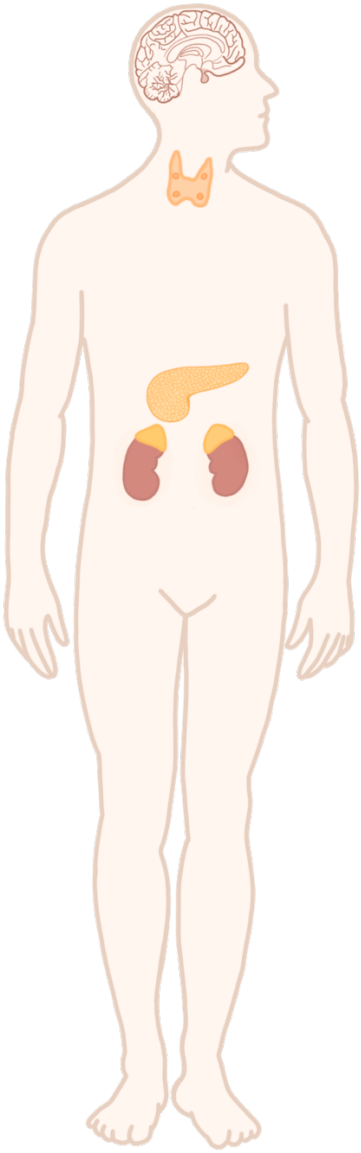

Endocrine Physiology

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First Edition
May 2020

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Booklet Disclaimer

About StudyAid

StudyAid is a student organization at the Jagiellonian University in Krakow. Throughout the academic year we host seminars in the major theoretical subjects: anatomy, physiology, biochemistry, immunology, pathophysiology, supplementing the lectures provided by the university. We are a group of 40 tutors, who are students at JUMC, each with their own field of specialty. To make our seminars as useful and relevant as possible, we teach in an interactive manner often using drawings and diagrams to help students remember the concepts. In addition to most seminars we create booklets, on which the seminars are based to aid the students in following the presentations. If you have any questions, do not hesitate to contact StudyAid at www.studyaid.no, we are always happy to answer any questions you may have academically related or not.

Table of Contents

Hormone Overview

Hormones and main function		
Anterior pituitary hormones	**Abbreviation**	**Main function**
Thyroid Stimulating Hormone	TSH	Release of thyroid hormone
Thyroid Hormone	TH	Increase metabolic rate
Follicle-Stimulating Hormone	FSH	Stimulates production of estrogen
Luteinizing Hormone	LH	Stimulates production of progesterone and estrogen
Growth Hormone	GH	Normal growth
Prolactin	-	Milk production
Posterior pituitary hormones	**Abbreviation**	**Main function**
Antidiuretic Hormone	ADH	Reabsorption of water
Oxytocin	-	Milk ejection
Sex Hormones	**Abbreviation**	**Main function**
Estrogen	-	Female development and reproduction
Testosterone	-	Male development
Other	**Abbreviation**	**Main function**
Parathyroid Hormone	PTH	Regulation of calcium concentration
Calcitonin	-	Decrease of calcium concentration
Vitamin D	-	Promotion of bone mineralization
Gonadotropin-releasing hormone	GnRH	Stimulates secretion of FSH and LH
Insulin	-	Stimulates intracellular movement and utilization of glucose
Glucagon	-	Stimulates glucose production in the liver
Somatostatin	-	Stops secretion of insulin, glucagon and gastrin

Section 1 – Introduction to the Endocrine System

1.1 – The Basics

I. What is a hormone?

- The endocrine system is responsible for a stable internal state in the body – called *homeostasis*. This system is regulated by release of hormones and their action on target tissues.
- Hormones are chemical substances, peptides, steroids or amines, which are secreted into the blood stream and attach to target receptors to produce a response.

Peptide hormones	Steroid hormones	Amine hormones
Most hormones in the body *Example:* Growth hormones, insulin, vasopressin	*Sex hormones* *Example:* Testosterone and estrogen	*Acute action hormones* *Example:* Epinephrine, norepinephrine, thyroid hormones
Synthesis		
mRNA ↓ Preprohormone (in the endoplasmic reticulum) ↓ prohormone (in the Golgi apparatus) ↓ **Peptide hormone**	Cholesterol ↓ removal or addition of side chains + hydroxylation or aromatization of the nucleus ↓ **Steroid hormone**	Tyrosine ↓ **Amine hormones**

1.2 – Regulation of Hormone Action

I. Homeostasis

- To keep an internal steady state, the body needs to send signals to the endocrine glands to tell them either to turn up or slow down production, and this process is called homeostasis.
- Neuronal mechanism: a nerve directly innervates the endocrine gland. This is seen in the secretion of catecholamine's after sympathetic nerve stimulation of the adrenal gland.
- Feedback mechanism: some part of the hormonal pathway gives feedback to the endocrine gland, telling it "there are enough of us – slow down", or "we need more!". Negative feedback is a lot more common than positive feedback.

Autocrine	Cell signal targets itself
Paracrine	Cell signal targets a nearby cell
Endocrine	Cell signal targets distant cells through the blood stream

II. Negative feedback

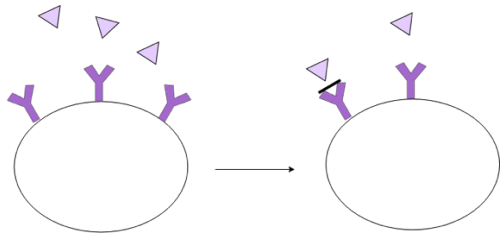
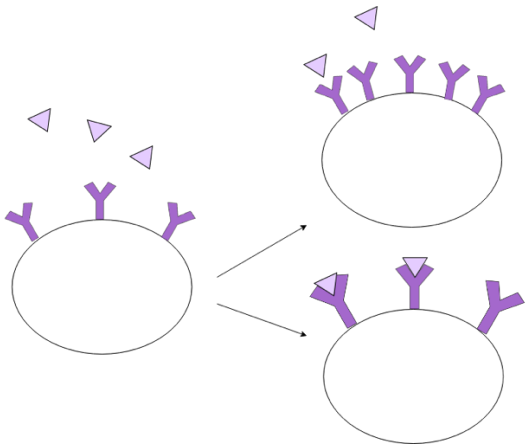
- The body's natural break. When a hormone reaches a certain level, it will either directly or indirectly "pull the break" on further production.
- *Example*: insulin is secreted by pancreatic β-cells after a meal. Its job is to facilitate the transport of glucose into the cells. This results in hypoglycemia (low blood glucose levels). Hypoglycemia works as a break on insulin secretion, decreasing the concentration of insulin and preventing hypoglycemic shock every time you eat.

III. Positive feedback

- The natural gas pedal of the body. Hormone actions stimulates more hormone secretion, «stepping on the gas» of production.
- *Example*: the estradiol surge seen in ovulation in reproductive women. See the «Female reproductive physiology» section for more details on this.

1.3 – Regulation of Hormone Receptors

- *Down-regulation* is a control mechanism to reduce the reaction of the body to a hormone if the hormone levels are high over time.
- *Up-regulation* is a mechanism where a hormone will increase the number of receptors or the affinity of the receptors in target tissues. This makes the tissue more sensitive to a hormone.

Down-regulation	Up-regulation
	
↓ sensitivity[1]	↑ sensitivity
↓ production of receptors ↑ degradation **↓ affinity**[2]	↑ production of receptors ↓ degradation ↑ affinity
Example: Triiodothyroine (T3) decreases the sensitivity of thyrothropin-releasing hormone (TRH) in the anterior pituitary. Chronically high levels of T3 will down-regulate the TRH receptor and decrease the production in the hypothalamic-pituitary-thyroid axis.	*Example: Prolactin increases its number of receptors in the breasts during pregnancy, increaseing the sensitivity of breast tissue to prolactin.*

[1]Sensitivity is the hormone concentration producing 50% of the maximal response possible.
[2]Affinity is the degree to which a substance tends to combine with another.

1.4 – Hormone Action on Target Cells

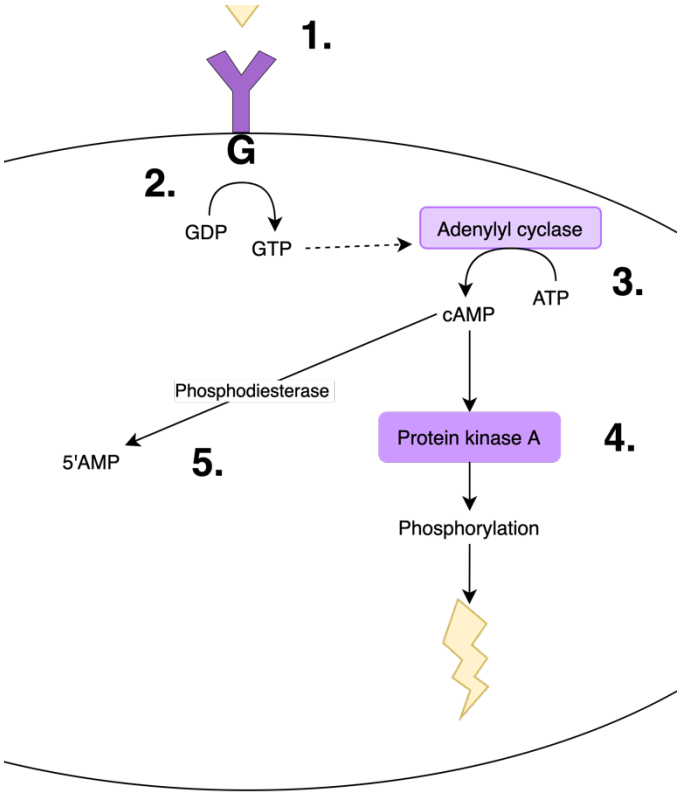
I. The hormone-receptor complex

- The hormone binds to the membrane receptor creating a hormone-receptor complex.
- This complex stimulates an effector protein that stimulate a second messenger which amplifies the hormonal signal and creates the physical action.
- There are many different types of receptor complexes, second messengers and responses. Below are some of the most common.

II. Adenylyl cyclase mechanism

- Some of the hormones that use the adenylyl cyclase mechanism are adrenocorticotropic hormone (ACTH), luteinizing hormone (LH), follicle-stimulating hormone (FSH) and parathyroid hormone (PTH).

Adenylyl cyclase



1. Hormone binds to receptor in cell membrane. GDP is replaced by GTP → activation of G protein

2. The *receptor-GTP complex* detaches and migrates within the cell membrane to bind and activate adenylyl cyclase

3. Activated adenylyl cyclase concerts ATP → cAMP[1]

4. cAMP activates protein kinase A and phosphorylates intracellular proteins, causing the final physiological action

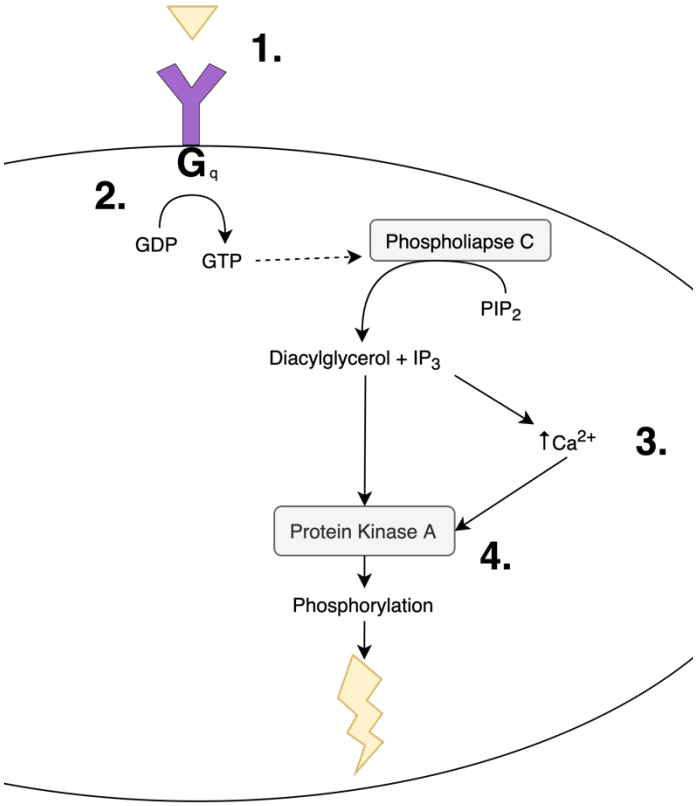
5. The enzyme phosphodiesterase inactivates cAMP by turning it into 5'AMP → ending the signal

[1] Cyclic adenosine monophopate

III. Phospholipase C mechanism

- Some of the hormones that use the phospholipase C mechanism are gonadotrophin-releasing hormone (GnRH), thyrotropin-releasing hormone (TRH), angiotensin and oxytocin.

Phospholipase C



1. Hormone binds to cell membrane receptor. GDP is replaced by GTP → Gq protein is activated

2. The *receptor-GTP complex* binds to and activates phospholipase C protein. This protein catalyzes phosphatidylinositol 4,5-diphosphage (PIP_2) into IP_3 + diacylglyceril

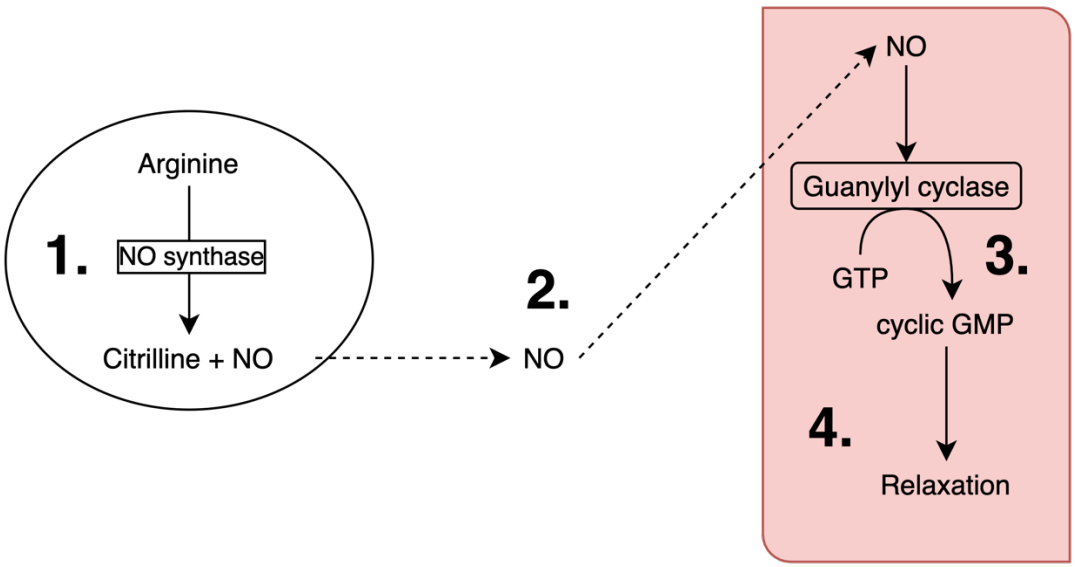
3. IP_3 stimulates release of Ca^{2+} from endoplasmic or sarcoplasmic reticulum

4. ↑ Ca^{2+} diacylglycerol activates protein kinase A, which phosphorylates proteins, causing the final physiological action

IV. Catalytic receptor mechanisms

- Some hormones bind to cell surface receptors that have enzymatic activity on the intracellular side of the cell membrane
- Guanylyl cyclase is one of those catalytic receptors, which is used by atrial natriuretic peptide (ANP) and nitric oxide (NO)

Nitric oxide (NO)



1. NO synthase cleaves arginine into citrulline + NO
2. NO diffuses out of the endothelial cell and into nearby vascular smooth muscle cells
3. NO binds to and activates cytosolic guanylyl cyclase. GTP is converted to cyclic GMP
4. ↑ cyclic GMP cause vascular smooth muscle relaxation

CLINICAL CORRELATION

Angina pectoris (chest pain)

NO is used therapeutically in angina pectoris. Atherosclerotic plaques can cause narrowing of the coronary vessels. When you have increased activity, the O_2 demand of the cardiac muscle cells will not be met, causing chest pain. Sublingual (rapid effect) nitroglycerin may be given and will in many cases give instant relief as NO will diffuse to the coronary vessel cells, stimulate guanylyl cyclase and cause vascular relaxation → widening of the lumen (vasodilation) and more blood to the cardiac muscle cells.

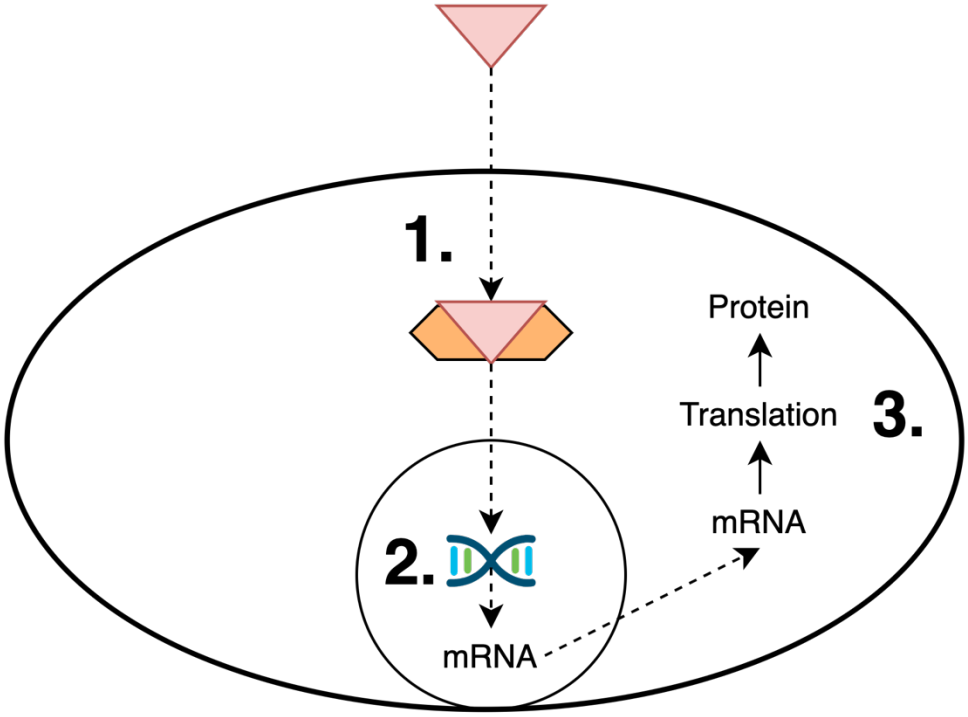
VI. Tyrosine kinase

- Hormones binds to extracellular receptors associated with intracellular tyrosine kinase
- Insulin and growth hormone are two examples of hormones using tyrosine kinase, and they will be discussed in further detail later in this booklet.

VII. Steroid and thyroid hormone receptors

- Steroid hormones bind to cytosolic receptors that initiate DNA transcription and synthesis of proteins.
- In contrast to the previously discussed receptors with adenylyl cyclase and phospholipase C mechanism, steroid hormones act slowly over several hours and not seconds/minutes.

