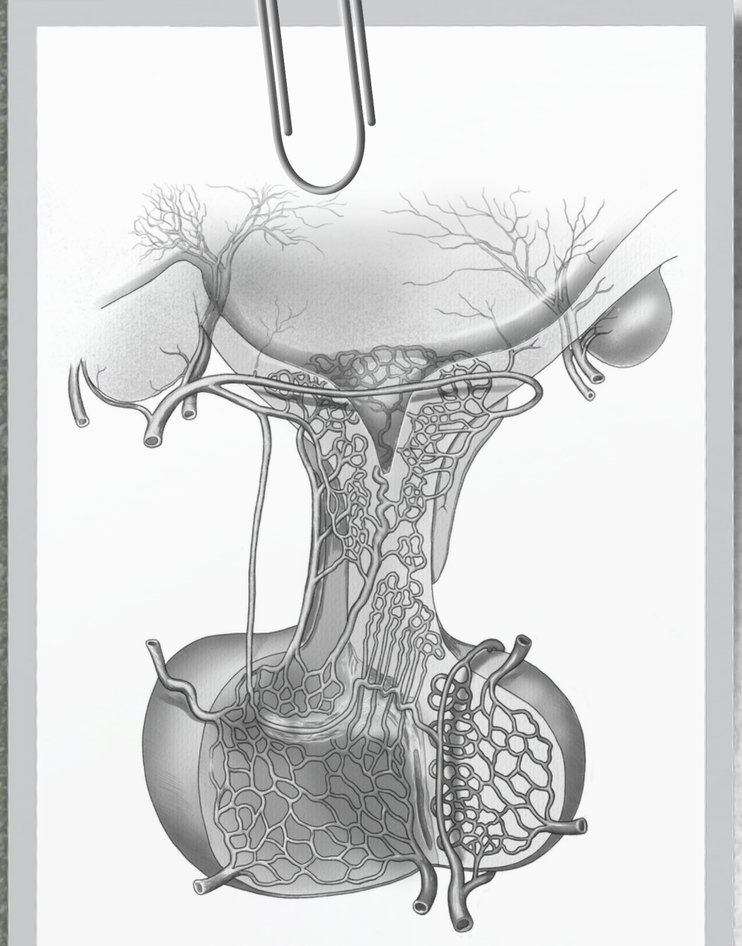
Endocrine Physiology/Anatomy

My collection of physiology notes about various endocrine glands. I am training to be a physician as such all basic science principles that are clinically relevant are on my study list

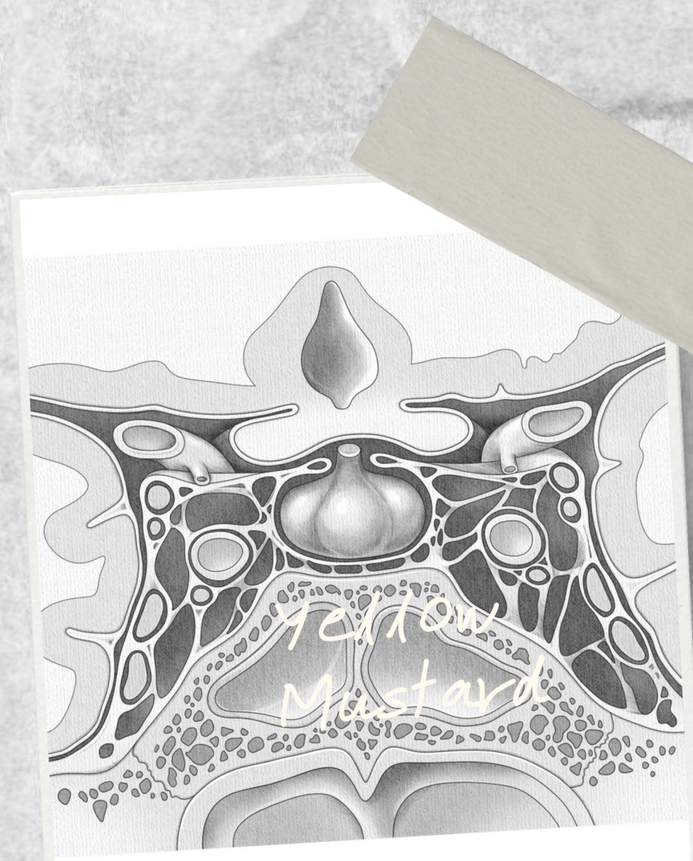


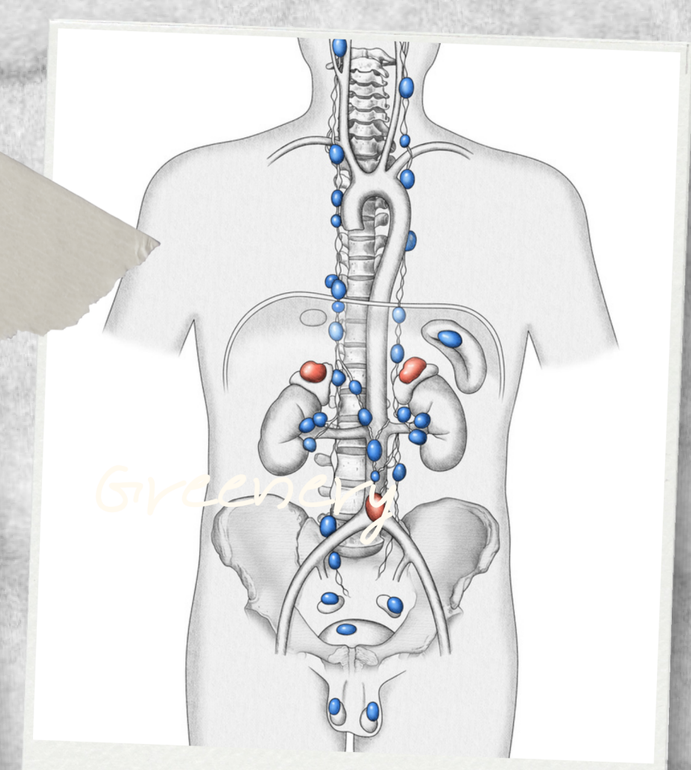
Reading

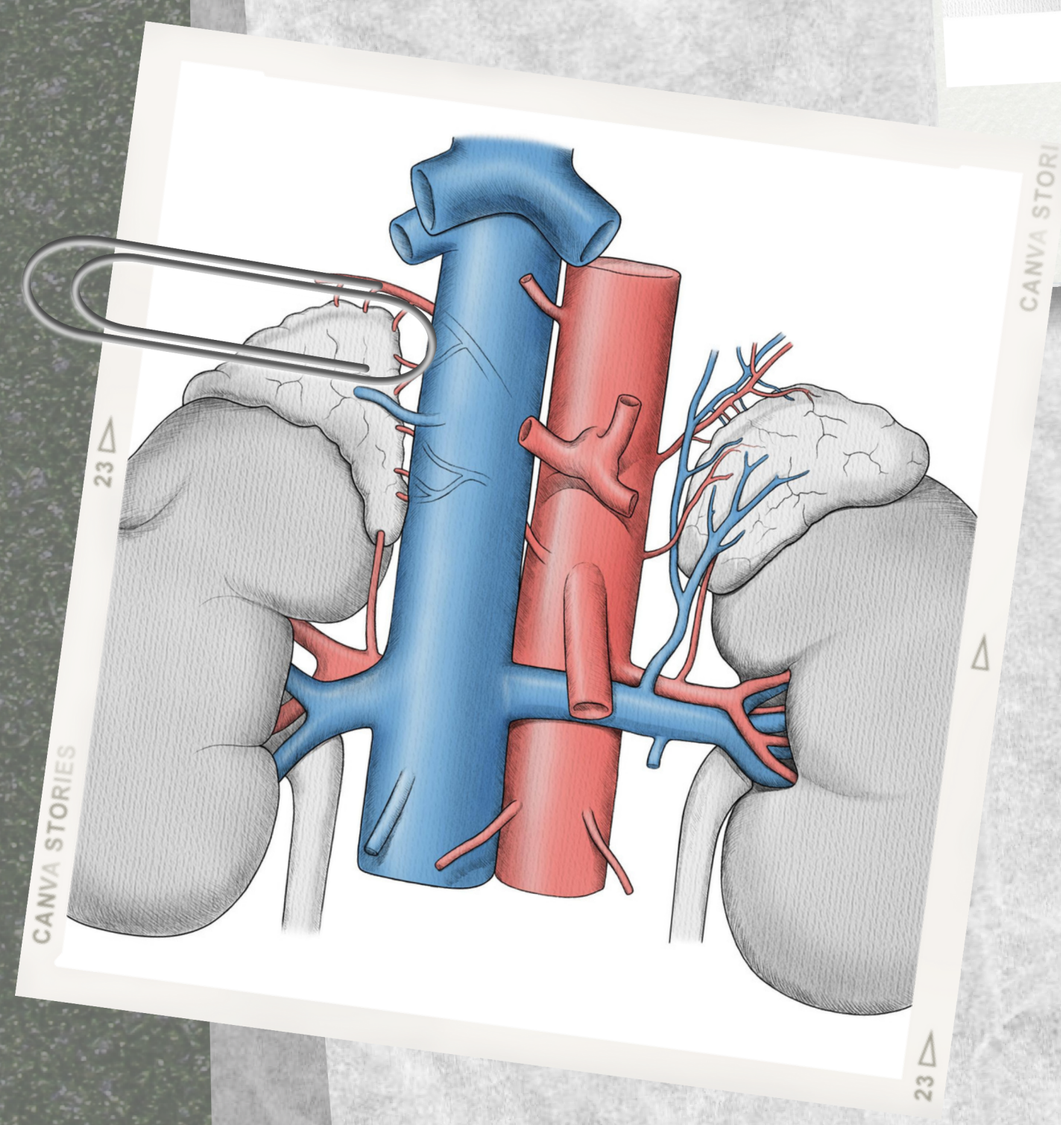
study partner

session at 2pm

on march 6th.







ADRENAL VEIN SAMPLING IN THE EVALUATION OF PRIMARY HYPERALDOSTERONISM

PITUITARY GLAND

ANATOMY

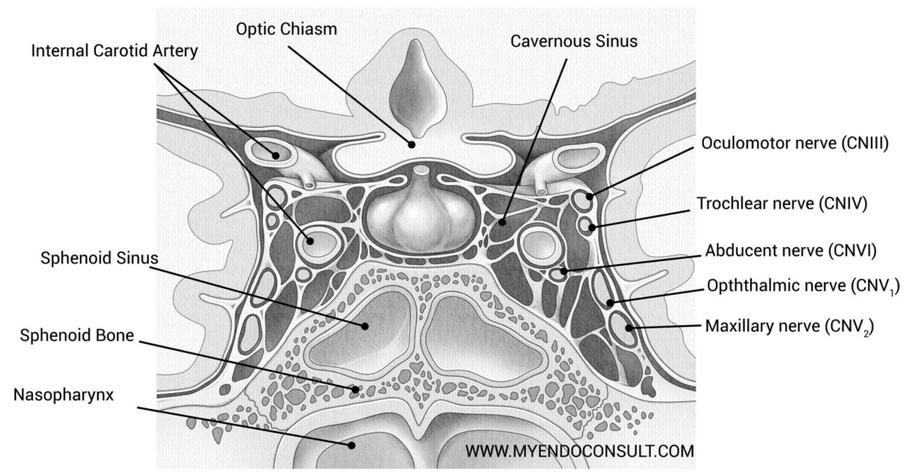
Parts of the Pituitary Gland : It is made up of an anterior lobe (2/3), the posterior lobe (1/3), and vestigial intermediate lobe

Location : Located within the **sella turcica** (bony roof of the sphenoid bone).

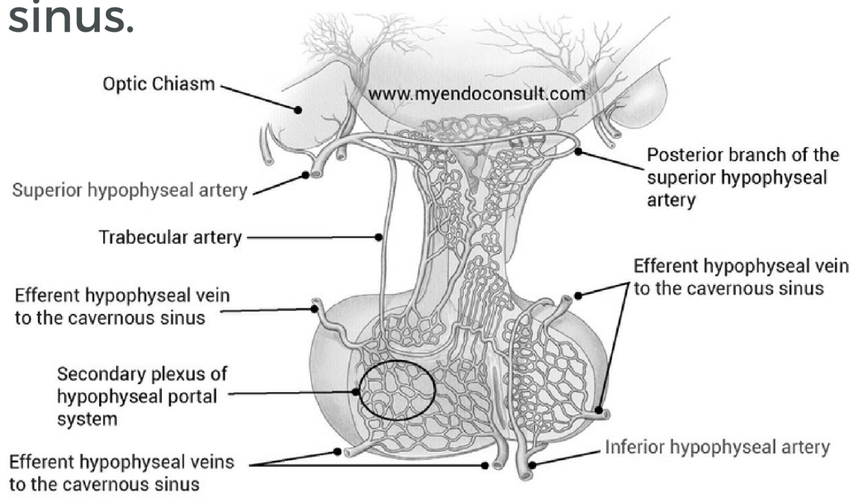
Blood supply: Receives arterial blood from the **inferior hypophyseal arteries**, venous drainage from the inferior petrosal sinuses. The hypophyseal portal system facilitates bidirectional flow of hormones between the hypothalamus and pituitary gland.

Embryology : Anterior pituitary (adenohypophysis) forms from Rathke's pouch. **Posterior pituitary** (neurohypophysis) arises from neural ectoderm associated with the development of the 3rd ventricle.

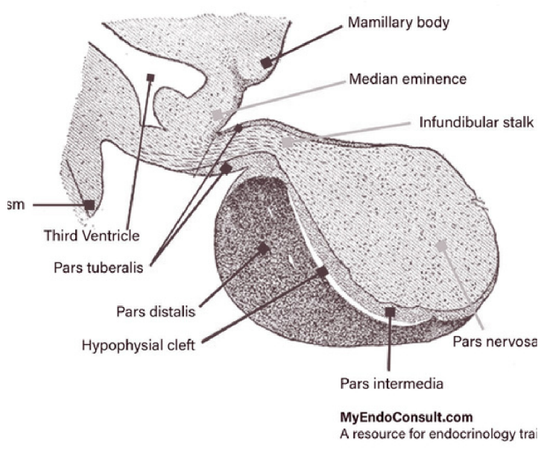
ANATOMIC RELATIONS



Superiorly : Dural Diaphragma sella and optic chiasm.
Laterally : Cavernous sinus through which the 3rd, 4th and 5th cranial nerves and internal carotid traverse.
Inferiorly : Bony roof of the sphenoid sinus.

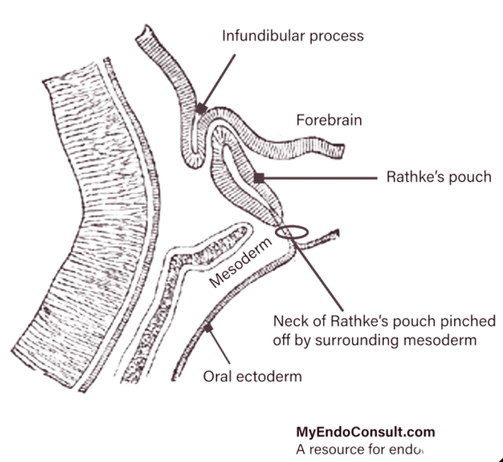


Arterial Supply : Inferior hypophyseal arteries (branches of the ICA and PCA)
Venous Supply : Drain into the inferior petrosal sinus



EMBRYOLOGY

The adenohypophysis is derived from a dorsal outpocketing of ectodermal tissue in the buccopharyngeal region. The neurohypophysis originates from the diencephalon.



PITUITARY GLAND

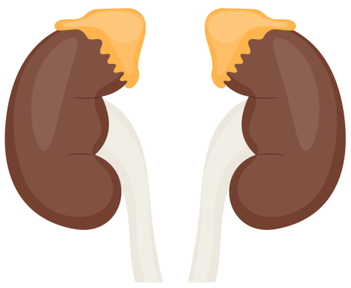
PHYSIOLOGY

The hormones produced by the **anterior pituitary gland** (adenohypophysis) are **growth hormone, prolactin, ACTH, TSH, FSH and LH.**

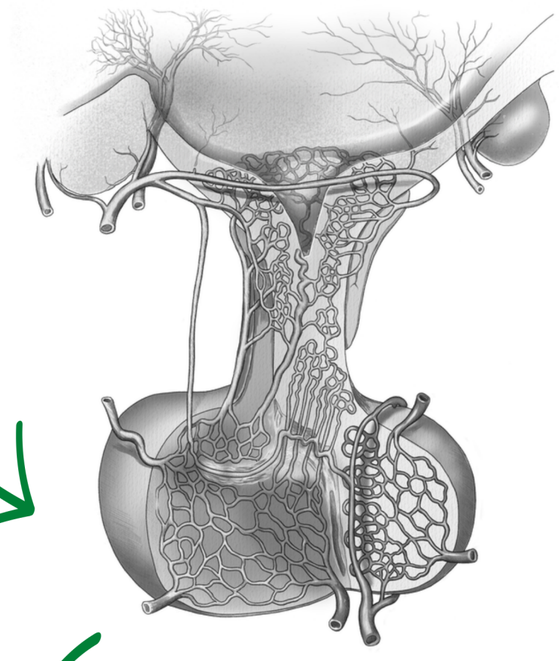
Hormone	Function	Stimulation	Inhibition
Growth Hormone (Somatotrophs)	Linear and organ growth	GHRH and Ghrelin	Somatostatin
Prolactin (Lactotrophs)	Lactational hormone	Oxytocin TRH	Dopamine
ACTH, POMC, MSH, Endorphins (Corticotrophs)	Metabolism and electrolyte homeostasis.	CRH (hypothalamus)	Cortisol
TSH (Thyrotrophs)	Metabolism	TRH (hypothalamus)	Thyroxine (T4) and T3 Somatostatin Dopamine
FSH and LH (Gonadotrophs)	Production of ova and spermatozoa. Steroidogenesis.	GnRH (hypothalamus)	Sex steroids Prolactin

PHYSIOLOGY AND ANATOMY

PITUITARY GLAND

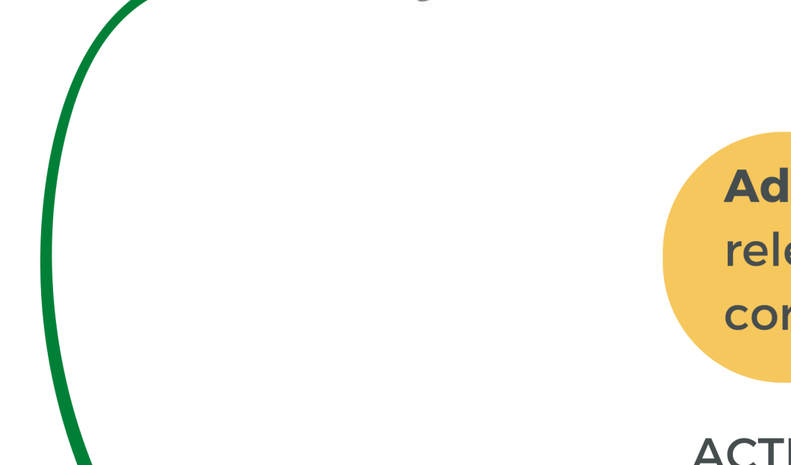


REGULATION OF CORTISOL



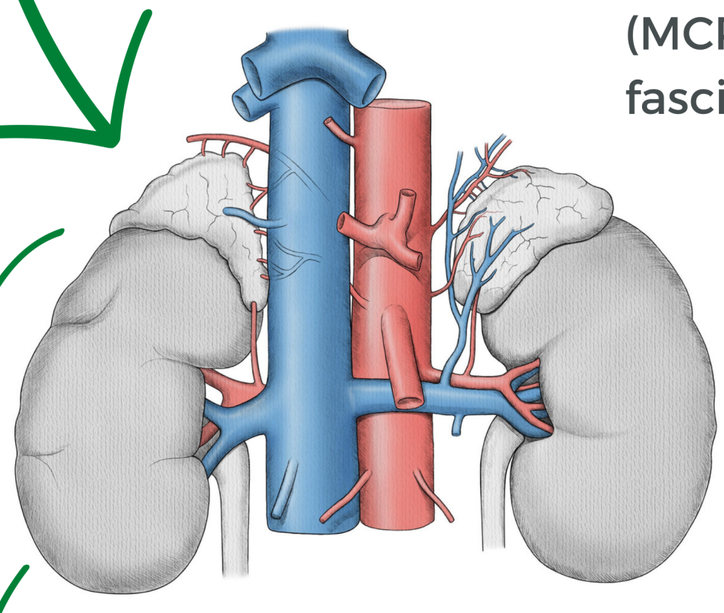
Corticotrophin-Releasing Hormone (CRH) produced by the paraventricular nucleus of the hypothalamus and ferried by the hypothalamic hypophyseal-portal venous system to corticotroph cells in the anterior pituitary.

CRH binds Corticotrophin releasing hormone receptor type 1 (CRH-R1) receptors on the surface of corticotrophs



Adrenocorticotrophic hormone (ACTH) is released by secretory vesicles in corticotrophs.

ACTH binds to the melanocortin-2 receptor (MCR-2) on cells present in the zona fasciculata of the adrenal cortex



Cortisol is released by cells in the zona fasciculata of the adrenal cortex.

Cortisol is involved in cellular metabolism and electrolyte homeostasis.

CRH

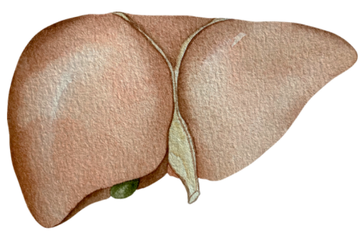
ACTH

Cortisol

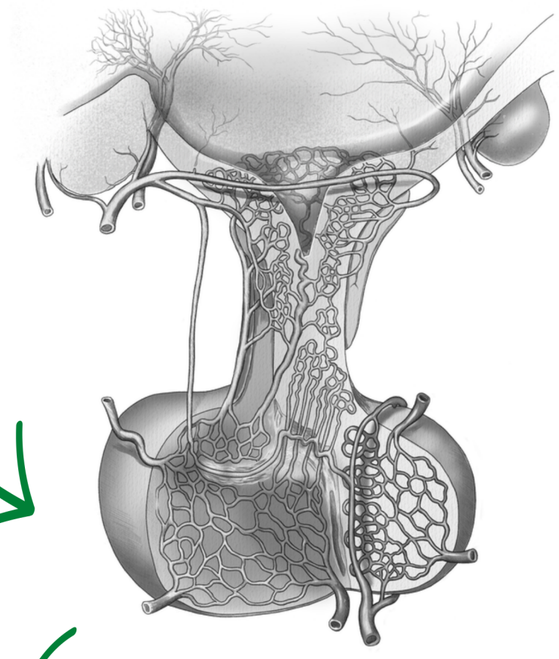
NEGATIVE FEEDBACK INHIBITION

PHYSIOLOGY AND ANATOMY

PITUITARY GLAND



REGULATION OF GROWTH HORMONE



GHRH

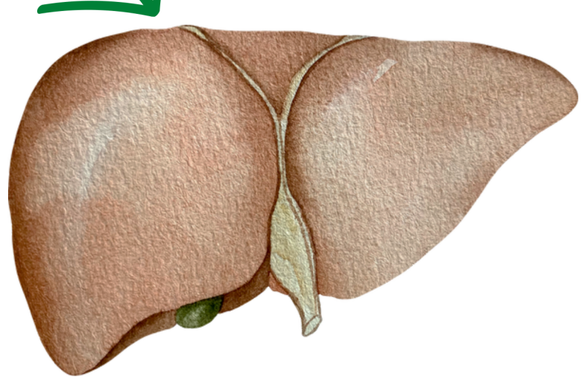
GH

1.
2.

Stimulates Growth Hormone

1.
2.

Inhibits Growth Hormone



NEGATIVE FEEDBACK INHIBITION

IGF-1

Growth Hormone Releasing Hormone (GHRH) is secreted in a pulsatile fashion and is carried from the hypothalamus to the anterior pituitary gland via the hypothalamo-hypophyseal vessels.

GHRH binds to GHRH-R on anterior pituitary somatotrophs

Growth Hormone is released by somatotrophs (anterior pituitary gland)

GH binds to the extracellular component of the **hepatic GH receptor (**GH-R) and induces a series of intracellular processes required for the transcription and translation of specific genes that encode **insulin-like growth factor 1 (IGF1)**, **IGF-binding protein 3 (IGFBP3)**, and an **acid-labile subunit (ALS)**

IGF-1 is released by hepatocytes

IGF-1 is involved in linear and organ growth

Somatostatin inhibits the release of growth hormone by somatotrophs.
Ghrelin (derived from gastric oxyntic cells) is a GH secretagogue (promotes GH release) that exhibits its effects by acting on hypothalamic GHRH cells in the median eminence.

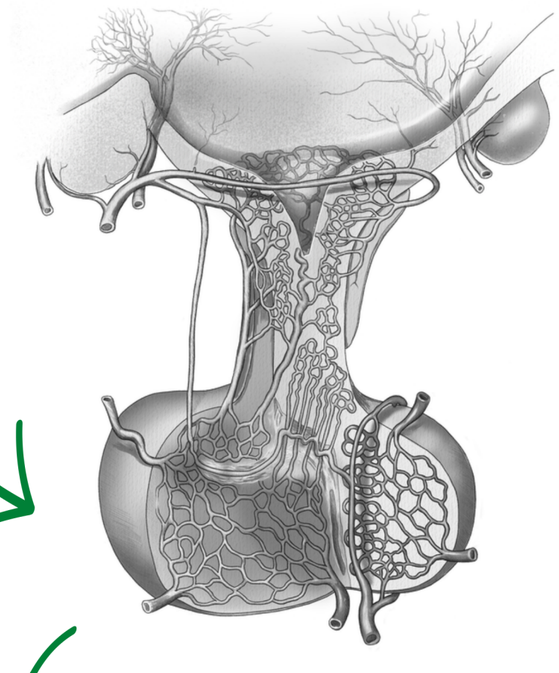
PHYSIOLOGY AND ANATOMY

PITUITARY GLAND

REGULATION OF THYROID HORMONE

NEGATIVE FEEDBACK INHIBITION

TRH



TSH

1.
2.

