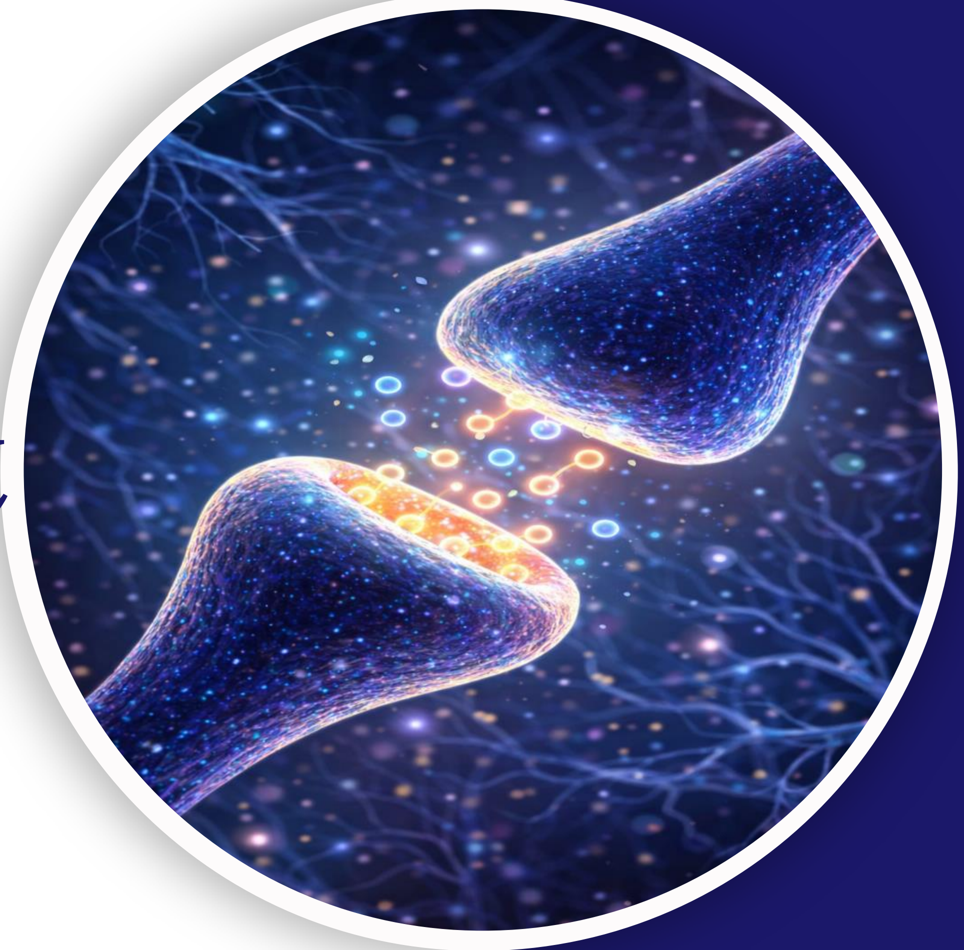
بسم الله الرحمـٰن الرحيم

(وَفَوْقَ كُلِّ ذِي عِلْمٍ عَلِيمٌ)

Endocrine Physiology | MID L3

Pituitary Hormones & their control Pt.1



Reviewed by : Leen Abukhalaf

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REMEMBER FROM GENERAL PHYSIOLOGY

- Glycoprotein receptors initiate signal transduction by binding extracellular ligands, activating intracellular pathways via conformational changes and second messengers.
- Protein (peptide) hormones are initially synthesized as large precursor peptides (pre-hormones) in the rough endoplasmic reticulum (ER) and then transported to the Golgi apparatus for post-translational modifications-slide 32.
- Dopamine is a catecholamine neurotransmitter synthesized from the amino acid tyrosine through the intermediate L-DOPA.

