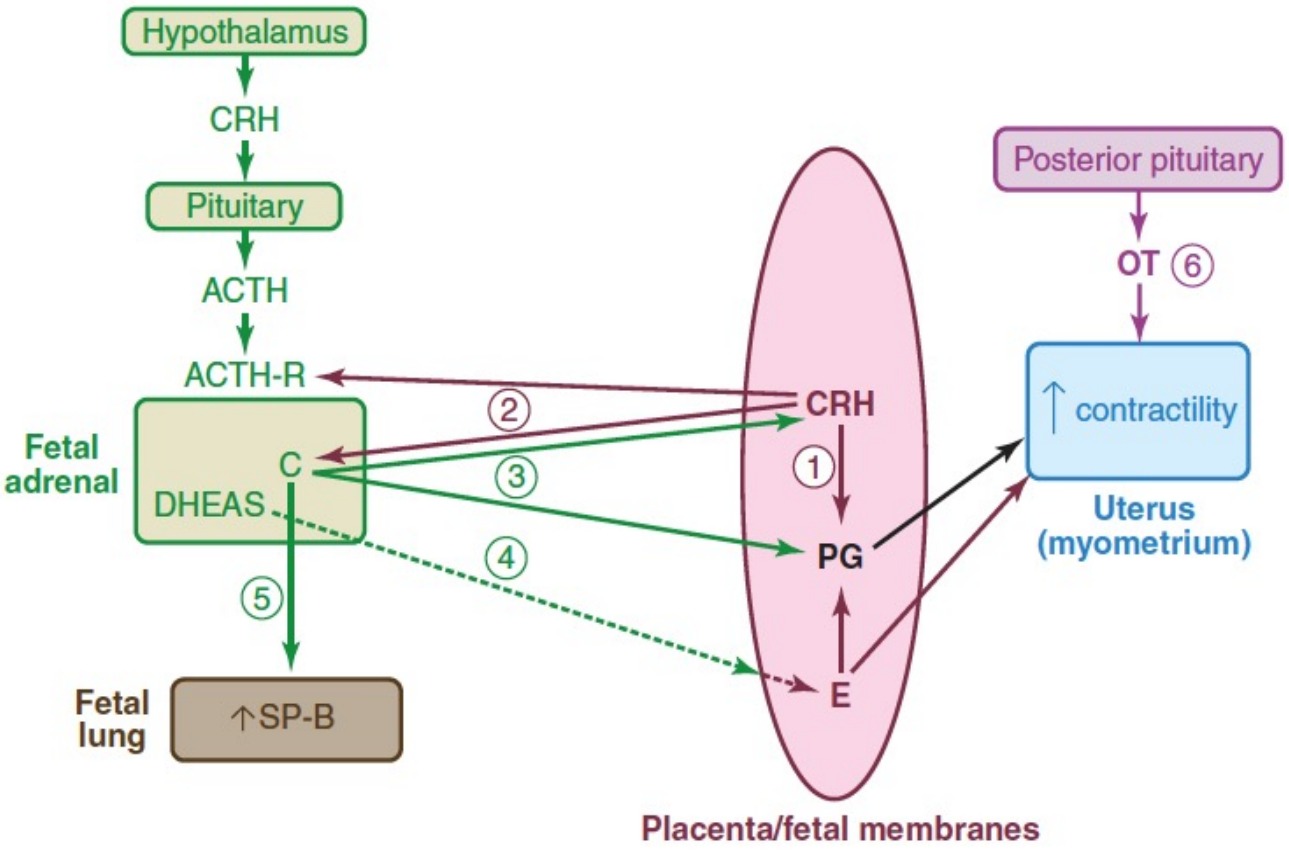
- A critical step in the birth of the newborn is the softening (or ripening) of the uterine cervix, which has functioned to retain the fetus throughout pregnancy, so that the fetus can be expelled when gestation is concluded.
- Several prostaglandins are produced in the cervix and the tissue contains both EP and FP receptors.
- It is likely that the mechanism of prostaglandin action in the cervix includes the induction of enzymes responsible for remodeling of collagen and proteoglycans that occurs during cervical softening.
- The local administration of PGE2 is a common way to stimulate the process, particularly when labor is being induced, and brings about the same changes as those seen in nontherapeutically assisted softening.