Inhibits TSH

Pituitary Gland

Free T4 and T3

Thyrotropin releasing hormone (TRH) is produced by cells in the paraventricular nucleus of the hypothalamus.

TRH acts on both **thyrotrophs** and **lactotrophs** of the anterior pituitary gland. Regulates a **circadian TSH rhythm** with maximal release at midnight and minimal concentrations in the late afternoon

Thyroid Stimulating Hormone is released by thyrotrophs (anterior pituitary gland)

TSH binds to TSH receptors of thyroid follicular cells to promote thyroid hormone synthesis

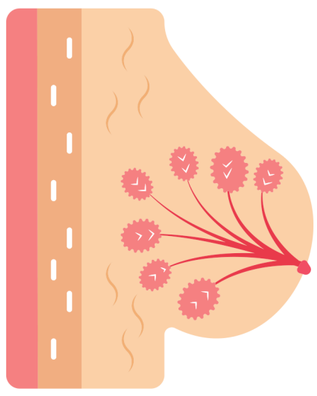
Thyroid hormone is produced by thyroid follicular cells

Thyroid hormone is involved in metabolism and heat production

Somatostatin and **Dopamine** released by specific hypothalamic neurones exert a tonic inhibitory action on TSH producing cells of the anterior pituitary gland (thyrotrophs)

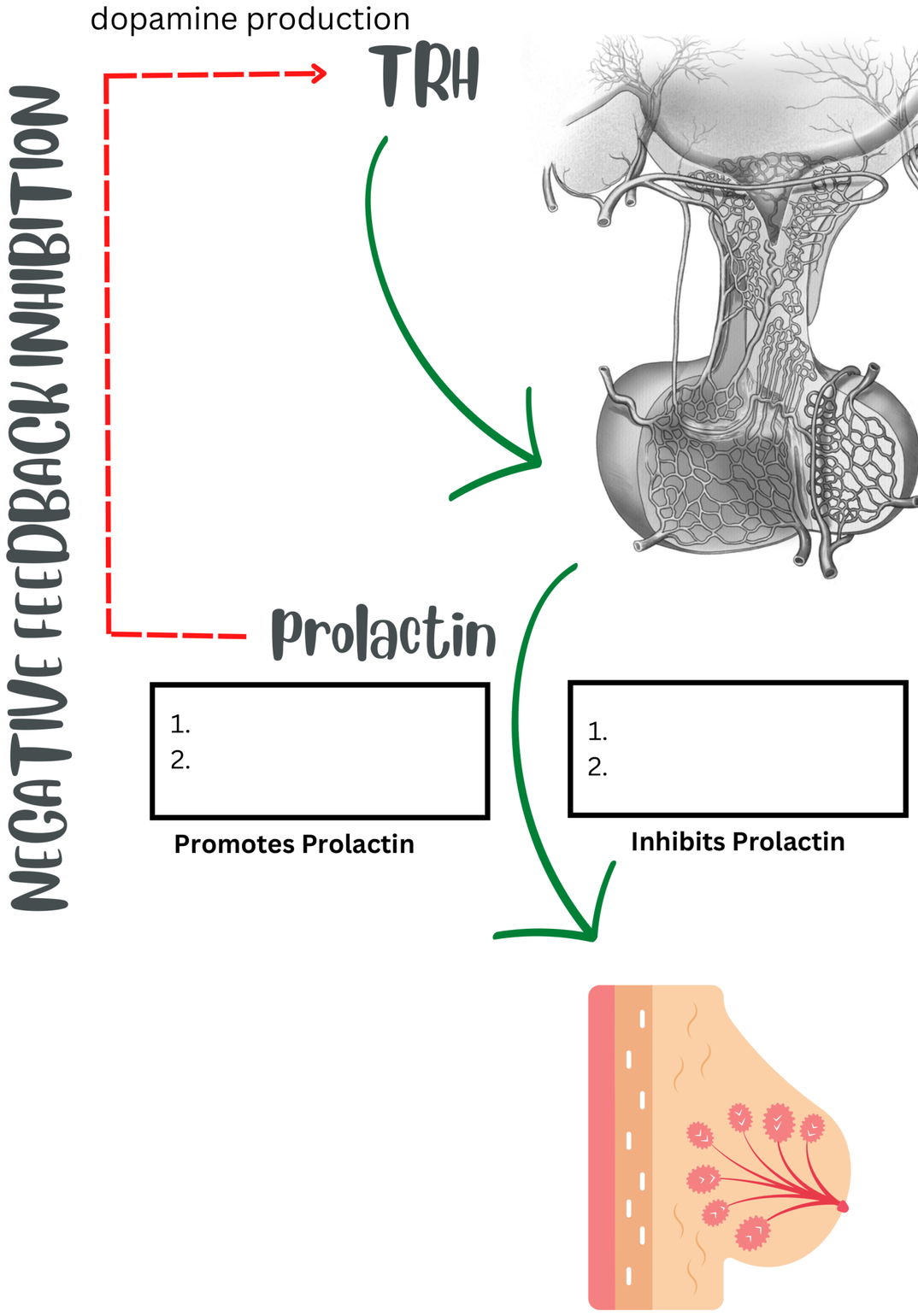
PHYSIOLOGY AND ANATOMY

PITUITARY GLAND



REGULATION OF PROLACTIN

Prolactin inhibits hypothalamic dopamine production



Thyrotropin releasing hormone (TRH) is produced by cells in the paraventricular nucleus of the hypothalamus.

TRH acts on **lactotrophs** of the anterior pituitary gland.

Prolactin is released by lactotrophs (anterior pituitary gland)

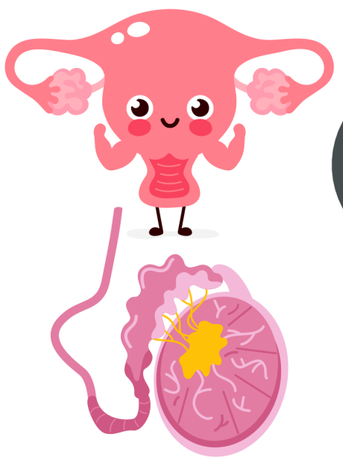
- Prolactin binds to mammary glands to promote milk "let-down"
- Prolactin also inhibits gonadal function.

How does prolactin inhibit gonadal function?

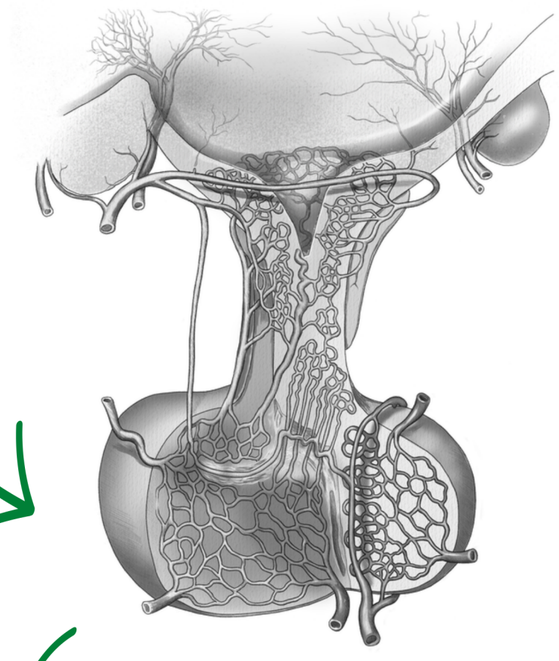
Important prolactin-releasing factors include **thyrotropin releasing hormone (TRH), oxytocin** (released by a baby suckling on the breast) and **stress** (physical or psychological)

PHYSIOLOGY AND ANATOMY

PITUITARY GLAND



REGULATION OF GONADOTROPINS



Gonadotropin releasing hormone (GnRH) is produced by cells in the hypothalamus.

GnRH is released in a pulsatile fashion that is critical in the release of gonadotropins - LH and FSH by the anterior pituitary.

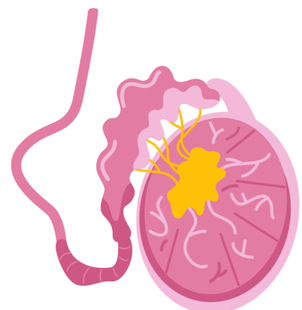
Luteinizing Hormone (LH) and Follicle Stimulating Hormone (FSH) are released by gonadotrophs (anterior pituitary gland)

LH and FSH are involved in gonadal steroidogenesis, spermatogenesis and ovarian follicle development.

GnRH

LH & FSH

NEGATIVE FEEDBACK INHIBITION



LH

A surge of LH at midcycle promotes ovulation and maintenance of corpus luteum

Stimulates the production of testosterone by the interstitial cells (Leydig) of the testes.

FSH

Promotes ovarian follicle development and subsequent production of estrogen

Promotes spermatogenesis by the Sertoli cells of the testes.

Testosterone and Estradiol

FSH stimulates the Sertoli cells of the testes to produce inhibin in men. In women, it stimulates the Granulosa cells to also produce inhibin. Inhibin provides the principal negative feedback inhbition of FSH synthesis in both men and women.

PHYSIOLOGY AND ANATOMY

PITUITARY GLAND

PHYSIOLOGY

The **posterior pituitary gland** does not synthesize hormones but contains **unmyelinated nerve fibers** originating from cell bodies in the **supraoptic nucleus (SON)** and **paraventricular nucleus (PVN)** of the hypothalamus.

Nerves fibers from the SON and PVN form the hypothalamo-hypophyseal tract of the pituitary gland.
These neurons produce **oxytocin** (SON) and **vasopressin** (PVN)

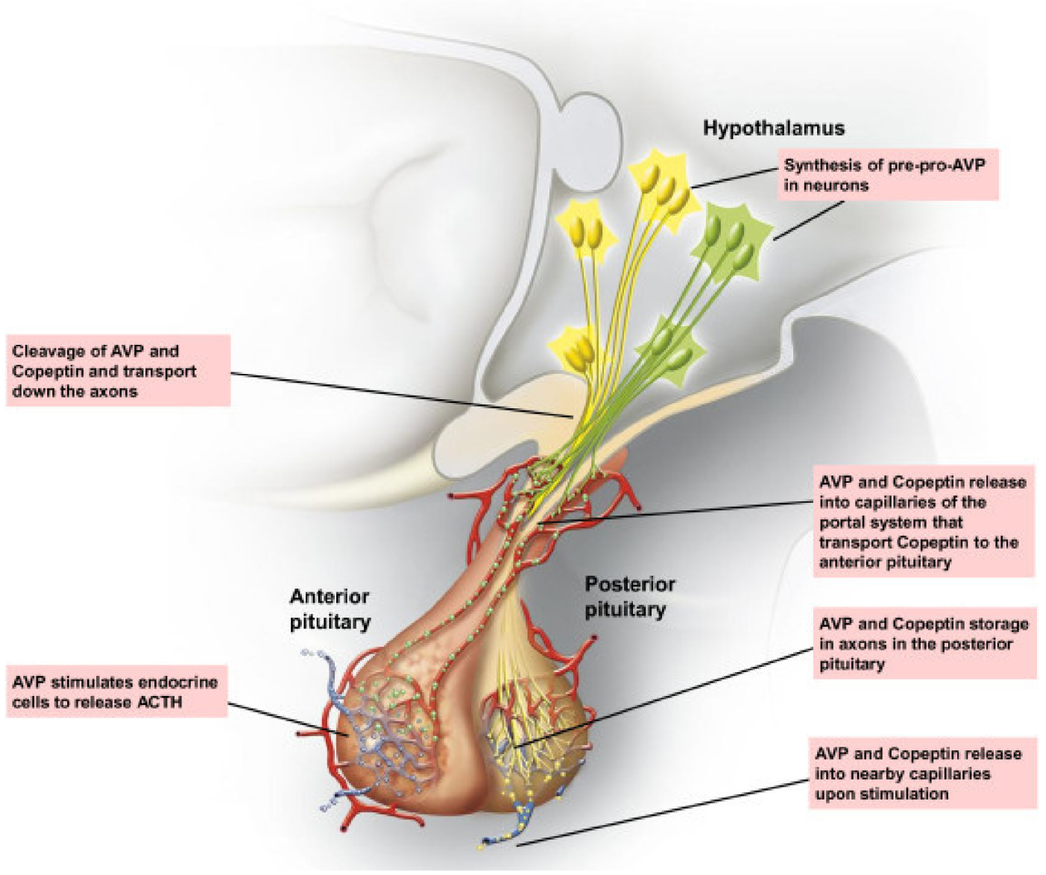
Stimulators of AVP release

- Increase in plasma osmolality
- Decrease in blood pressure (baroreceptor response(
- Emotions (pain or fear)
- Nicotine
- Angiotensin II

Inhibitors of AVP release

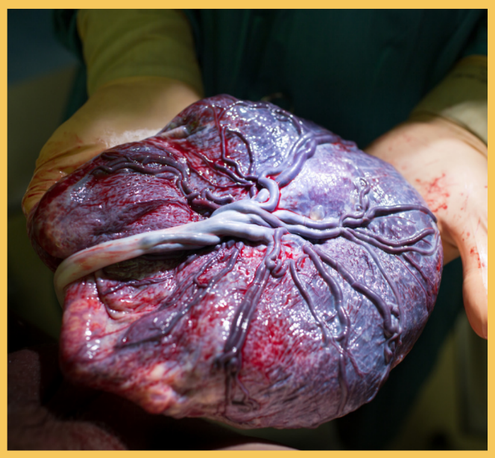
- Alcohol

POSTERIOR PITUITARY



What are the physiologic effects of oxytocin?

- It stimulates rhythmic contractions of uterine smooth muscle during childbirth
- It simulates contraction of myoepithelial cells on alveolar secretory cells.



CLINICAL APPLICATION

Synthetic oxytocin (Syntocinon) as a slow intravenous infusion is utilized in the induction of labor. It stimulates uterine contractions and reduces the dangers of uterine hemorrhage.

PHYSIOLOGY AND ANATOMY

THYROID GLAND

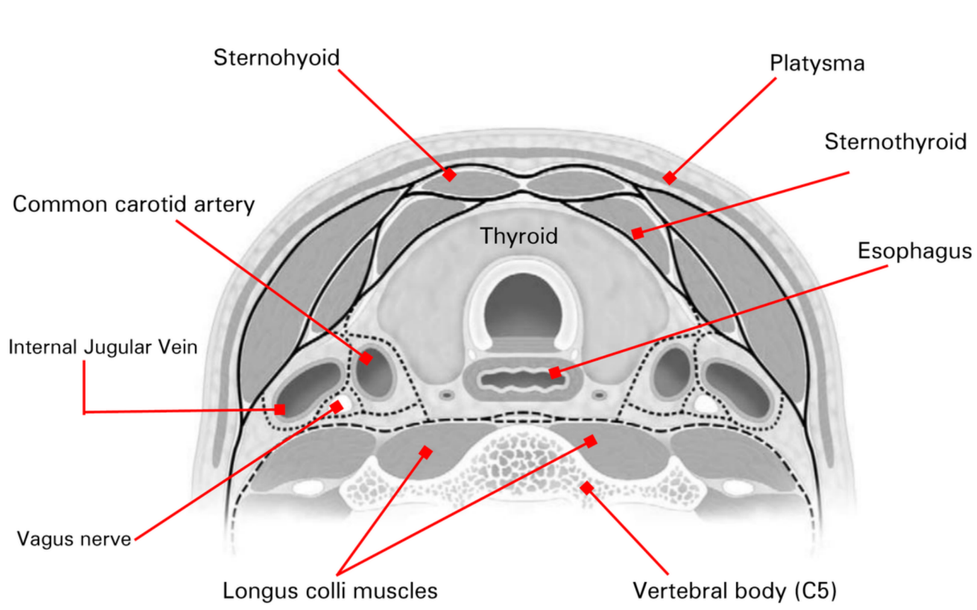
ANATOMY

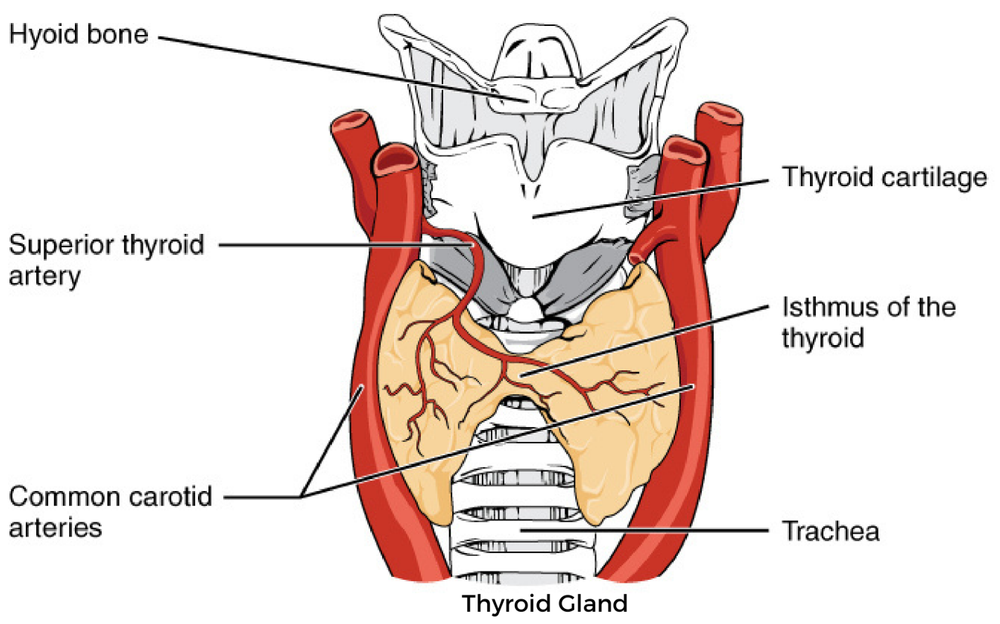
Thyroid Gland : Thyroid, which in Greek means **"shield-shaped,"** is a term credited to **Bartholomeus Eustachius** of Rome. He aptly described the thyroid gland as **"a single glandulamthyroideam"** with two lobes connected via ridge (or isthmus).

The normal thyroid gland hugs the trachea anterolaterally and is bound laterally by the carotid sheath (containing the common carotid artery, internal jugular vein and vagus nerve) and sternomastoid muscles.

The **strap muscles** (sternohyoid, sternothyroid, and omohyoid) cover most of the anterior aspect of the thyroid gland. The gland usually measures anywhere from 15 to 25g in weight. The lateral lobes are about 4cm in length and 2cm in width. The isthmus (which connects both lateral lobes) crosses the trachea in front of the first two tracheal rings.

ANATOMIC RELATIONS

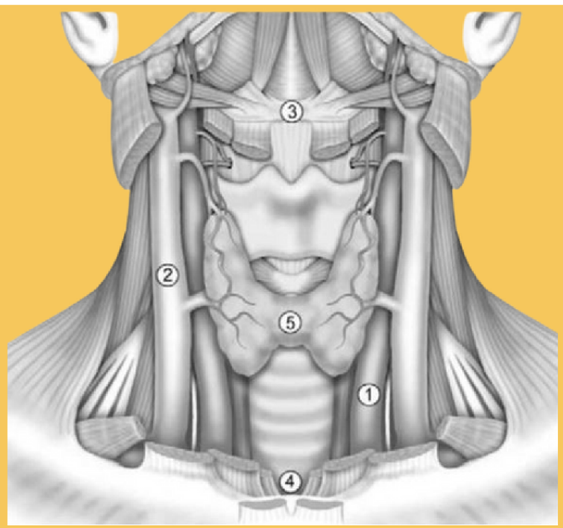




Thyroid Gland

The **superior thyroid artery** arises on each side as the first branch of the **external carotid artery**. It supplies the upper, anterior, and lateral portions of the lateral lobes.

The **inferior thyroid artery** is a branch of the **thyrocervical trunk** which also arises from the first portion of the subclavian artery. It supplies the inferior, posterior and medial parts of the organ on either side.



POP QUIZ

Anatomy of the central compartment of the neck, depicting important relations of the **thyroid gland**(5). The **carotid artery**(2) and **internal jugular vein** (1) lying laterally, **hyoid bone** (3) superiorly, and **suprasternal notch** (4) inferiorly.

PHYSIOLOGY AND ANATOMY

THYROID GLAND

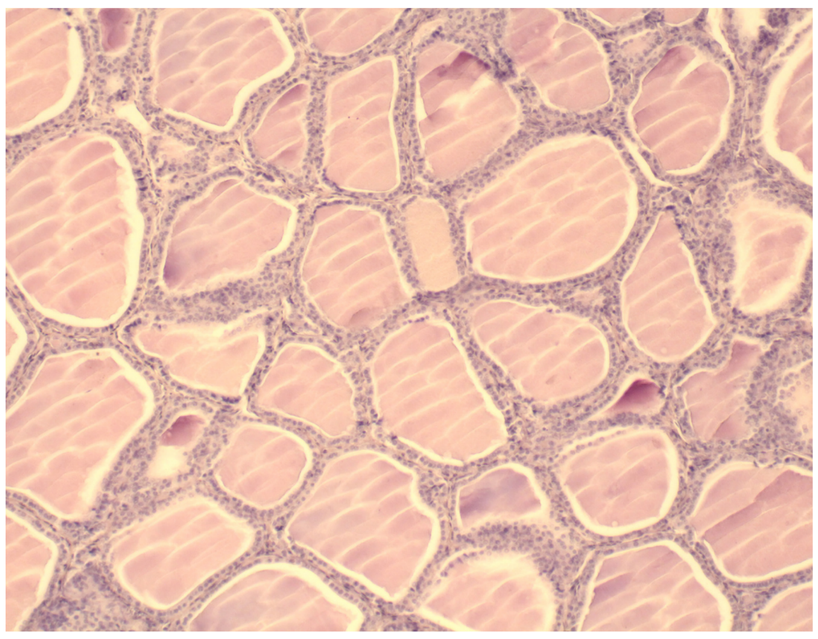
EMBYROLOGY

Thyroid Gland : The thyroid gland appears very early in embryonic life. In the human embryo (approximately 3.5 to 4 mm in length), an entodermal outpocketing forms in the floor of the oral cavity, just beneath the **buccopharyngeal membrane** and between the first pair of pharyngeal pouches.

At the bottom of this small pit, an epithelial bud protrudes into the underlying mesenchyma. The primordium becomes displaced caudally, but remains attached to the floor of the pharynx by the **thyroglossal duct**.

During its descent, the originally compact bud becomes bilobed and differentiates into a mass of irregularly arranged epithelial cords, which later form the isthmus and the lateral lobes of the gland.

HISTOLOGY



At an embryonic age of about eight weeks, the **epithelial cords** of the **thyroid primordium** disintegrate into small vesicles, the primary or two-cell follicles, which contain small amounts of colloidal material.

From these, rounded or rod-shaped secondary (definitive) follicles sprout out and enlarge. The follicles of the mature gland measure up to 1 mm in diameter.

They contain a **gelatinous colloid** and are lined by a simple epithelium, the depth of which varies widely according to the functional state of the gland.

Recall Box

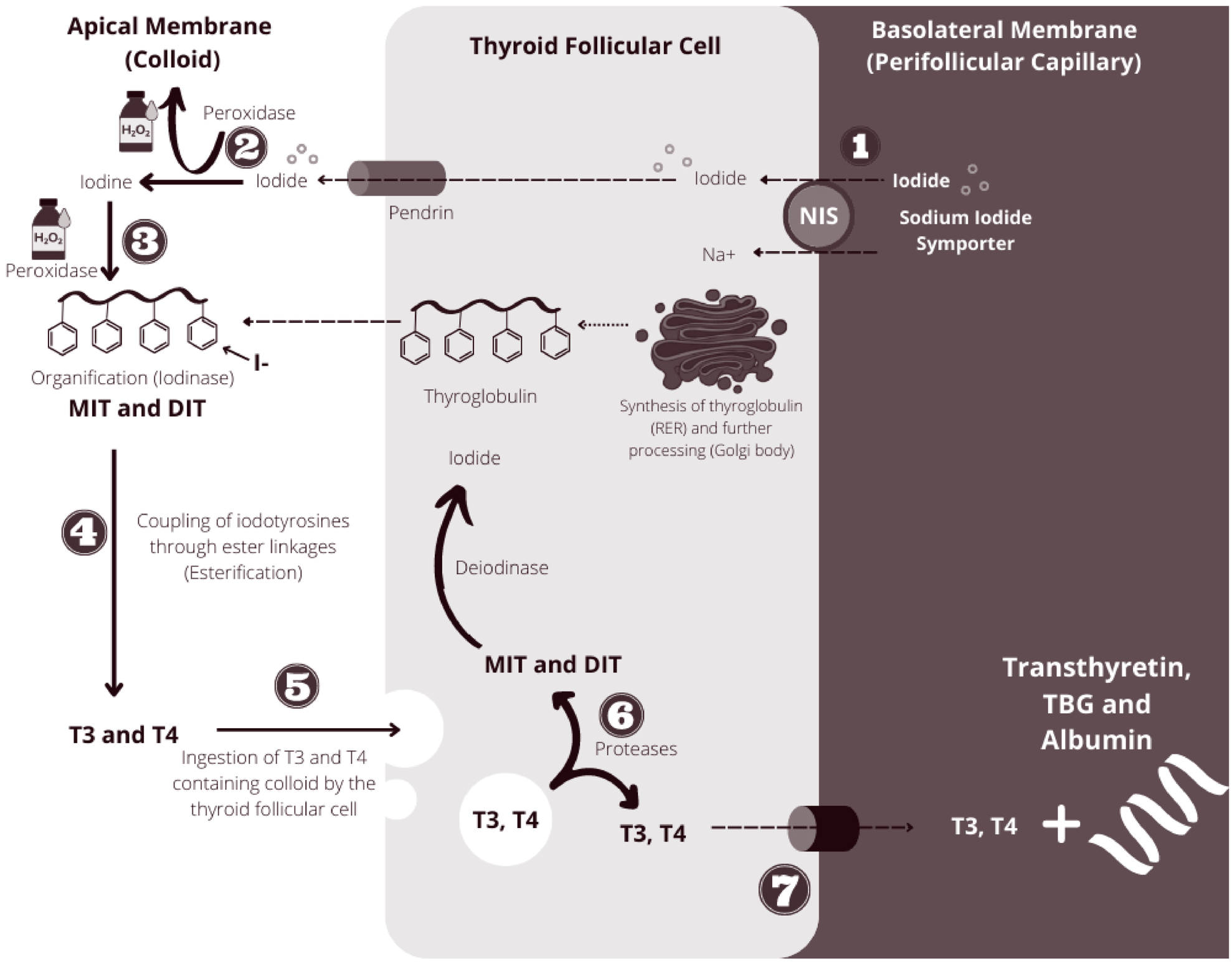
Outline the anatomic relations of the thyroid gland, and details about its vascular supply

PHYSIOLOGY AND ANATOMY

THYROID GLAND

HORMONE SYNTHESIS

The efficient synthesis of thyroid hormone requires about 1 g of iodine per week. Indeed, iodine absorbed from the intestine travels in the blood, bound mainly to serum albumin.