Pituitary Hormones and Their Control by the Hypothalamus

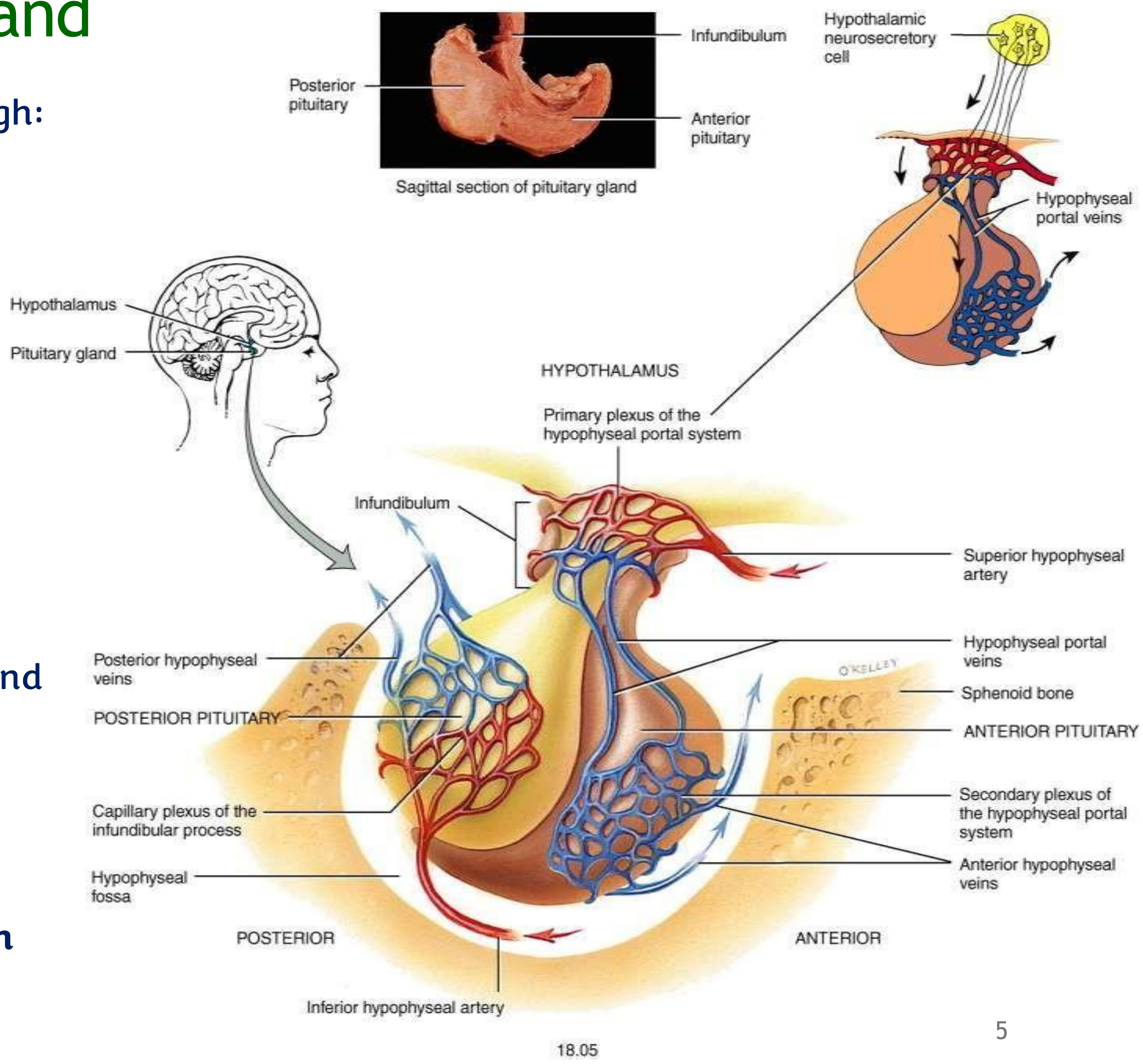
Objectives

- Give an account of the importance of the relationship of the hypothalamus and pituitary
- List anterior pituitary hormones
- Give an account for the action of anterior pituitary hormones
- Follow up the control of anterior pituitary hormones
- Track the abnormalities of anterior pituitary
- List the posterior pituitary hormones
- Give an account of the function of posterior pituitary hormones
- Explain abnormalities of those hormones

Hypothalamus and Pituitary Gland

The pituitary gland receives its blood supply through:
Superior hypophyseal artery
Inferior hypophyseal artery
Because of this special blood supply, we call it the **hypophyseal portal circulation**.