Steroid hormone



1. Steroid hormone, being hydrophobic, diffuses into the target cell. Here it binds to the specific receptor protein located either in the cytosol or nucleus. The hormone-receptor complex diffuses into the nucleus.

2. Hormone-receptor complex dimerizes and binds to a specific part of the DNA, called *steroid-responsive element* (SRE), located on the 5' region of the target gene.

3. The complex is now a transcription factor. New mRNA is transcribed. It will leave the nucleus and translate into a protein.

1.5 – Test Yourself

1) Fill in the table

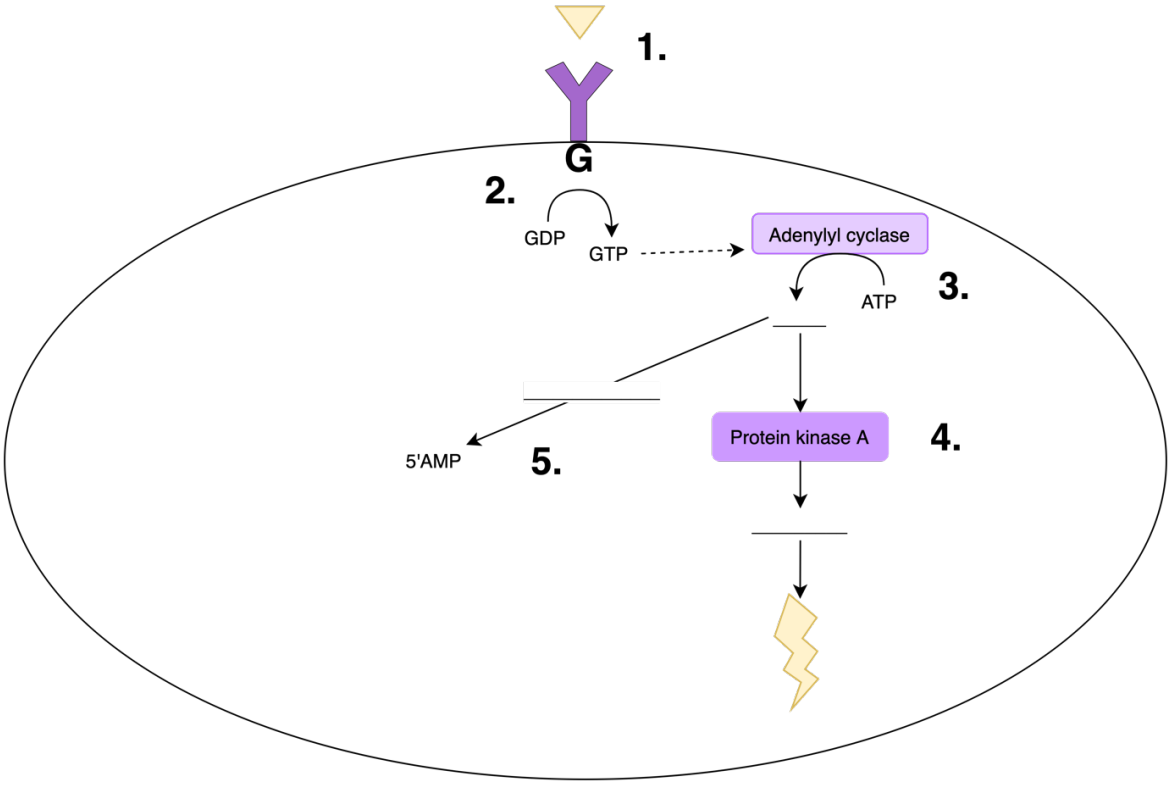
Autocrine	
Paracrine	
Endocrine	

2) Which of the following is <u>not</u> seen in down-regulation of a hormone receptor?

a) ↑sensitivity
b) ↓affinity
c) ↓production of receptors
d) ↑degradation of receptors

3) Fill in the gaps

Use 3 of the following words: cAMP, IP_3, PIP_2, dephosphorylation, phosphorylation, NO synthase, Phosphodiesterase, Phosphate kinase A



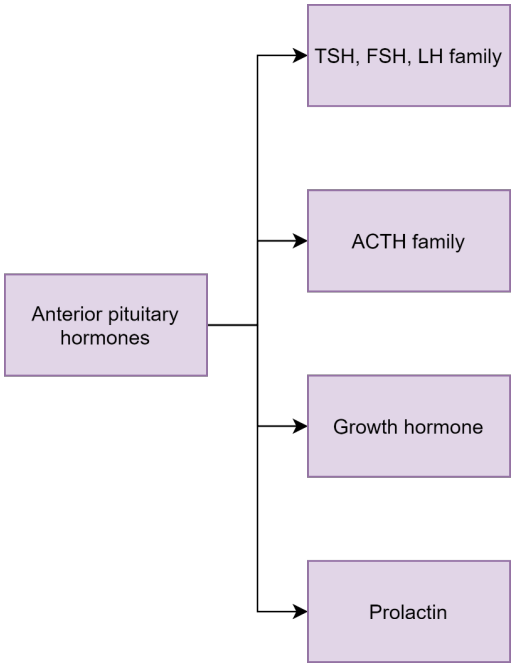
4) Sort the following hormones according to the second-messenger system they use

Insulin	Growth hormone	Oxytocin
ACTH	PTH	LH
GnRH	Angiotensin	FSH

Adenylyl-cyclase system	Phospholipase C	Tyrosine kinase

Section 2 – The Anterior Pituitary

2.1 – Overview

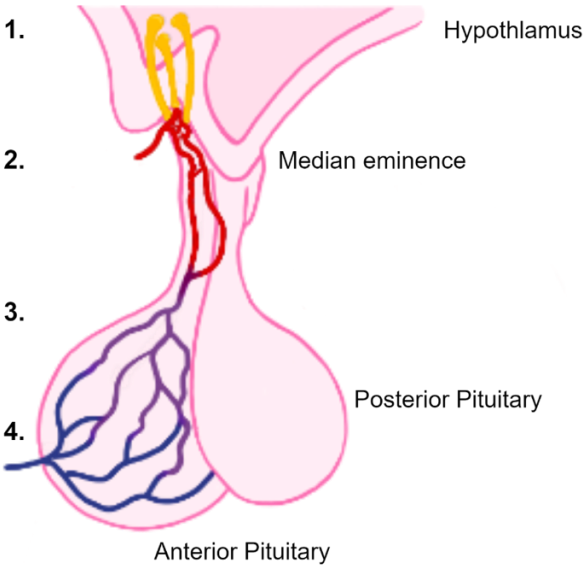


I. The hypothalamus and the pituitary gland

- The hypothalamus and the pituitary gland function together to regulate other glands, such as the thyroid, adrenal, and reproductive glands.
- The pituitary gland, also known as the hypophysis, consists of two lobes: the anterior lobe; the adenohypophysis, and the posterior lobe; the neurohypophysis.
- The hypothalamus controls the pituitary by neural and hormonal mechanisms, initiating the secretion of pituitary hormones.

II. The relationship between the hypothalamus and anterior pituitary

- The anterior pituitary gland is a collection of endocrine cells. The connection between the hypothalamus and anterior pituitary is both neural and endocrine.
- The hypothalamus and anterior pituitary are linked by portal blood vessels. Consequently, most of the blood supply of anterior pituitary is venous blood from the hypothalamus.



1. The hypothalamus synthetizes its own hypothalamic-releasing or inhibiting hormones in its own cell bodies
2. The hormones travel down the axons to the median eminence of the hypothalamus. There, hormones are secreted into the nearby capillary plexus upon stimulation.
3. The venous blood from those capillaries drains into hypophyseal portal vessels and delivers the hypothalamic hormones to the anterior pituitary
4. The hypothalamic hormones stimulate or inhibit secretion of the anterior pituitary hormones into systemic circulation

2.2 – Growth Hormone

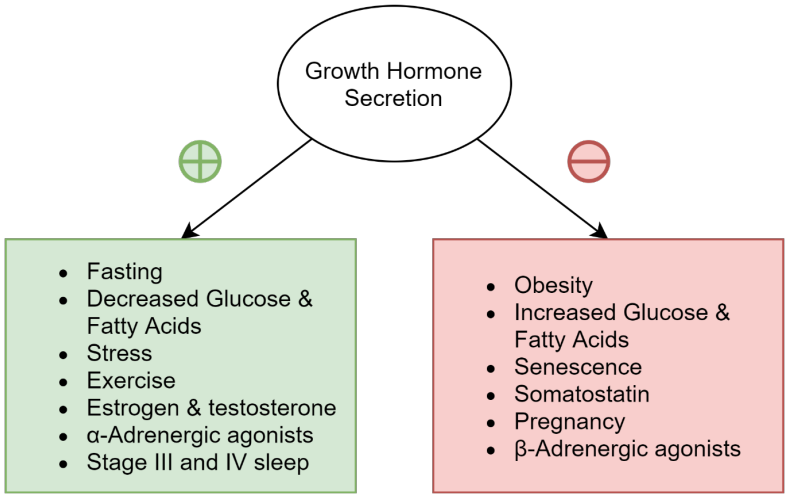
I. Overview

- The growth hormone, also known as somatotropin, is responsible for normal growth to adult stature, secreted throughout life.
- The highest rates of secretion are during puberty, causing the growth spurt. The secretory burst is induced by estrogen in females and by testosterone in males.
- Lowest levels of secretion are seen in the elderly

Regulation of secretion	Synthesis is stimulated by GHRH[1] from hypothalamus. Secreted in a pulsatile pattern every 2 hours.
Actions	<u>Diabetogenic</u> ↓ glucose utilization and ↑ lipolysis → ↑ blood glucose and ↑ insulin levels → insulin resistance, over time <u>Increased organ growth</u> ↑ protein synthesis and uptake <u>Increased bone growth</u> ↑ production of IGF[2] in the liver resulting in ↑ DNA synthesis ↑ DNA synthesis causes lengthening of long bones, widening of epiphyseal plates, and proliferation of chondrocytes
Deficiency	- Affects children - Manifests as short stature, mild obesity, delayed puberty - Treated with hormone replacement therapy
Excess production	- Affects both children and adults - Manifests as tall stature, enlarged hands and feet, and coarse facial features - Treated with somatostatin analogues, like octreotide, by decreasing production

[1]Growth hormone releasing hormone
[2]Insulin-like growth factors

II. Factors influencing growth hormone secretion



2.3 – Prolactin

- Major functions are growth, development, and lactation of breasts during pregnancy
- Prolactin is only active during pregnancy and lactation

Regulation of secretion	Unless pregnant or lactating, prolactin is physiologically inhibited by dopamine
Actions	<u>Breast development</u> Along with estrogen and progesterone, prolactin stimulates proliferation of mammary ducts at puberty and growth of mammary alveoli during pregnancy <u>Lactogenesis</u> - Prolactin levels ↑ during pregnancy, but its receptors in the breasts are inhibited by estrogen and progesterone until after delivery - Milk production is stimulated by suckling <u>Inhibition of ovulation</u> - Prolactin inhibits GnRH - It is responsible for ↓ fertility during breast-feeding

<u>CLINICAL CORRELATION</u>

Prolactinoma

- The most common pituitary adenoma (tumor in the pituitary gland), that results in excess prolactin (hyperprolactinemia)
- Manifests as galactorrhea (lactation in men or non-breastfeeding women)
- Treated with a dopamine agonist

2.4 – Test Yourself

1) Fill in the blanks

The connection between the hypothalamus and anterior pituitary is both _____and _____.
Most of the blood supply of anterior pituitary is venous blood from the _____.
The secretion of the anterior pituitary hormones into systemic circulation is stimulated or inhibited by _____or_____.

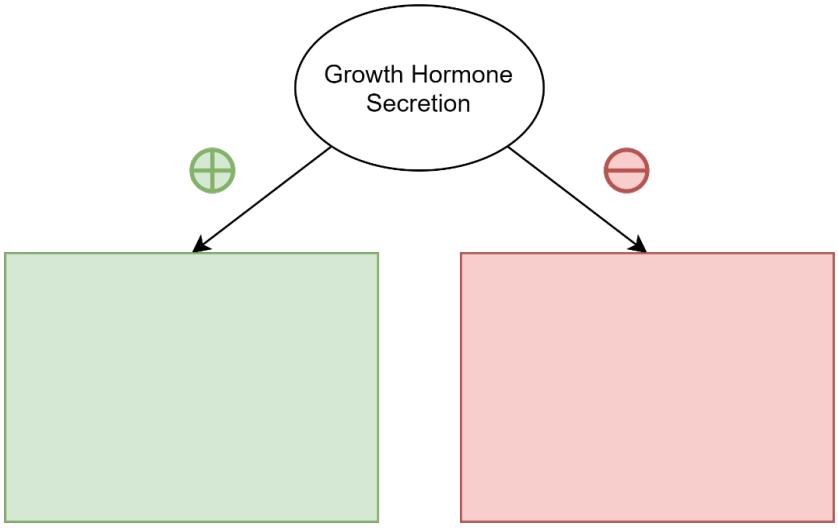
2) When is growth hormone secreted the most?

_____

_____

3) Arrange the following factors for growth hormone secretion into the proper boxes:

Sleep, Stress, Estrogen, Somatostatin, Increased Glucose, Pregnancy, Fasting



4) Which of the following is NOT an action of growth hormone?

a) increased insulin resistance
b) increased glucose utilization
c) increased lipolysis
d) increased organ growth
e) increased linear bone growth

5) What are the actions of prolactin?

a) Breast development
b) Lactogenesis
c) Ovulation
d) a and b
e) all of the above

6) Which hormone physiologically inhibits prolactin?

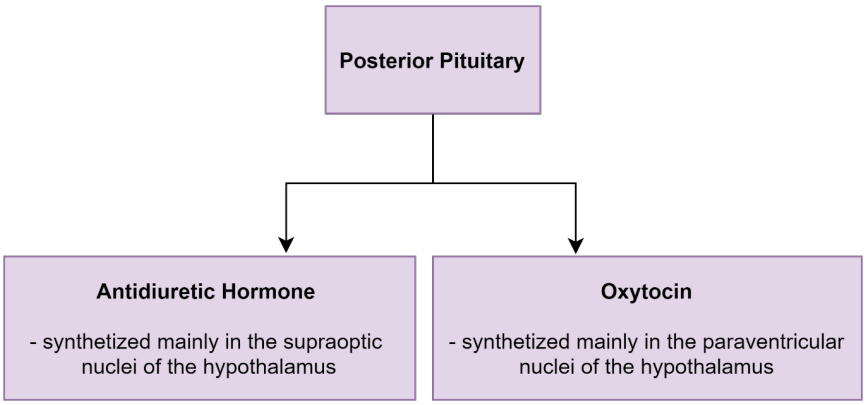
a) Estrogen
b) Progesterone
c) Testosterone
d) Dopamine
e) Norepinephrine

Section 3 – The Posterior Pituitary

3.1 – Overview

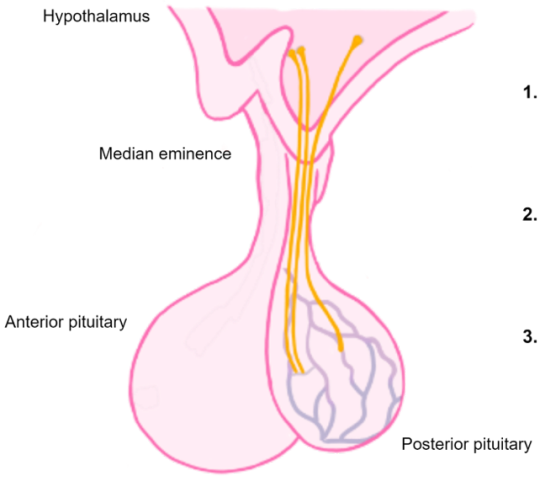
I. The hormones

- The posterior pituitary secretes two hormones (neuropeptides): antidiuretic hormone (ADH) and oxytocin.
- The main function of ADH is reabsorption of water
- The main function of oxytocin is milk letdown.



II. Relationship between the hypothalamus and the posterior pituitary

- The posterior pituitary is a collection of nerve axons whose cell bodies are in the hypothalamus. The connection between the hypothalamus and posterior pituitary is neural.



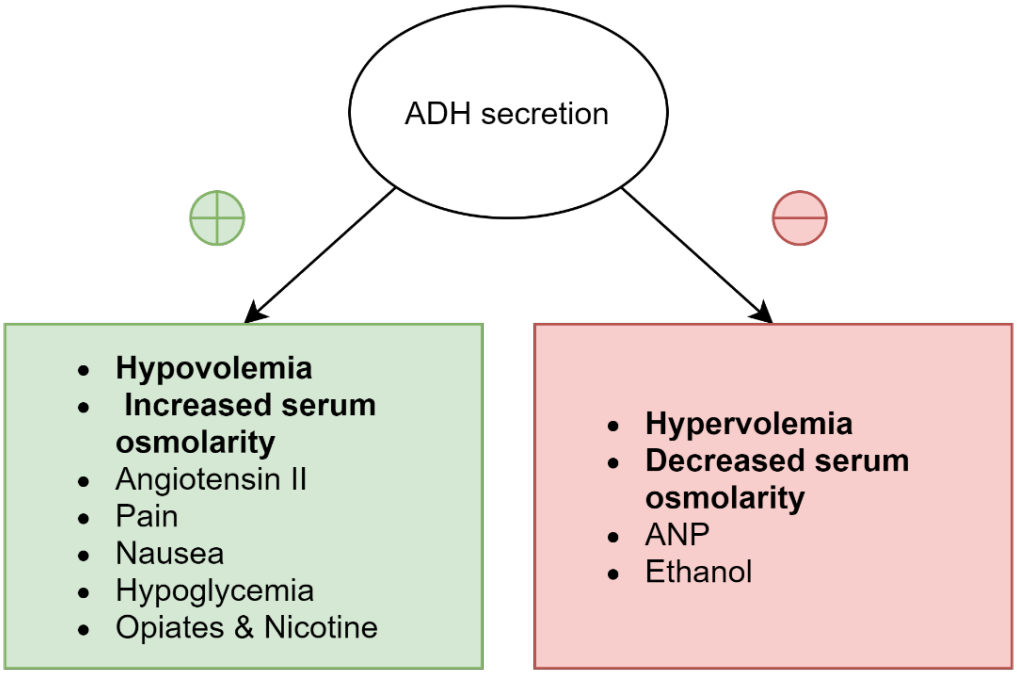
1. The cell bodies located in the hypothalamus synthetize ADH and oxytocin
2. The two hormones are transported down the axons in neurosecretory vesicles to be stored in nerve terminals of the posterior pituitary
3. Once the cell body is stimulated, the vesicles are released by exocytosis into systemic circulation to their target tissues

3.2 – Antidiuretic Hormone

I. Overview

- Antidiuretic hormone (ADH) is also called vasopressin
- Plays a major role in controlling serum osmolality