MNEMONIC DEVICE

This is a simple mnemonic (memory device) for recalling the 7 critical steps of thyroid hormone synthesis is **SOO-3Ps** (Sow Three Peas).
S : Sodium Iodide Symporter **O** : Oxidation **O** : Organification
3 : Esterification **P** : Pinocytosis **P** : Proteases **P** : Peripheral deiodination

Scan this QR Code (by Pointing your active camera) to watch our short youtube video about thyroid hormone synthesis

PHYSIOLOGY AND ANATOMY

THYROID GLAND

THYROID FUNCTION TESTS

The appropriate use of thyroid function tests in the management of thyroid disorders.

TSH

A sensitive test for diagnosing most forms of disordered thyroid function. Difficult to interpret in patients with nonthyroidal illness (sick euthyroid syndrome), pregnancy, exposure to high dose steroids or dopamine.

- Primary hypothyroidism
- Pituitary TSH secreting tumor
- Thyroid Hormone Resistance Syndromes

- Primary hyperthyroidism
- Central Hypothyroidism

Total Thyroxine T4

A measure of both bound (part of thyroid hormone attached to binding proteins) and free thyroid hormone (T3 and T4). Over 99% of thyroid hormone is bound to thyroxine bindng globulin. Clinical states that alter binding proteins can affect total thyroxine levels.

- Primary hyperthyroidism
- Thyroid Hormone resistance syndrome
- Pituitary TSH secreting Tumor

- Primary hypothyroidism
- Central Hypothyroidism

T3 Resin uptake (T3RU)

An indirect assessment of the binding capacity of the patient's serum proteins. It is typically used in conjunction with the total T4 measure to evaluate the free thyroxine index.

- Primary hyperthyroidism
- low TBG states

- Primary hypothyroidism
- High TBG states

Scan this QR Code (by Pointing your active camera) to watch our short youtube video about the reverse T3 Test

ADRENAL GLAND

ANATOMY

They are **pyramidal in shape** located above the upper poles of kidneys. In the adult, each of the **adrenal glands** weighs about **3-5 g**.

They are situated retroperitoneally and on the superomedial aspect of the anterior aspect of the kidneys.

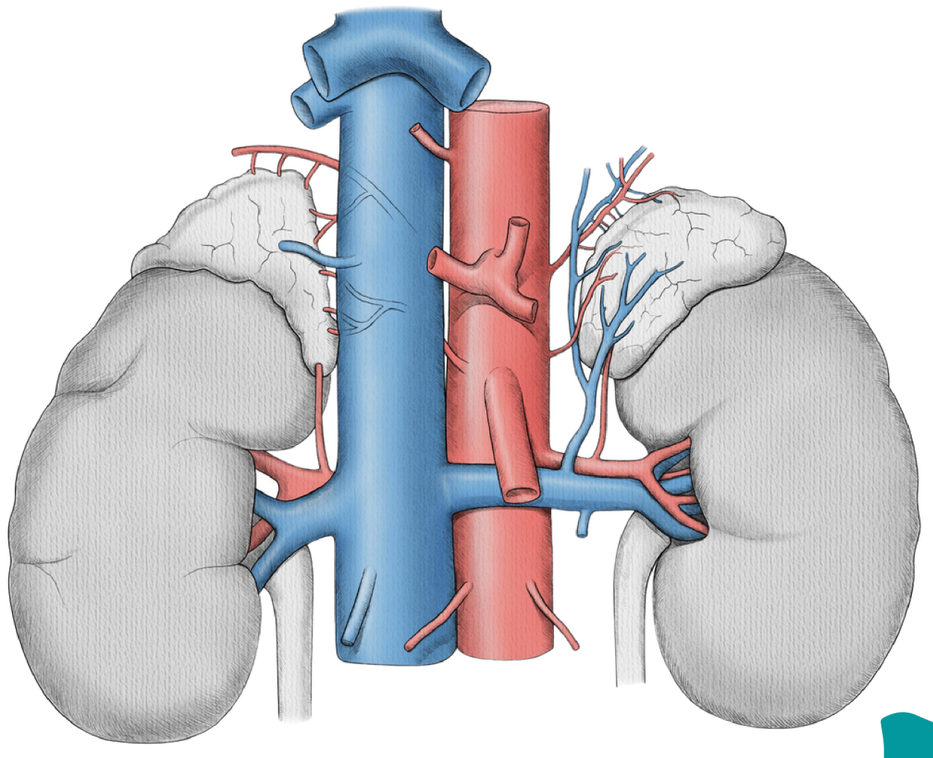
Both glands are surrounded by adipose tissue and by the renal fasciae, to which they adhere firmly.

The **cortex** makes up 90% of adrenal weight, medulla makes up 10%.

Blood supply
Arteries: superior arteries (from inferior phrenic arteries), middle (from aorta), and inferior adrenal arteries (from renal arteries)

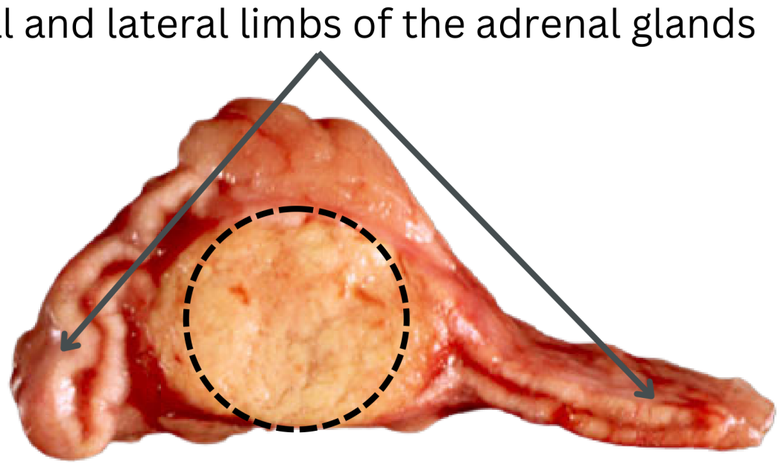
Veins: right adrenal vein → inferior vena cava; left adrenal vein → left renal vein.

VASCULAR SUPPLY

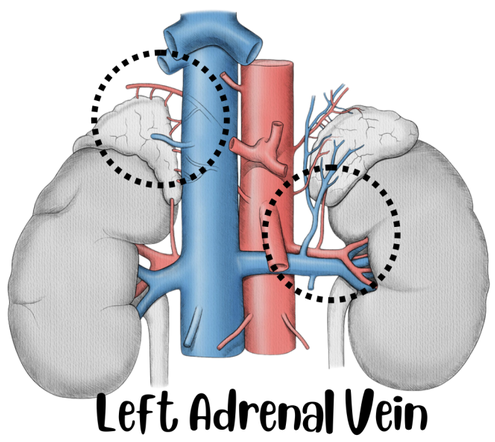


Label the Vasuclar Supply of the Adrenal Gland

Medial and lateral limbs of the adrenal glands



An Aldosterone secreting tumor in the body of the adrenal gland



ADRENAL VEIN SAMPLING

To reduce the lag time between samples, the **right adrenal vein** (the most difficult to cannulate since it abuts the IVC at an acute angle) is sampled first, followed by the left adrenal vein, and finally from the external iliac vein. Aldosterone and cortisol levels are drawn from each site.

Scan this QR Code (by Pointing your active camera) to learn more about adrenal vein sampling in hyperaldosteronism.

PHYSIOLOGY AND ANATOMY

ADRENAL GLAND

EMBYROLOGY

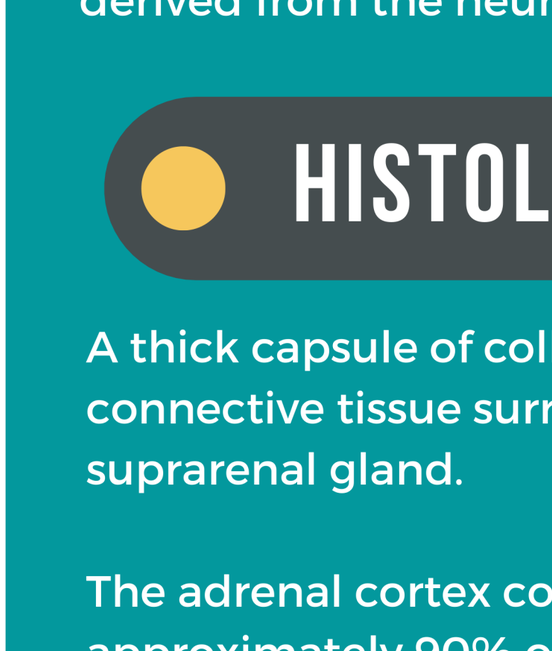
The two **main components** of the adrenal (suprarenal) gland, the **cortex,** and the **medulla**, differ not only in morphology and function but also in origin.

The cortex develops from cells of the celomic epithelium and is, therefore, of mesodermal origin, while the chromaffin and sympathetic ganglion cells of the medulla are derived from the neural ectoderm.

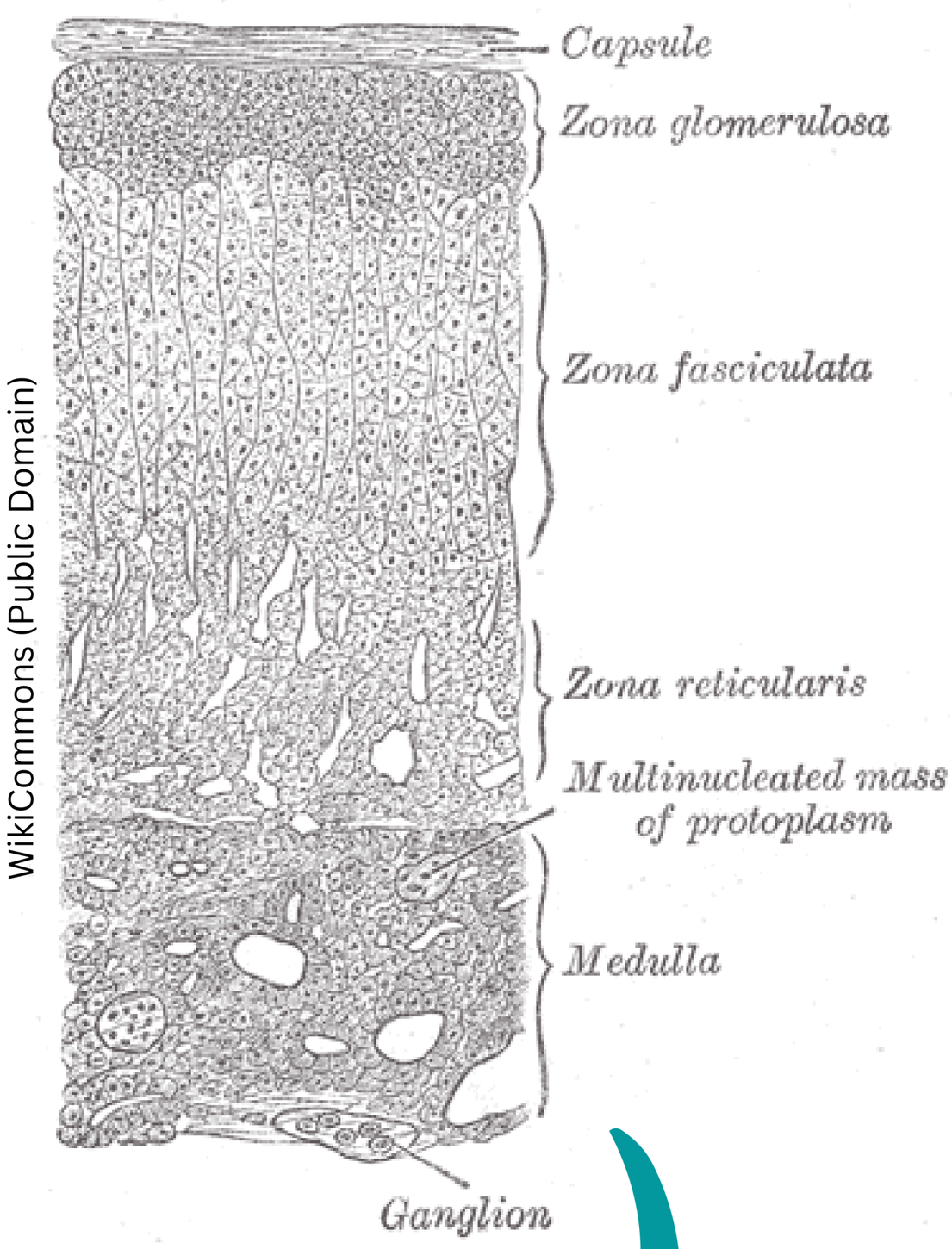
HISTOLOGY

A thick capsule of collagenous connective tissue surrounds the suprarenal gland.

The adrenal cortex constitutes approximately 90% of the total organ volume and is composed of three easily distinguishable **concentric zones**.



HISTOLOGY



WikiCommons (Public Domain)

MEMORY DEVICE

The layers of the cortex can be remembered with the mnemonic GFR: **G** - glomerulosa, **F** - fasciculata, **R** - reticularis.

Products of the adrenal cortex, from outer to inner layer
Salt, sugar, sex; **“the deeper you go, the sweeter it gets.”**
Salt = Aldosterone, **Sugar** = Glucocorticoids (cortisol), **Sex** = sex steroids (Androgens)

ADRENAL GLAND

PHYSIOLOGY

Glucocorticoids (Z. Fasciculata)
Cortisol circulates mostly bound to cortisol-binding globulin (~ 75%) and albumin (~ 15 %); only~ 10% is free in plasma.

Mineralocorticoids (Z. Glomerulosa)
Controlled by renin-angiotensin-aldosterone system Renin release is stimulated by low sodium chloride load, low renal perfusion, sympathetic nervous system activation, angiotensin II, and atrial natriuretic peptide.

Hyperkalemia and high concentrations of ACTH also directly stimulate aldosterone release.

Aldosterone circulates primarily bound to albumin and, to a lesser extent, **cortisol-binding globulin**; – 50% is free

Adrenal androgens (Z. Reticularis)
Function mostly as precursors for peripheral conversion to the active androgens (testosterone and dihydrotestosterone) . Both bind the androgen receptor

In adult males with normal gonadal function, the effect of adrenal androgen is negligible compared to testicular sources of androgens.

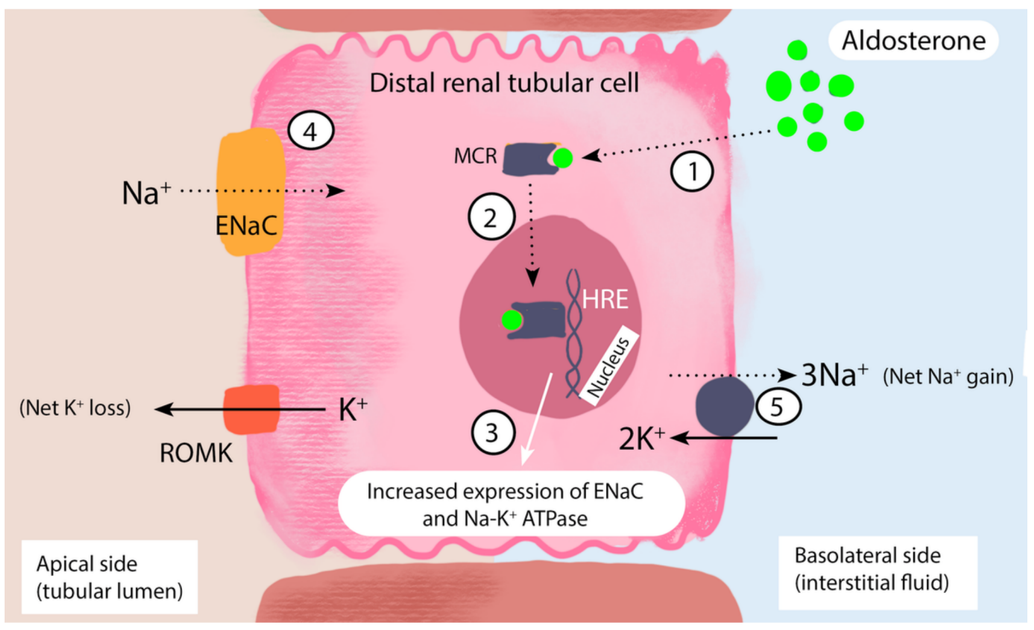
However, in females, adrenal androgens contribute ~ 50% of total androgens

WATER CONSERVATION

Aldosterone is a hormone that plays an essential role in the regulation of sodium and water balance in the body.

The adrenal glands secrete it in response to blood pressure, electrolyte levels, and fluid status changes.

Under normal circumstances, aldosterone helps conserve sodium and water by promoting reabsorption in the kidney.



Aldosterone, a lipid-soluble steroid hormone, diffuses through the cell membrane of the ductal epithelial cell and binds to the cytosolic mineralocorticoid receptor (MCR) (step 1).

The **aldosterone-MCR complex** is then translocated into the nucleus where it attaches to the **hormone response element (HRE)** (step 2) required for transcription and translation of the **epithelial sodium chloride (ENaC) channel** and **sodium-potassium adenosine triphosphatase (Na-K ATPase) pump** (step 3).

ENaC and Na-K+ ATPase both play an active role in sodium reabsorption from the filtered renal sodium load present in the collecting duct and distal convoluted tubule.
The net effect is the transfer of sodium from the apical to the basolateral side of the renal tubular cell (steps 4 and 5).

Aldosterone also promotes the expression of **renal outer medullary potassium (ROMK)** channels. The insertion of ROMK channels on the apical membrane facilitates potassium and hydrogen ion loss.

PHYSIOLOGY AND ANATOMY

ADRENAL GLAND

PHYSIOLOGY

The **juxtaglomerular apparatus** is composed of the macula densa cells present in the **distal convoluted tubule (DCT)**, **juxtaglomerular cells** (present in the entire glomerular vasculature but more prominent in the afferent arteriole) and the **glomerular afferent arteriole(AT)**.

Renin, a rate limiting enzyme released from **juxtaglomerular cells**, initiates a cascade of reactions, which leads to the eventual formation of Angiotensin II.

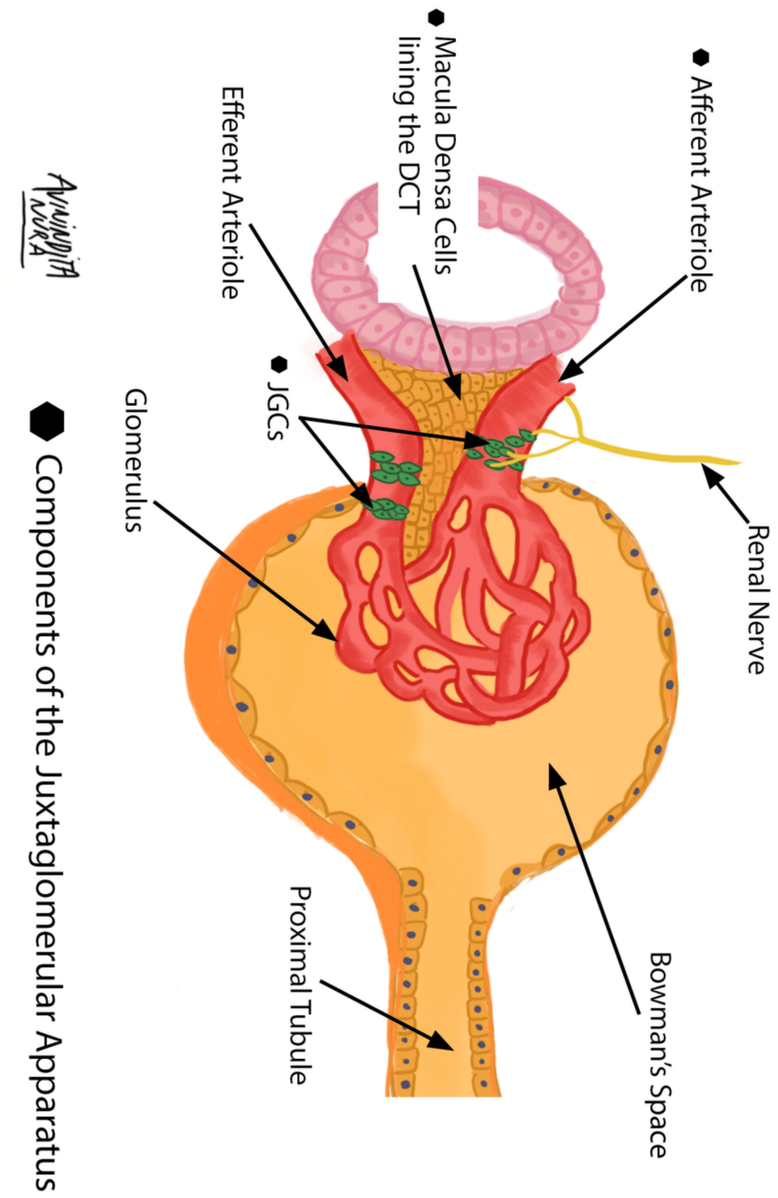
Triggers of **renin secretion** include a low sodium load presented to macula densa cells (located in the DCT), adrenergic stimulation from renal nerves innervating JGCs in the afferent arteriole and a reduced tensile stretch of the afferent arteriole of the glomerulus.

Renin, the **rate-limiting enzyme** in the renin-angiotensin-aldosterone-system (RAAS) is critical in maintaining intravascular volume and blood pressure.

Renin release is also controlled by long and short negative feedback loops mediated by the effect of ATII on the collecting tubule and JGCs, respectively

MECHANISM OF RENIN RELEASE

- Change in **sodium chloride load** presented to the macula densa cells (a group of 15-20 cells in the distal convoluted tubule) influences the eventual release of renin from the **juxtaglomerular cells (JGCs)**, through some signaling mediators. A high sodium load inhibits renin release from the juxtaglomerular cells, whereas a low sodium load does the opposite.
- A change in **blood pressure** at the **afferent arteriole** controls renin release from the JGCs. Low tension in the afferent arteriolar wall increases renin release, which ultimately enhances sodium conservation and maintenance of intravascular volume.
- Activation of **beta-adrenergic sympathetic nerves** terminating in the juxtaglomerular cells promotes renin release.

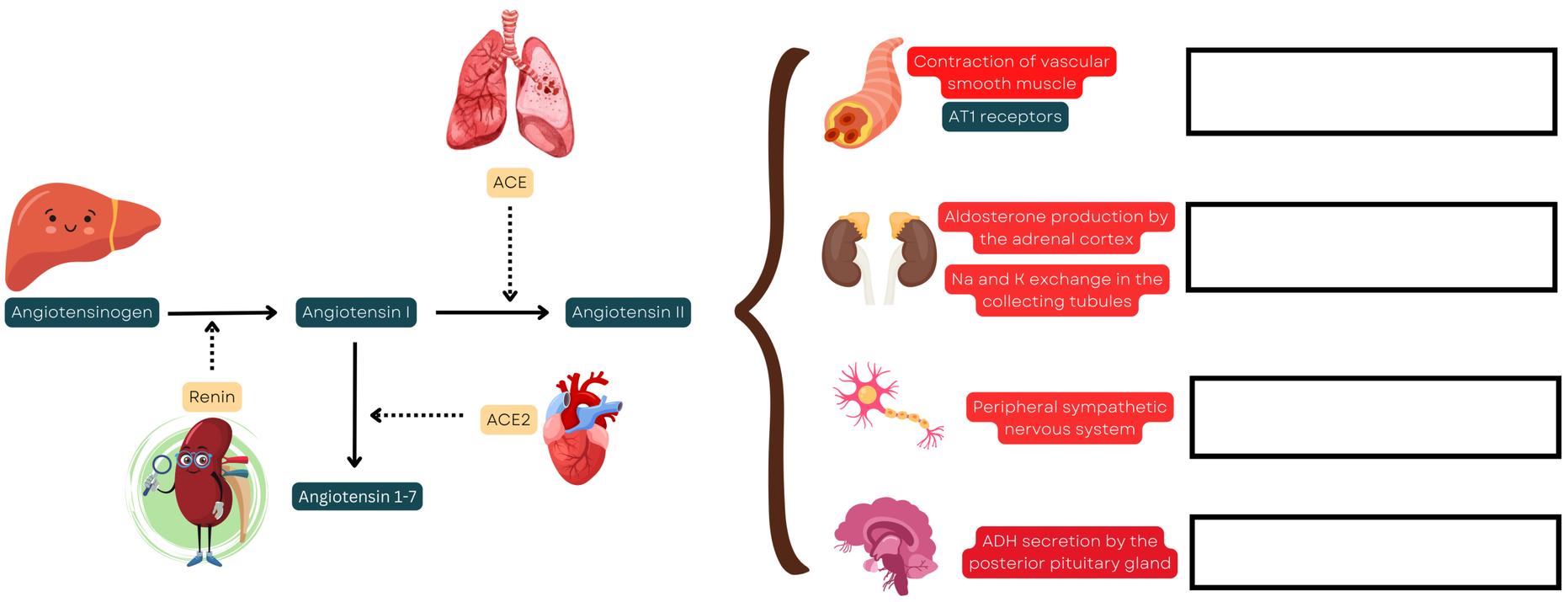


PHYSIOLOGY AND ANATOMY

ADRENAL GLAND

PHYSIOLOGY

Regulation of the Renin Angiotensin Aldosterone Axis



Renin catalyzes the conversion of **angiotensinogen**, the renin substrate produced and secreted by the liver, to a decapeptide called **angiotensin I**. Angiotensin I has no biological action by itself but is the substrate of another endothelial cell-associated peptidase abundant in the human body but primarily localized in the pulmonary vasculature, called **angiotensin-converting enzyme (ACE)**.