Prostaglandins in reproduction

4. Parturition/Preterm Labor

- The biological effect of the first prostaglandins studied was their powerful ability to contract uterine smooth muscle.
- PGE2 is a potent abortifactant and is used in the early termination of pregnancy. It has been known for three decades that aspirin and indomethacin, both cyclooxygenase inhibitors that, at low doses, are specific for COX-1, delay parturition (birth) in humans and other animals.
- At higher doses these NSAIDs both inhibit COX-2 as well. The cyclooxygenases occur in the placenta and fetal membranes and during normal labor, prostaglandin production by COX-1 is regulated by other hormones involved in parturition.
- Preterm labor, on the other hand, which shares physiologic features with inflammatory processes, is mediated largely by COX-2. Clinically, preterm labor can be curtailed with systemic or vaginally delivered local doses of indomethacin, attesting to the importance of prostaglandins in parturition.

Hormonal interactions in parturition



Placental CRH plays a central role in parturition.

1. Placental (pink oval) CRH stimulates myometrial contractile activity through the increased production of prostaglandins (PG), which are directly responsible for increasing uterine contractions (black arrow).
2. CRH also stimulates the fetal adrenal (green box) to increase steroidogenesis both directly and indirectly by increasing the ACTH receptors and thus the responsiveness of the fetal adrenal to the pituitary hormone (magenta arrows).
3. Increased cortisol from the fetal adrenal stimulates increased CRH production by the placenta in a positive feedback loop and also stimulates PG levels (green arrows).
4. Increased fetal adrenal steroidogenesis results in greater sulfated DHEAS leading to increased estrogen synthesis in the placenta (dashed green arrow). Estrogen stimulates contractions of the uterus both directly and by stimulation of PG production (magenta arrows).
5. Cortisol from the fetal adrenal is required for several aspects of the final development of the fetus, including lung (brown box) maturation through the increased synthesis of surfactant protein B (SP-B; green arrows).
6. As labor progresses, secretion of oxytocin (OT) from the posterior pituitary increases and the myometrium, through an increase in OT receptor number, becomes more sensitive to the hormone, further strengthening and coordinating uterine contractions.

Leukotrienes in Human Disease

1. Asthma and Other Upper Respiratory Conditions

- Asthma is a complex disease resulting in part from narrowing of the airways.
- For decades the agent that causes the bronchoconstriction of asthma was known as the slow-reacting substance of anaphylaxis (SRS-A), but was not structurally characterized until the early 1980s.
- The identification of SRS-A as a mixture of leukotrienes led to the elucidation of the 5-LO pathway and, in particular, the role of the products of LTC4 synthase, the cysteinyl leukotrienes (cys-LTs), in the pathogenesis of bronchial asthma.
- In the 1990s, the efficacy of the 5-LO inhibitor zileurton in human asthma was demonstrated and effective anti-asthma drugs became available.
- In addition to asthma, reactions such as immediate hypersensitivity to allergens and hyperactivity in response to cold and exercise are mediated by leukotrienes.

2. Atherosclerosis

- Atherosclerosis is a chronic inflammatory vascular disease.
- There is much evidence supporting a role for the 5-lipoxygenase and, in particular, LTB4 in the development of human atherosclerosis.
- Blocking the pathway with a BLT1 antagonist protected against atherosclerosis in a mouse model. Also in mice, genetic removal of 5-LO pathway decreases the size of atherosclerotic plaques and specific inhibition of 5-LO reduces monocyte adhesion and infiltration.
- In humans atherosclerotic plaque levels of 5-LO correlate positively with disease stage.
- Genetic polymorphism studies in humans suggest that individuals with some variants of 5-LO show a greater risk of myocardial infarction and stroke.

Leukotrienes in Human Disease

TABLE 8-3 Leukotrienes: Biological Actions and Human Disease

	LTB_4	cys-LTs
	LTA_4 hydrolase	LTC4 synthase
Production from LTA_4	Macrophages Neutrophils	Macrophages Eosinophils Mast cells Dendritic cells
Target cells ↑Activity	*Neutrophils* Chemotaxis, aggregation, degranulation *Mast cells* Recruitment of immature mast cells *Smooth muscle cells* Proliferation, migration *Dendritic cells* Chemotaxis, accumulation in lymph nodes *Macrophages* IL-6, MCP-1, TNF-α production *Lymphocytes* T-cell recruitment to peripheral tissue	*Endothelial cells* Microcirculation permeability and leakage *Mast cells* IL-5, IL-8, TNF-α production *Smooth muscle cells* Vaso- broncho- constriction *Dendritic cells* Migration from epidermis to lymph nodes *Macrophages* TNF-α, MMP-9 production *Lymphocytes* Allergen sensitization in pulmonary tract, Th2 immune reaction
Associated Diseases	Arthritis Atherosclerosis Cancer Dermatitis	Asthma Allergic rhinitis Aortic aneurysm Ischemia/stroke

IL, interleukin; MCP, monocyte chemoattractant protein; MMP, matrix metalloproteinase; TNF, tumor necrosis factor; COPD, chronic obstructive pulmonary disease; IBD, irritable bowel disease.