II. Factors influencing ADH secretion



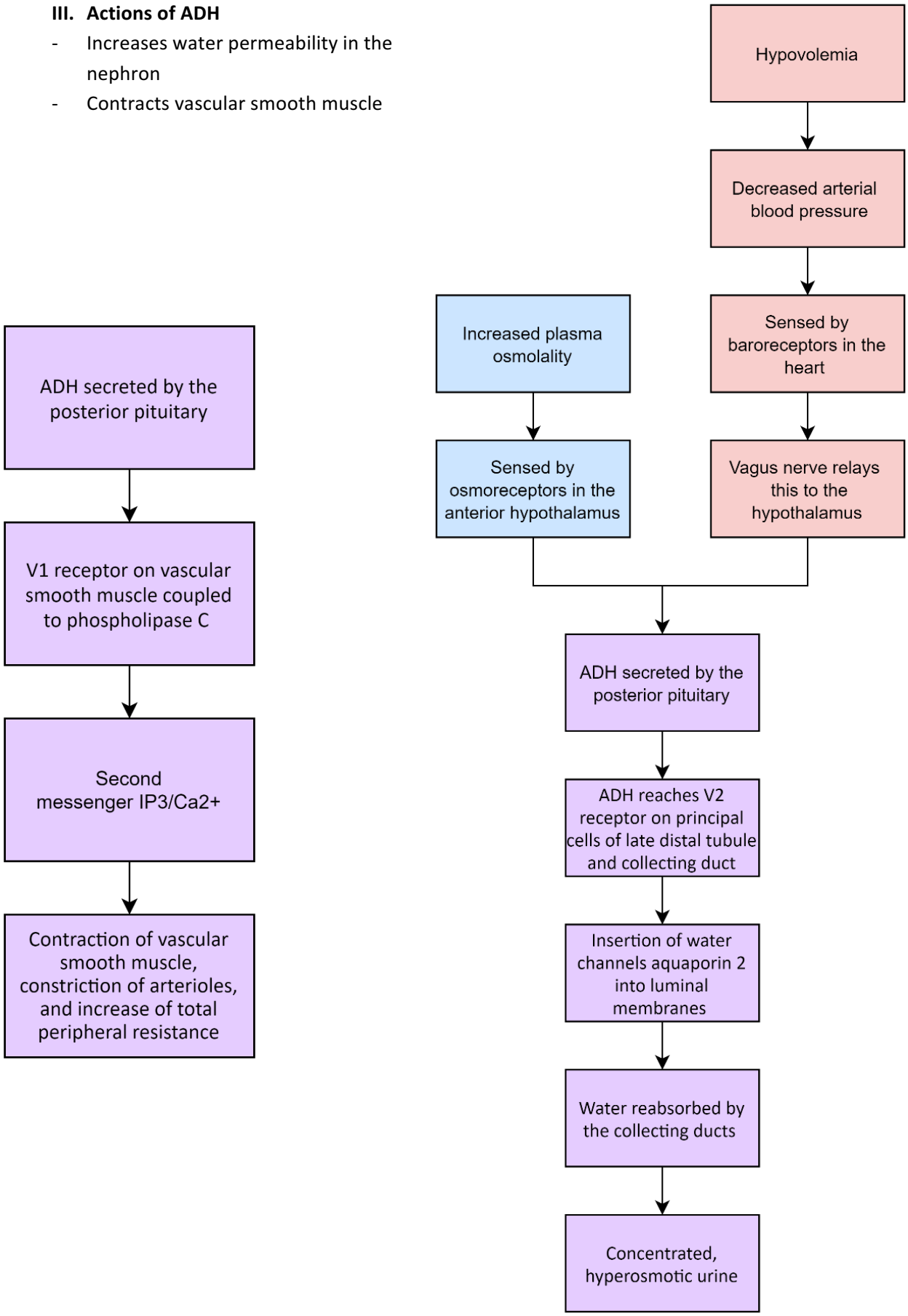
CLINICAL CORRELATION

Diabetes Insipidus

- A disorder where there is ↓ action of ADH; either by ↓ secretion or by receptor resistance
- Results in dilute urine with increased serum osmolality

III. Actions of ADH

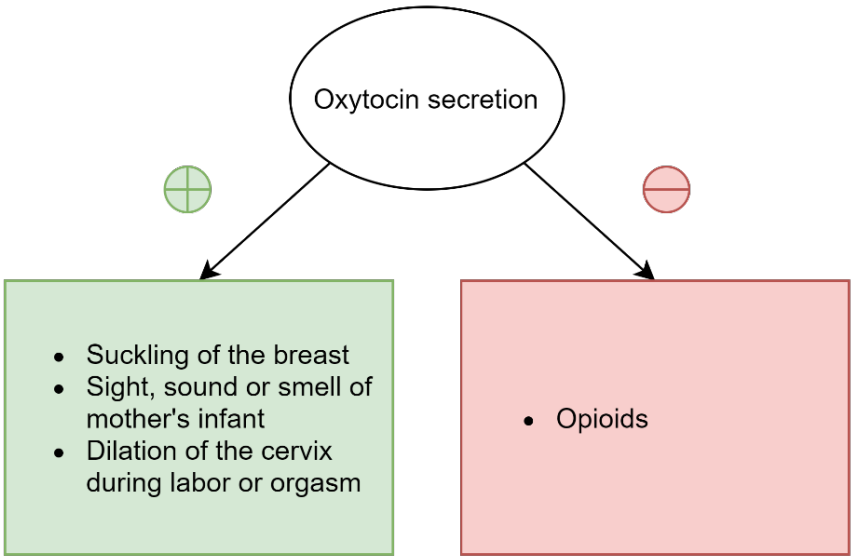
- Increases water permeability in the nephron
- Contracts vascular smooth muscle



3.3 – Oxytocin

- Stimulates milk ejection from the lactating breast

I. Factors influencing oxytocin secretion



II. Actions of oxytocin

- Milk letdown: Stimulation → contraction of myoepithelial cells in mammary alveoli and ducts → milk flows into larger ducts
- Uterine contraction: Undefined role during labor

CLINICAL CORRELATION

Therapeutic use of oxytocin

Oxytocin is used therapeutically for inducing labor and decreasing postpartum bleeding.

3.4 – Test Yourself

1) Fill in the blanks

The posterior pituitary is a collection of _____ whose cell bodies are in the _____.
Therefore, the connection between the hypothalamus and posterior pituitary is _____.
The posterior pituitary hormones are transported down the axons in _____ to be stored in nerve terminals of posterior pituitary.

2) Where is Oxytocin mainly produced?

a) paraventricular nuclei of the hypothalamus
b) supraoptic nuclei of the hypothalamus
c) paraventricular nuclei of the posterior pituitary
d) supraoptic nuclei of the posterior pituitary

3) What are the two main actions of ADH?

_____

_____

_____

4) Water reabsorption induces by ADH occurs mainly in which part of the nephron?

a) proximal convoluted tubule
b) descending loop of Henle
c) ascending loop of Henle
d) distal convoluted tubule
e) collecting duct

5) What are the two main roles of Oxytocin?

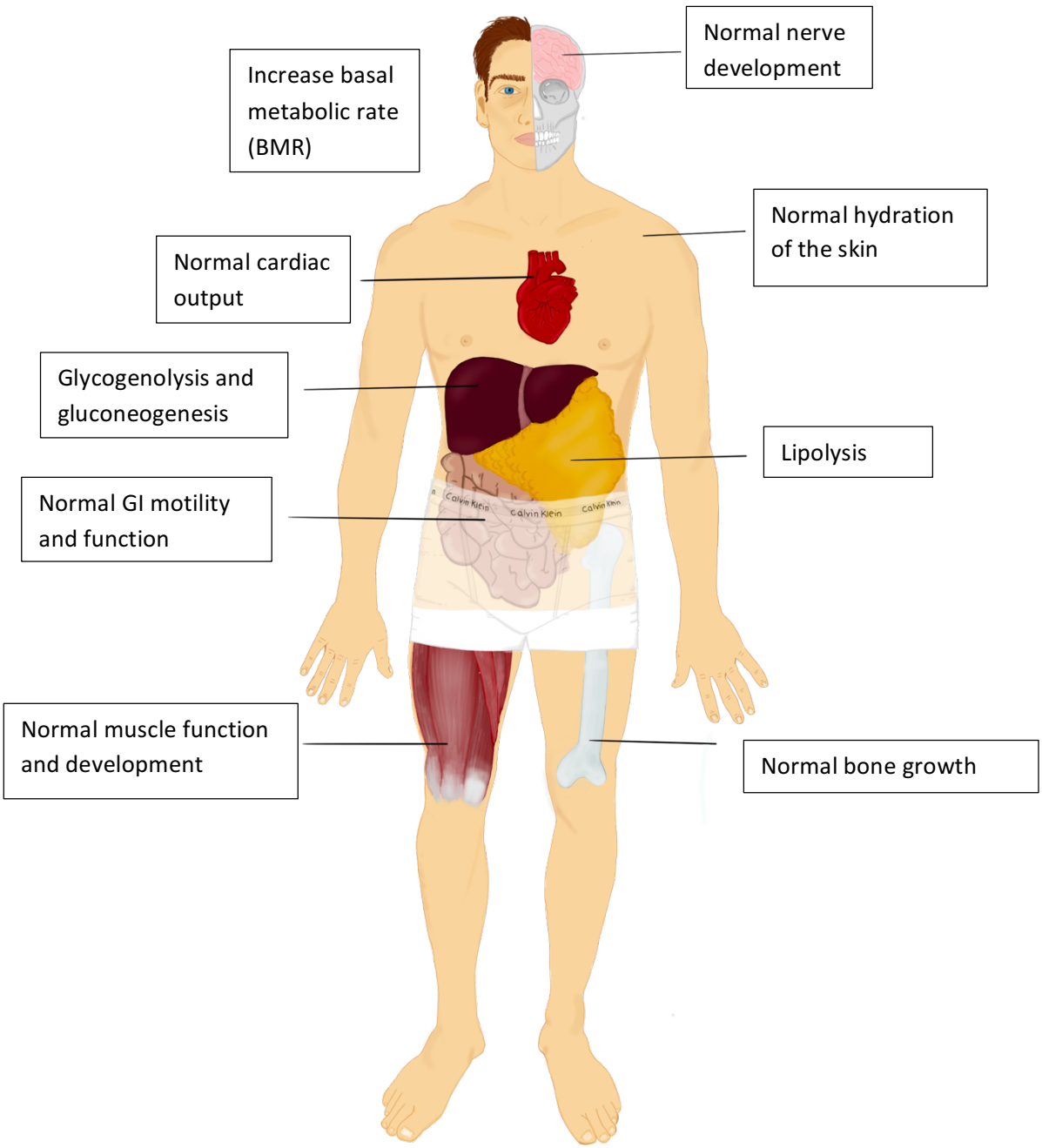
_____

_____

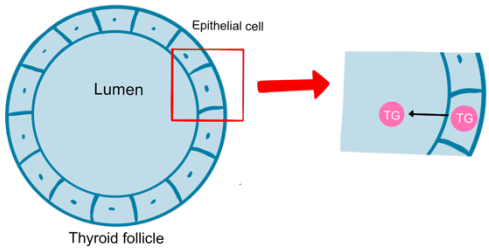
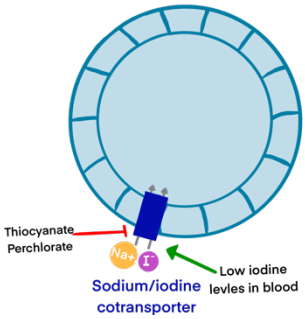
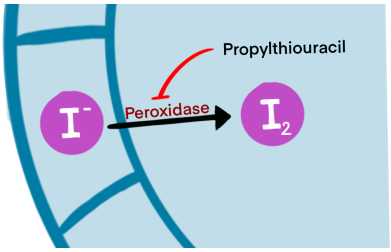
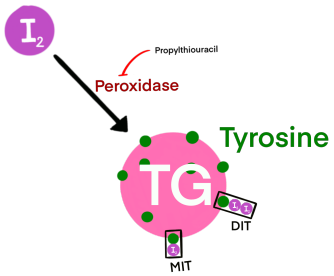
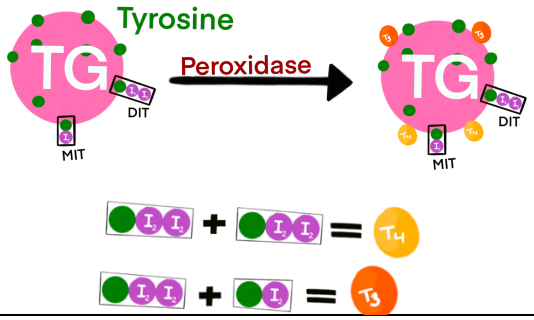
_____

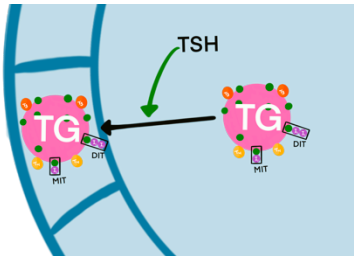
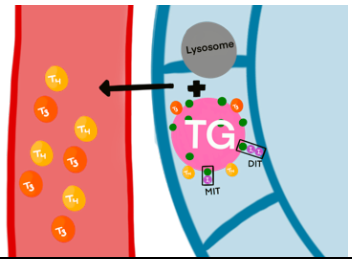
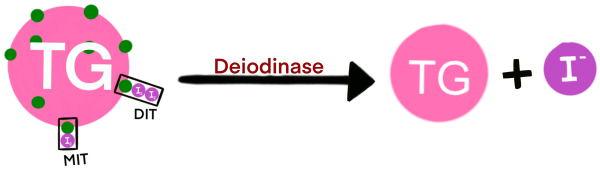
Section 4 – The Thyroid Gland

4.1 – General Function of the Thyroid Gland



4.2 – Synthesis of Thyroid Hormones

Steps		
1		Follicular epithelial cells Thyroglobulin (TG) Thyroglobulin is then secreted into the follicular lumen
2		In response to low Iodine levels in the blood the Sodium (Na^+)/Iodine (I^-) cotransporter is activated to work against the electrochemical gradient
3		I^- is oxidized to I_2 by the enzyme peroxidase
4		I_2 binds tyrosine moieties on thyroglobulin to form mono- and diidotyrosine (MIT and DIT respectively)
5		MIT and DIT bind together and form the thyroid hormones

6		Thyroglobulin with thyroid hormones, MIT and DIT moieties move from the lumen to the follicular epithelial cells in response to thyroid stimulating hormone (TSH)
7		Thyroglobulin fuse with lysosome and the bonds between thyroglobulin and thyroid hormones are hydrolyzed. The free thyroid hormones move into the blood
8		MIT and DIT is “recycled” and the free thyroglobulin and I- enters the synthesis cycle again

4.3 – Transport of Thyroid Hormones in the Blood

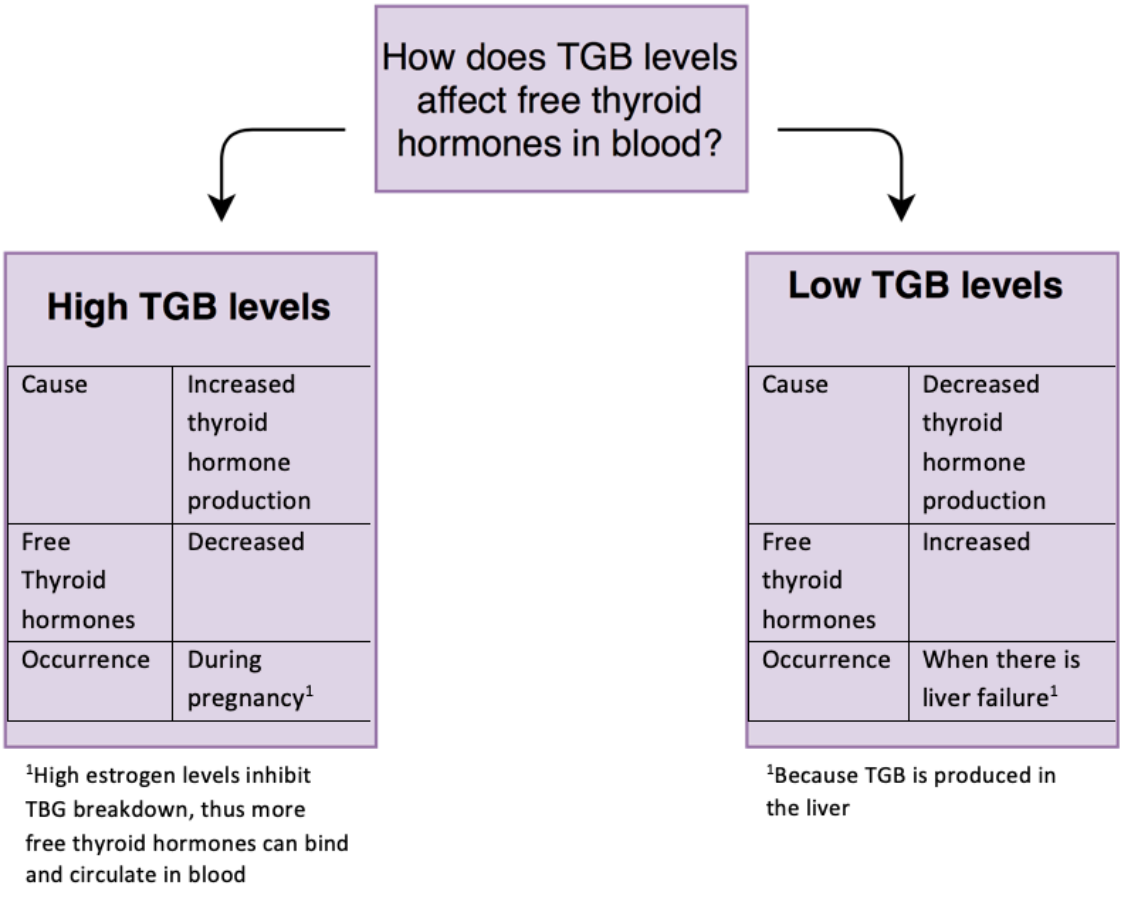
- The thyroid hormones, T3 and T4, can travel in the blood freely or bound to plasma proteins such as thyroxine-binding globulin (TBG). The free thyroid hormones are active, while the bound hormones are inactive.