ACE cleaves the terminal dipeptide of angiotensin I to generate an octapeptide known as **Angiotensin II**. Furthermore, there is an **isoform** of an **angiotensin-converting enzyme** called ACE2, which catalyzes the conversion of angiotensin I to an additional peptide known as **Angiotensin 1–7** (which binds a vascular endothelial receptor known as MAS).

Angiotensin II exerts its biologic actions by binding to a family of surface trans-membrane receptors widely distributed in the body, known as **type 1** and **type 2 angiotensin II receptors** (AT1 and AT2 receptors).

Activation of **AT1 receptors** by angiotensin II results in the contraction of vascular smooth muscle cells, which increases peripheral vascular resistance and elevates blood pressure. These effects are partially counterbalanced by **AT2 receptor activation** by **angiotensin I** and **MAS receptor activation** by **angiotensin 1–7**, which result in vasodilation.

In addition to the regulation of vascular tone, Angiotensin II stimulates sodium reabsorption directly in the distal convoluted tubules of the nephron. Also, **Angiotensin II** indirectly augments the production from the adrenal cortex of **Aldosterone**, the most potent mineralocorticoid hormone that regulates the **sodium–potassium exchange** in the collecting tubules of the kidney.

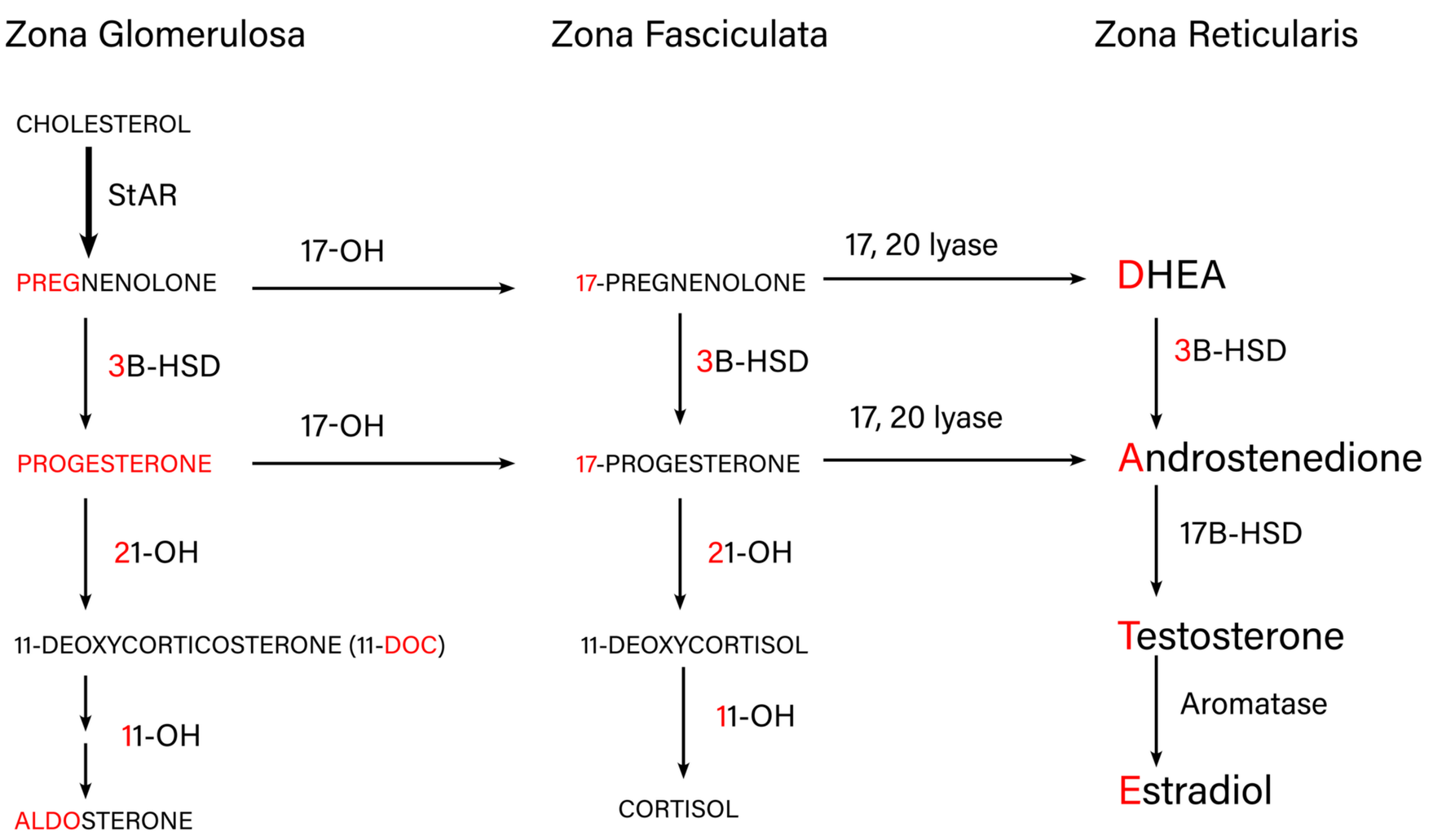
Angiotensin II enhances the activity of the peripheral **sympathetic nervous system (SNS)** and also promotes ADH secretion by the posterior pituitary gland. ADH then stimulates water reabsorption in the collecting duct.

PHYSIOLOGY AND ANATOMY

ADRENAL GLAND

PHYSIOLOGY

Adrenal enzyme deficiencies, specifically congenital adrenal hyperplasia (CAH), and their corresponding effects are frequently tested in board exams (USMLE and ABIM). This is a simple mnemonic for remembering all the critical steps in the adrenal steroid hormone synthesis pathway. I have used this approach to simplify this daunting pathway for medical students



Zona reticularis, is responsible for the formation of 17 ketosteroids. These are the sex steroids. A simple memory aid is that “SEX may occur after a DATE”.

MyEndoConsult.com
A resource for endocrinology trainees

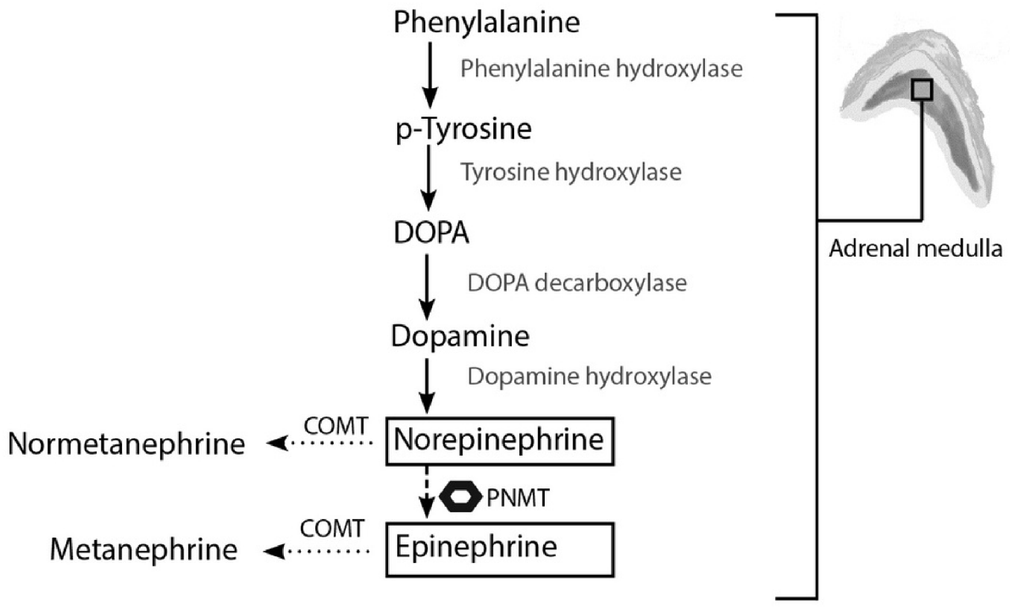
Scan this QR Code (by Pointing your active camera) to review the detailed steps in using this mnemonic for adrenal steroidogenesis and Congenital Adrenal HyperPlasia

ADRENAL GLAND

PHYSIOLOGY

Catecholamine (Epinephrine and norepinephrine) (Secreted by the medulla)

- **Action:** sympathetic stimulation through adrenergic receptors (increased heart rate, blood pressure, metabolic rate)
- **Stimulus:** hypotension, physical/psychological stress, hypoglycemia
- **Excess:** Pheochromocytoma
- **Deficiency:** Questionable endocrine significance



Which tissues contain PNMT?

1.
2.

CATECHOLAMINE SYNTHESIS

The **rate-limiting step** in the synthesis of catecholamine occurs at the initial conversion of **L-tyrosine** into **L-3,4-dihydroxyphenylalanine (DOPA)** via the **tyrosine hydroxylase enzyme**. DOPA is subsequently converted to dopamine. Dopamine is hydroxylated into L-norepinephrine, which is then converted into epinephrine.

The conversion of norepinephrine to epinephrine requires the cortisol-induced enzyme, **phenylethanolamine-N-methyl transferase (PNMT)**(dashed arrow). This is the reason why epinephrine and its metabolite (metanephrine) are only produced by PNMT-containing organs such as chromaffin cells in the adrenal gland and the organ of Zuckerkandl (located at the aortic bifurcation).

Norepinephrine and epinephrine are converted into their metabolites, i.e., normetanephrine and metanephrine, respectively, by **catechol-O-methyltransferase (COMT)**(dotted arrow)

What are metanephrines.
Scan QR Code

FRACTIONATED METANEPHRINES

This refers to the **metabolites** of **epinephrine** and **norepinephrine (catecholamines),** which are metanephrine and normetanephrine. **Metanephrines** represent an umbrella term for the metabolites metanephrine and normetanephrine

PHYSIOLOGY AND ANATOMY

ADRENAL GLAND

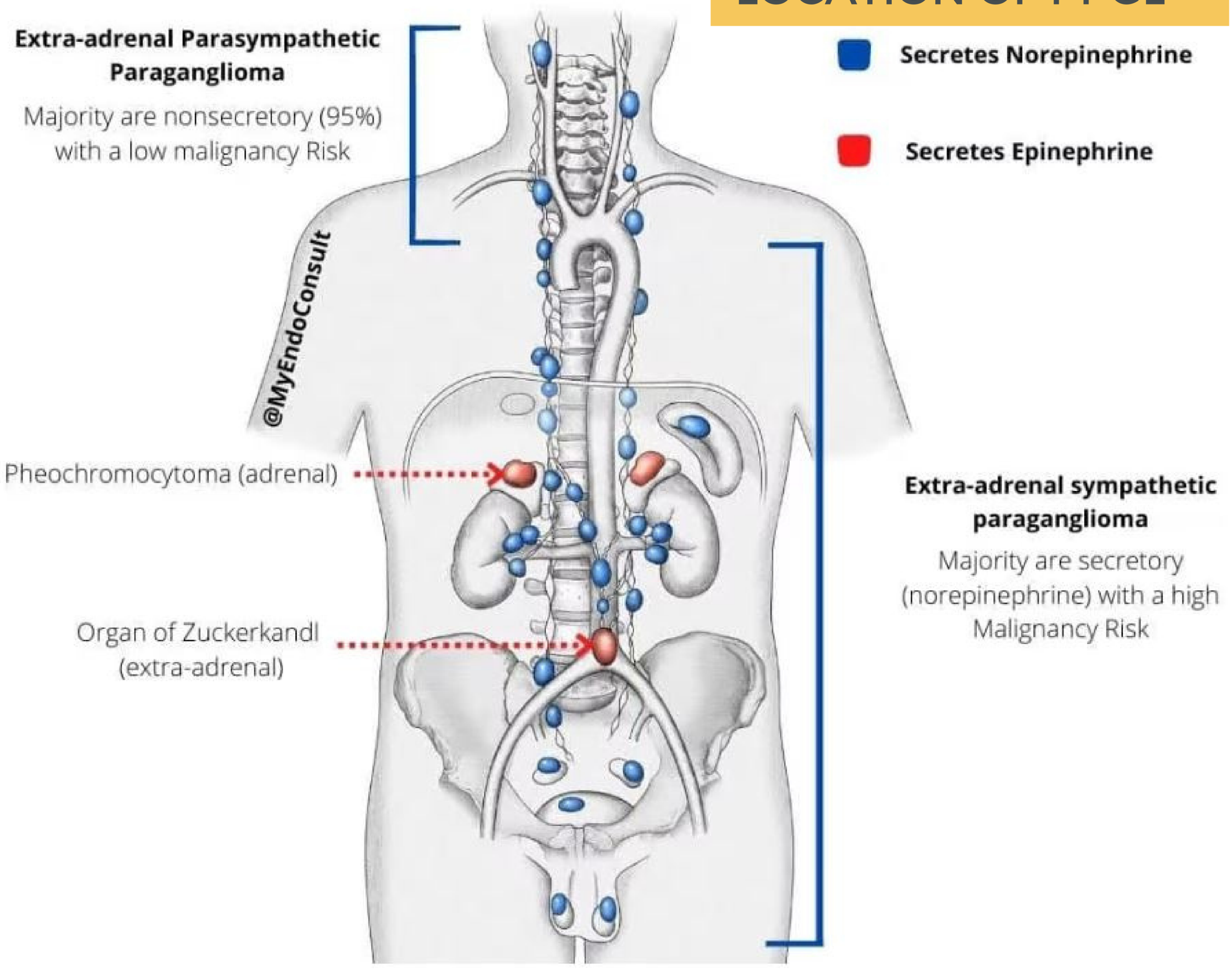
PATHOLOGY

Hereditary paraganglioma-pheochromocytoma (PPGLs) syndromes refers to paragangliomas (tumors derived from neuroendocrine tissues found along the paravertebral axis extending from the skull base to the pelvis) and by pheochromocytomas (paragangliomas of the adrenal medulla).

Although **paragangliomas** can produce hormones, they do not produce metanephrine (a metabolite of epinephrine) due to the lack of paracrine stimulation by **PNMT** (lack of cortisol).

Conversely, **pheochromocytomas** can produce either metanephrine or normetanephrine (a metabolite of norepinephrine).

LOCATION OF PPGL



PHYSIOLOGY AND ANATOMY

PARATHYROID GLAND

ANATOMY

The **parathyroid glands** are ovoid glands that measure **4-6mm x 2-4mm x 0.5-2mm in size**.

They weigh approximately **30mg** in size, with the inferior parathyroids being significantly larger than the superior parathyroids.

The four **parathyroid glands** lie within the cervical fascial sheath of the thyroid gland and are attached to the back of the **lateral lobes** of the thyroid glands.

The **superior parathyroid glands** are located near the superior pole of the thyroid gland and are lateral to the position of the recurrent laryngeal nerve (as a surgical anatomic reference).

The **inferior parathyroid glands** are located medial to the position of the recurrent laryngeal nerve (as a surgical anatomic reference).

DISCOVERY OF PARATHYROIDS

The **parathyroids** were first discovered in an **Indian rhinoceros**. The first description in humans was reported in a monograph by **Ivar Sandstrom** (a Swedish medical student) in 1880.

HORMONE HISTORY BUFF

The discovery of the parathyroid glands has been credited to Ivar Sandström, who published the discovery in 1880 in a paper titled **“on a New Gland in Man and Several animals.”** Due to the late anatomical description of these glands, they have often been referred to as “the last anatomic discovery.”

PHYSIOLOGY AND ANATOMY

PARATHYROID GLAND

EMBRYOLOGY

The primordial tissue that forms the **parathyroid glands** is formed from the epithelium lining the dorsal portions of the **third** and **fourth pharyngeal pouches**.

- Inferior parathyroid glands (third branchial pouches)
- Superior parathyroid glands (fourth branchial pouches)

On the other hand, the epithelium lining the ventral portion of the **third pharyngeal pouch** differentiates into the primordia of the **thymus**.

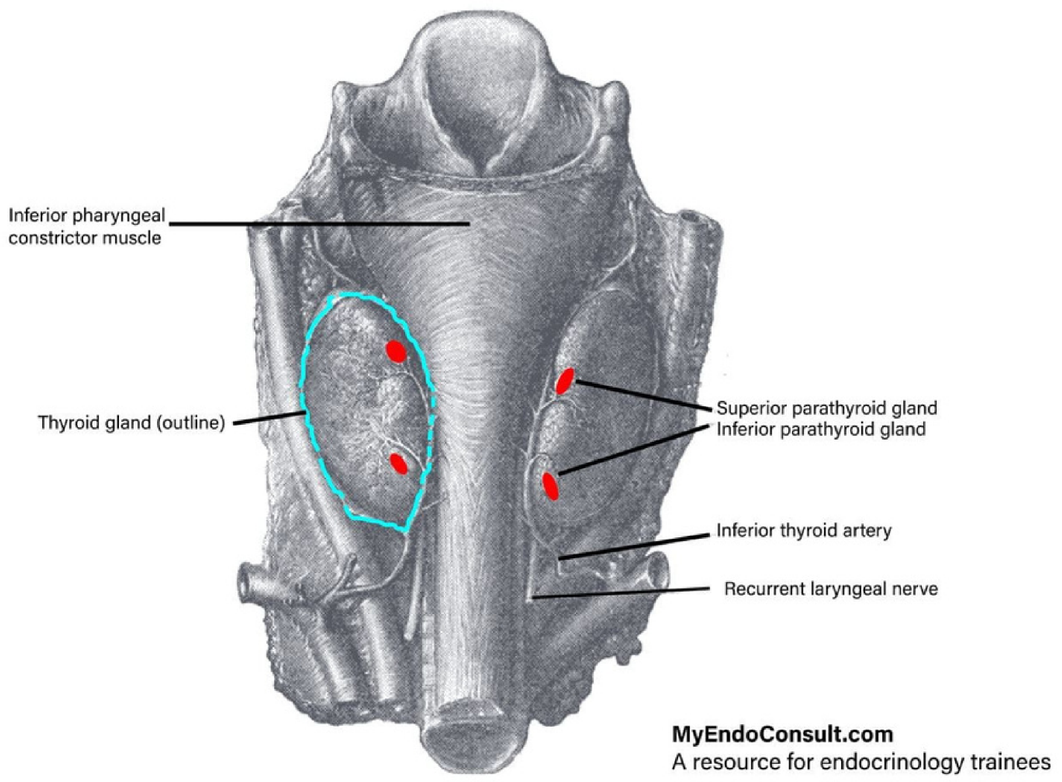
HISTOLOGY

There are two major cells in the parathyroid glands.

Chief cells : Produce Parathyroid Hormone (PTH) and are the predominant epithelial cell type.

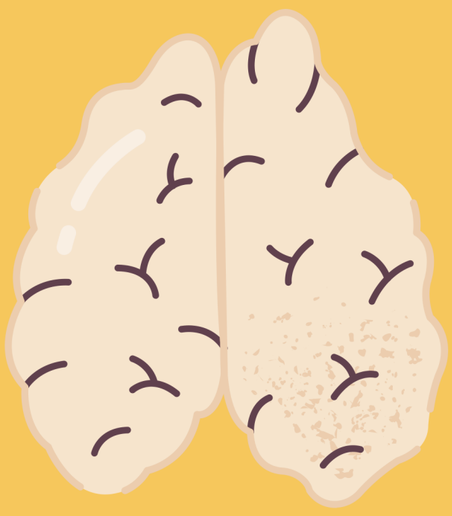
Oxyphil cells : These are mitochondria rich cells with a granular cytoplasm.

VASCULAR SUPPLY (PARATHYROIDS)



The **inferior thyroid arteries** supply both the **superior** and **inferior parathyroid glands** (over 90%). Additional tributaries from the other cervical vessels such as the superior thyroid artery, thyroidea ima artery, laryngeal, esophageal, and tracheal vessels supply the parathyroids as well.

The **parathyroid veins** are drained by **superior**, **middle**, and **inferior thyroid veins**. Superior and middle thyroid veins lead into the internal jugular vein and then into the systemic circulation. The inferior thyroid veins drain directly into the brachiocephalic vein.



ECTOPIC PARATHYROIDS

Approximately 10– 20% of humans have fifth parathyroid gland, often located in the mediastinum (**especially the thymus**)

PHYSIOLOGY AND ANATOMY

PARATHYROID GLAND

PHYSIOLOGY

Calcium is the most abundant mineral in the human body, with about 99% found in bone.

The skeletal system comprises calcium and phosphorus-containing **hydroxyapatite crystals**, **collagenous** and **noncollagenous proteins**.

It is essential in several biochemical processes, including hormone secretion, bone mineralization, maintenance of cell integrity, coagulation of blood, neuromuscular contraction, and signal transduction.

Several hormones with regulatory effects on the **parathyroid glands**, intestine, bone, and kidneys ensure the maintenance of serum calcium within a narrow physiologic range.

FORMS OF CALCIUM

1. **Free** or **ionized form** (about 50% of circulating calcium)
2. **Albumin-bound** (~40%)
3. **Complexed form** (~10% bound to anions such as bicarbonate, citrate, phosphates, and citrate)

REGULATION OF PTH ACTION

- ↑ ionized Ca2 + **activates CaSR** and **suppresses PTH** secretion
- ↓ ionized Ca2 + **stimulates PTH** secretion

- ↓ Mg2 + **inhibits PTH** secretion action
- ↑ Mg2 + **activates CaSR** and **suppresses PTH** secretion

PTH ACTION IN BONE

PTH has a **dual effect** on bone remodeling (resorption-formation sequence), depending on whether the skeleton is **continuously** or **intermittently** exposed to PTH.
Chronic and **persistent exposure** of the skeleton to elevated levels of PTH typical of Primary hyperparathyroidism results in **bone resorption**, while **intermittent exposure** (for example, treatment of osteoporosis with PTH analogs) promotes **bone formation**. Osteoblasts are the primary target for PTH action in bone.

PHYSIOLOGY AND ANATOMY

PARATHYROID GLAND

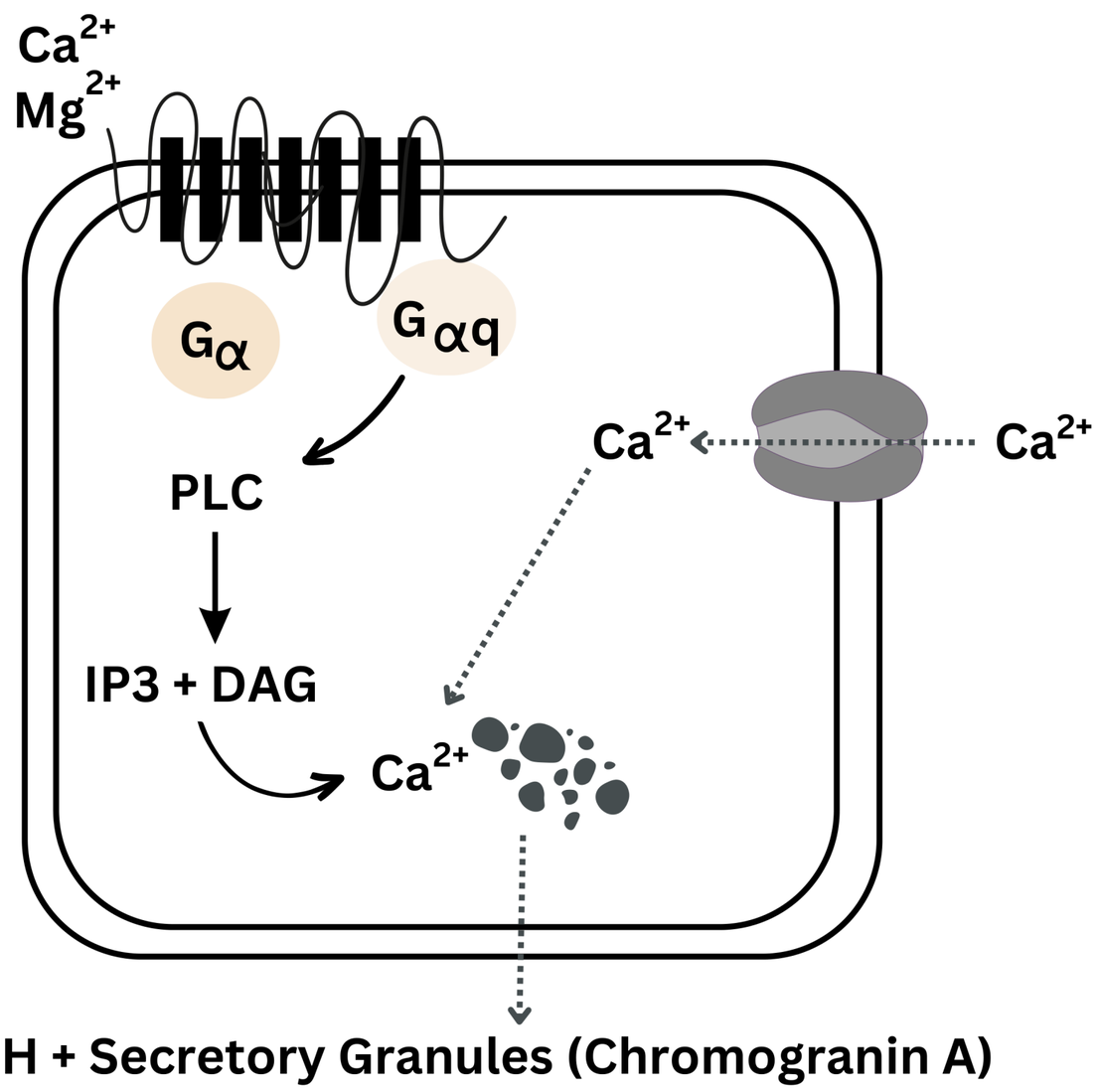
PHYSIOLOGY

The Calcium Sensing Receptor

The calcium-sensing receptor (CaSR), a G-protein coupled receptor expressed by chief cells of the parathyroid gland, C cells of the thyroid, and renal tubules, plays a pivotal role in regulating serum calcium.