Clinically Relevant Endocrine Disorders

Disease	Description
Acromegaly	Inappropriate and continued secretion of growth hormone by a tumor of pituitary cells which leads to soft tissue swelling and hypertrophy of the skeletal extremities (usually in the third or fourth decade).
Addison's disease	Adrenocortical insufficiency resulting from a deficient production of glucocorticoids and/or mineralocorticoids due to a destruction of the adrenal cortex.
Bartter's syndrome	Characterized by increased angiotensin, renin, aldosterone, secretion, hypokalemia, alkalosis, and hyperplasia of the renal juxtaglomerular cells, but with normal blood pressure; the disease, which is possibly an autosomal-dominant disorder, usually appears in late infancy or early childhood; the primary defect may be a lesion in chloride reabsorption in the kidney loop of Henle.
Celiac disease	An intestinal malabsorption disorder occurring in some individuals who may lack an enzyme necessary for the hydrolysis of *N*-glutamyl peptides in the small intestine. As a consequence, the affected individual is intolerant of some proteins, usually those derived from wheat, oats, barley, or rye; the disease is also referred to as gluten-sensitive enteropathy.
Chiari-Frommel syndrome	The occurrence of galactorrhea (non-nursing-related lactation) and amenorrhea (absence of expected menstrual periods) during the postpartum period; the disease may be due to the presence of a prolactin-secreting tumor.
Cretinism	Characterized by a permanent neurological and skeletal retardation and results from an inadequate output of thyroid hormone during uterine and neonatal life; may be caused by iodine deficiency, thyroid hypoplasia, genetic enzyme defects, or excessive maternal intake of goitrogens.
Cushing's disease	Hypercortisolism resulting from the presence of small pituitary tumors which secrete ACTH leading to excess production of cortisol by the adrenals.
Cushing's syndrome	The circumstance of glucocorticoid excess without specification of the specific etiology; it may result from endogenous causes but is more commonly iatrogenic.

Clinically Relevant Endocrine Disorders

Diabetes insipidus	A deficient secretion of vasopressin which is manifested clinically as *diabetes insipidus;* it is a disorder characterized by the excretion of an increased volume of dilute urine.
Diabetes mellitus	A disease characterized by a chronic disorder of intermediary metabolism due to a relative lack of insulin which is characterized by hyperglycemia in both the postprandial and fasting state (see also types I and II *diabetes mellitus*).
Diabetes mellitus (insulin-dependent or type I diabetes)	The form of diabetes which appears in the second and third decade of life and is characterized by a destruction of the pancreas B cells; this form of the disease is normally treated with daily administration of insulin.
Diabetes mellitus (insulin-independent or type II diabetes)	The form of diabetes arising after the fourth decade, usually in obese individuals; this form of the disease does not normally require treatment with insulin.
Empty sella syndrome	Empty sella is a term that describes *sellae* that fill with air during pneumoencephalography. It is frequently associated with the flattening of the pituitary gland. The etiology of the disease is unknown; the pituitary function is usually normal.
Fanconi syndrome	A renal tubular defect in the absorption of a variety of substances including H_2O, phosphate, sodium, bicarbonate, and amino acids; frequently an osteomalacic bone disease and a distal tubular acidosis may accompany the disease.
Feminization	Feminization of males, usually manifested by enlargement of the breasts (gynecomastia) which can be attributed to an increase in estrogen levels relative to the prevailing androgen levels.
Froehlich's syndrome	A condition usually caused by craniopharyngioma (a tumor of the hypothalamus) which results in a combination of obesity and hypogonadism; sometimes termed adiposogenital dystrophy.
Galactorrhea	The persistent discharge from the breast of a fluid that resembles milk and that occurs in the absence of parturition or else persists postpartum (4–6 months) after the cessation of nursing.
Gigantism	This condition appears in the first year of life and is characterized by a rapid weight and height gain; affected children usually have a large head and mental retardation; to date no specific endocrine abnormalites have been detected.