4.3.1 – Thyroxine-Binding Globulin (TGB)

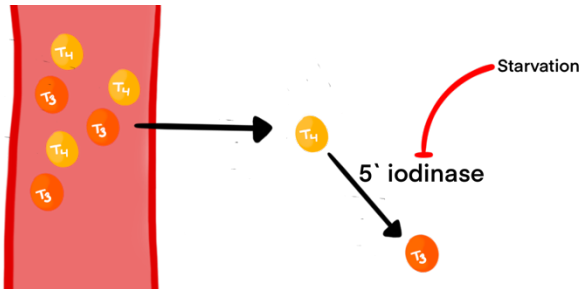
I. Function of TBG

- TBG functions to transport thyroid hormones in blood.
- It allows the body to keep inactivated thyroid hormones in blood which can be activated when they are needed

II. Pathologic levels of TBG



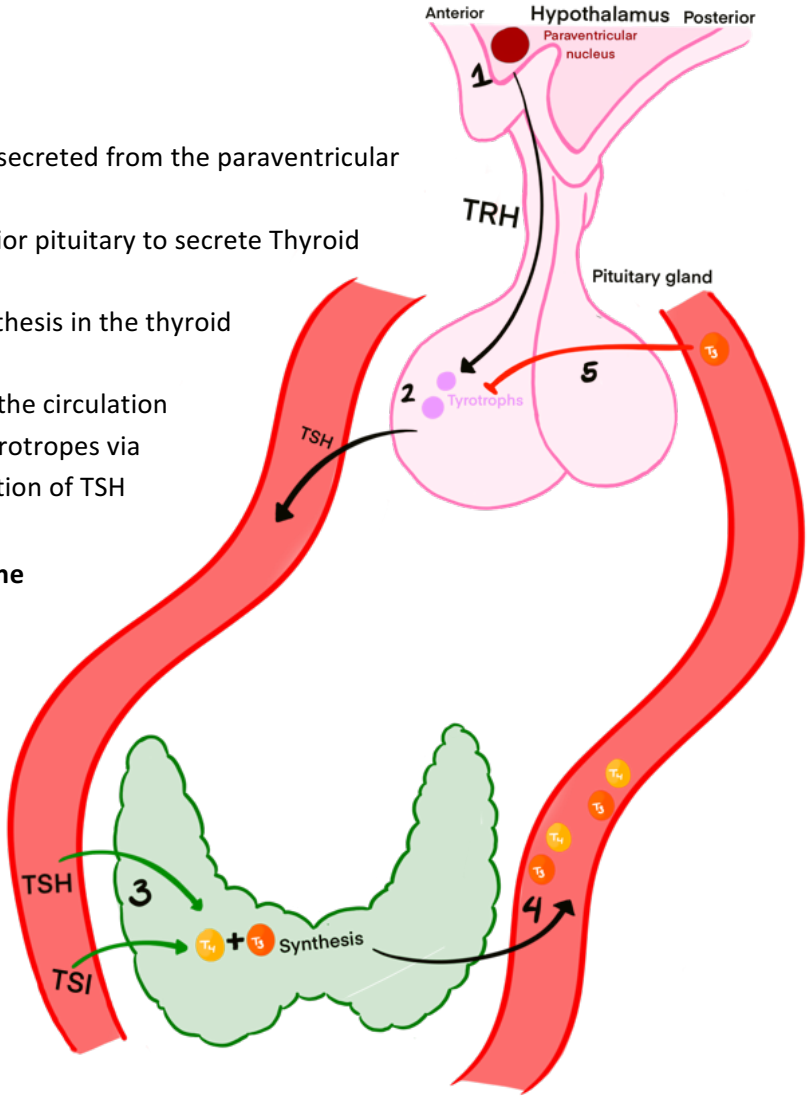
4.4 – Thyroid Hormones in Tissue



- The thyroid gland mainly secretes T4, which is less active than T3.
- *5´iodinase* is needed in the tissue to convert T4 to the active thyroid hormone, T3.
- It removes an I_2 group from T4 resulting in higher levels of T3 in the tissue.
- *5´iodinase* is inhibited by starvation.

4.5 – Regulation of Thyroid Hormones

4.5.1 – Negative Inhibition Pathway



1. Thyroid Releasing Hormone (TRH) is secreted from the paraventricular nucleus in the hypothalamus
2. TRH acts on thyrotropes in the anterior pituitary to secrete Thyroid Stimulating Hormone (TSH)
3. TSH stimulates thyroid hormone synthesis in the thyroid gland
4. Thyroid hormones are secreted into the circulation
5. High levels of free T3 inhibits the thyrotropes via negative feedback to decrease secretion of TSH

4.5.2 – Other Stimulators of Thyroid Hormone Synthesis

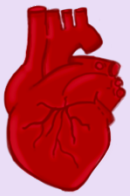
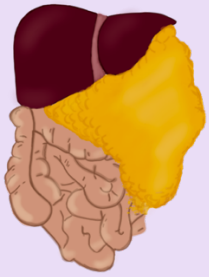
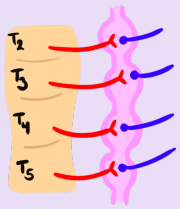
- Thyroid-stimulating Immunoglobins (TSI) are fragments of immunoglobulin G (IgG).
- TSI can stimulate and bind to the TSH receptor the same way TSH does stimulating thyroid hormone production

CLINICAL CORRELATION

Graves Disease

- Hyperthyroidism caused by high levels of circulation TSI
- The high levels of thyroid hormones inhibit the secretion of TSH
- A patient with Grave's disease will have low serum levels of TSH and high levels of circulating T3/T4

4.6 – Actions of Thyroid Hormones

Location	Action
	- The effect of thyroid hormones on CNS depends on age. - In the perinatal period: it is important for normal maturation of CNS - In adults: it is important for cognitive function and general energy and capacity.
	- To increase the oxygen consumption, thyroid hormones increase the cardiac output. This way more oxygenated blood goes to tissues due to the higher oxygen demand.
	INTESTINE - Promote absorption of glucose from intestine LIVER - Breakdown of glycogen[1] via glycogenolysis - Production of glucose via gluconeogenesis FAT - Break down and utilization of stored fat via lipolysis
	- Important in proper growth and especially in bone formation, promoting the ossification of bone - If a person has a chronic thyroid hormone deficiency (hypothyroidism), they will have a “younger skeleton” than their actual age. This can result in growth retardation in children.
	Regulates the balance between protein catabolism and anabolism (breaking down vs building up muscle)
	- Thyroid hormones affect the autonomic nervous system to produce effects similar to those of catecholamines - This results in increased BMR[2] and heat production, and increase heart rate and stroke volume

[1]Gycogen = stored glucose

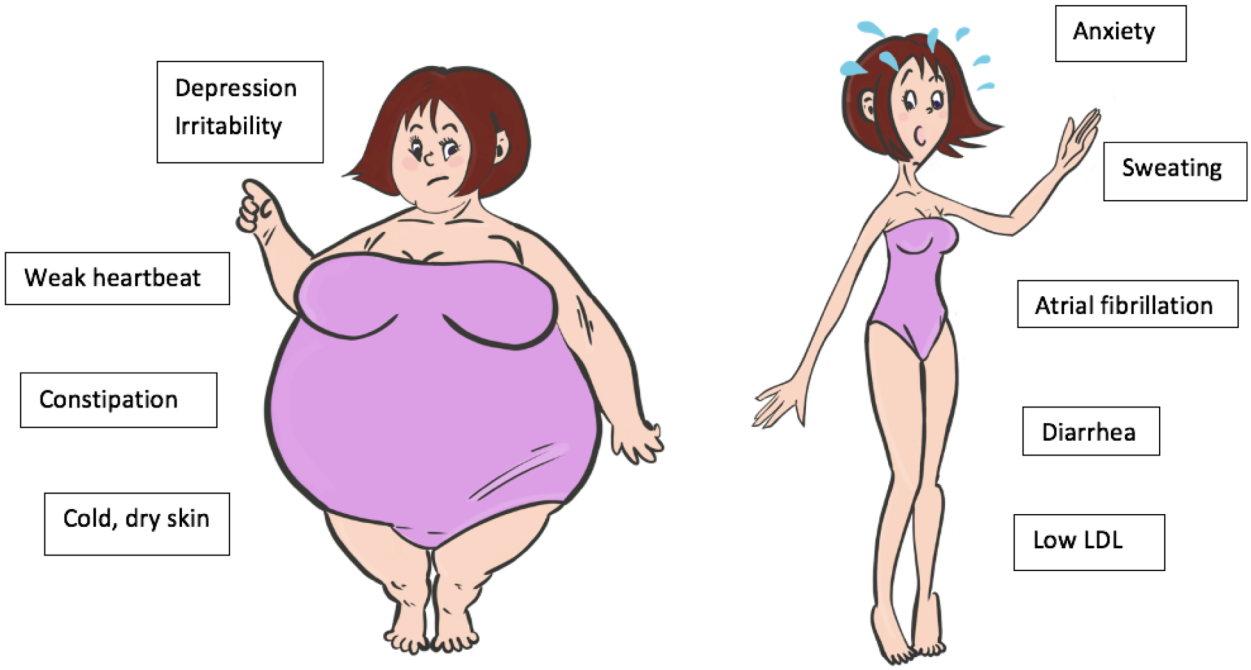
[2]Basic metabolic rate

CLINICAL CORRELATION

Hypothyroidism – deficiency of thyroid hormones in the blood

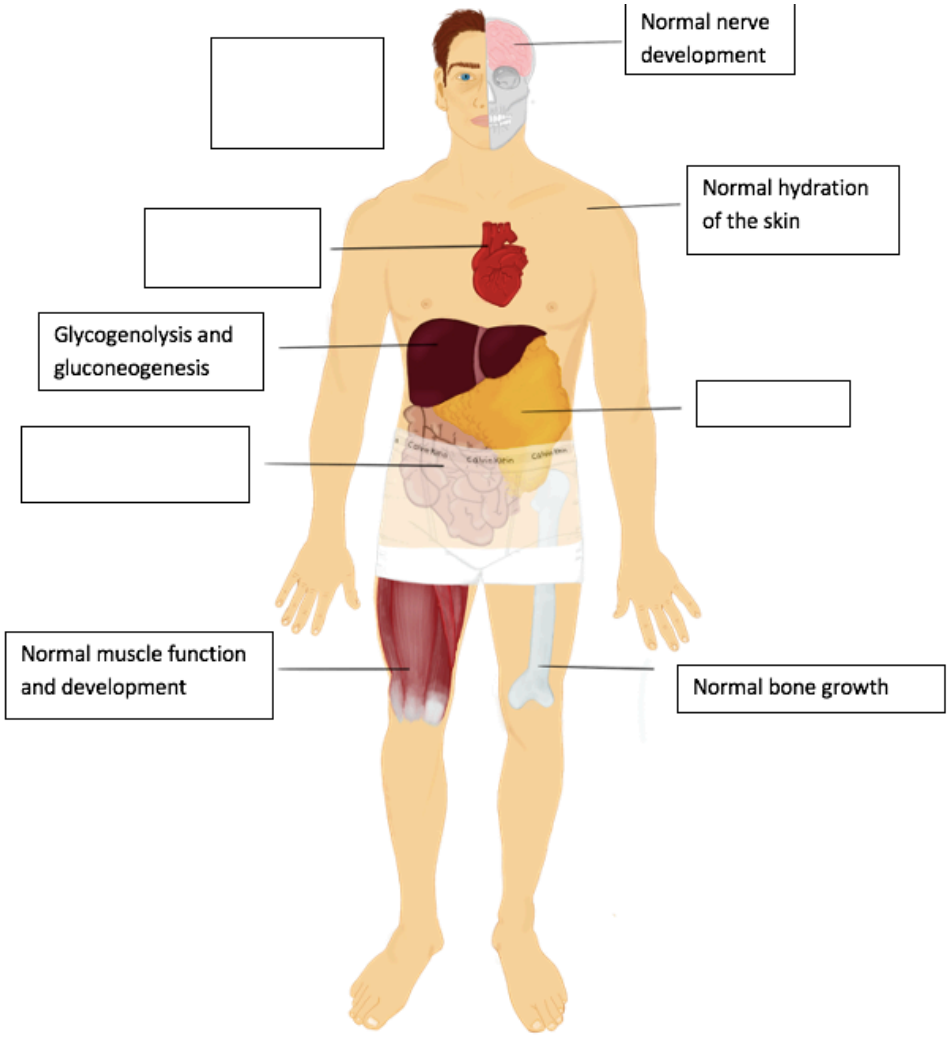
Hyperthyroidism - excess of thyroid hormones in the blood

Hypothyroidism **VS** **Hyperthyroidism**



4.7 – Test Yourself

1) Fill in the blanks

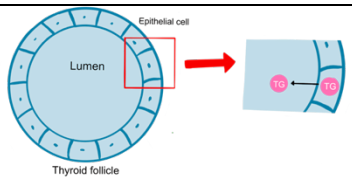
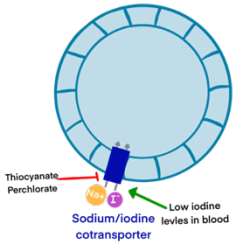
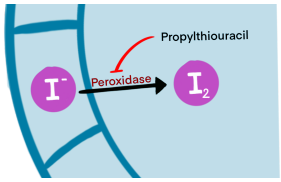
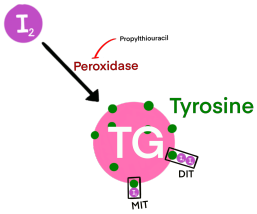
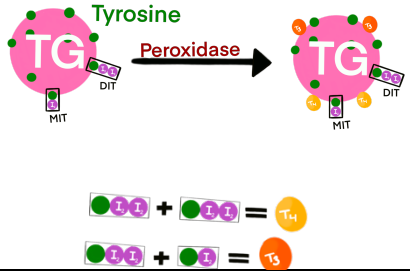
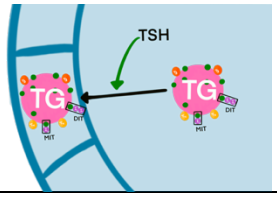
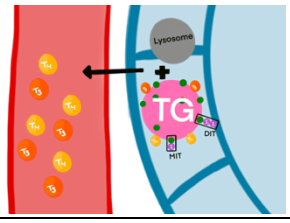
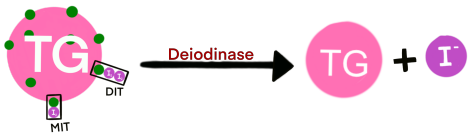


2) What enzyme is needed in tissues to convert T4 to T3? And what can inhibit this enzyme?

3) What is the function of Thyroxine-binding globulin (TBG)?

4) What hormone stimulates thyroid hormone synthesis and where does thyroid hormone synthesis take place?

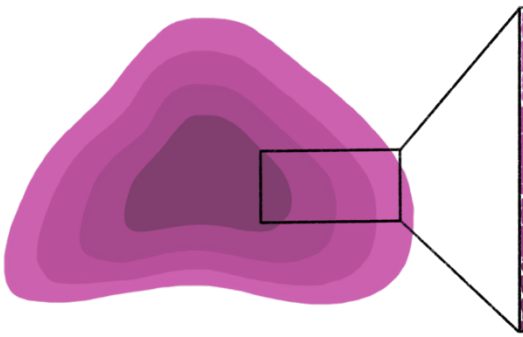
5) Place the steps of thyroid hormone synthesis in the right order

		Follicular epithelial cells Thyroglobulin (TG) MIT and DIT bind together and form the thyroid hormones
		Thyroglobulin fuse with a lysosome and the bonds between thyroglobulin and thyroid hormones are hydrolyzed. The free thyroid hormones move into the blood
		Thyroglobulin is then secreted into the follicular lumen
		I_2 binds tyrosine moieties on thyroglobulin to form mono- and diidotyrosine (MIT and DIT respectively)
		Thyroglobulin with thyroid hormones, MIT and DIT moieties move from the lumen to the follicular epithelial cells in response to thyroid stimulating hormone (TSH)
		MIT and DIT is “recycled” and the free thyroglobulin and I^- enters the synthesis cycle again
		In response to low Iodine levels in the blood the Na^{2+}/I^- cotransporter is activated to work against the electrochemical gradient
		I^- is oxidized to I_2 by the enzyme peroxidase

Section 5 – The Adrenal Gland

5.1 – Overview

5.1.1 – Layers of the Adrenal Gland



Layer	Hormone	Function
Zona glomerulosa	Mineralocorticoids	Salt balance in blood
Zona fasciculata	Glucocorticoids	Sugar balance in blood
Zona reticularis	Androgens	Male sex characteristics
Medulla	Catecholamines	Fight or flight response

MNEMONIC

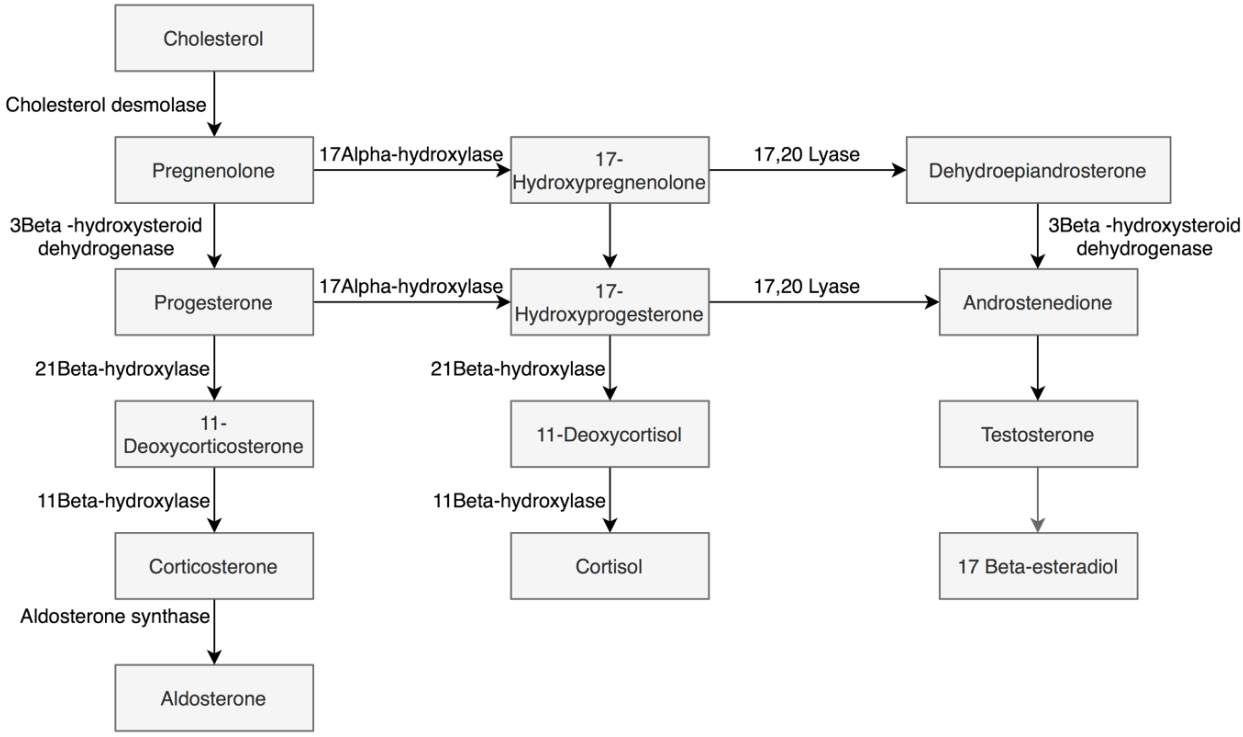
Go Find Rex – Make Good Sex

G – glomerulosa **M – mineralocorticoids**

F – fasiculata **G – glucocorticoids**

R – reticularis **S – sex hormones**

5.1.2 – Synthesis of Adrenal Cortex Steroid Hormones



I. Cholesterol

- The precursor for all adrenal cortex hormones, provided through the circulation and to a smaller degree produced de novo in the adrenal cortex.
- May by stored until the adrenal cortex needs to make more hormones.