The activation of CaSR blunts the synthesis and eventual **release of PTH by the parathyroids**, **augments calcitonin release by C cells** of the thyroid, and finally **inhibits renal calcium reabsorption** (independent of PTH action)

CASR ACTIVATION



At the level of the parathyroid glands, **CaSR's activation** by ionized calcium (an extracellular first messenger) results in downstream processes (Phospholipase C-Inositol triphosphate-diacylglycerol pathway), which increases the liberation of calcium from its stores in the endoplasmic reticulum.

Increased intracellular calcium inhibits the fusion of **PTH-containing vesicles** with the plasma membrane, which results in reduced secretion of PTH. Additionally, the transcription of PTH is regulated by **1α,25(OH)2D** (binding of active vitamin D to vitamin D response elements in the promoter region of the **PTH gene promotes PTH synthesis**)(not shown). Similarly, magnesium, another relevant extracellular divalent cation, can also activate the **CaSR** and **impair PTH synthesis**.

CINACALCET & HYPERPARATHYROIDISM

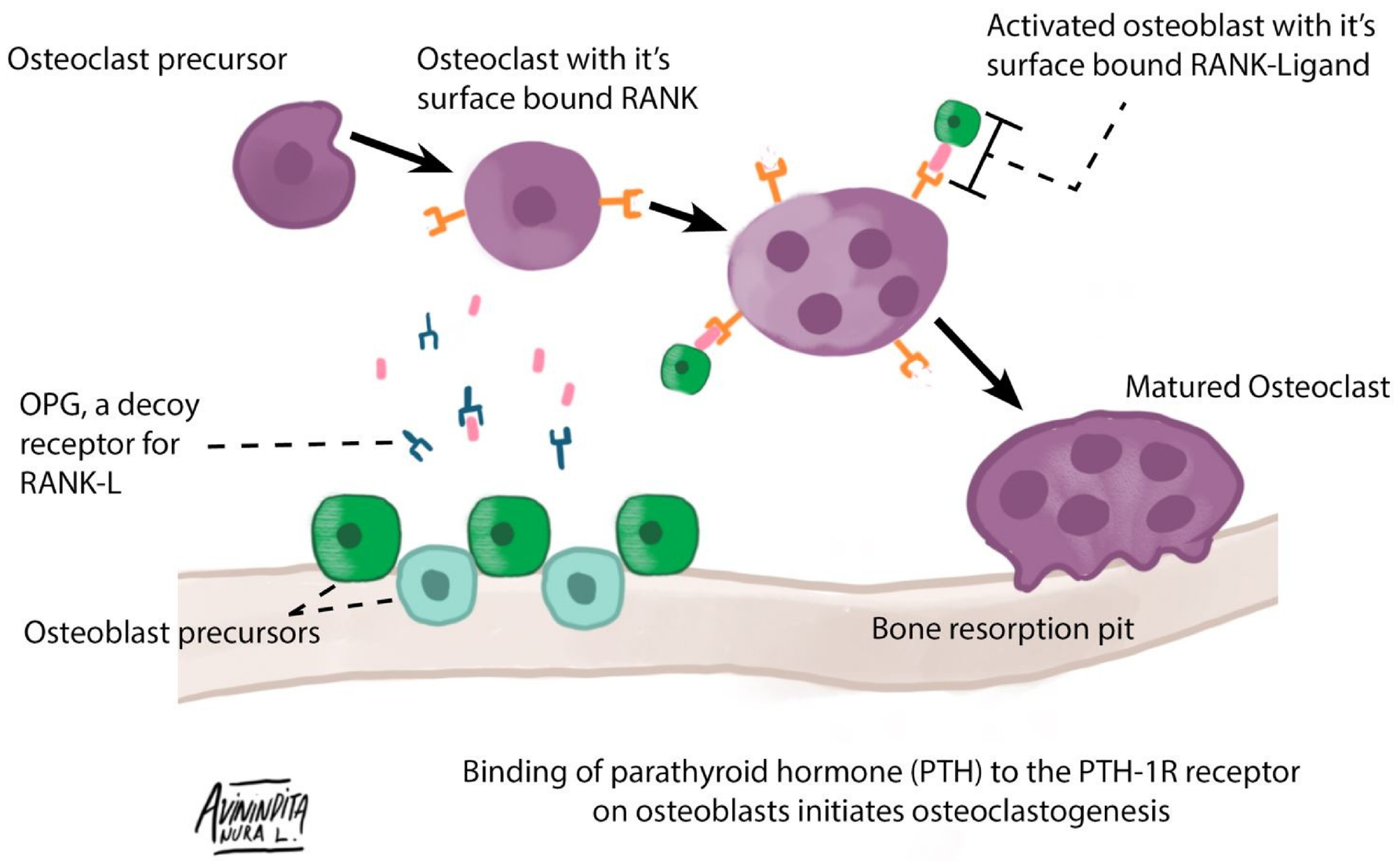
Calcimimetics promote the sensitivity of the CaSR to serum calcium by lowering the set point for activation of the receptor. This, in effect, leads to the activation of the CaSR even at lower levels of ionized calcium, a process that inhibits PTH release

PHYSIOLOGY AND ANATOMY

PARATHYROID GLAND

PHYSIOLOGY

The role of PTH in osteoblast-osteoclast interaction.



Binding of parathyroid hormone (PTH) to the PTH-1R receptor on osteoblasts initiates osteoclastogenesis

PTH binds to its cognate **PTH-1R receptor** on **osteoblasts** (derived from mesenchymal stem cells), thereby initiating the process of bone resorption.

Consequently, osteoblast surface-bound **receptor activator of nuclear factor kappa-B ligand** (RANK-L) will bind to the RANK receptor present on osteoclasts (derived from hematopoietic stem cells). This results in the activation and differentiation of a precursor osteoclast into a matured osteoclast.

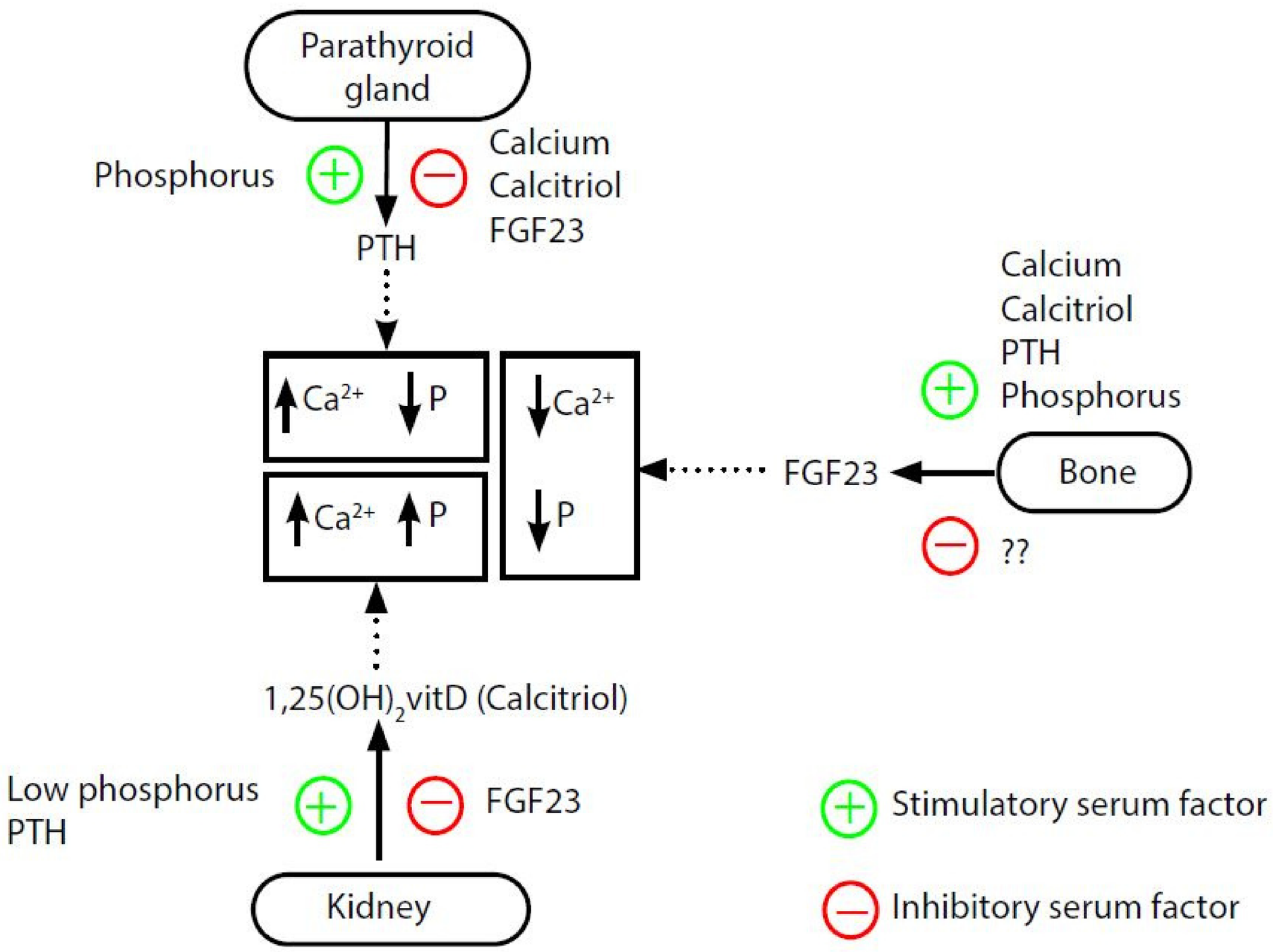
The liberation of calcium and phosphorus from **hydroxyapatite crystals** by matured osteoclasts occurs in bone resorption pits. OPG, a decoy receptor (alternate binding site) for RANK-L, reduces osteoclast activation

PHYSIOLOGY AND ANATOMY

PARATHYROID GLAND

PHYSIOLOGY

Role of parathyroid hormone, fibroblast growth factor 23 (FGF-23), and calcitriol in calcium and phosphate balance



CALCIUM PHYSIOLOGY

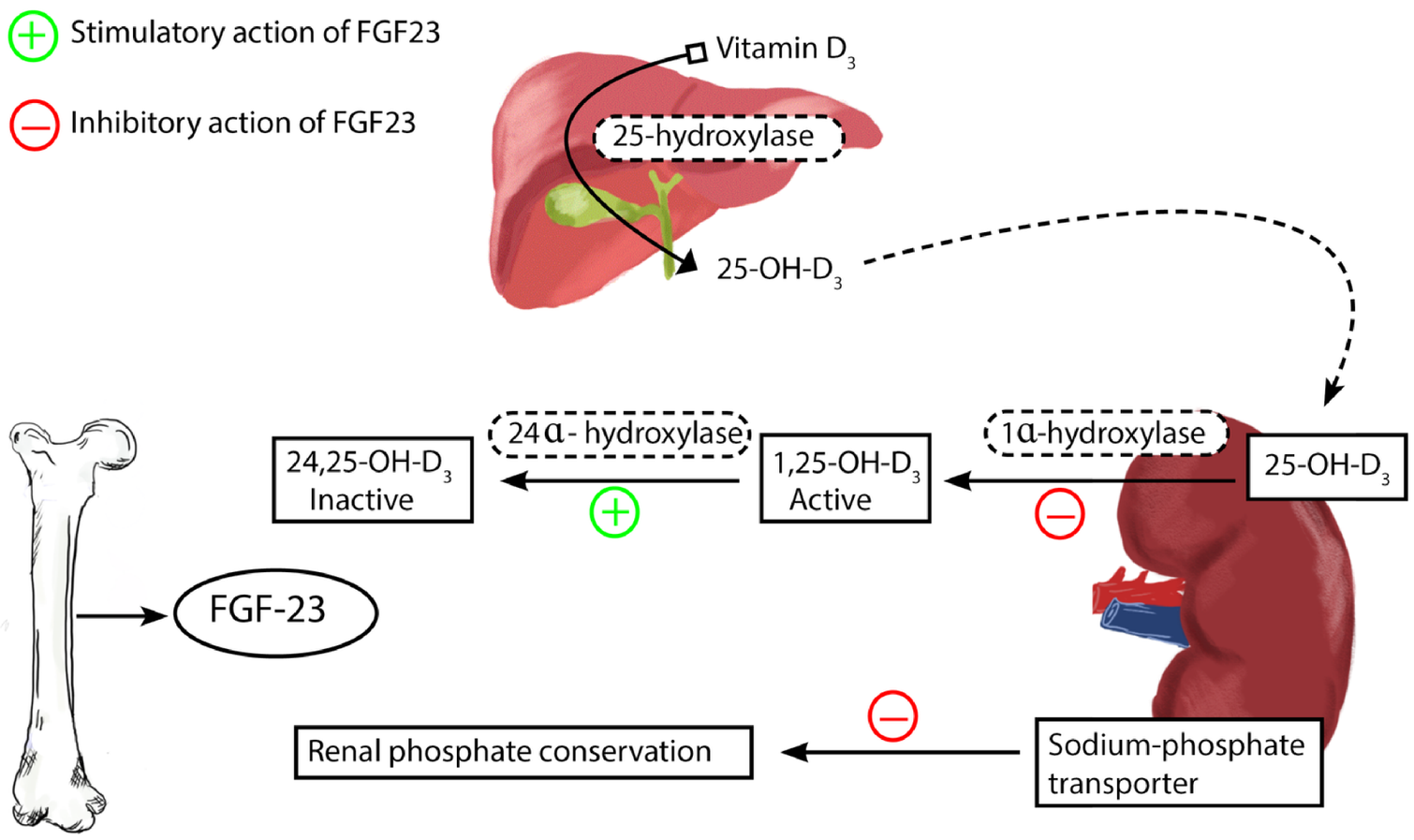
Learn more about the regulation of both serum calcium and phosphorus in this blog post.

PHYSIOLOGY AND ANATOMY

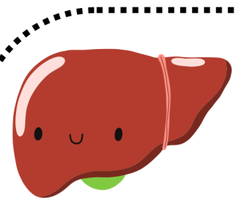
PARATHYROID GLAND

PHYSIOLOGY

Regulation of calcitriol by FGF-23

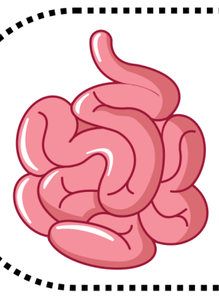


Vitamin D3 is synthesized in the skin from **7-dehydrocholesterol** though the direct effects of **UV light**. **Vitamin D2 (ergocalciferol)** is an alternative source of vitamin D derived from a **plant sterol (ergosterol)**.



These sources of vitamin D undergo **hydroxylation in the liver**, leading to the formation of **25 hydroxyvitamin D**. The **1 alpha hydroxylase enzyme** subsequently converts 25 hydroxyvitamin D to **1,25-dihydroxyvitamin D**.

This final hydroxylation step which leads to the formation of active vitamin D occurs in the kidneys, although this process occurs at extra-renal sites such at the skin, intestine, pancreas, thyroid, and parathyroids .



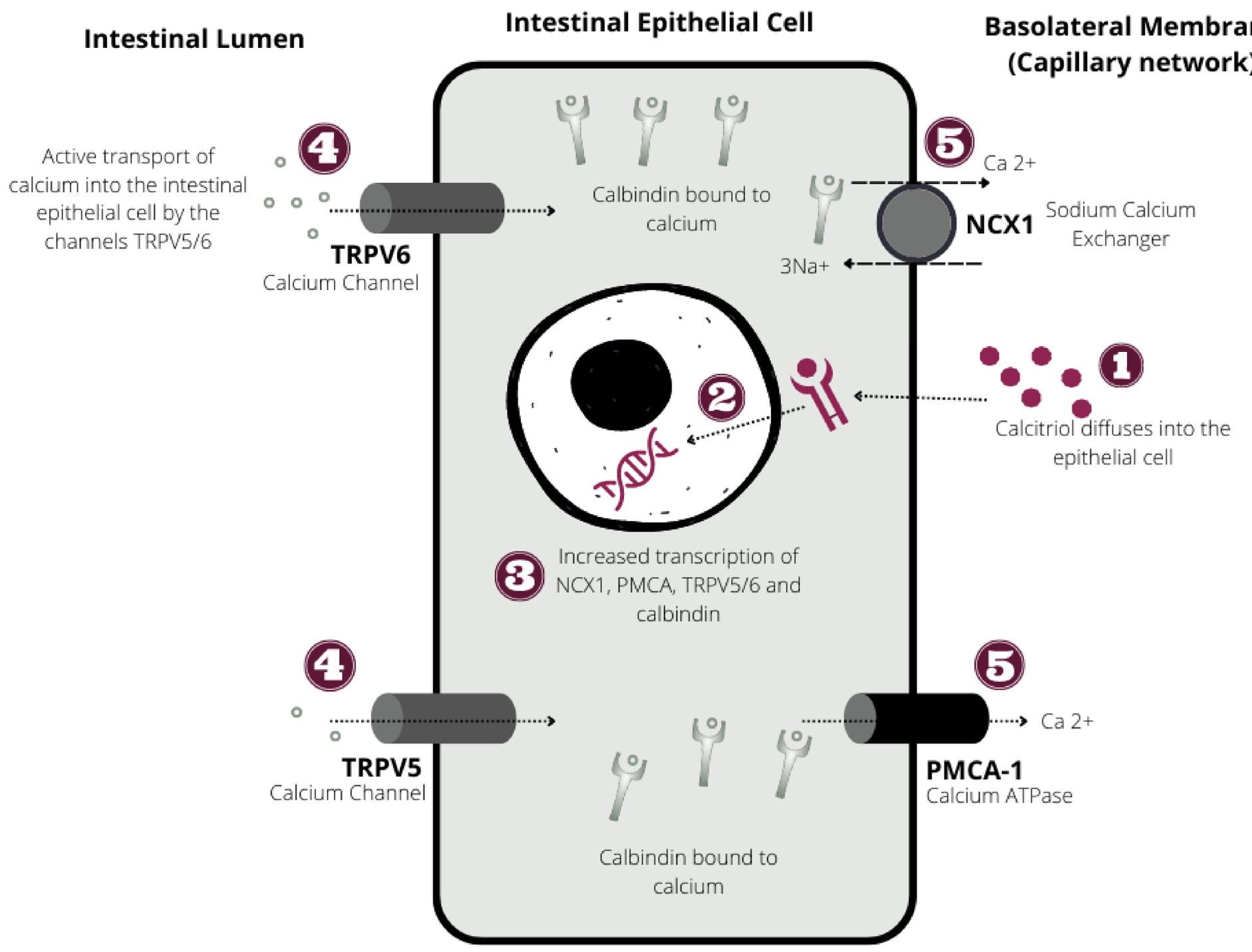
Active vitamin D is a hormone that exerts it effects by binding to the ubiquitous vitamin D receptor (VDR) in various tissues. It is noteworthy that VDR is indeed a transcription factor that in conjunction with other modulators, regulates gene transcription in various tissues.

Active vitamin D is **inactivated** by the **24 hydroxylase enzyme** into **24,25-dihydroxyvitamin D**. FGF23 promotes the inhibitory action of the 24 hydroxylase enzyme on active vitamin D. In addition, FGF-23 inhibits 1 alpha-hydroxylase activity. The net effect is a reduction in circulating levels of active vitamin D. **FGF-23** also inhibits renal phosphate conservation by downregulating the expression of renal sodium phosphate transporters.

PARATHYROID GLAND

PHYSIOLOGY

- 1α,25(OH)2D, also referred to as **calcitriol** (active vitamin D) plays a central role in the handling of **renal** and **intestinal calcium.**
- Calcitriol has a short half-life (t 1/2) of 4-6 hours. Consequently, it has a quick onset of action (1-3 days)



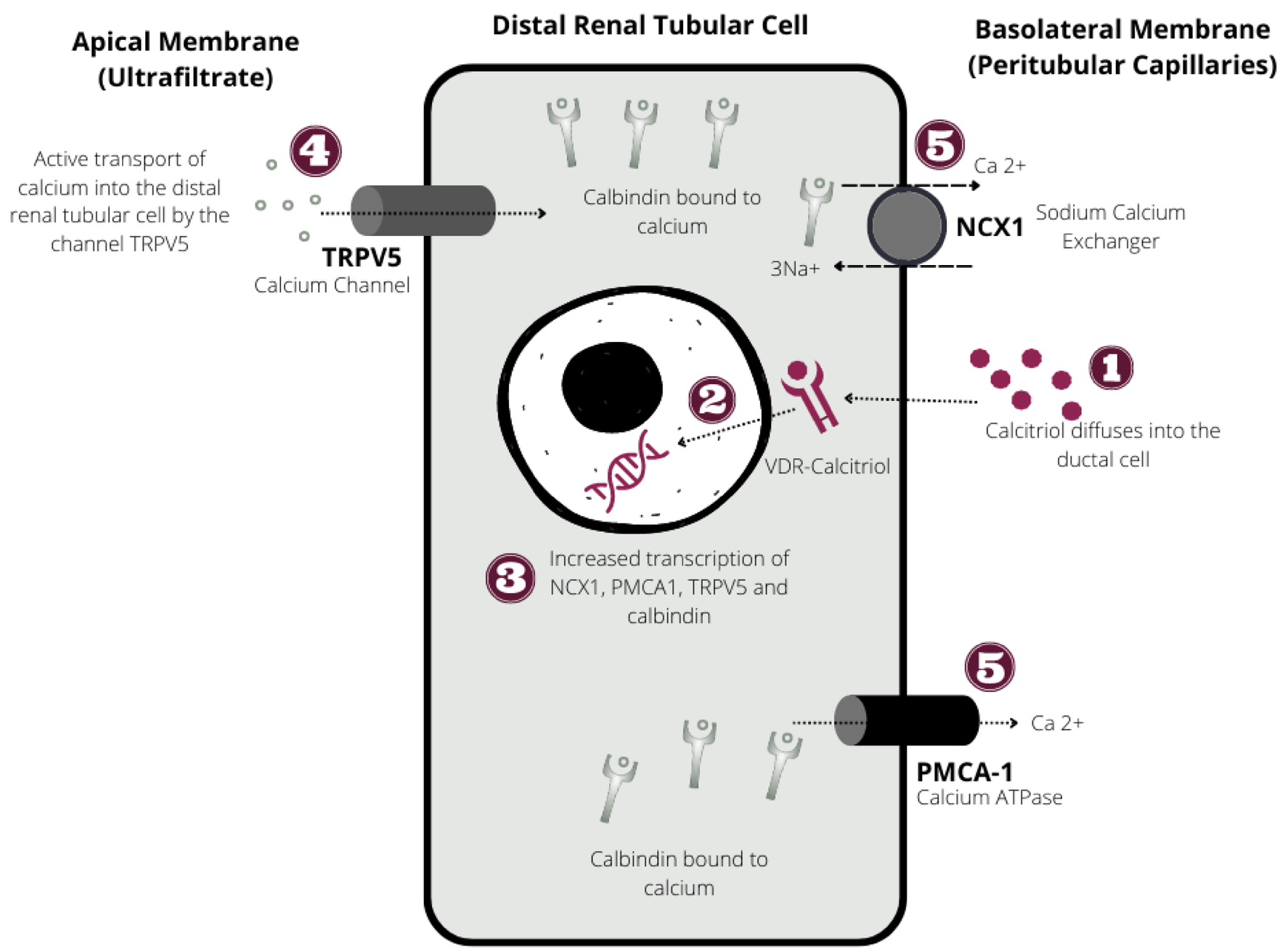
Calcitriol-mediated intestinal calcium absorption: Calcitriol binds to its **intracellular vitamin D receptor (VDR)**. The calcitriol–VDR complex then binds to **hormone response elements (HREs)** on DNA and induces transcription of multiple **calcium channels** (TRPV6, TRPV5), and electrolyte exchangers (NCX1), calcium ATPase (PMCA1), and calcium-binding proteins, **calbindin** (CB).

Insertion of calcium channels on the apical membrane of the enterocyte allows the influx of calcium into the enterocyte. CB carries calcium from the apical to the basolateral side of the enterocyte. Calcium-ATPase, an ATP-dependent transporter, is involved in pumping calcium out of the cytosol into the capillary network on the basolateral side of the intestinal epithelial cell.

PARATHYROID GLAND

PHYSIOLOGY

Calcitriol-mediated calcium absorption at the distal renal tubule



Calcitriol-mediated calcium absorption at the **distal renal tubule**: Calcitriol diffuses through the basolateral membrane of the distal renal tubular cell to bind its cytosolic vitamin D receptor (VDR).

The **calcitriol–VDR complex** binds to **hormone response elements (HREs)** on DNA to initiate transcription of calcium channels (TRPV5), calcium exchangers (NCX1), and calcium ATPase (PMCA1). Calcium channels (TRPV5) present on the apical membrane are involved in the direct translocation of calcium from the renal tubule into the cytosol of the distal renal tubular cell.

This step is then followed by cytosolic transfer of ionized calcium by calbindin (calcium-binding protein) to the basolateral surface of the distal tubular cell. The extrusion of calcium into the peritubular vasculature is facilitated by NCX1 and PMCA1.

PHYSIOLOGY AND ANATOMY

PARATHYROID GLAND

PHYSIOLOGY

Calcitonin is a 32 amino acid peptide secreted by the parafollicular or C cells of the thyroid gland.