(*Continued*)

Clinically Relevant Endocrine Disorders

Disease	Description
Goiter	Goiter may be defined as a thyroid gland that is twice its normal size; endemic goiter is the major thyroid disease throughout the world. Goiter is frequently associated with a dietary iodine deficiency; in instances of sporadic goiter it may occur as a consequence of a congenital defect in thyroid hormone synthesis.
Grave's disease	An autoimmune disease characterized by the presence in serum of a long-acting thyroid stimulator (LATS) that is an antibody for the receptor for TSH. Grave's disease is the most common cause of thyrotoxicosis.
Gynecomastia	Abnormal breast enlargement which may occur in males during puberty.
Hartnup's disease	An intestinal transport disorder. The condition may be diagnosed by the massive urinary excretion of monoamino-monocarboxylic amino acids; frequently there are pellagra-like rashes after exposure to sunlight as well as attacks of cerebellar ataxia.
Hermaphroditism	True hermaphroditism is defined as the presence of both testicular and ovarian tissue in the same individual; pseudohermaphroditism is a discrepancy between gonadal and somatic sex.
Hirsutism	An increase in facial hair in women which is beyond that cosmetically acceptable; this condition may be associated with a number of masculinizing disorders including Cushing's syndrome, congenital adrenal hyperplasia, and polycystic ovary syndrome.
Hyperaldosteronism	An inappropriate secretion of aldosterone. It can occur as a primary adrenal problem (e.g., adrenal tumor) or can be secondary to other metabolic derangements that stimulate its release; it is often characterized by inappropriately high levels of plasma renin.
Hyperparathyroidism	Inappropriately high secretion of PTH leading to hypercalcemia. Frequently associated with hyperparathyroidism is a metabolic bone disease characterized by excessive bone calcium reabsorption; frequently attributable to an adenoma of the parathyroid gland.
Hypoparathyroidism	Inappropriately low secretion of PTH leading to hypocalcemia; the disease is either idiopathic or iatrogenically induced.
Hypophosphatasia	An autosomal recessive trait characterized by elevated serum and urine inorganic pyrophosphate, a low serum alkaline phosphatase, and frequently hypercalcemia; may be related to a dysfunction of the osteoblasts.

Clinically Relevant Endocrine Disorders

Klinefelter's syndrome	Typically characterized by male hypogonadism; the presence of extra X chromosomes is likely the fundamental underlying etiological factor. It is characterized by varying degrees of decreased Leydig cell function and seminiferous tubule failure.
Milk-alkali syndrome	Affected subjects have hypercalcemia, nephrocalcinosis, soft tissue calcification, renal impairment, alkalosis, and hyperphosphatemia; the syndrome can result as a consequence of an excessive dietary intake of milk and other absorbable alkali (e.g., Na_2CO_3 or $NaHCO_3$); it is uncommon today.
Myxedema	Hypothyroidism clinically manifested by the presence of a mucinous edema; the disease may appear at any time throughout life and is attributable to disorders of the thyroid gland or to pituitary insufficiency.
Nelson's syndrome	A pituitary adenoma occurring in 10% of patients with Cushing's disease; afflicted subjects have a severe skin pigmentation.
Osteomalacia	A bone disease in adults characterized by a failure of the skeletal osteoid to calcify; it is usually caused by an absence of adequate access to vitamin D.
Polycystic ovary syndrome	A complex of varying symptoms ranging from amenorrhea to anovulatory bleeding often associated with obesity and hirsutism. The term denotes an absence of ovulation in association with continuous stimulation of the ovary by disproportionately high levels of LH.
Pseudohypoparathyroidism	A familial disorder characterized by hypocalcemia, increased circulating levels of PTH and a peripheral unresponsiveness to the hormone; afflicted individuals frequently are of short stature, with mental retardation and short metacarpals and/or metatarsals.
Rickets	A failure in the child of the skeletal osteoid to calcify; it is usually caused by an absence of adequate amounts of vitamin D; it is characterized by a bowing of the femur, tibia, and fibulas.
Turner's syndrome	A condition present in females with a 45, XO chromosome pattern (i.e., complete absence of the X chromosome). The XO individual is typically short with a thick neck and trunk and no obvious secondary sex characteristics.
Waterhouse-Friderichsen syndrome	Acute adrenal insufficiency resulting from severe systemic infection by *meningococcus* characterized by a high fever, meningeal irritation, and vascular collapse.
Werner's syndrome	Multiple endocrine neoplasia, type 1, caused by an autosomal recessive inheritance. It is often characterized by a severe testicular atrophy and a mild insulin-resistant diabetes.
Zollinger-Ellison syndrome	Tumors of the pancreas which result in excessive secretion of gastrin; the afflicted subject has recurrent duodenal ulcers and diarrhea caused by hypersecretion of gastric acid.

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