II. Synthesis of cortex hormones

- The enzymes needed for production of cortex hormones from cholesterol require; cytochrome P-450, molecular oxygen, and NADPH.
- The illustration above show pathways that occur in different layer in the cortex, all the pathways do not occur in the same layer.

5.1.3 – Regulation of Adrenal Cortex Hormones

I. Adrenocorticotropic hormone (ACTH)

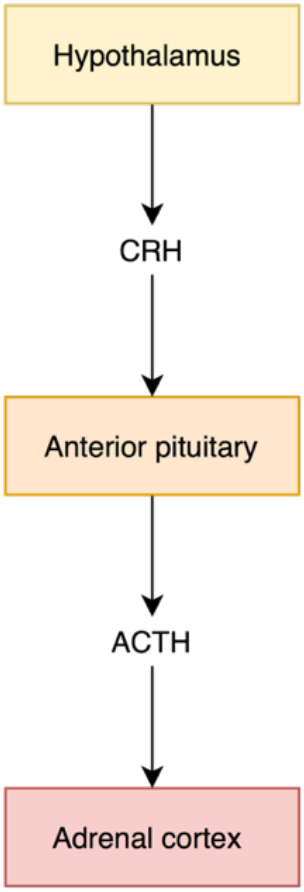
- Secreted by the anterior pituitary in response to corticotropin-releasing hormone (CRH) secreted from the hypothalamus
- The first step in the synthesis of cortex hormones is the conversion of cholesterol to pregnenolone. This step requires *cholesterol desmolase* which depends on the circulation levels of ACTH.

II. Glucocorticoid and androgen secretion

- Regulated only by the hypothalamic-pituitary axis

III. Androgens

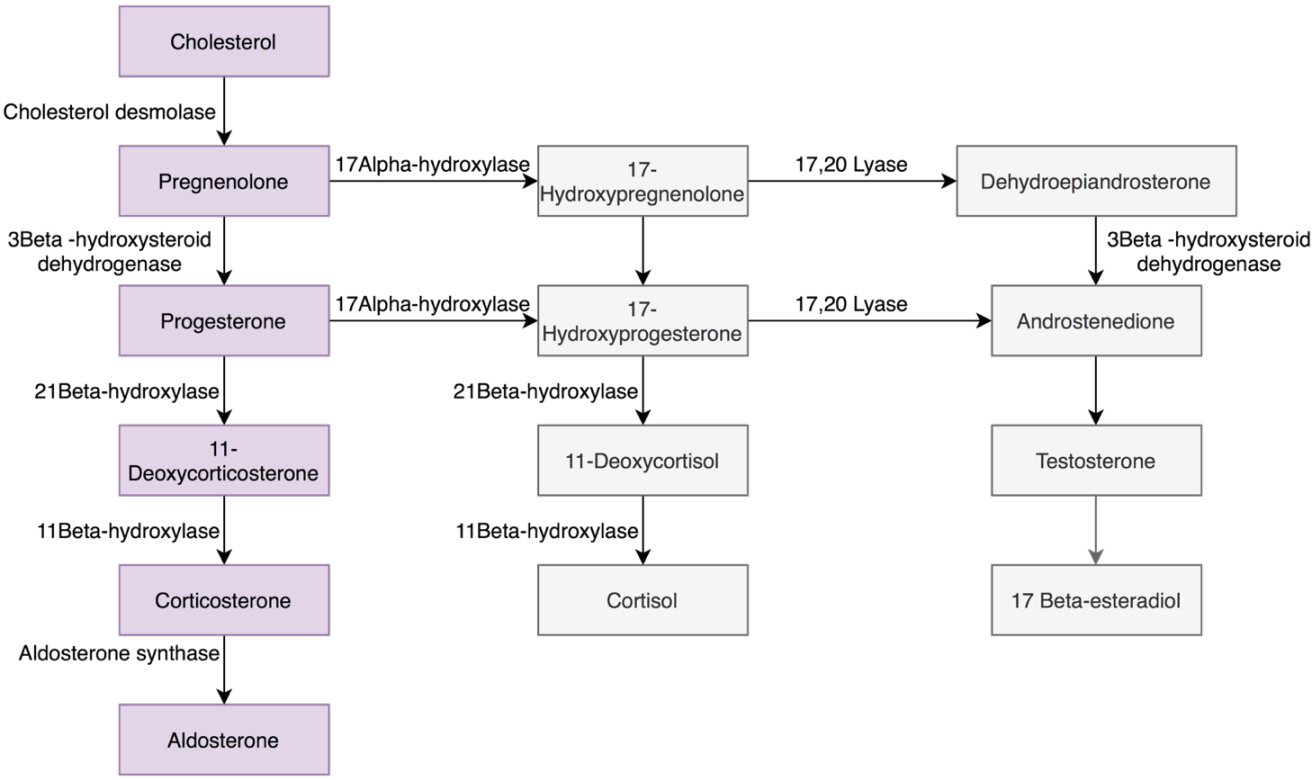
- Regulated by the hypothalamic-pituitary axis
- Further they are regulated by the renin-angiotensin-aldosterone system (RAAS).



5.2 – Mineralocorticoids

5.2.1 – Synthesis of Mineralocorticoids

- We are starting from the outermost layer of the adrenal gland working our way in.
- In the outermost layer, the zona glomerulosa, mineralocorticoids are produced.
- The major mineralocorticoid is *aldosterone*.

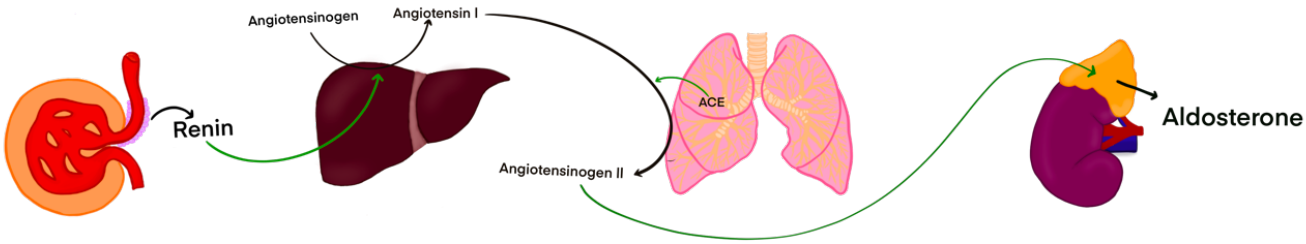


- The pathway shown in purple illustrates the production pathway of aldosterone, the major mineralocorticoid
- The most important thing to remember is that the reason why the zona glomerulosa cannot produce cortisol is because it lacks the enzyme *17- alpha-hydroxylase*.
- If there is an enzyme deficiency within the aldosterone producing pathway there will not be any aldosterone production

5.2.2 – Regulation of Mineralocorticoids

- Changes in the extracellular fluid (ECF) volume is the main regulator of aldosterone secretion.
- The ECF volume is affected by both changes in RAAS and in potassium (K^+) levels.

I. The renin-angiotensin-aldosterone system



1. Renin is secreted from the juxtaglomerular cells in the glomerulus of the kidney in response to low blood pressure and low glomerular filtration rate (GFR)
2. Renin acts on the liver by hydrolyzing angiotensinogen to angiotensin I
3. Angiotensin I is secreted into the blood and travel to the lungs where the engiotensin converting enzyme (ACE) convert angiotensin I to angiotensin II
4. Angiotensin II then acts on the adrenal cortex to stimulate aldosterone secretion

II. Serum potassium (K^+) levels

K^+ concentration	Aldosterone secreted	Mechanism
Low	Low	- Absent or low levels of K^+ results in that voltage-gated Ca^{2+} channels remain closed. - Aldosterone is not released from the adrenal cortex
High	High	- When there are high levels of K^+ this results in depolarizes voltage gated Ca^{2+} channels. - Increasing intracellular Ca^{2+} concentration - Initiating aldosterone release from the adrenal cortex

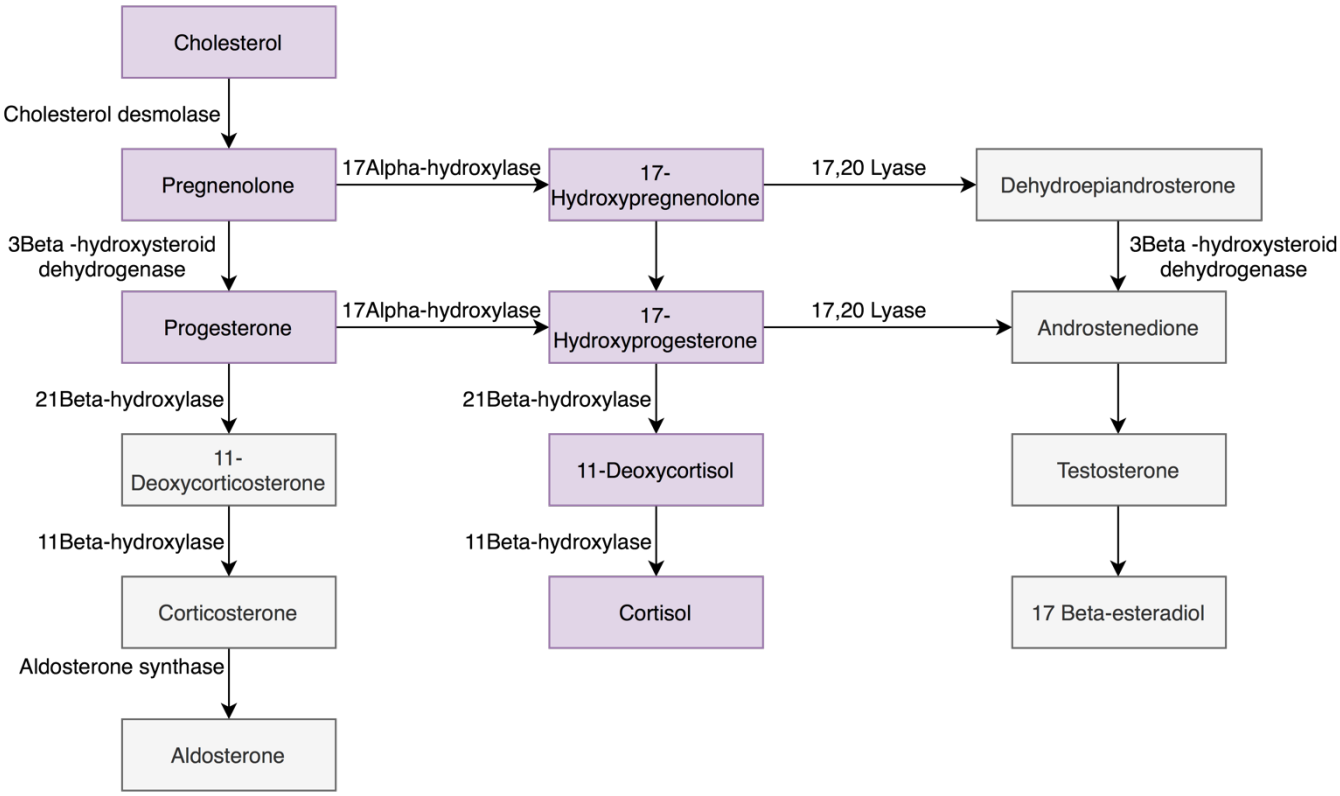
5.2.3 – Actions of Mineralocorticoids

- Maintain electrolyte balance and blood pressure regulation by
    1. Increasing *Na^+ reabsorption*
    2. Increasing *K^+ and H^+ excretion*
    3. Water reabsorption → Increased blood pressure

5.3 – Glucocorticoids

5.3.1 – Synthesis of Glucocorticoids

- In the next layer, the zona fasiculata, glucocorticoids are produced.
- The main glucocorticoid is *cortisol*.



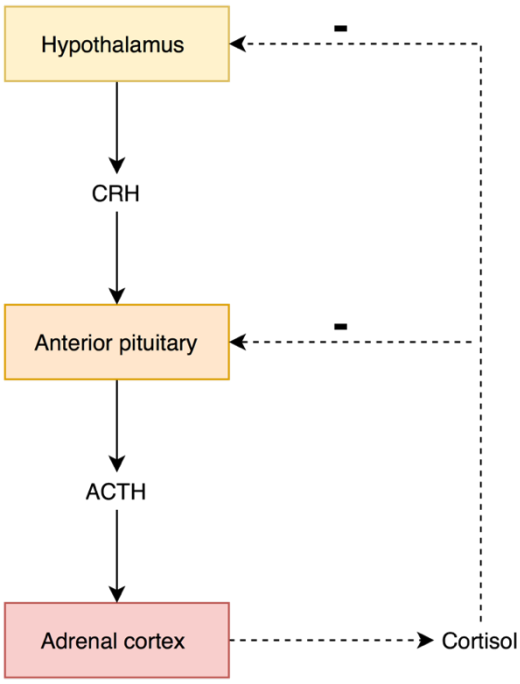
- The zona fasciculata, compared to zona glomerulosa, contains all the enzymes required to produce cortisol and corticosterone.
- 17-hydroxyprogesterone is converted to cortisol via *21- and 11-beta-hydroxylase*
- *21- and 11-β-hydroxylase* are also responsible for converting progesterone into corticosterone.

CLINICAL CORRELATION

17 alpha-hydroxylase deficiency

- Corticosterone can function similarly to cortisol
- A 17 alpha-hydroxylase deficiency will result in inadequate cortisol production
- Corticosterone production will increase and will function as cortisol

5.3.2 – Regulation of Glucocorticoids



I. Mechanism of secretion

1. CRH is secreted from the hypothalamus
2. Stimulating the anterior pituitary to secrete ACTH
3. Activation of cortisol production and secretion from the zona fasiculata

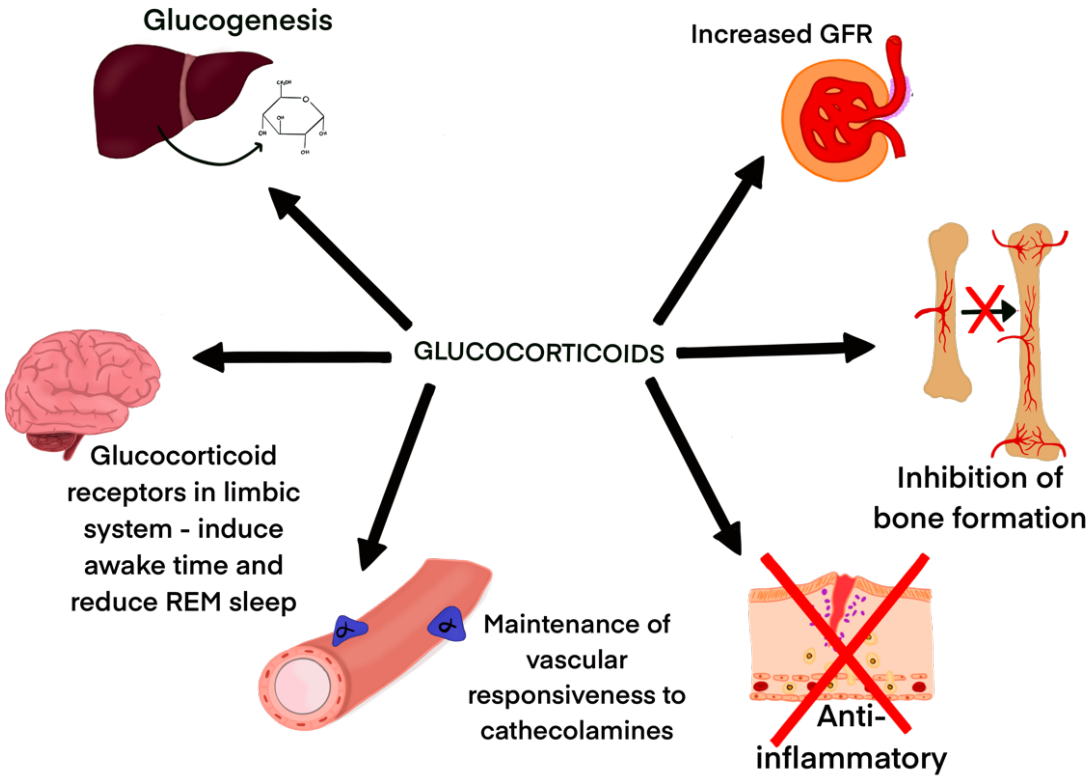
- This occurs in a pulsatile manner, meaning that the secretory pattern has about 10 secretory bursts a day.

II. Negative feedback inhibition

- The only mechanism of regulation of glucocorticoid levels is the product of production.
- Meaning that if the zona fasciculata secretes a lot of cortisol, the high amount of cortisol will inhibit both the anterior pituitary from secreting ACTH and the hypothalamus from secreting CRH.
- The result is less production of cortisol, which is favorable when cortisol levels are high.

5.3.3 – Actions of Glucocorticoids

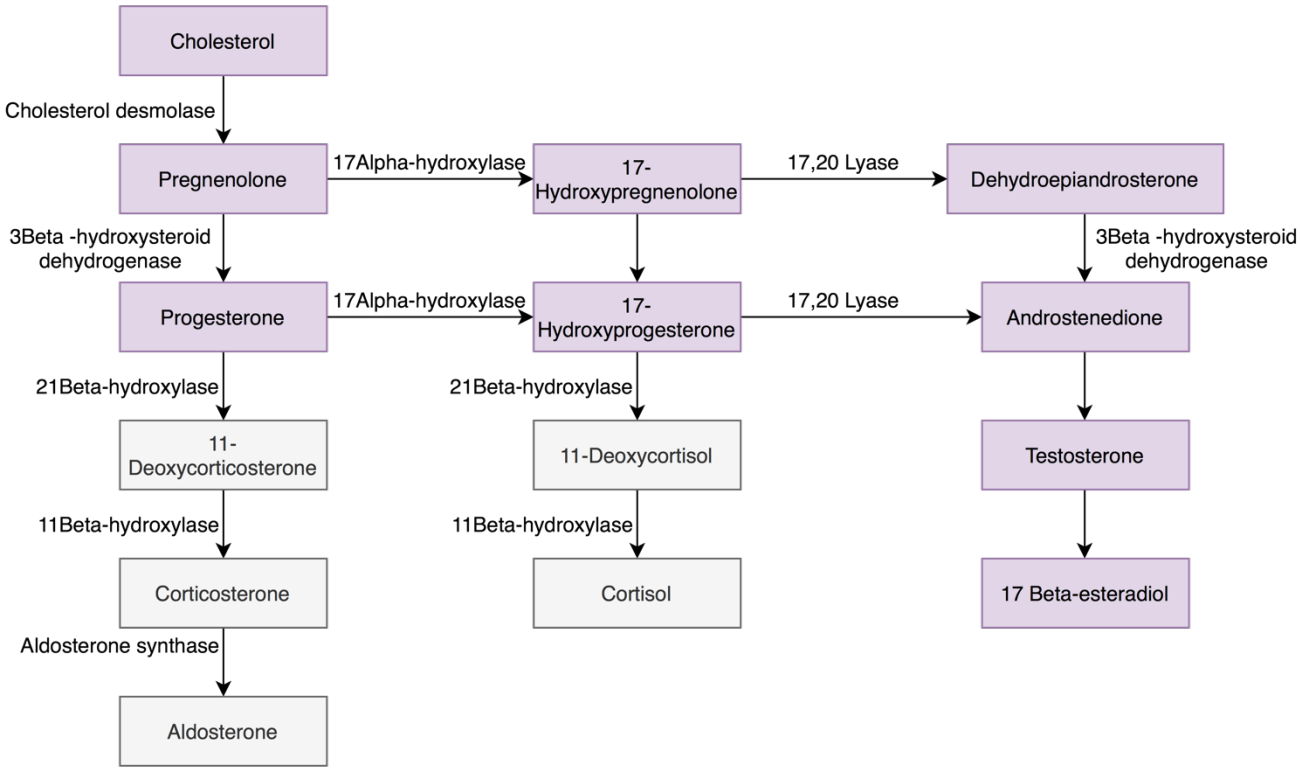
- Glucocorticoids, such as cortisol, are responsible for glucose formation (gluconeogenesis), immunosuppression, blood pressure elevation, and inhibition of bone formation.