Procalcitonin, a 116 amino acid peptide, is the precursor to calcitonin. Under normal physiologic conditions, it is largely produced by the **C cells of the thyroid**, however, in the setting of significant bacterial sepsis, the calcitonin gene is induced in several extra-thyroidal sites.

Calcitonin secretion is dependent on levels of serum calcium. Hypercalcemia induces the production of calcitonin. On the other hand, hypocalcemia inhibits the release of calcitonin

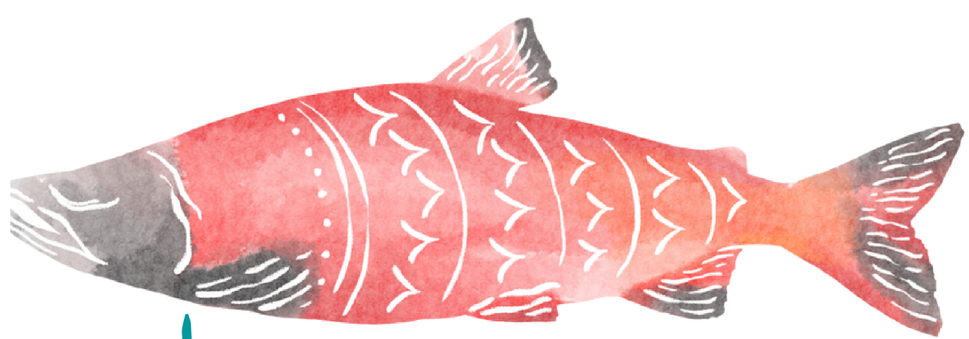
Human calcitonin has a half-life of approximately 10 minutes. **Salmon calcitonin**, which differs from human calcitonin by 16 amino acids, is more potent, is cleared more slowly, and has a stronger affinity for the CTR than human calcitonin

MECHANISM OF ACTION

Calcitonin secretion is dependent on levels of serum calcium. **Hypercalcemia** induces the production of calcitonin. On the other hand, **hypocalcemia** inhibits the release of calcitonin.

The **calcitonin receptor (CTR)** is a **G-protein coupled receptor** that activates various intracellular processes (cyclic adenosine monophosphate/protein kinase A pathway) upon its activation by calcitonin.

In summary, activation of CTR at the level of the osteoclast impairs osteoclast cell adhesion, ion transport, and enzyme activity, all critical processes in bone resorption. Inhibition of bone resorption impairs the liberation of calcium from **hydroxyapatite crystals** and ultimately restores serum calcium in the setting of hypercalcemia.



PROCALCITONIN AND SEPSIS

Plasma **procalcitonin levels > 2.0 µg/L** indicates a high probability of **systemic bacterial infection** and risk for progression to sepsis or septic shock. **Procalcitonin levels < 0.5 µg/L** indicate a low likelihood systemic bacterial infection and low risk of progression to sepsis or septic shock

♂ REPRODUCTION

ANATOMY

The testes are primarily responsible for the production of testosterone and spermatozoa, with most of their volume being germ cells and seminiferous tubules.

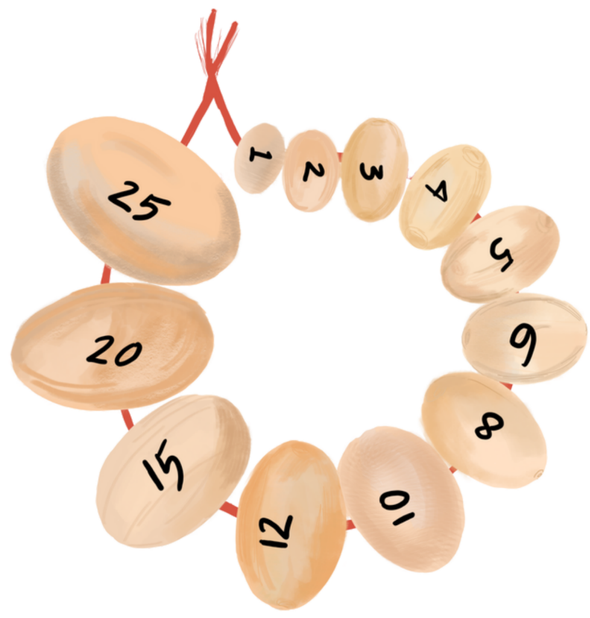
The testes are paired organs, each 15–30 ml volume (3.5– 5.5 cm length, 2– 3 cm width)

Epididymis : A coiled tubule 3– 6 m in length connecting testes to vas deferens. A site of sperm storage (estimated 155– 200 million sperm stored in each epididymis).

Seminal vesicle: collagenous tubular structure with outer muscular layer, secretes up to 80% of seminal plasma (alkaline fluid containing fructose, prostaglandins, coagulants)

Prostate: secretes thin, acidic fluid (20% of semen volume) containing citric acid, acid phosphatase, proteolytic enzymes

THE ENDOCRINE ROSARY



The **orchidometer** consists of a series of 12 graduated beads that range in size from 1 to 25 milliliters (ml). **Testicular volume** assessment using an orchidometer allows objective measurement of testicular size. The beads are graded by volume, starting at **1 to 3ml** for **prepubertal testicles**, **4 to 12 ml** for **puberty** and **15 to 25ml** for **adult-sized** testicles.
The examiner places the largest-sized bead next to each testicle. Scrotal skin should be taut over the testicle being measured. If the testicle does not match, the next largest sphere is placed until a fit is found. The sizes of the two testicles are then compared and recorded.

HORMONE HISTORY

In a rather crude experiment carried out in 1889, **Brown-Séquard** injected testicular extracts from a dog and guinea pig into his subcutaneous tissue. In a letter published in **The Lancet journal**, he described various effects of his extract, including an increase in muscle strength, improved urinary flow, and improved cognition

♂ REPRODUCTION

PHYSIOLOGY

Testosterone is present in plasma, either bound to circulating proteins or an unbound free form.

- Approximately 53-55% of testosterone is bound to albumin.
- 43-45% bound to sex hormone binding globulin (SHBG).
- 1-2% in an active free form

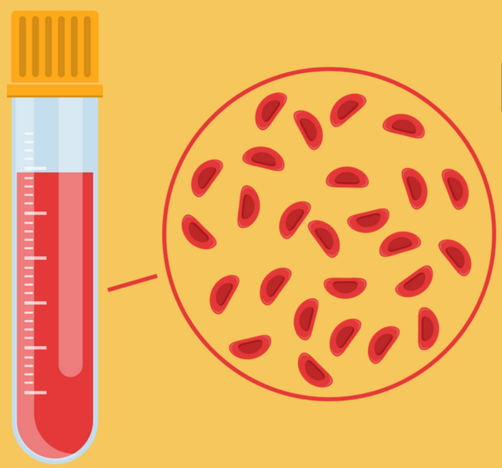
SHBG is a glycoprotein with an affinity for various sex steroids, including testosterone, dihydrotestosterone, and estradiol

Effects of estrogen on bone resorption

1.
2.

EFFECTS OF TESTOSTERONE

- Promotes **bone formation** by binding to androgen receptors on osteoblasts
- Promotes insulin-like growth factor 1 mediated proliferation of chondrocytes and osteoblasts.
- Estrogen (produced through the action of aromatase on testosterone) inhibits RANKL-mediated bone resorption.
- Growth of **androgen-dependent hair** by activating androgen receptors on dermal papilla cells.
- Androgen receptors on sebaceous glands are activated by testosterone leading to an increased risk for acne.
- The mechanism underlying muscle protein synthesis and hypertrophy is unknown.
- Descent of the testes, spermatogenesis, phallic and testicular enlargement.
- Increase in **libido**.
- increased **synthesis of erythropoietin**
- Suppression of hepcidin (an inhibitor of intestinal iron absorption)
- Increase in iron mobilization



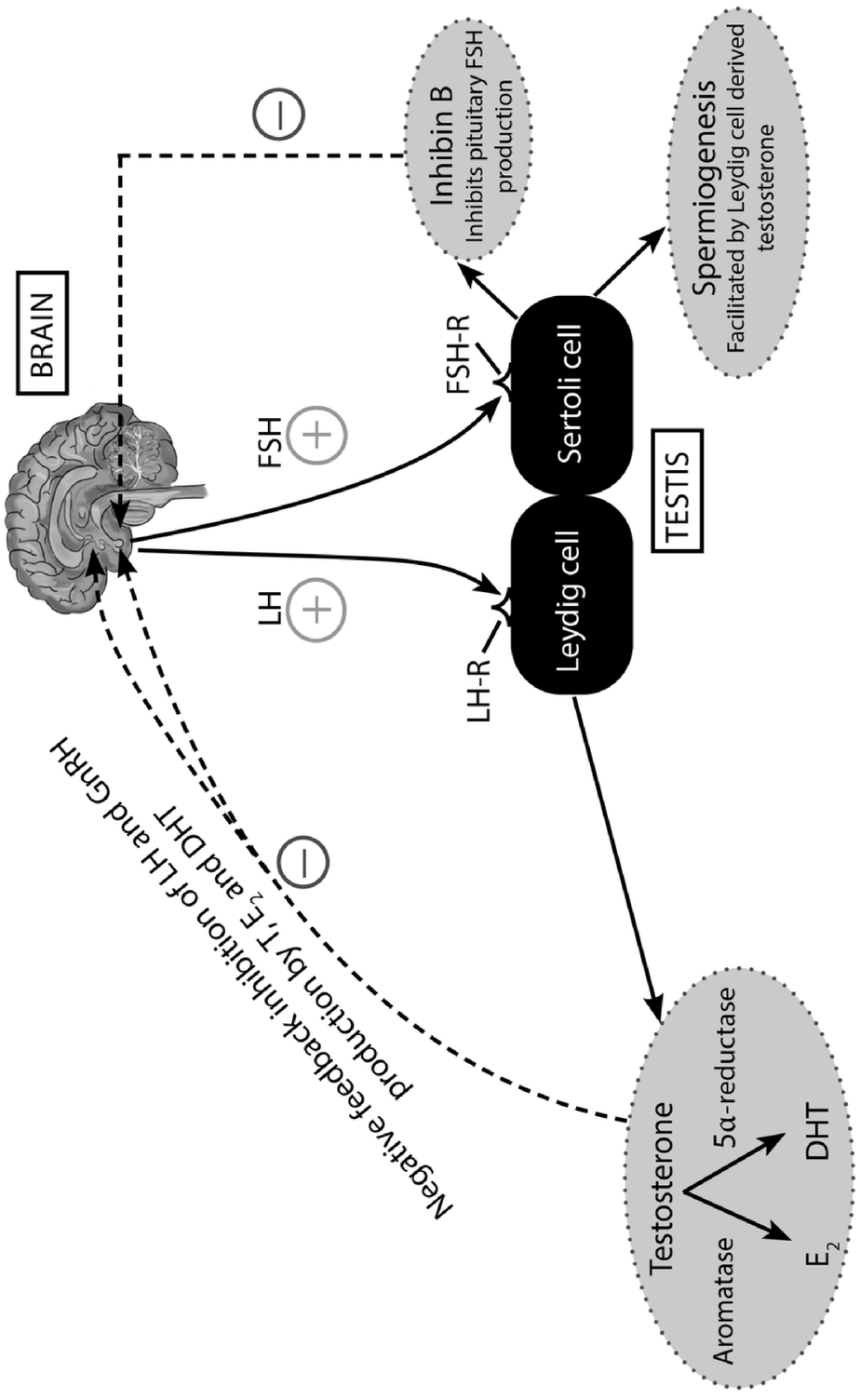
EVALUATING MALE HYPOGONADISM

- The secretion of testosterone occurs in a pulsatile and diurnal fashion, with peak concentrations around 8 am and nadir around 8 pm.
- Testosterone is best drawn by 9am (fasting)

♂ REPRODUCTION

PHYSIOLOGY

1. **The seminiferous tubules :** Responsible for the differentiation of germ cells into spermatozoa. Sertoli cells are essentially "nursing cells" for germ cells and possess receptors for FSH and androgens. **Sertoli cells** produce inhibin, Anti-Mullerian Hormone and androgen-binding protein.
2. **Interstitial cells** : contains **Leydig cells** which are responsible for the production of testosterone. They possess receptors for LH.



HPT AXIS

Gonadotropin-releasing hormone (GnRH) produced from the hypothalamus stimulates pituitary gonadotrophs to produce **gonadotropins (FSH and LH)**. Luteinizing hormone (LH) binds to its cognate G-protein coupled LH receptor (LH-R) on the Leydig cell and subsequently stimulates the production of testosterone.

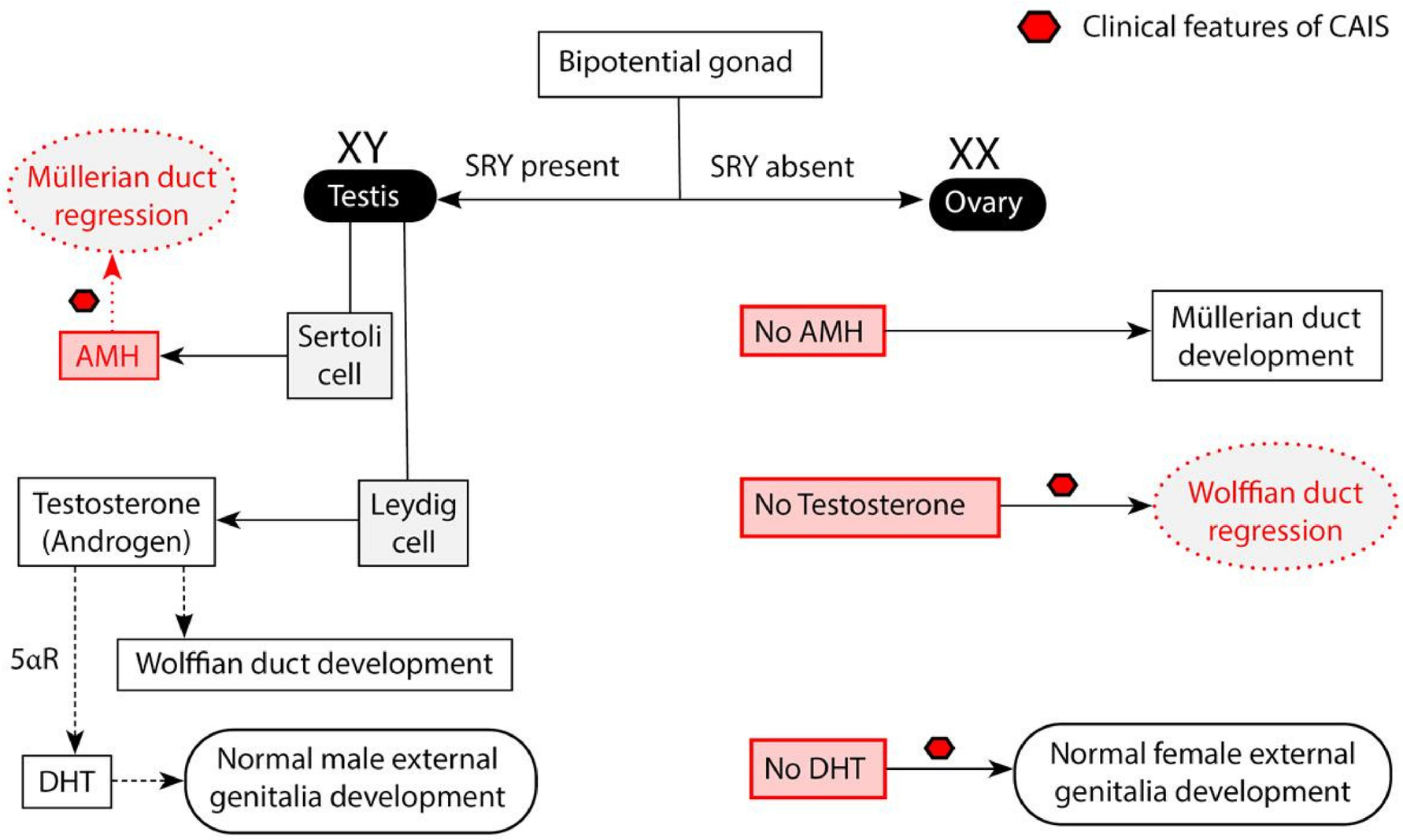
Subsequently, testosterone (T) is converted to estradiol and dihydrotestosterone (DHT) by peripheral aromatase (enzyme) and 5α reductase enzymes, respectively (solid lines). Also, negative feedback inhibition of both pituitary gonadotrophs and hypothalamic GnRH neurons is mediated by testosterone and estradiol (E2) (broken lines).

Also, **Follicle-stimulating hormone (FSH)** binds to its corresponding G-protein coupled FSH receptor (FSH-R) on the Sertoli cell of the testis. This action promotes the formation of **spermatozoa (spermatogenesis)**, **androgen-binding proteins (ABPs)**, and **inhibin B** (solid lines). It is worth noting; however, that sustained spermatogenesis in the Sertoli cell requires the presence of intratesticular testosterone (Leydig cell-derived testosterone). Finally, inhibin B suppresses FSH release via a negative feedback loop (broken lines).

♂ REPRODUCTION

PATHOLOGY

Complete androgen insensitivity syndrome (CAIS) occurs as a result of a mutation of the gene responsible for the translation of the androgen receptor (AR).



In utero, the **bipotential gonad** differentiates into either male or female gonad with ultimate phenotypic features being under the influence of the transcription factor, SRY (Sex-determining region of the Y chromosome), androgens and anti-Mullerian hormone (AMH).

In a **genetic male (XY)**, the **SRY transcription factor** present on the short arm of the Y chromosome plays a pivotal role in the differentiation of the bipotential gonad into a testis. **AMH** secreted by the **Sertoli cells of the testes** causes regression of the **Mullerian ducts**, which are responsible for the formation of the upper female genital structures (upper 1/3rd of the vagina, uterus and fallopian tubes).

Androgens from the testes bind to androgen receptors and mediate the development of the **Wolffian duct** into male internal genital structures (seminal vesicles, epididymis, and vas deferens). Due to the mutation of the AR, the Wolffian ducts regress as well, leading to the formation of the lower female genitalia (lower 2/3rd vagina, labia, and clitoris).
SRY = Sex-determining region of the Y chromosome, **5αR** = 5 alpha-reductase

REPRODUCTION

ANATOMY

Uterus :

- Measures 3 x 2 x 1 inches in nulliparous females
- Pelvic location in nonpregnant females
- Its normal anatomic orientation is an anteverted-anteflexed position.

Ovaries :

- Paired ovaries each link to the uterus via the fallopian tubes.
- Principal glands of the female reproductive system.
- Measure 3 x 1.5 x 1 cm in size.
- Each ovary contains thousands of follicles. A dominant follicle is released by an ovary once a month during the reproductive years.

VASCULAR SUPPLY

Arterial Supply :

The **uterine artery** is a branch of the anterior division of the internal iliac artery. It has a complicated course but eventually anastomoses with branches of the ovarian artery within the broad ligament.

The **ovarian artery** is a branch of the abdomina aorta. The ovarian artery courses through the suspensory ligament of the ovary.

Venous Supply :

The **uterine vein** follows the course of its corresponding uterine artery and eventually drains into the internal iliac vein.

The right ovarian veins empties into the inferior vena cava. The left ovarian vein empties into the left renal vein.

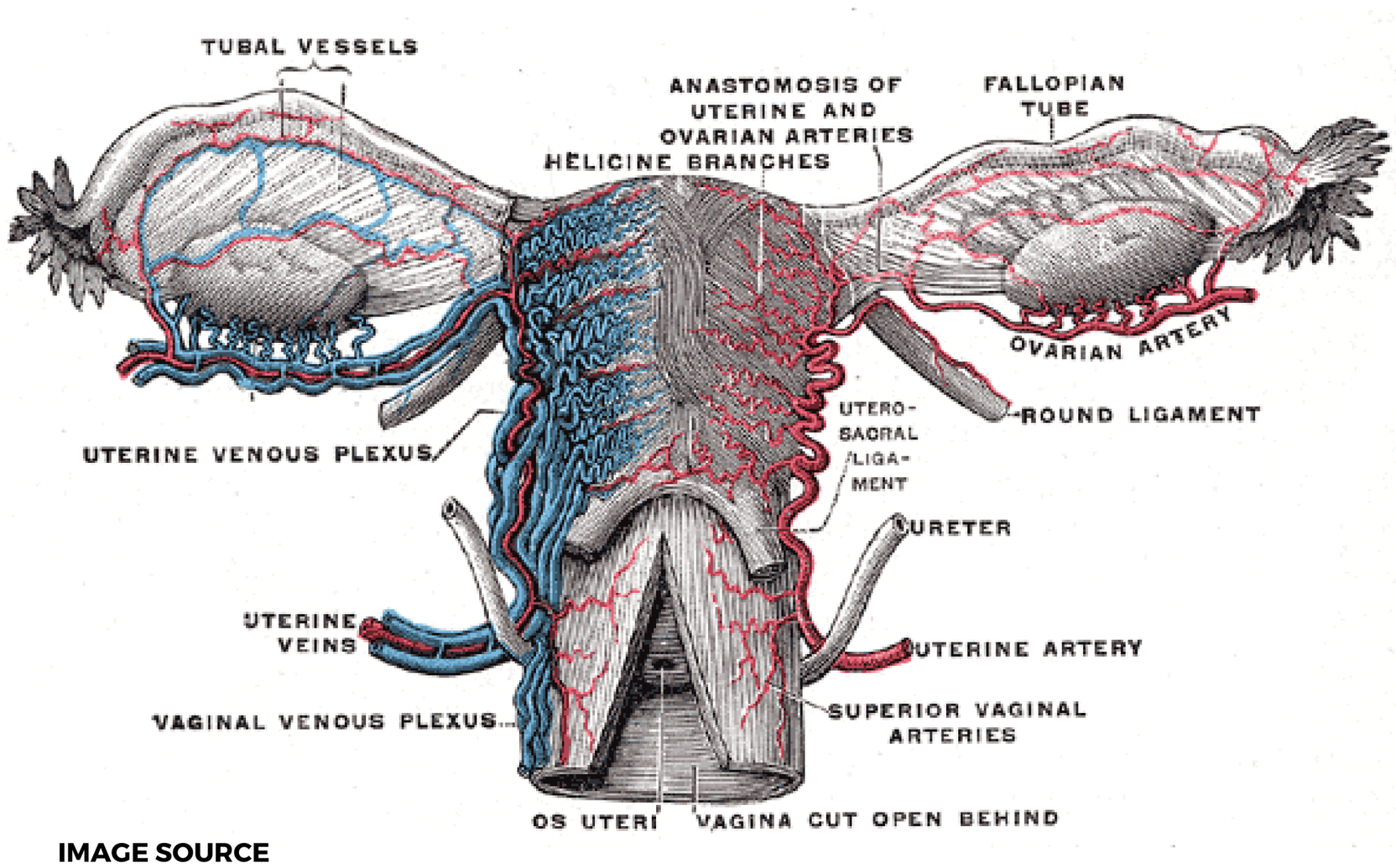


IMAGE SOURCE
@WIKICOMMONS

REPRODUCTION

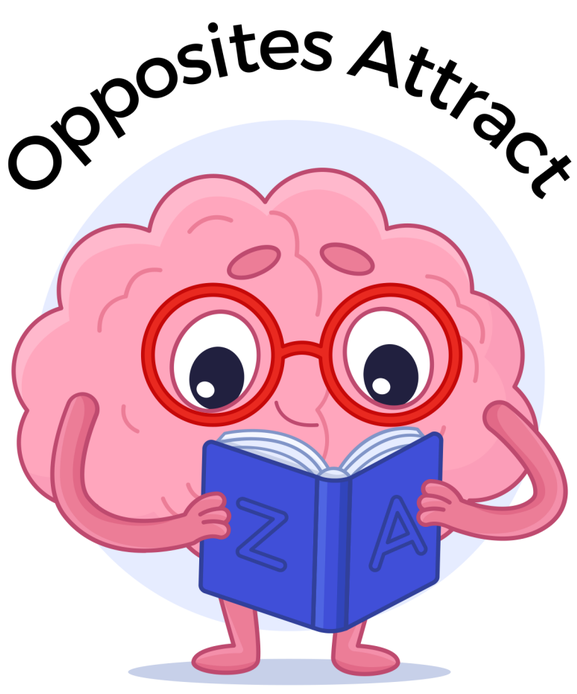
EMBRYOLOGY

Paramesonephric Duct :

- Also known as the **Mullerian Duct**
- The embryonic origin of the genital ducts.
- The uterus, cervix and fallopian tubes are derived from the upper two thirds of the mullerian duct.
- The vagina is derived from the urogenital sinus in conjunction with the lower third of the mullerian duct.

Mesonephric Duct :

- Also known as the **Wolffian Duct**
- This structure regresses in females except a small portion of its cranial aspect (epoophoron and paroophoron)
- The caudal portion forms Gartner's duct cyst.



Wolffian = Men
Mullerian = Woman

CLINICAL CORRELATES

What is the risk associated with a retroverted uterus?
A normal uterus is in an anteverted and anteflexed position. A retroverted uterus is associated with **postpartum hemorrhage**.

Significance of a bicornuate uterus
This embryologic defect of the uterus due to incomplete fusion of paired Mullerian ducts results in bicornuate uterus - associated with **infertility** and first trimester spontaneous **miscarriages**.

Ligation of the uterine artery during hysterectomy
The uterine artery courses above the ureter. Unintentional transection of the ureters can occur if this anatomic relationship is dismissed by a surgeon.

What is the role of the SRY transcription factor in sex determination?

Recall Box

REPRODUCTION

PHYSIOLOGY

FSH

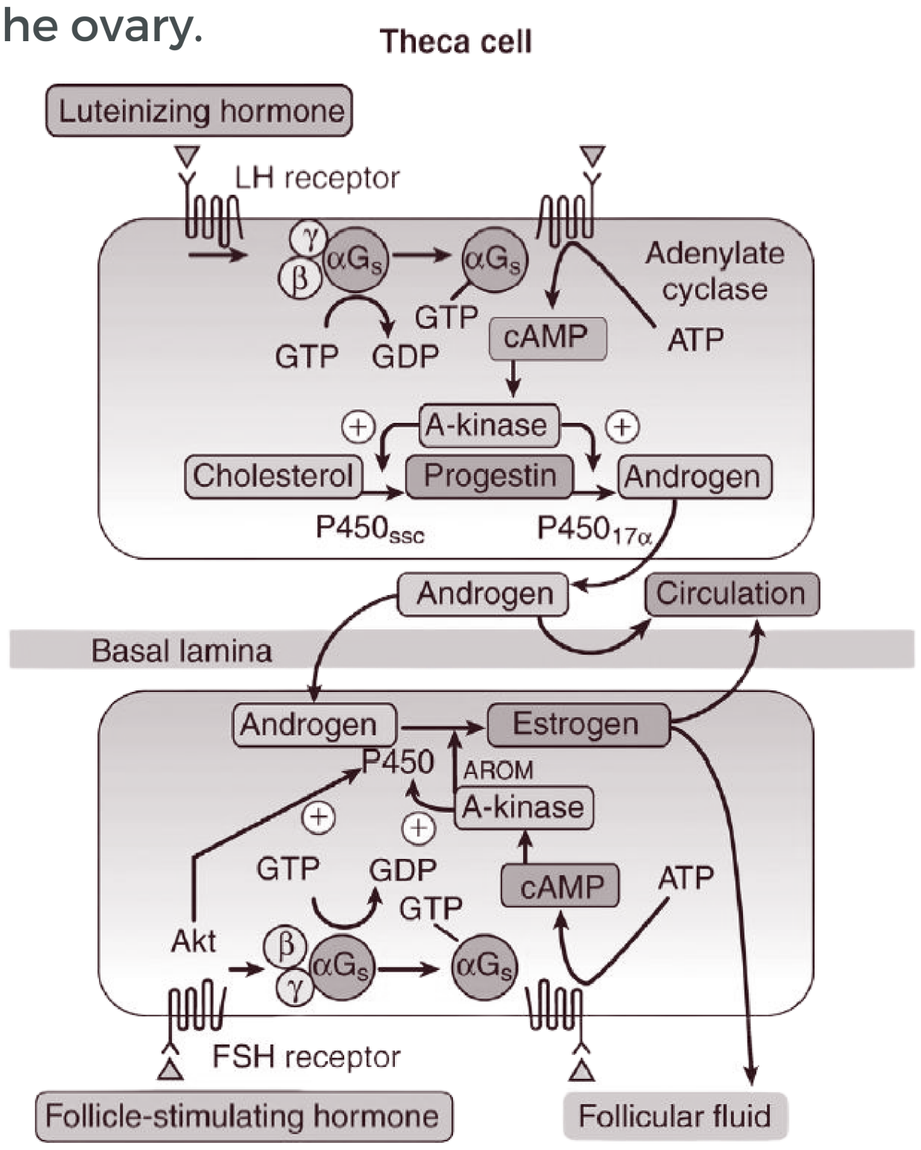
- A glycoprotein
- Secreted predominantly in the follicular phase of the menstrual cycle
- Stimulates granulosa cells of the ovary to produce estradiol
- Stimulates ovarian follicle development

LH

- A glycoprotein
- A critical level of estradiol promotes the LH surge
- Stimulates Leydig cells of the ovary to produce androgens
- Promotes the development and maintenance of the corpus luteum.

ESTROGEN BIOSYNTHESIS

The **classic two cell, two gonadotropin model** of **estrogen synthesis** was first proposed by Armstrong et al. in 1979. This model is sometimes referred to as the Armstrong-Dorrington “two-cell” model. It posits that **FSH receptors** are exclusively on **granulosa cells**, whilst **LH receptors** are expressed primarily by **theca cells** of the ovary.



2 CELL 2 GONADOTROPIN

The two-cell two gonadotropin theory is central to our understanding of ovarian steroidogenesis. The origin, simplified model, and intracellular signaling mechanisms involved in this pathway... (scan the QR code)

REPRODUCTION

PHYSIOLOGY

Ovarian follicular development can be categorized into two distinct but interrelated stages, often described as the **gonadotropin-independent** and **gonadotropin-dependent phases**.

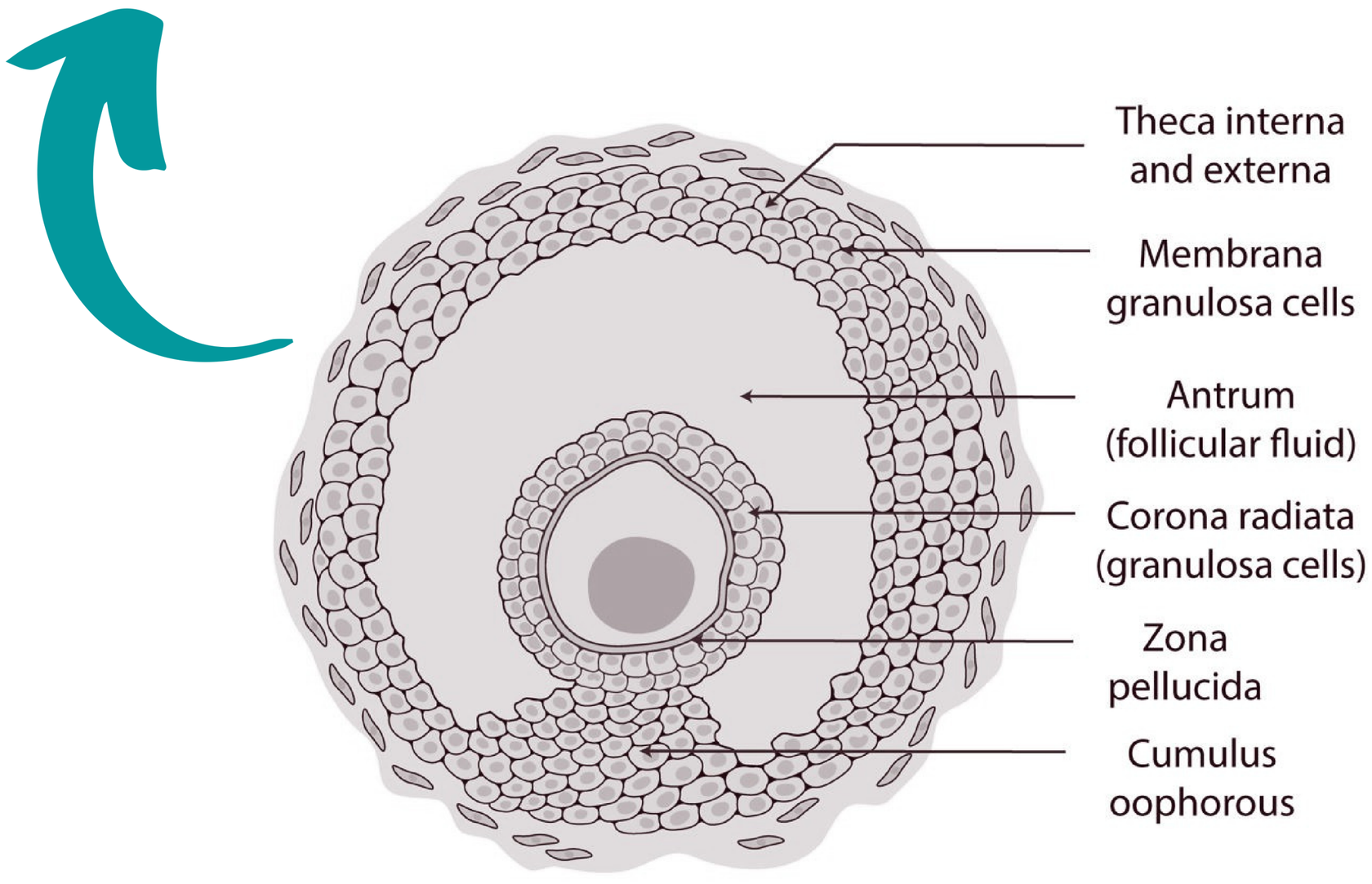
- The **gonadotropin independent phase** is characterized by the growth of a primordial ovarian follicle into a pre-antral follicle (before the follicle develops a fluid-filled space or antrum).
- **Gonadotropin dependent phase** promotes the development and release of the dominant follicle

MENSTRUAL CYCLE

The **menstrual cycle** and, in effect, ovarian follicular development is regulated by the hypothalamus, pituitary gland, and ovaries.

The frequency of firing of the **GnRH pulse generator** at various stages of the menstrual cycle determines the extent of synthesis and secretion of **follicle-stimulating hormone** and **luteinizing hormone**.

The term gonadotropins refer to follicle-stimulating hormone and luteinizing hormone. Follicle-stimulating hormone is critical in the recruitment and development of ovarian follicles, while luteinizing hormone mediates the process of ovulation



REPRODUCTION

GONADOTROPIN INDEPENDENT

The **primordial follicle** has a nucleus surrounded by a single layer of squamous granulosa cells.

Recruited primordial follicles transform into primary follicles (transition of squamous to cuboidal granulosa cells).

Subsequently, primary follicles develop into **secondary follicles** (transition from a cuboidal to stratified columnar epithelium).

Additionally, the secondary follicle has an internal theca interna layer and an outer theca externa layer.

Next, the secondary follicle differentiates into a **pre-antral follicle**. Formation of the pre-antral follicle marks the transition point from gonadotropin-independent to gonadotropin-dependent folliculogenesis.

This phase of follicular development is controlled by various intraovarian regulators, including growth factors and cytokines

GONADOTROPIN DEPENDENT

Granulosa and theca interna cells of the pre-antral follicle express FSH and LH receptors, respectively.

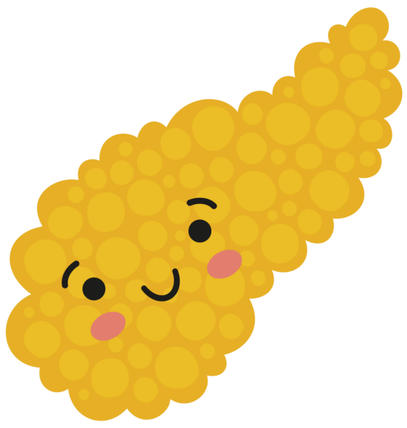
FSH binds to its cognate FSH receptor on the granulosa cells of the pre-antral follicle, leading to follicular growth and development of a fluid-filled follicular space (antrum).

Also, the binding of LH to LH receptors on theca interna cells results in the production of androgens.

Androgens paradoxically promote both follicular growth and regression, depending on the stage of follicular development

Stimulation of androgen receptors on granulosa cells of follicles in the early gonadotropin-dependent phase augments FSH-mediated follicular development. Conversely, during the late preovulatory stage, elevated levels of androgens lead to arrested antral follicular development.

PHYSIOLOGY AND ANATOMY



PANCREAS

HISTOLOGY

The islets cells of the pancreas (also known as islets of Langerhans) are somewhat ovoid groupings of pancreatic endocrine cells embedded within a rich background of acinar exocrine tissue.

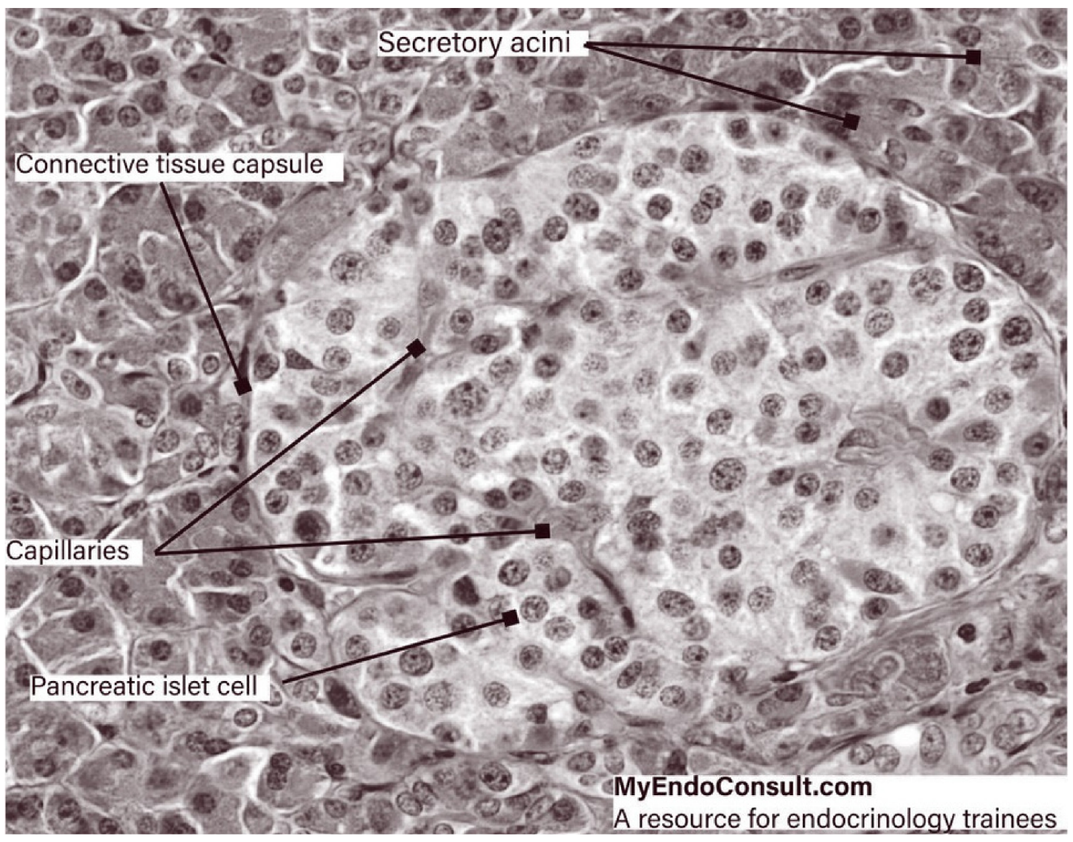
Endocrine cells of the pancreas represent about **2% of the pancreatic volume**, with most of the islets being present in the tail of the pancreas.

The islets of Langerhans in the pancreas are composed of various cells, including **beta**, **alpha**, **delta**, **PP**, **epsilon**, **G**, and **EC cells**.

A normal adult pancreas is composed of approximately one million islet cells.

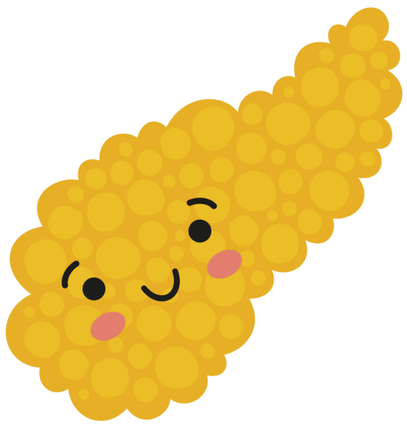
- The **beta cells** are polyhedral in shape and evenly dispersed throughout the pancreas.
- **Alpha cells** are columnar in shape and are present principally in the body and tail of the pancreas.
- The **delta cells** have a dendritic and are variably distributed.
- The **PP cells** are present in the head and uncinate process of the pancreas.

ISLET OF LANGERHANS



The **endocrine pancreatic islet** appears as a pale-staining complex in the middle of the field. It lies on a background of deeply staining pancreatic secretory acini (exocrine pancreas). Also, the pancreatic islet contains a rich vascular supply (capillaries) and multiple islet cells encased in a thin connective tissue capsule.

Can you recall the hormones produced by various components of the islets?

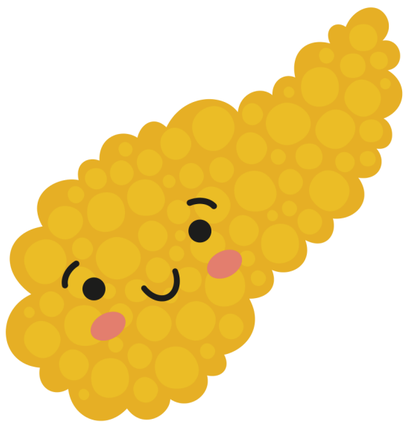


PANCREAS

EMBYROLOGY

The islets of Langerhans develop from epithelial cells of the outgrowing pancreatic ducts during fetal life. They are, therefore, of entodermal origin. Even in the embryo of 18 mm in length (age about 7 weeks), the terminal and side buds of the primitive ducts contain a few granular cells. These cells multiply and form single solid sprouts which enlarge to become the fetal (and early post-natal) islets.

Islet cell (frequency)	Hormone produced	Effects(s)
Beta cells (50-70%)	Insulin and amylin	Insulin increases peripheral glucose uptake and reduces hepatic gluconeogenesis and glycogenolysis. Amylin slows gastric emptying and stimulates satiety
Alpha cells (20-30%)	Glucagon	Stimulates hepatic gluconeogenesis and glycogenolysis. Stimulates hepatic ketogenesis during a prolonged fast
Delta cells (10%)	Somatostatin	Inhibits the secretion of insulin, glucagon, and PP
PP cells (2%)	Pancreatic polypeptide	Inhibition of glucagon secretion and acts as a satiety hormone
Epsilon cells (1%)	Ghrelin	Inhibits insulin release after a glucose load. Stimulates GH secretion and is also called the "hunger hormone."
G cells (absent)	Gastrin	Pancreatic gastrin-producing cells are present during embryonic development but undergo involution in adults. Re-expression of gastrin can, however, occur in the setting of pancreatic neuroendocrine tumorigenesis (Zollinger-Ellison Syndrome).
EC cells (rare)	Serotonin	Classic features of carcinoid syndrome



PANCREAS

PHYSIOLOGY

Insulin is a 51 amino acid peptide hormone that consists of two chains (A and B) linked by a pair of disulfide bonds.

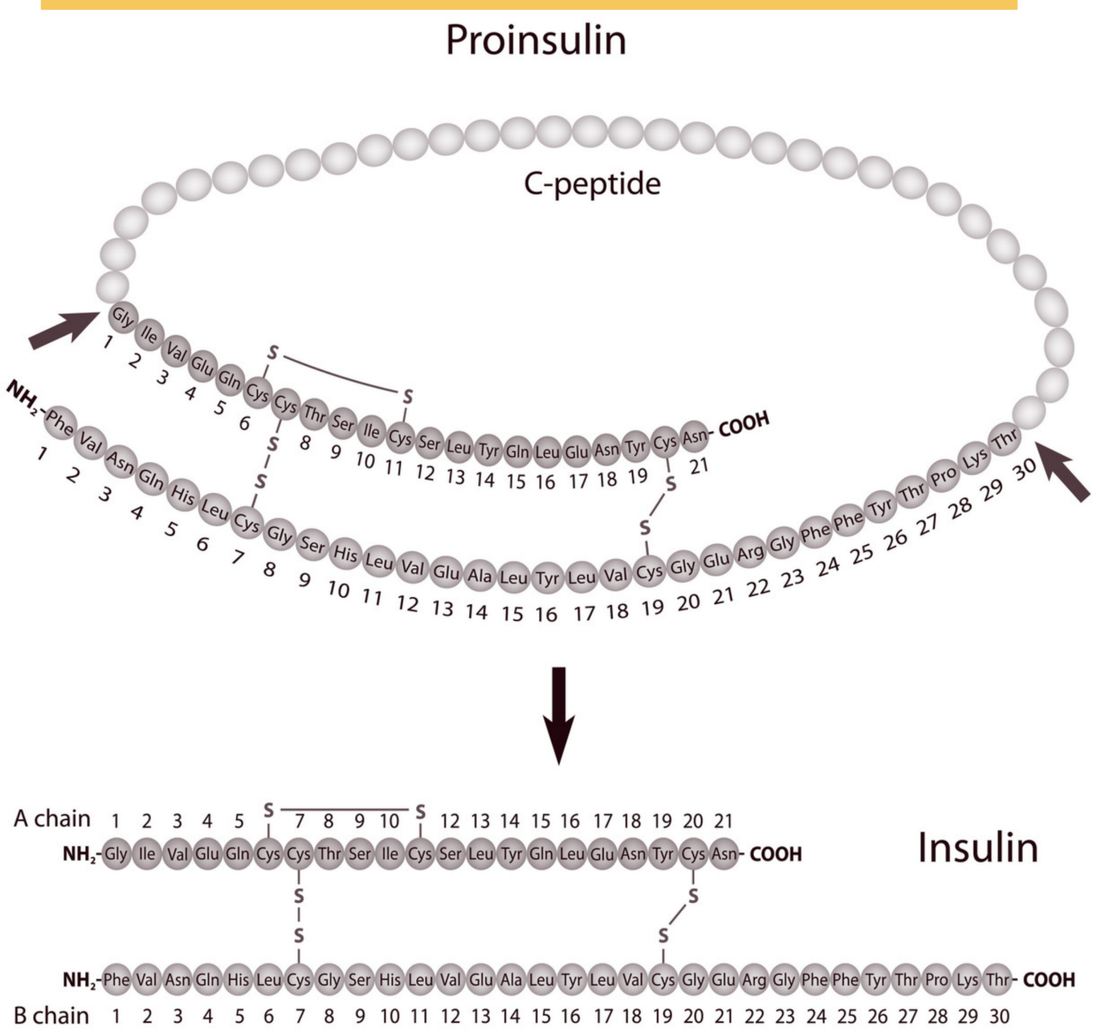
The **A (21 amino acids)** and **B (30 amino acids)** chains of insulin are linked by an intervening sequence of amino acids known as the **connecting peptide (c-peptide)**.

The gene that encodes for human insulin produces an mRNA transcript that is translated into a large 110 amino acid polypeptide sequence known as preproinsulin.

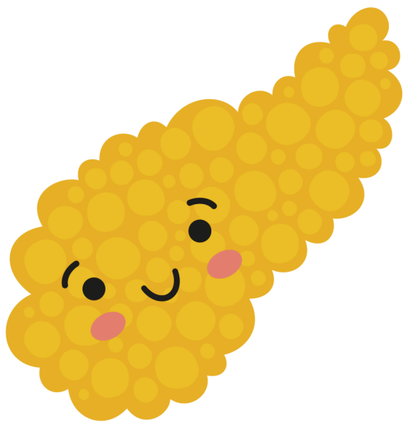
Preproinsulin then undergoes further processing in the lumen of the rough endoplasmic reticulum to produce proinsulin. **Proinsulin** is then ferried into the Golgi apparatus, where it is subsequently cleaved into the native insulin peptide and c-peptide.

Along with these products of proinsulin processing, amylin and other intermediate peptides are packaged into secretory granules by the pancreatic beta cell.

STRUCTURE OF INSULIN



- **Endogenous insulin** is secreted via either **high-frequency pulses** every 5-15 minutes or **low-frequency ultradian pulses** every 80-120 minutes.
- After an oral glucose challenge, about 40-80% of insulin released into the portal vein undergoes first pass metabolism in the liver.
- This phase of hepatic metabolism enables insulin to exert various effects on glucose metabolism such as **promotion of glycogenolysis**, **inhibition of glycogenesis**, **increased gluconeogenesis**, and a **reduction in glucagon secretion.**



PANCREAS

PHYSIOLOGY

Incretins are gut-derived factors that enhance insulin release by pancreatic beta cells.

These factors are produced by selective posttranslational modification of **proglucagon**, a 160-residue peptide expressed by the **α-cells of the pancreas**, **K** and **L** cells of the small intestine.

The **incretin effect** is described as enhanced insulin secretion in response to an oral glucose load (~6–1.7-fold) compared with intravenous glucose administration.

The incretin effect is mainly attributed to the action of two hormones gut hormones, including **glucose-dependent insulinotropic peptide (GIP)** and **glucagon-like peptide 1 (GLP-1)**.

K cells are responsible for the production of GIP and the L cells for GLP-1.

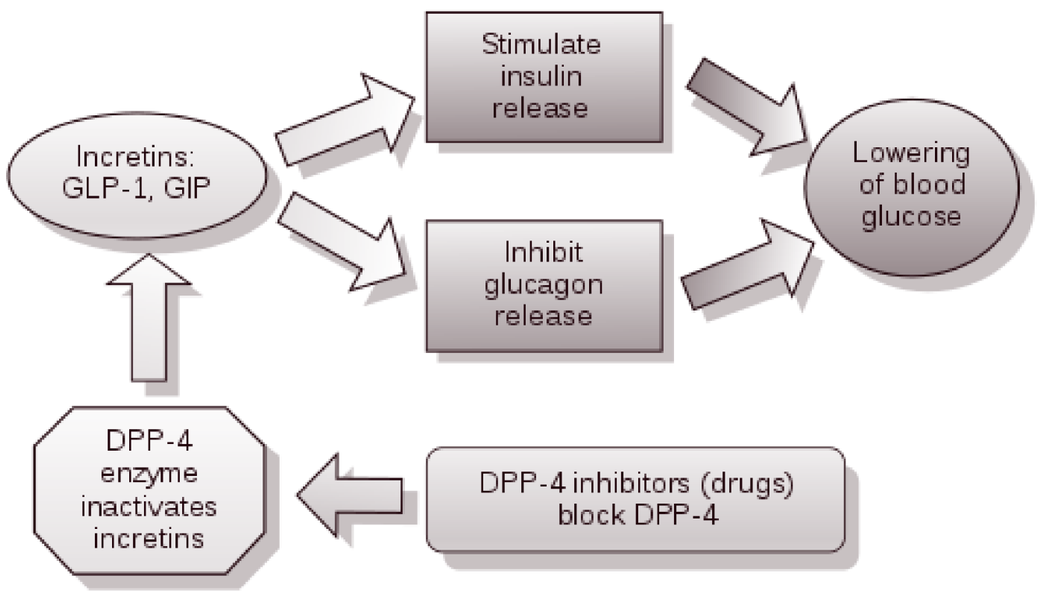
EFFECTS OF GLP-1

- GLP-1 is released in the gut in proportion to ingested calories.
- Reduction in gastric emptying and suppression of gastric acid secretion
- Anorexegenic effects

EFFECTS OF GIP

Along with GLP-1, GIP acts as an incretin to potentiate **glucose-stimulated insulin release**.