5.4 – Androgens

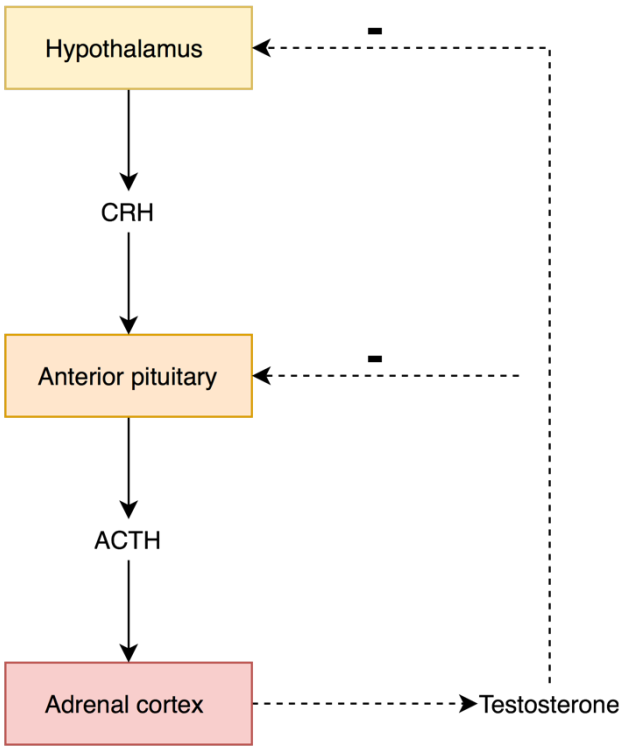
5.4.1 – Synthesis of Androgens

- In the innermost layer of the cortex, the zona reticularis, androgens are produced.
- The main androgens produced are *dehydroepiandrosterone (DHEA)* and *androstenedione*.



- DHEA and androstenedione are weak androgens
- They are transported via the blood to the testes where they are converted to testosterone, a strong androgen.

5.4.2 – Regulation of Androgens



5.4.3 – Actions of Androgens

Male	Female
- DHEA and androstenedione secreted from the zona reticularis is converted to testosterone in the tests. - The tests also make its own testosterone, thus the androgens from the adrenal cortex is less important.	- DHEA and androstenedione secreted from the zona reticularis and these are the major androgens in female. - They are responsible for development of pubic and axillary hair and for libido

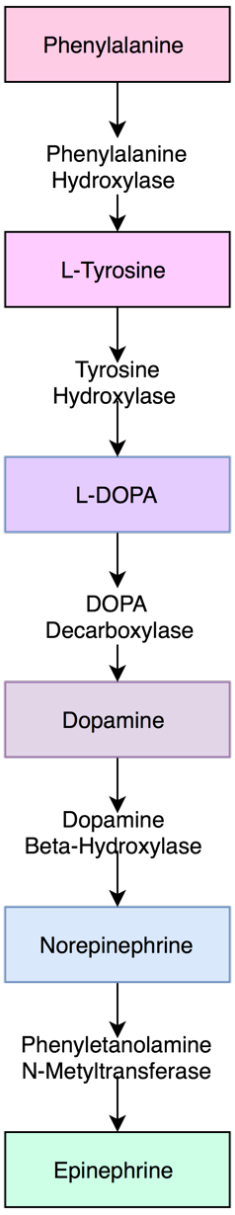
5.5 – Catecholamines

- Catecholamines such as epinephrine and norepinephrine, are synthesized in the adrenal medulla, as well as other sites in the body like the central nervous system and postganglionic adrenergic neurons.
- Take part in fight-or-flight response

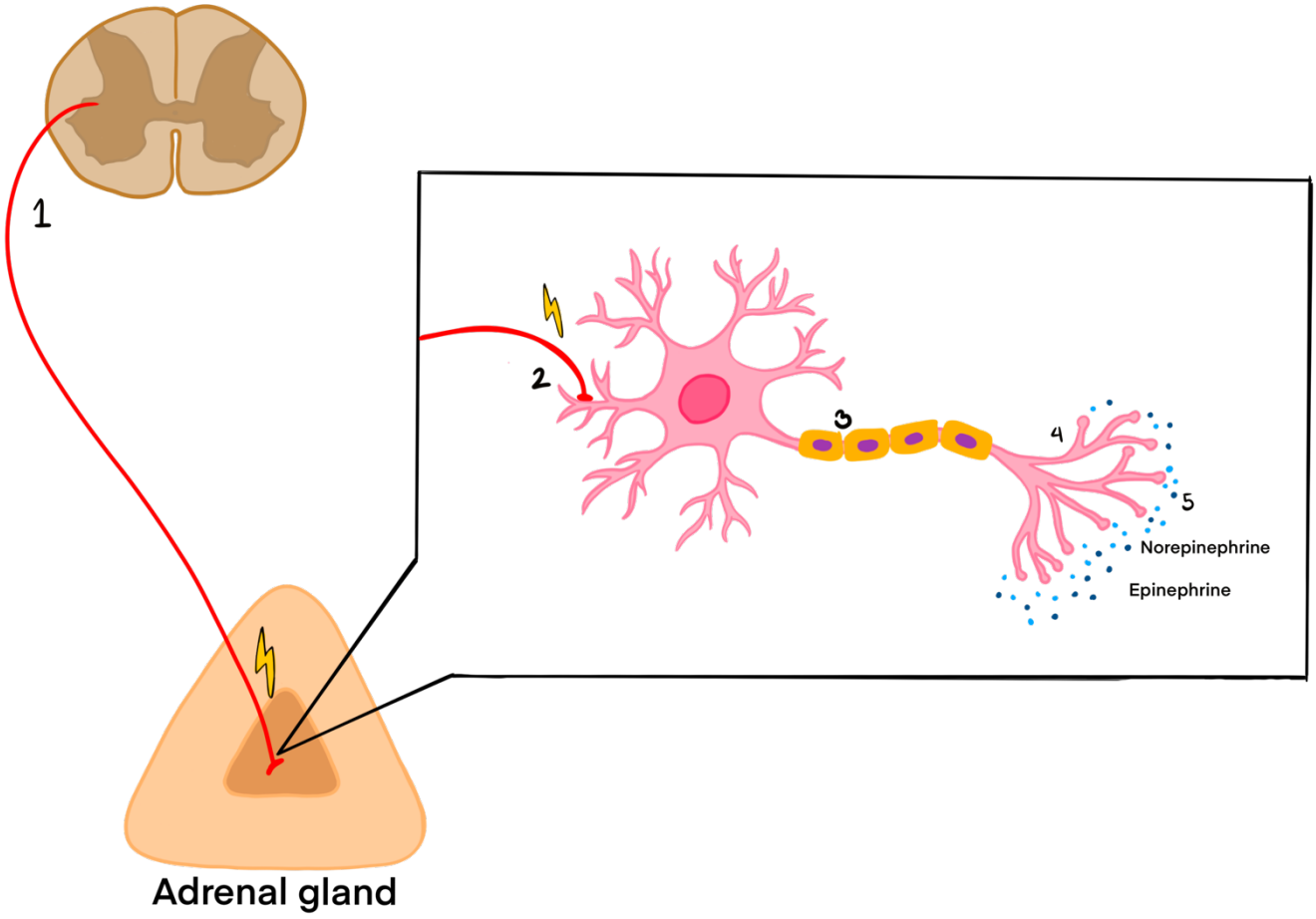
5.5.1 – Structure of the Adrenal Medulla

- The adrenal medulla is composed of neural tissue called *chromaffin cells* which are cell bodies of the post-ganglionic motor-neurons of the sympathetic nervous system
- Nerves that supply the adrenal medulla arise in the thoracolumbar outflow (T1-L2) in the lateral grey horn of the spinal cord.

5.5.2 – Synthesis of Catecholamines

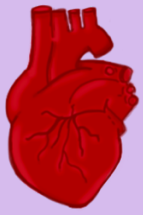
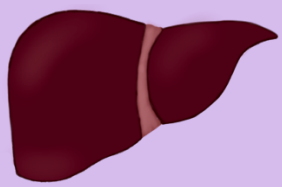
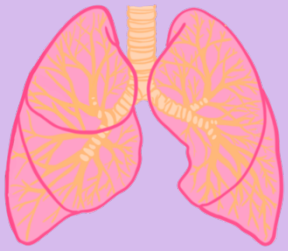
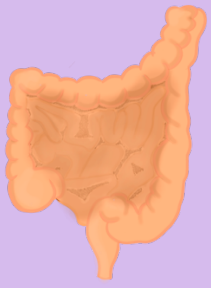


5.5.3 – Pathway of Catecholamine Release



1. Cholinergic neurons arise in the ventral grey horn of the spinal cord
2. They travel to the adrenal medulla and synapse on the chromaffin post ganglionic neurons, stimulating the synthesis of catecholamines (see flow chart)
3. The depolarization of the chromaffin cell body travel along its axon
4. The action potential stimulates Ca^{2+} influx at the axon terminal
5. This stimulates the release of the epinephrine and norepinephrine

5.5.4 – Action of Catecholamines

Location	Action
	Stimulate β1-adrenergic receptors on the sinoatrial node ↓ Increased the heart rate
	Glucose production via glycogenolysis and gluconeogenesis ↓ Hyperglycemia
	Stimulate β2-adrenergic receptors located in the bronchi ↓ Bronchodilation and increased respiration
	Redirection of blood flow from the intestine to working muscles ↓ Inhibits digestion
	Activation of hormone sensitive lipase (HSL) in adipose tissue ↓ Production of free fatty acids (FFA) and glycerol used by the muscle to produce energy

5.6 – Adrenal Gland Disorders

- When you understand the physiology of the adrenal cortex and its hormones it is easier to understand what happens when the adrenal gland is not functioning properly
- Here are 32examples of what happens when there is disruption of the physiologic functions

	Addison disease ***Primary adrenal insufficiency***	**Exogenous Cushing syndrome** ***Hypercorticolism***
Adrenocortical hormone(s)	Decreased	Increased
Caused by	Autoimmune destruction of adrenal cortex	Elevated cortisol levles[1]
Clinical features	Hypoglycemia Hyponatremia[2] Hyperkalemia[3] Metabolic acidosis Decreased pubic hair in females Hypotension	Hyperglycemia Moon face and central obesity Dyslipidemia[4] Osteoporosis Menstrual disturbances in females Hypertension
ACTH levels	Increased[4]	Decreased
Treatment	Glucocorticoids and mineralocorticoids	Lower pharmacologic doses of glucocorticoids

[1]Either caused by high pharmacologic doses of cortisone
[2]Low serum sodium level
[3]High serum potassium level
[4]High levels of total cholesterol
[5]ACTH levels are increased due to the decrease in circulating adrenocortical hormones

Explanation of clinical features

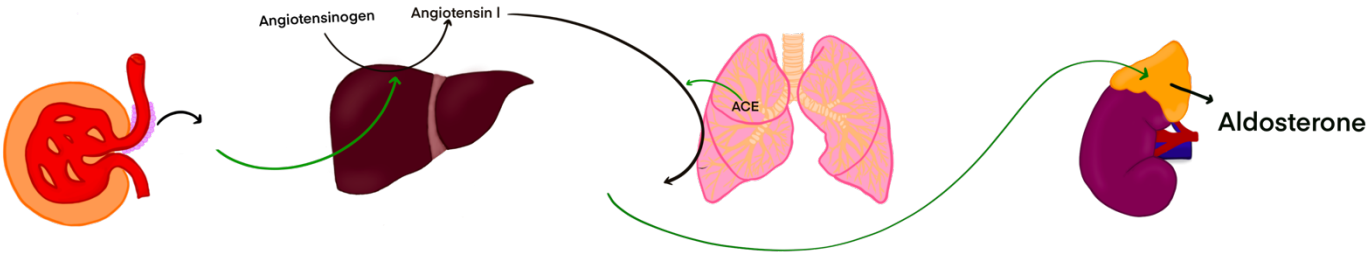
Addison syndrome		Cushing syndrome	
Hypoglycemia	Decreased gluconeogenesis Increased glycolysis	**Hyperglycemia**	Increased gluconeogenesis
Hyponatremia	Decreased aldosterone → salt loss	**Moon face + obesity**	Redistribution of fat
Hyperkalemia	Decreased aldosterone → decreased compensation	**Dyslipidemia**	Increased lipolysis
Metabolic acidosis	Decreased aldosterone → increased H^+ in blood	**Osteoporosis**	Cortisol inhibits the function of vitamin D
Decreased pubic hair	Decreased DHEA	**Menstrual disturbances**	Inhibition of GnRH
Hypotension	Decreased catecholamines → less vasoconstriction	**Hypertension**	Activation of RAAS → vasoconstriction

4.6 – Test Yourself

1) What 2 hormones are only regulated by negative feedback?

a) Cortisol and Aldosterone
b) Testosterone and Cortisol
c) Aldosterone and Testosterone
d) Aldosterone and DHEA

2) Fill in the blanks



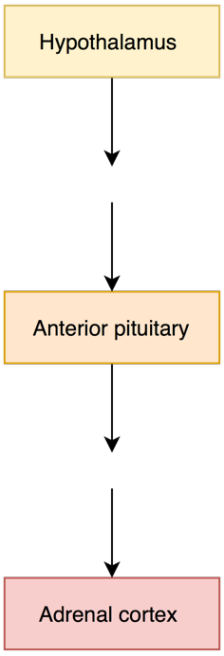
3) What hormones are regulated by RAAS?

a) Mineralocorticoids
b) Glucocorticoids
c) Androgens

4) In what disease do you have decreased adrenocortical hormone concentration in blood?

a) Addison Disease
b) Graves' Disease
c) Cushing's Syndrome
d) Cushing´s Disease

5) Fill in the blanks



6) Why are the androgens produced by the zona reticularis more important in females than in males?

7) Fill in the blanks

K^+ concentration	Aldosterone secreted	Mechanism
	Low	- Absent or low levels of K^+ results in that voltage-gated Ca^{2+} channels remain closed. - Aldosterone is not released from the adrenal cortex
High		- When there are high levels of K^+ this results in depolarizes voltage gated Ca^{2+} channels. - Increasing intracellular Ca^{2+} concentration - Initiating aldosterone release from the adrenal cortex

8) What amino acid is the precursor in catecholamine synthesis?

a) Tyrosine
b) Phenylalanine
c) Dopamine
d) Norepinephrine

9) Aldosterone is important for maintaining electrolyte balance, what 3 electrolytes does it regulate?

Section 6 – The Parathyroid Glands

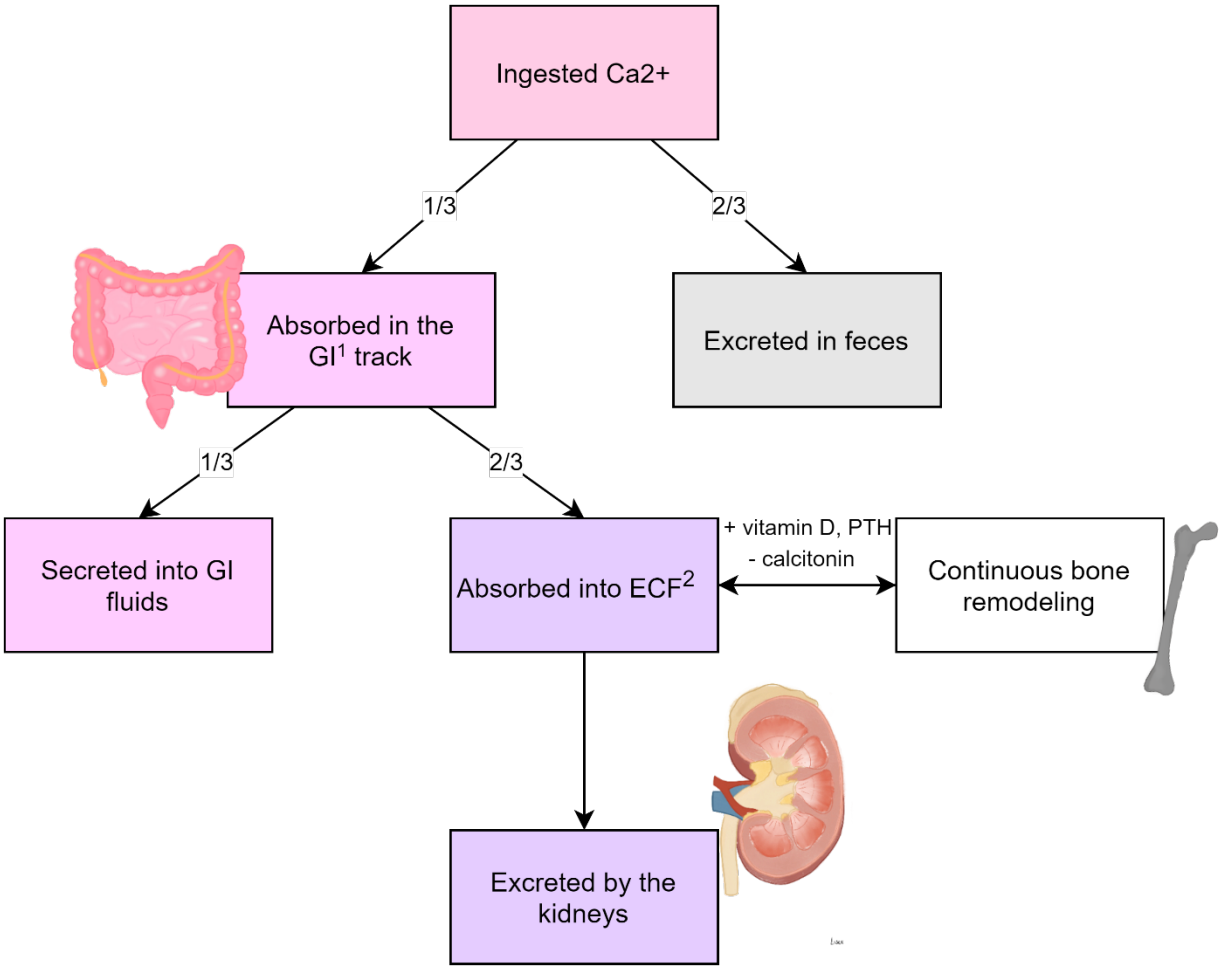
6.1 – Overview

I. General function

- Four, oval-shaped endocrine glands located in the posterior surface of the thyroid gland
- Their function is to secrete parathyroid hormone (PTH) in response to low calcium (Ca^{2+}) levels in the blood