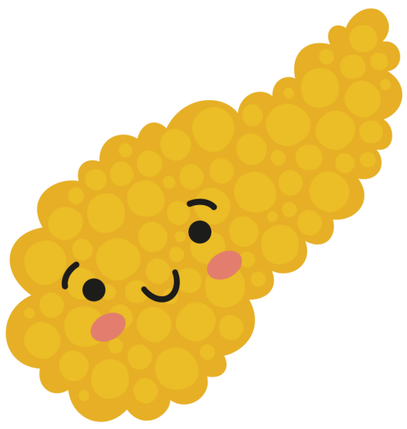
Direct **anabolic effects on adipose tissue**, including...
o Stimulation of glucose uptake
o Fatty acid synthesis
o Lipogenesis
o Inhibition of lipolysis



Clinical Cases, Ilmari Karonen, CC BY-SA 3.0, via Wikimedia Commons

LEARN MORE...

Mechanism of action of incretin mimetics. Beyond the basics.



PANCREAS

PHYSIOLOGY

Glucose homeostasis depends on the action of insulin and a host of other counterregulatory hormones. This finely tuned system depends on the action of hormones, neural stimuli, cytokines, and other regulatory cytokines working together in various organs to control plasma glucose. Indeed, the pancreatic beta-cell is pivotal in directing the orchestra of this complex homeostatic system.

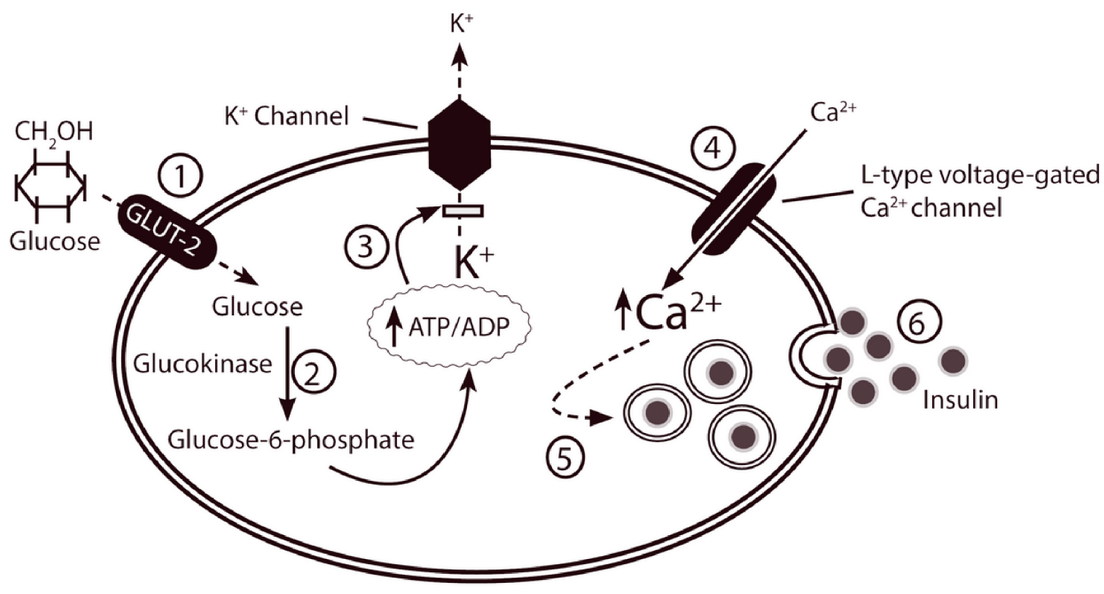
Fasting State

- Reduction in insulin promotes fatty acid oxidation in adipose tissue
- Glucagon promotes hepatic gluconeogenesis and glycogenolysis.

Postprandial State:

- Inhibition of hepatic glucose output (reduction in glycogenolysis and gluconeogenesis)
- Promotion of glucose uptake by peripheral tissues (muscle and adipose tissue
- Reduction in lipolysis (adipose tissue)

MECHANISM OF INSULIN RELEASE



Pancreatic beta cell

Glucose transporter 2 channels ferry glucose into the pancreatic beta-cell. This is followed by the phosphorylation of glucose into glucose-6-phosphate by **glucokinase**.

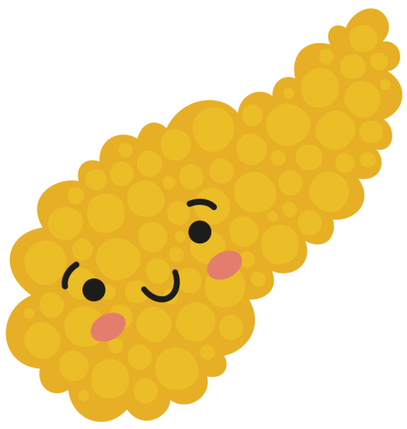
ATP generated as a consequence of glycolysis blocks **potassium channels** on pancreatic cell membranes, which consequently results in depolarization of the cell membrane.

Depolarization of pancreatic beta-cell membrane activates pancreatic **L-type voltage-gated calcium channels** – a process that funnels calcium into the pancreatic beta-cell. I**ncreased intracellular calcium** leads to the liberation of endocytic stores of insulin into the systemic circulation.

GLUCOSE TRANSPORTERS

Glucose transporters are required from shuttling glucose from the extracellular to intracellular compartment.

PHYSIOLOGY AND ANATOMY



PANCREAS

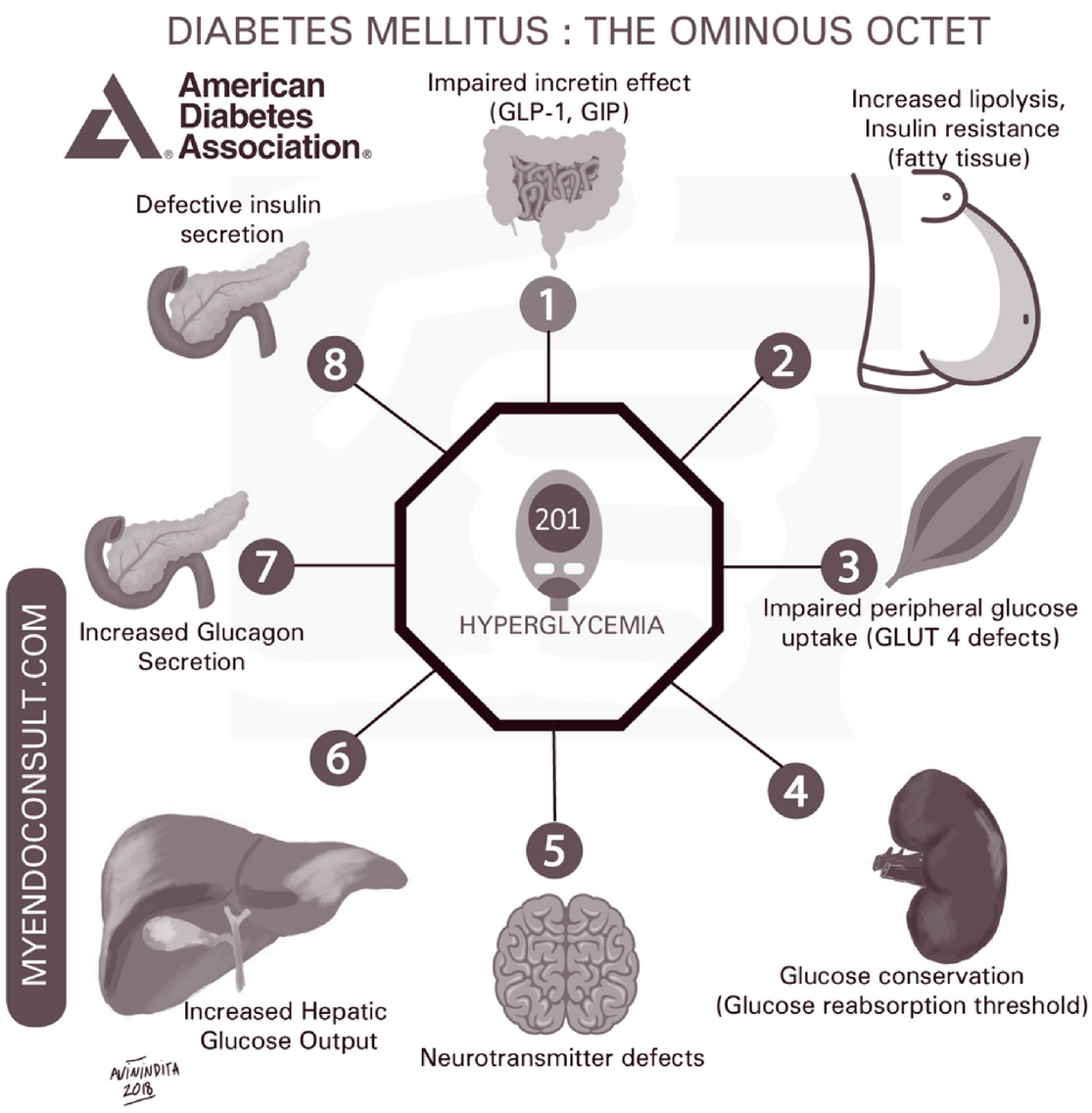
PATHOLOGY

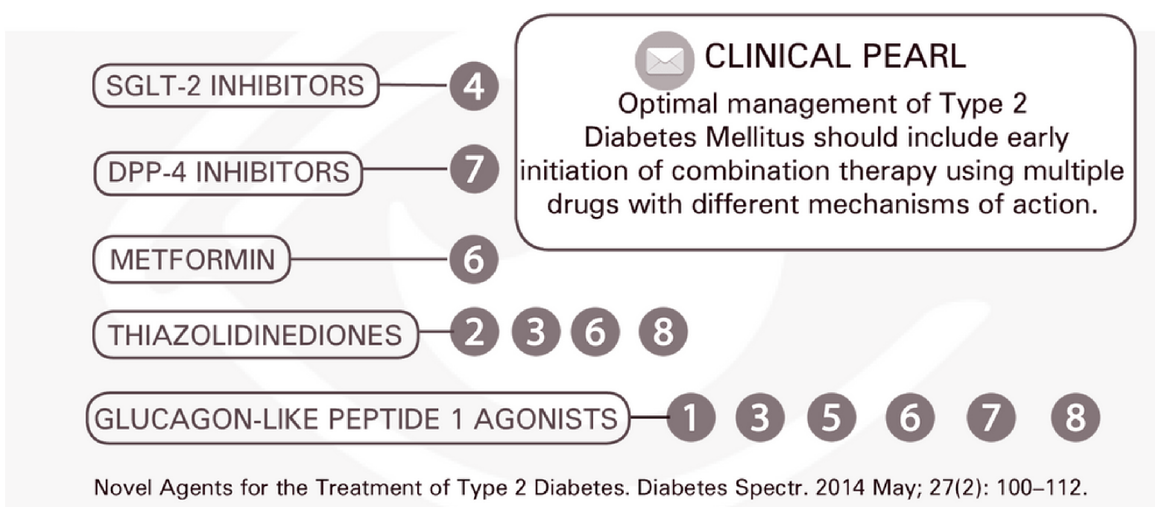
There are eleven known pathophysiologic defects that Type 2 diabetes mellitus (T2DM) is characterized by. These eleven features are often referred to as the **"egregious eleven"**.

The egregious eleven refers to the 11 core pathophysiologic defects of type 2 diabetes mellitus.

1. Pancreatic beta cell dysfunction
2. Loss of the incretin effect
3. Pancreatic alpha cell dysfunction
4. Adipose tissue dysfunction (insulin resistance)
5. Muscle tissue dysfunction (insulin resistance)
6. Liver dysfunction (insulin resistance)
7. Brain dysfunction
8. Colon dysfunction (Gut dysbiosis)
9. Immune system dysfunction
10. Low amylin levels
11. Kidney dysfunction

OMINOUS OCTET OF TYPE 2 DIABETES





PATHOPHYSIOLOGY OF T2DM

Learn about the core pathophysiologic defects in type 2 diabetes mellitus, from the ominous octet to the egregious eleven...

PHYSIOLOGY AND ANATOMY

LIPID METABOLISM

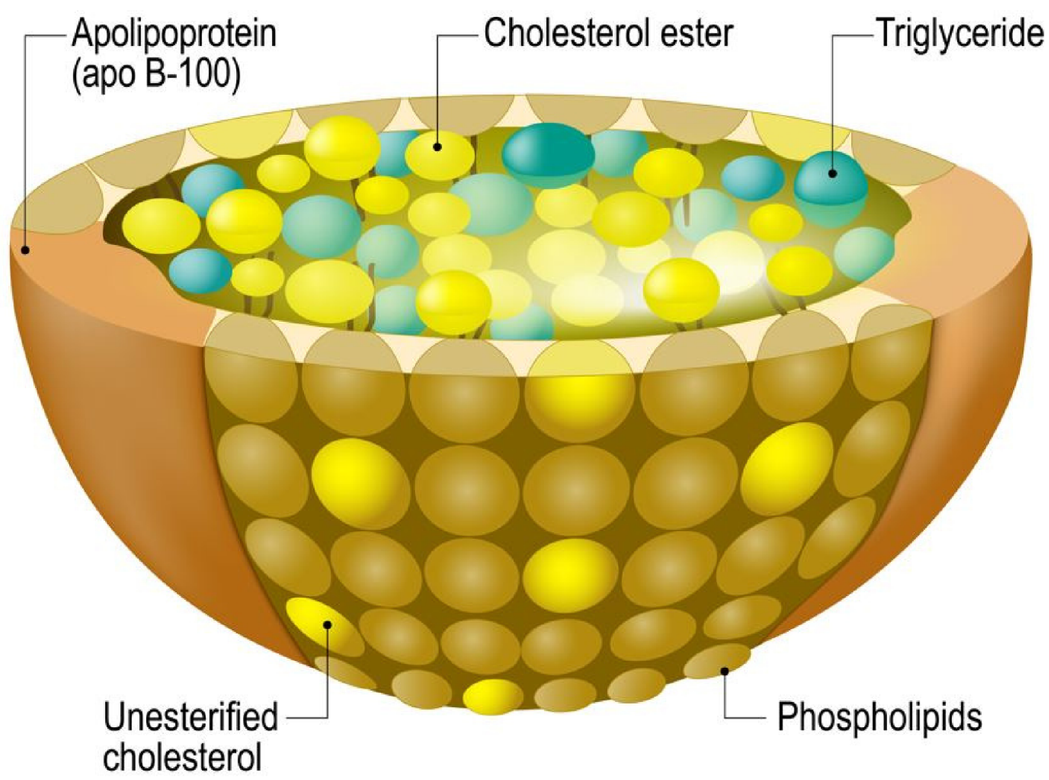
PHYSIOLOGY

What are lipoproteins?
They are a complex composition of cholesterol esters and triacylglycerols in a dense lipid core, with a circumferential rim of **free cholesterol**, **apolipoproteins**, and **phospholipids**.

This intricate configuration allows water-insoluble cholesterol and triacylglycerols to be ferried through the circulatory system to their target tissues.

The classification of lipoproteins depends on their size, lipid composition, and specific apolipoprotein subtype.
There are various lipoproteins, including....
low-density lipoprotein (LDL), high-density lipoproteins (HDL), very low-density lipoproteins (VLDL), intermediate-density lipoproteins (IDL) and chylomicrons.

STRUCTURE OF LIPOPROTEINS



WHAT ARE APOLIPOPROTEINS?

These **complex proteins** present on the surface of **lipoproteins** play critical roles in lipoprotein physiology by providing structural integrity to lipoproteins, modulating **lipoprotein-related enzymatic action**, and serving as ligands for various lipoproteins at specific target tissues

LIPOPROTEIN METABOLISM

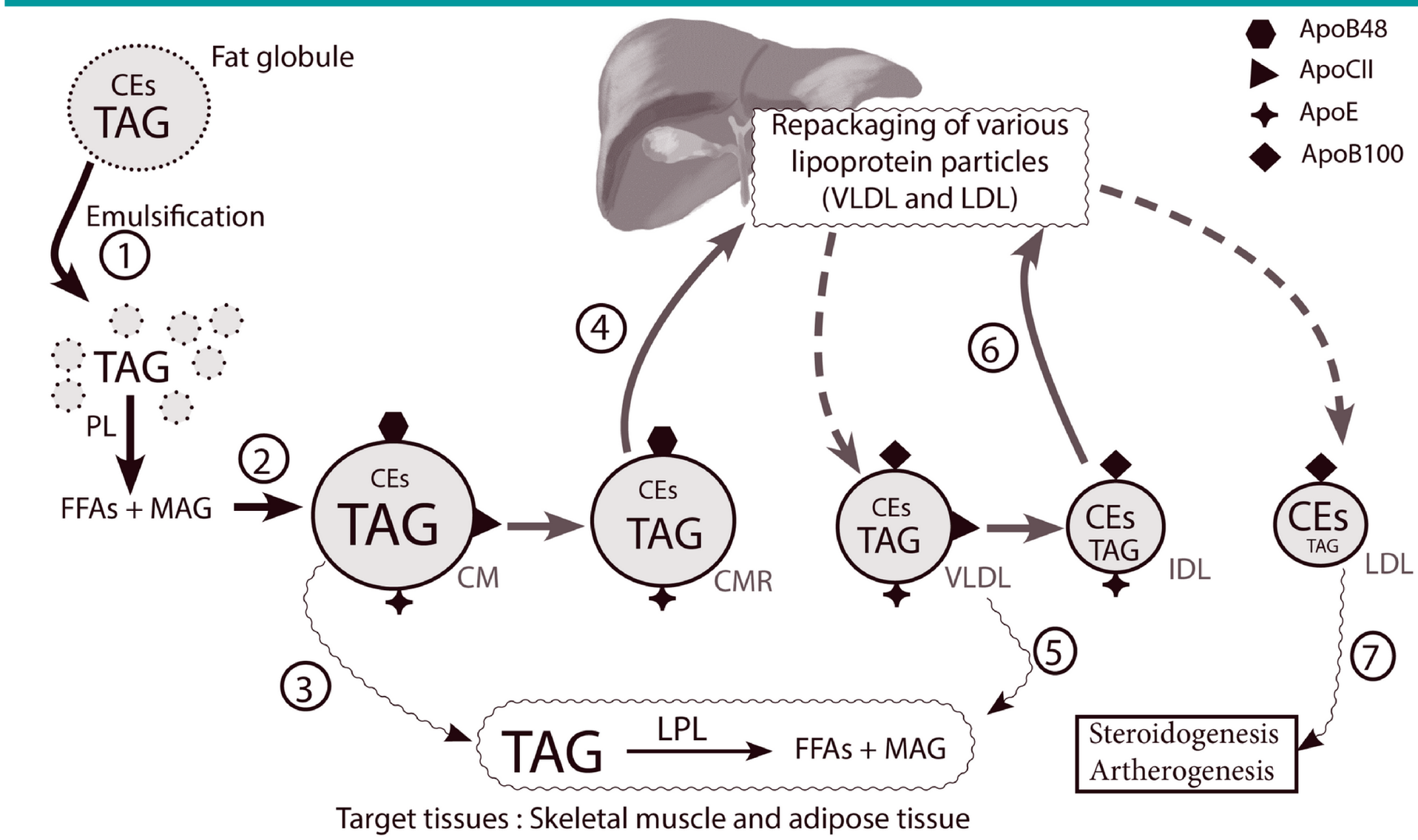
Review lipoprotein metabolism in this article.

LIPID METABOLISM

PHYSIOLOGY

Exogenous and Endogenous Lipoprotein Pathway

Lipoprotein metabolism aims to transfer dietary sources of triglycerides to both muscle and adipose tissue for energy metabolism and storage, respectively. It also facilitates the cycling of cholesterol between the liver and peripheral tissues, a process critical for the formation of steroid hormones, cell membranes, and bile acids.



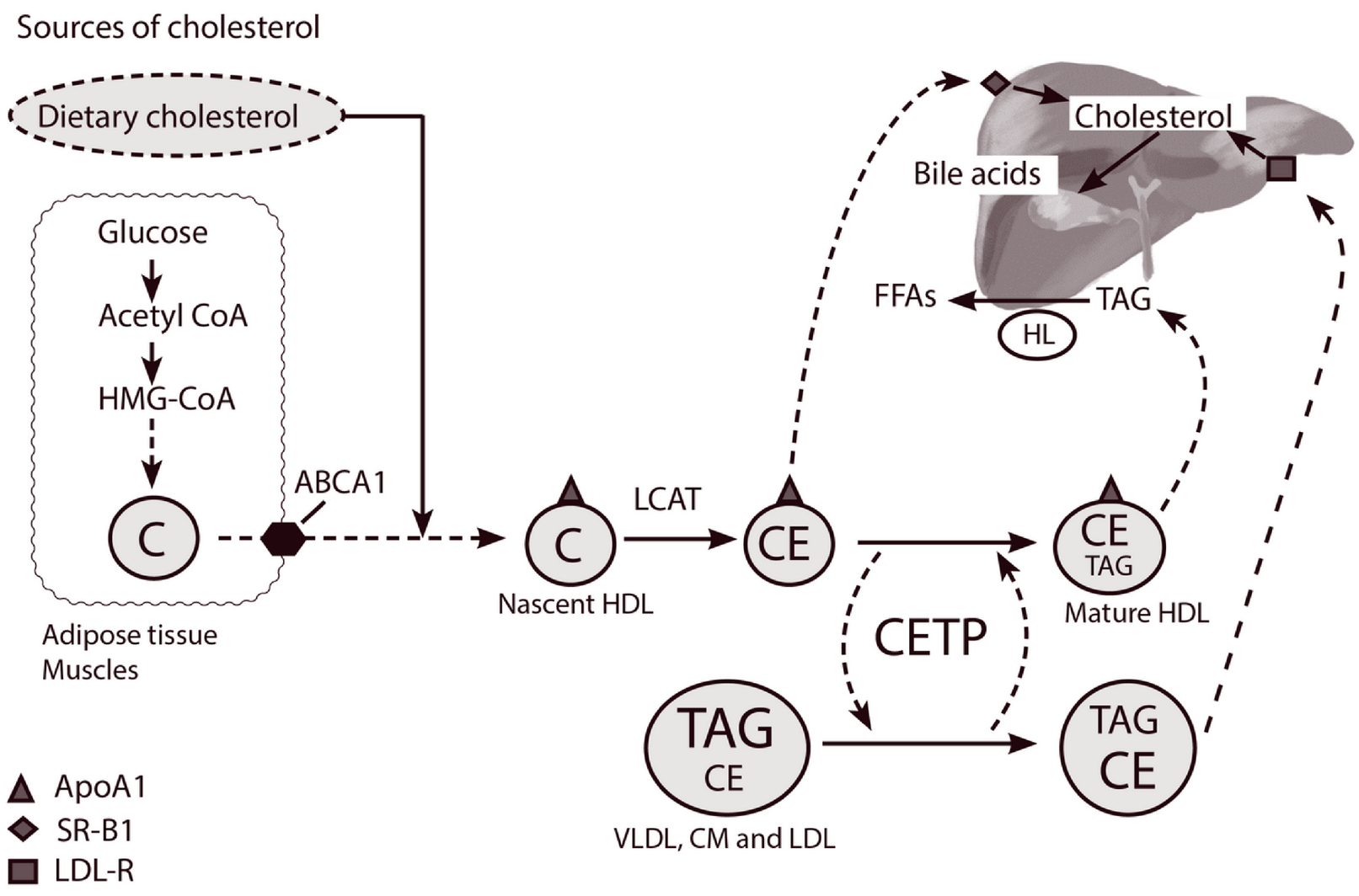
Emulsification of fat globules into tiny fat droplets by bile **(step 1)**, facilitates the hydrolysis of triacylglycerides (TAG) into free fatty acids (FFAs) and monoacylglycerol (MAG) by pancreatic lipase (PL) in the intestinal lumen. Chylomicron (CM) formed from repackaged TAG, cholesterol esters (CEs), and various apoproteins **(step 2)** are delivered to target tissues where TAG is hydrolyzed by lipoprotein lipase (LPL) **(step 3).** Chylomicron remnants (CMR) are transported to the liver for further processing **(step 4)**. VLDL released from the liver is destined for adipose tissue and skeletal muscle, where stores of TAG are released for hydrolysis by LPL**(step 5)**. IDL formed after VLDL processing in target tissues is destined for the liver **(step 6)**. LDL, a cholesterol ester (CE) rich lipoprotein, is critical in steroidogenesis in various tissues and plays a central role in atherogenesis(step 7)

LIPID METABOLISM

PHYSIOLOGY

Reverse Cholesterol Transport Pathway

HDL is responsible for transferring cholesterol and triglycerides from peripheral tissues back to the liver[19] and finally into the intestine for excretion



Free cholesterol from extrahepatic tissues (muscles and adipose tissue) is transferred to ApoA-1 to form the nascent HDL particle; this process is facilitated by **ATP-binding cassette transporter A1 (ABCA1)** present on the cell membrane of extrahepatic tissues (muscles, adipose tissue, and intestine).

Cholesterol (C) is then converted to cholesterol esters by **Lecithin cholesterol acyltransferase (LCAT)**, which is critical in the formation of mature HDL[10]. Cholesterol ester transfer protein (CETP) is essential in the transfer of cholesterol esters and triglycerides between other circulating lipoproteins (chylomicrons, VLDL, LDL) and HDL. CETP transfers CE's from HDL to other lipoproteins and carries TAGs from these lipoproteins back to the mature HDL particle. HDL, therefore, becomes rich in TAGs at the expense of CEs.

HDL binds to the **hepatic scavenger SR-B1 receptor**, where it releases its cholesterol esters without being internalized by the liver. It then returns to circulation as a smaller HDL particle, to repeat the process of cholesterol and triglyceride acquisition. HDL may also be hydrolyzed by hepatic lipase (HL) into FFAs, converting it back to a smaller HDL particle, which can then be recycled in the process of cholesterol acquisition. HDL can also bind the hepatic LDL-R receptor, a process that facilitates the release of cholesterol to the liver for bile acid synthesis