II. Calcium homeostasis

- Calcium homeostasis is regulated by three organ systems; bone, kidney, and intestine, and three hormones; PTH, calcitonin, and vitamin D
- PTH and vitamin D act to increase Ca^{2+} concentration, while calcitonin acts to decrease Ca^{2+} concentration

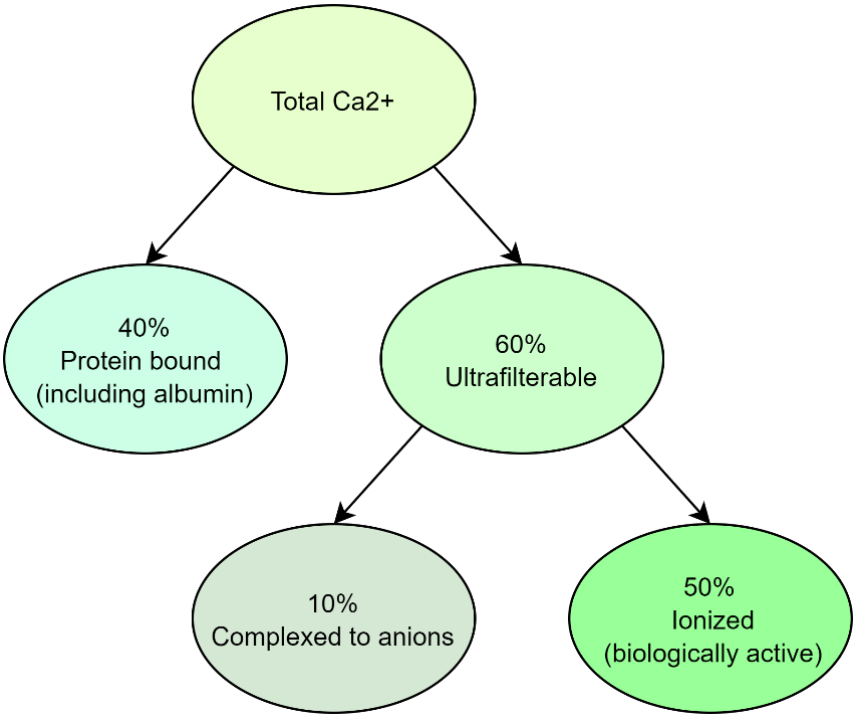


[1]Gastrointestinal
[2]Extracellular fluid

III. Calcium concentrations in the body

- Ionized Ca2+ concentration is affected by changes in anion concentration and acid-base abnormalities

Changes in anion concentration	Acid-base abnormalities
Inverse relationship: ↑ anion concentration causes more Ca^{2+} to be complexed with anions and less Ca^{2+} to be ionized	- Acidemia: ↑ ionized Ca^{2+}, as ↑ H^{+} displaces Ca^{2+} from albumin - Alkalemia: ↓ ionized Ca^{2+}, as ↓ H^{+} frees binding sites on albumin



CLINICAL CORRELATION

Hypocalcemia

(↓ Ca^{2+} concentration in the blood stream)

- Chvostek sign: tapping on the facial nerve elicits facial muscle twitching
- Trousseau sign: spasmic contractions of hands and feet upon inflating the blood pressure cuff

6.2 – Parathyroid Hormone

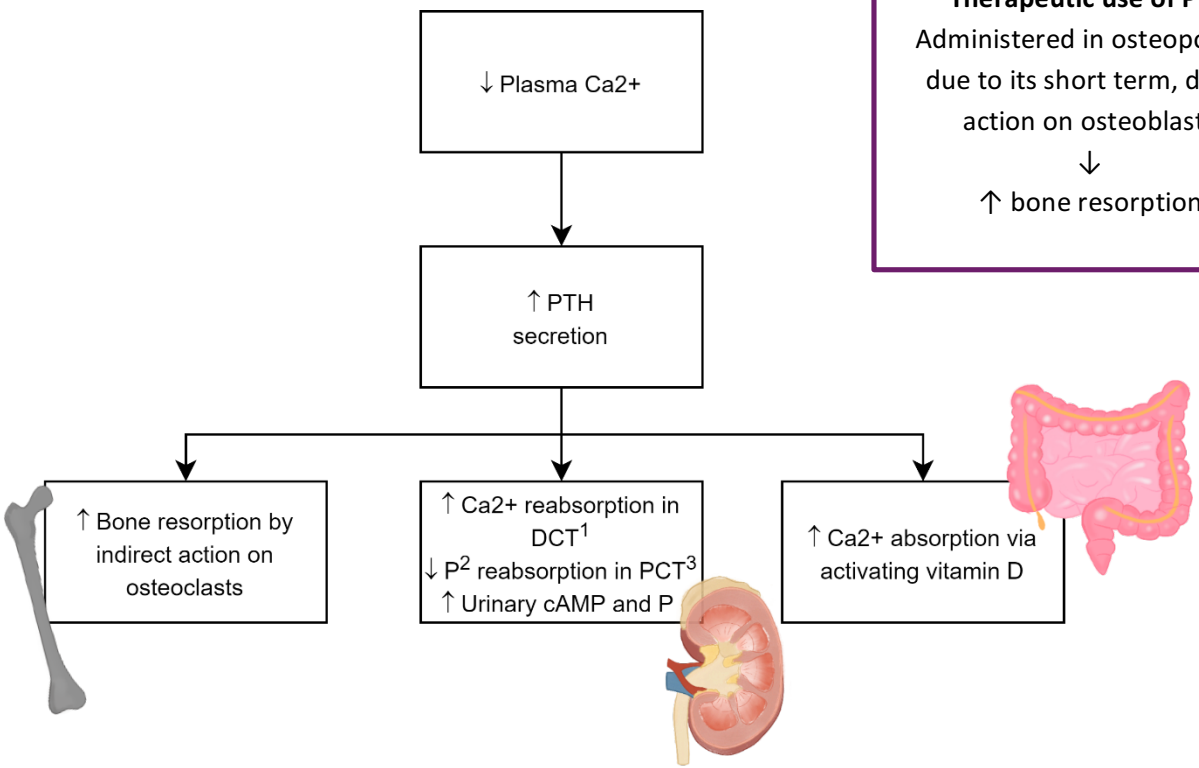
I. General function

- PTH is secreted from the chief cells located in the four parathyroid glands
- It is responsible for regulating Ca^{2+} concentration in extracellular fluid by acting on the bones, the kidneys and the intestines
- PTH secretion is stimulated by low calcium concentration in the blood, and it is inhibited by high levels of circulation calcium
- Calcium-sensing receptors are linked to phospholipase C via the Gq protein
- Low levels of serum magnesium also have a small effect on stimulating PTH secretion

II. Actions of PTH

CLINICAL CORRELATION

Therapeutic use of PTH
Administered in osteoporosis due to its short term, direct action on osteoblasts
↓
↑ bone resorption



[1]Distal convoluted tubule, [2]Phosphate, [3]Proximal convoluted tubule

III. Calcitonin

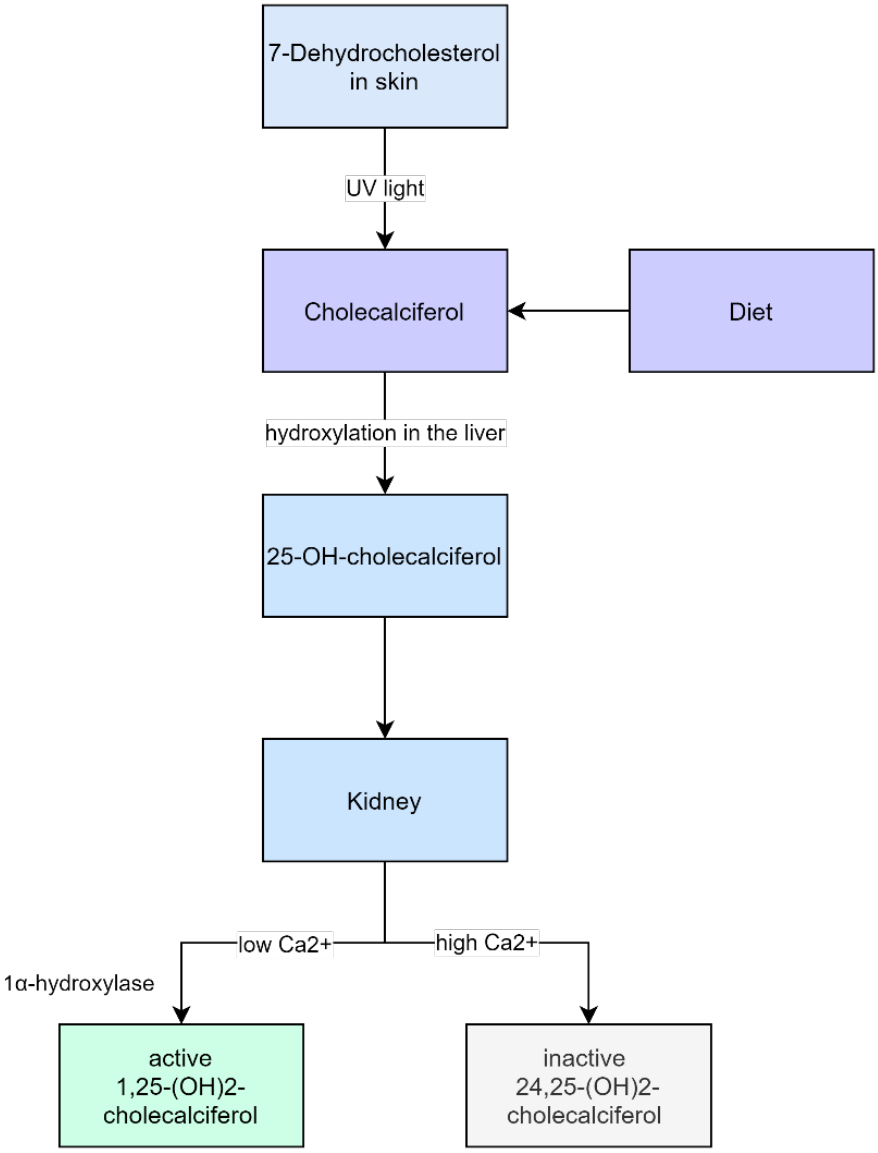
- Secreted by the parafollicular "C" cells of the thyroid gland
- Stimulated in response to ↑ Ca^{2+} concentration
- Decreases Ca^{2+} concentration by inhibiting osteoclastic bone resorption
- Its role in regulating Ca^{2+} homeostasis is uncertain and it is considered to be minor

6.3 – Vitamin D (Calcitriol)

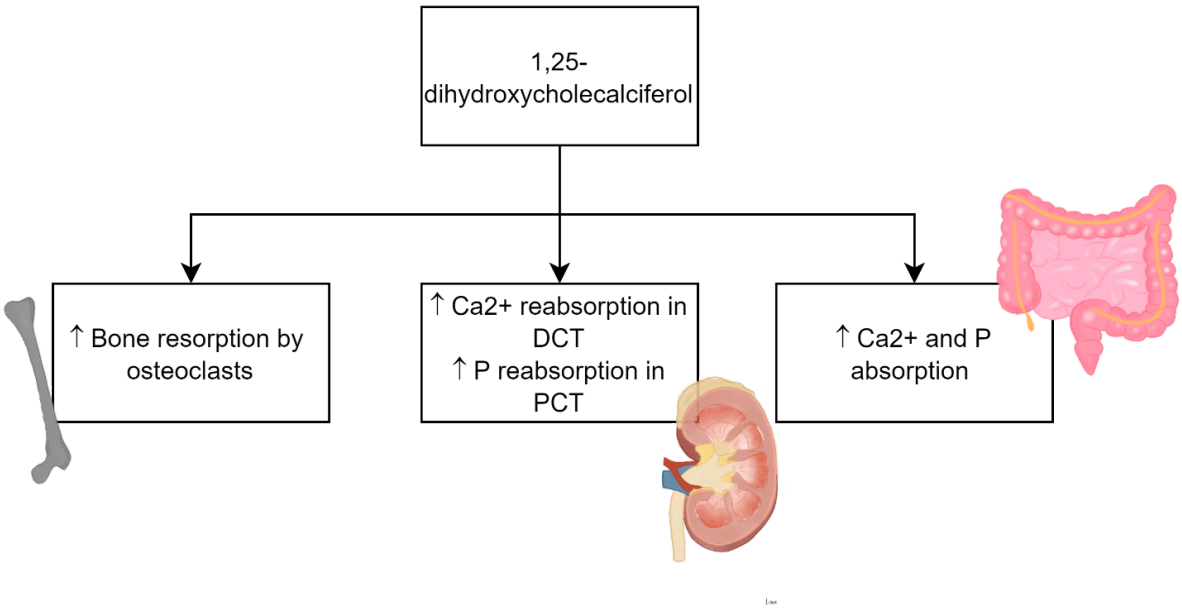
I. Main finctions

- The main role of vitamin D is to promote bone mineralization
- Vitamin D acts on the bones, the kidneys and the intestines like PTH, however unlike PTH it *increases both Ca^{2+} and phosphate concentration*
- It is produced in the skin from cholesterol upon UV light stimulation and it is also acquired in the diet

II. Synthesis of vitamin D



III. Actions of Vitamin D



CLINICAL CORRELATION

Vitamin D deficiency

- Causes rickets in children, characterized by growth failure and skeletal deformities.
- Causes osteomalacia in adults, characterized by softening of the bones.

6.4 – Test Yourself

1) Approximately what percentage of Ca^{2+} is ionized (biologically active)?

a) 10%
b) 40%
c) 50%
d) 60%

2) Fill in the blanks with ↓ or ↑ appropriately

Acidemia ___ ionized Ca^{2+}, as ___ H^+ displaces Ca^{2+} from albumin
Alkalemia ___ ionized Ca^{2+}, as ___ H^+ frees binding sites on albumin

3) What is NOT an action of PTH?

a) increasing bone resorption
b) increasing Ca2+ reabsorption in DCT of the kidney
c) increasing P- reabsorption in PCT of the kidney
d) increasing Ca2+ absorption from the intestines

4) What is the one action of Calcitonin?

_____

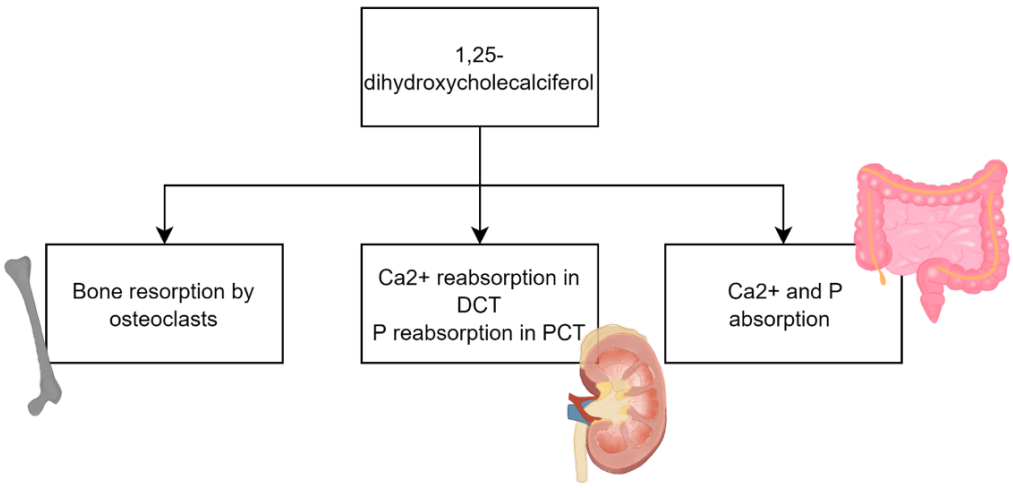
_____

_____

5) Where is vitamin D converted into an active substance?

a) Kidney
b) Skin
c) Liver
d) Intestines
e) Pancreas

6) Fill in the blanks with ↑ or ↓



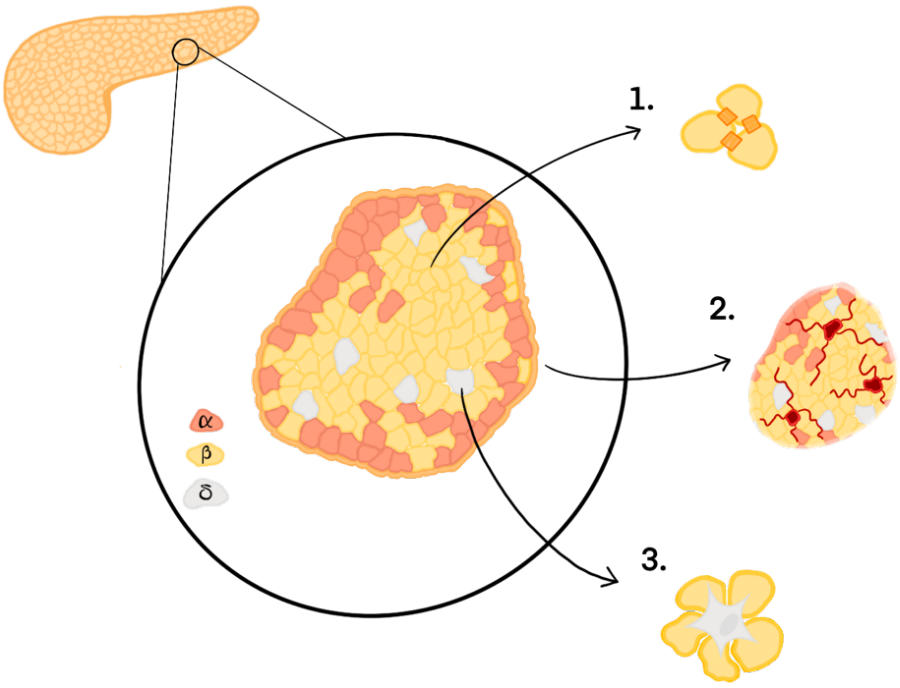
Section 7 – The Endocrine Pancreas

7.1 – The islets of Langerhans

I. Cell distribution

Cell type	Percentage	Location	Product
β-cells	65%	Central islet	Insulin
α-cells	20%	Outer rim of islet	Glucagon
δ-cells	10%	Mixed	Somatostatin + gastrin

II. Communication



1. Gap-junctions between cells facilitate easy *paracrine communication*
2. The islets of Langerhans are highly vascularized, receiving 10% of the total pancreatic blood flow. The blood distributes from the core of the islet through a network of fenestrated capillaries converting to venules at the rim of the islet.
3. Neuronal innervation by adrenergic, cholinergic and peptidergic innervation. The δ cells even have dendrite-like processes into the β cells, suggesting intraislet neural communication.

CLINICAL CORRELATION

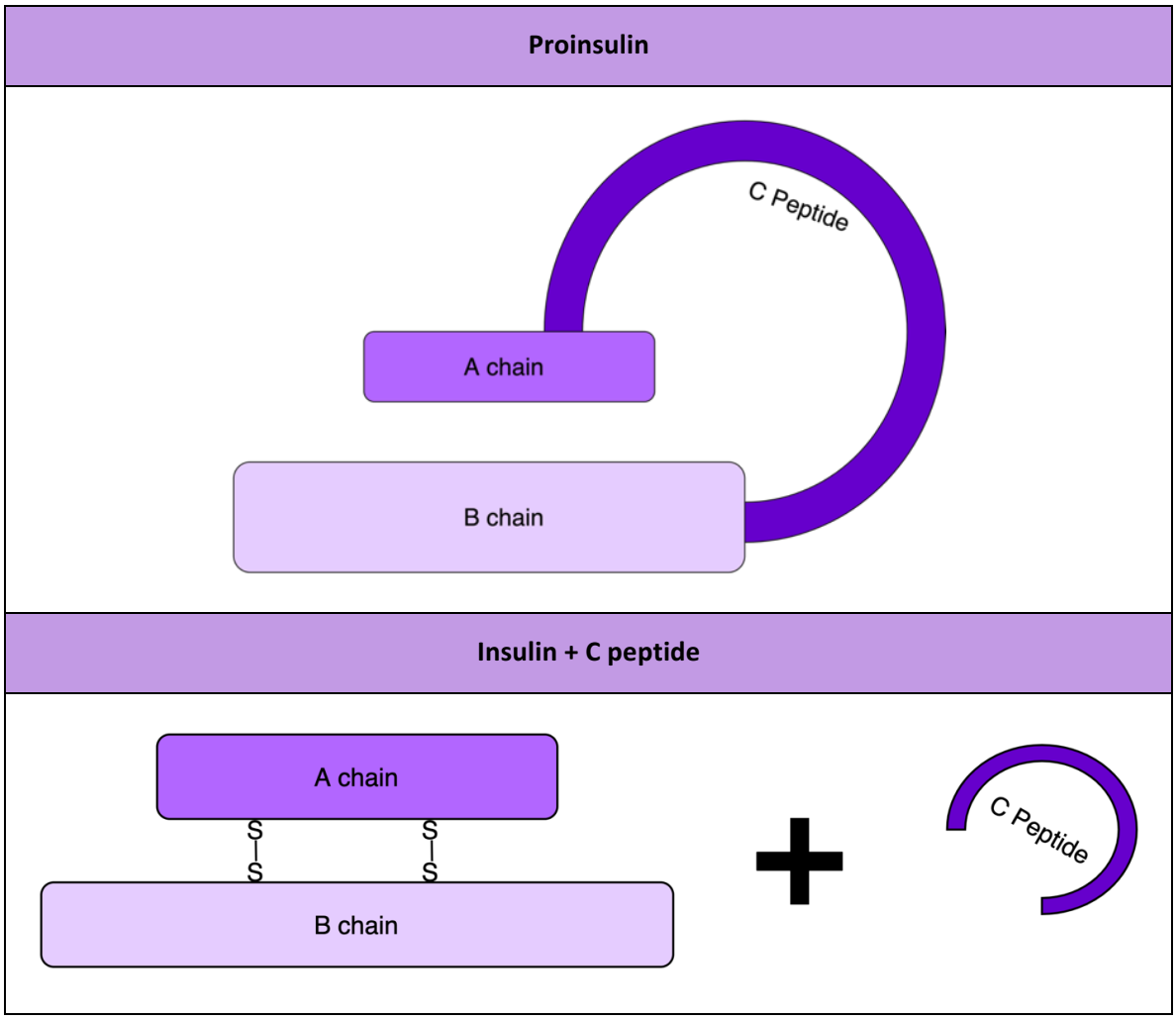
Diabetes mellitus (DM) type 1

In DM type 1 you have autoimmune destruction of the β-cells and therefore decreased production of insulin. The symptoms will not develop before 90% of the β-cells are damaged!

7.2 – Insulin

I. Structure of Insulin

- Insulin is transcribed from a gene on chromosome 11, the mRNA directs production of *preproinsulin*, which is cleaved into *proinsulin*.
- *Proinsulin* consists of an A chain + B chain + connecting peptide (C peptide).
- Disulfide bridges are formed between A and B chain in the endoplasmic reticulum.
- The C peptide is cleaved off in the Golgi apparatus leaving granules consisting of ready insulin + C peptide which are ready to be released from β-cells on stimulation.



CLINICAL CORRELATION

Diabetes mellitus type 1

C-peptide is released together with insulin and its concentration can be used to monitor the β-cell function. A patient with no β-cell function not have any measurable C-peptide, and has to receive exogenous insulin.

II. Regulation of insulin secretion

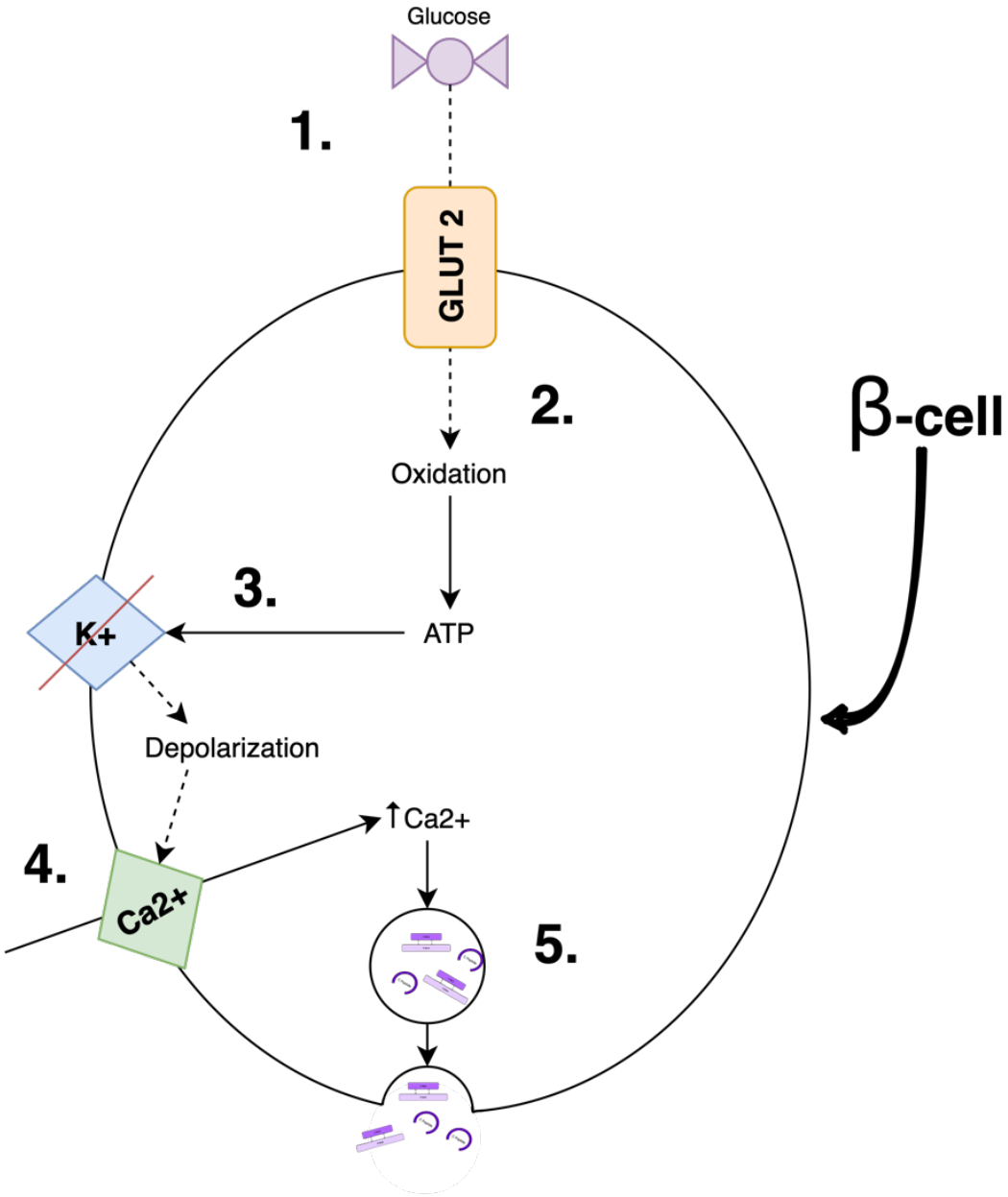
- Insulin is the key to get glucose into the cells and is essential for the cells in the body to exploit the nutrients available in the blood stream.
- Secretion of insulin is *stimulated* by increased concentration of nutrients in the blood and with parasympathetic stimulation ("rest and digest").
- Secretion of insulin is *inhibited* by fasting, exercise or α-adrenergic stimulation ("fight or flight" response).

Stimulatory factors	Inhibitory factors
↑ [glucose][1] ↑ [amino acids] ↑ [fatty acids and ketoacid] Cortisol Glucagon GIP[2] Potassium Acetylcholine	↓ [glucose] Fasting Exercise Somatostatin Norepinephrine and epinephrine

[1]Strongest stimulatory factor of insulin secretion

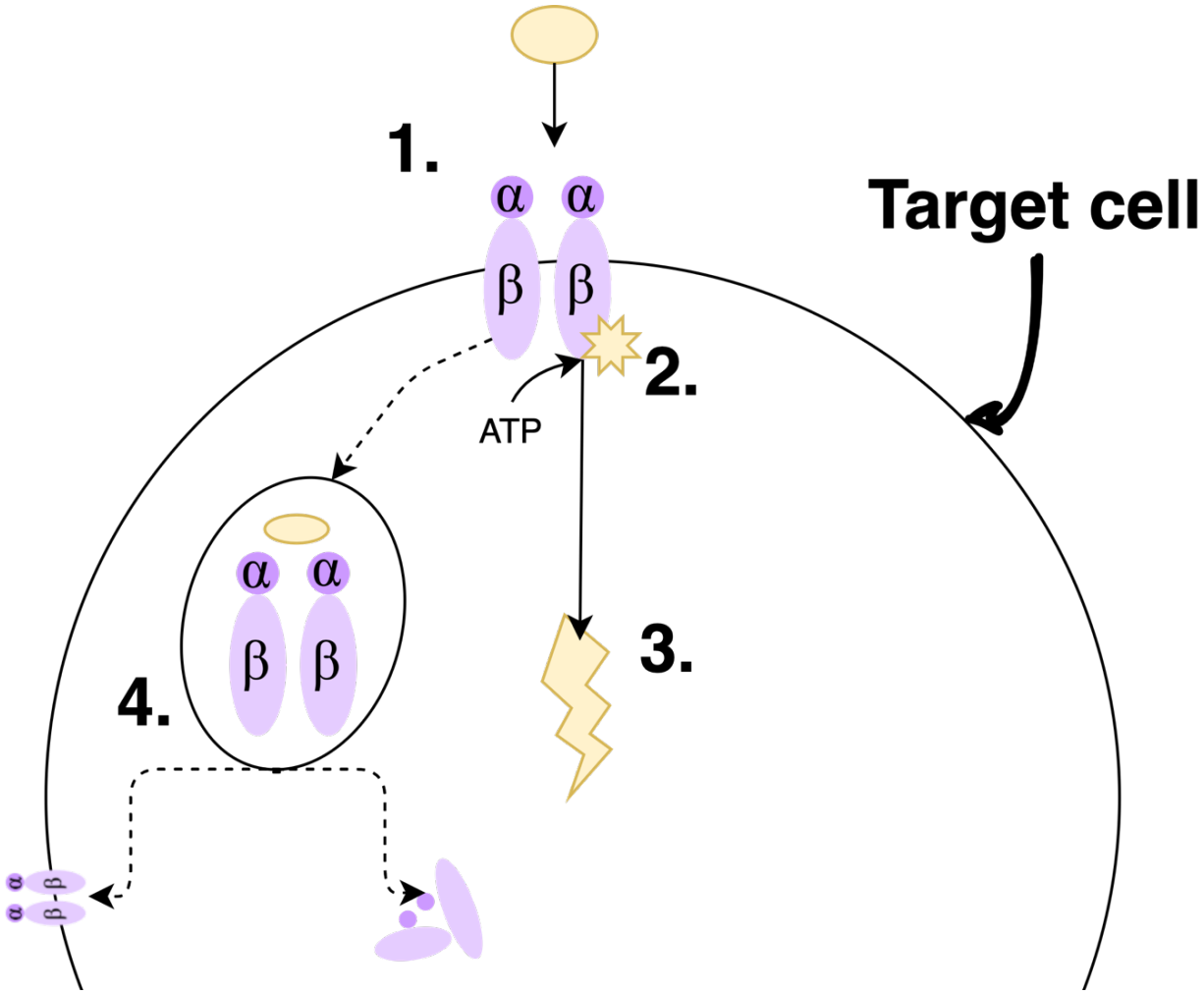
[2]Glucose-dependent insulinotropic peptide

III. Secretion of insulin from β-cells



1. Glucose is transported into β-cells by *GLUT 2 transporters* by facilitated diffusion
2. Glucose is oxidized, producing ATP
3. ↑ATP results in closure of the ATP-sensitive K^+ channels → depolarization of cell membrane
4. Depolarization opens voltage-gated Ca^{2+} channels → ↑Ca^{2+}
5. ↑Ca^{2+} intracellularly stimulates exocytosis of granules filled with insulin + C peptide in equimolar amounts

IV. Mechanism of action of insulin on target tissues



1. Insulin binds to the extracellular *α-units* of the insulin receptor
2. The binding of the α-units activates the *β-units*. Activated β-units phosphorylates itself in the presence of ATP.
3. Phosphorylated insulin receptors activate enzymes involved in the physiological action of insulin. In addition, insulin binds to elements in the nucleus, Golgi apparatus and endoplasmic reticulum, *stimulating gene transcription*.
4. The insulin-insulin receptor complex is taken into the target cell by endocytosis. Here it is either recycled out in the cell membrane, or degraded. In this way, insulin can down-regulate its own receptor if exposed to high amounts of glucose over time.

RECALL

Section 1.3 – Down-regulation
The degeneration of insulin receptors when exposed to high amounts of glucose is a good example of down-regulation.

V. Action of insulin on target tissue

↓ blood glucose concentration
- Insulin inserts *GLUT4* into cell membrane of target cell, facilitating intracellular movement of glucose. - Insulin promotes conversion of glucose → glycogen in liver and muscle cells. -Insulin inhibits gluconeogenesis[1] by increasing the production of fructose 2,6-diphosphate and therefore directing the substrate away from glucose formation.
↓ blood fatty acid + ketoacid concentration
- Insulin stimulates fat deposition and inhibits lipolysis in adipose tissue - Insulin inhibits ketoacid formation in the liver
↓ blood amino acid concentration
- Insulin has an anabolic effect on protein metabolism, increasing uptake of amino acids and proteins by tissues and therefore decreasing the blood concentration. - Insulin increases protein synthesis and inhibits protein degradation
Hypokalemia (↓K^+)
- Insulin promotes intracellular transport of K^+, by increasing the Na^+/K^+ ATPase.

[1]Synthesis of glucose

VI. Pathophysiology of insulin

- The major disorder of insulin is called diabetes mellitus and there are two major types

	Type 1 ***insulin-dependent***	**Type 2** ***non-insulin dependent***
Mechanism	Autoimmune destruction of β-cells stops endogenous production of insulin	Chronically increased amounts of glucose in the body cause down-regulation of insulin receptors on target tissue and insulin resistance
	↑ blood glucose ↑ fatty acids ↑ amino acids and proteins ↑ ketoacids[1]	The β-cell secretion of insulin is usually normal for a long time, but it is no longer able to activate the receptors in target tissue
	No link to obesity	Linked to obesity
Treatment	Insulin supplementation!	- Caloric restrictions and weight loss - Sulfonylurea drugs[2] - Metformin[3]

[1]Results in metabolic acidosis called diabetic ketoacidosis (DKA)

[2]stimulate ↑ release of insulin from β-cells

[3]↑ insulin receptors on target tissue

7.3 – Glucagon

- Glucagon has the opposite actions of insulin
- It is known as the "hormone of starvation"

I. Regulation of glucagon

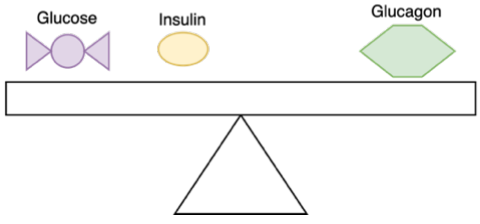
Stimulatory factors	Inhibitory factors
Fasting Intense exercise ↓ glucose ↑ amino acid concentration[1] CCK[2] β-adrenergic agonists ACh[3]	Insulin Somatostatin ↑ fatty acids ↑ ketoacids

[1]Arginine especially
[2]Cholecystokinin
[3]Acetylcholine

II. Action of glucagon on target tissues

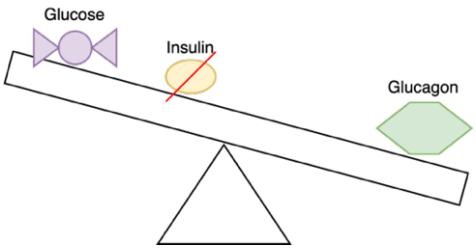
↑ blood glucose concentration
- Glucagon stimulates glycogenolysis - Glucagon inhibits glycogen formation from glucose - Glucagon increase gluconeogenesis by decreasing the production of fructose 2,6-bisphosphate
↑ blood fatty acid + ketoacid concentration
- Glucagon increases lipolysis and decreases fatty acid synthesis, releasing fatty acids to the blood stream

Normally functioning endocrine pancreas



↓ glucose - stimulation of glucagon
↑ insulin - inhibition of glucagon
= Balanced glucagon secretion

Diabetes mellitus type 1



↓glucose - stimulation of glucagon
NO insulin → NO inhibition of glucagon
= ↑↑ secretion of glucagon

- Patients with diabetes mellitus type 1 have an increased risk of severe hyperglycemia, as the regulation of glucagon balance is lost.

7.4 – Somatostatin

- Somatostatin is secreted by the δ-cells of the islets of Langerhans.
- Somatostatin stops the secretion of insulin, glucagon and gastrin after the signal of ingestion of food

I. Regulation of somatostatin

Stimulate secretion by:	Inhibit secretion by:
Ingestion of all forms of nutrients GI hormones Glucagon β-adrenergic agonists	Insulin[1]

[1]via paracrine communication

7.5 – Test yourself

1) What is the strongest stimulator of insulin secretion?

a) Exercise
b) ↑ph
c) ↑glucose
d) A-adrenergic stimulation

2) How does insulin cause lowered blood glucose?

3) Which of the following transporters facilitate glucose diffusion into β-cells?

a) GLUT-1
b) GLUT-2
c) GLUT-3
d) GLUT-4

4) Fill in the gaps

(increased/decreased)

Insulin is stimulated by _____ blood glucose and _____ fatty acids.

Glucagon is stimulated by _____ blood glucose and _____ amino acid concentration.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