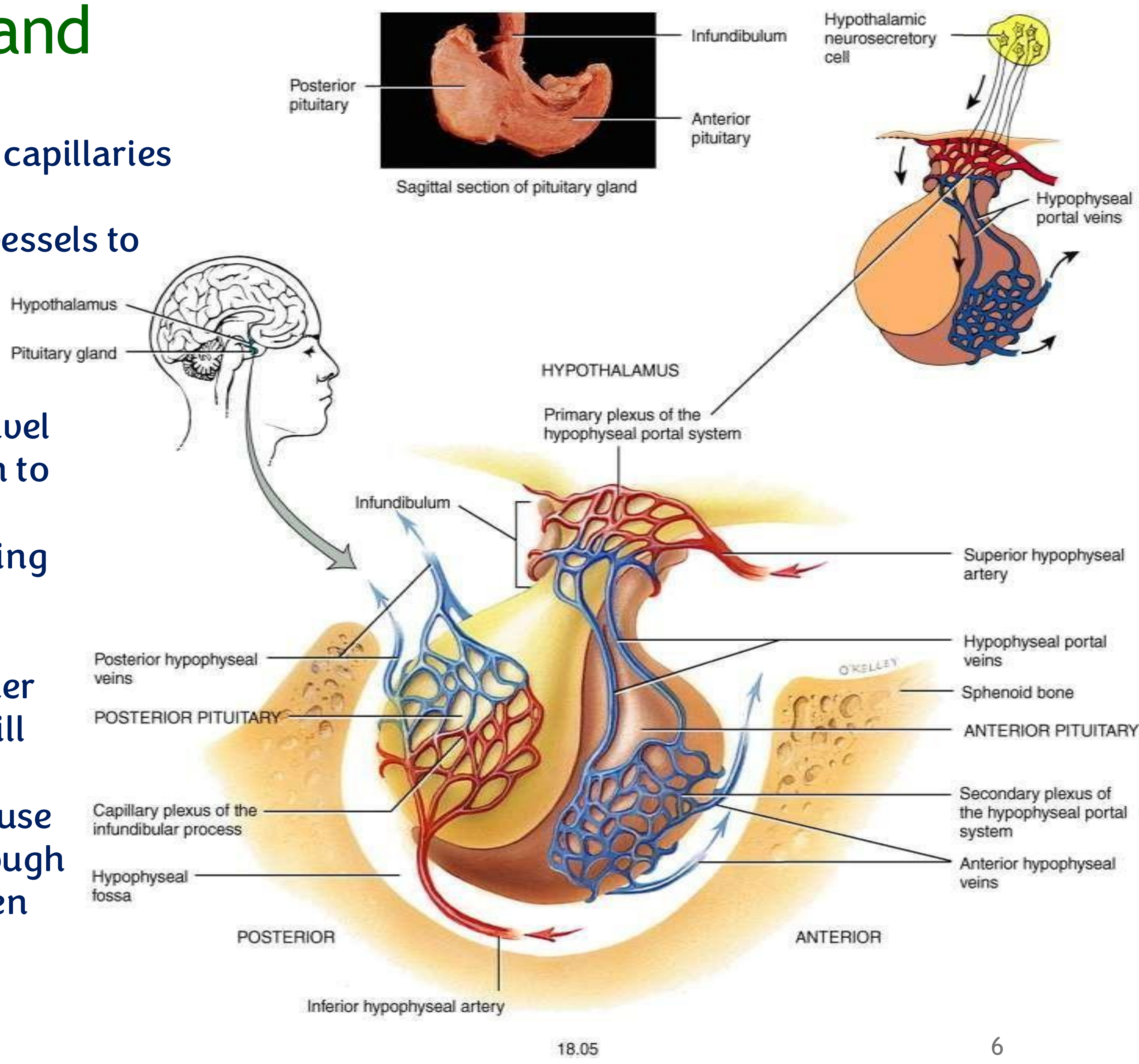
What is a portal circulation?
A **portal system** is a circulation in which blood passes through **two capillary beds in sequence** before returning to the heart.
Normal systemic circulation:
Artery → Capillary → Vein
Portal circulation:
Artery → First capillary bed → Portal veins → Second capillary bed → Vein
This arrangement is very important because the hypothalamic hormones are carried directly to the anterior pituitary **without being diluted in the systemic circulation**.
As a result, they reach the anterior pituitary in **high concentrations**, making them effective.



Hypothalamus and Pituitary Gland

Median Eminence
The hypothalamic hormones are secreted into the capillaries of the median eminence.
They then travel through the hypophyseal portal vessels to the anterior pituitary in high concentrations.

Why is the Portal System Important?
The hormones released from the hypothalamus travel only a short distance through the portal circulation to the anterior pituitary.
Therefore, they remain highly concentrated, allowing the anterior pituitary to function normally.
The doctor gave an example:
If the anterior pituitary were transplanted to another place in the body (for example, the leg), it would still function because it still receives blood supply.
However, it would not function as efficiently, because the hypothalamic hormones would first travel through the entire systemic circulation, become diluted, then eventually reach the anterior pituitary in very low concentrations, making them much less effective.



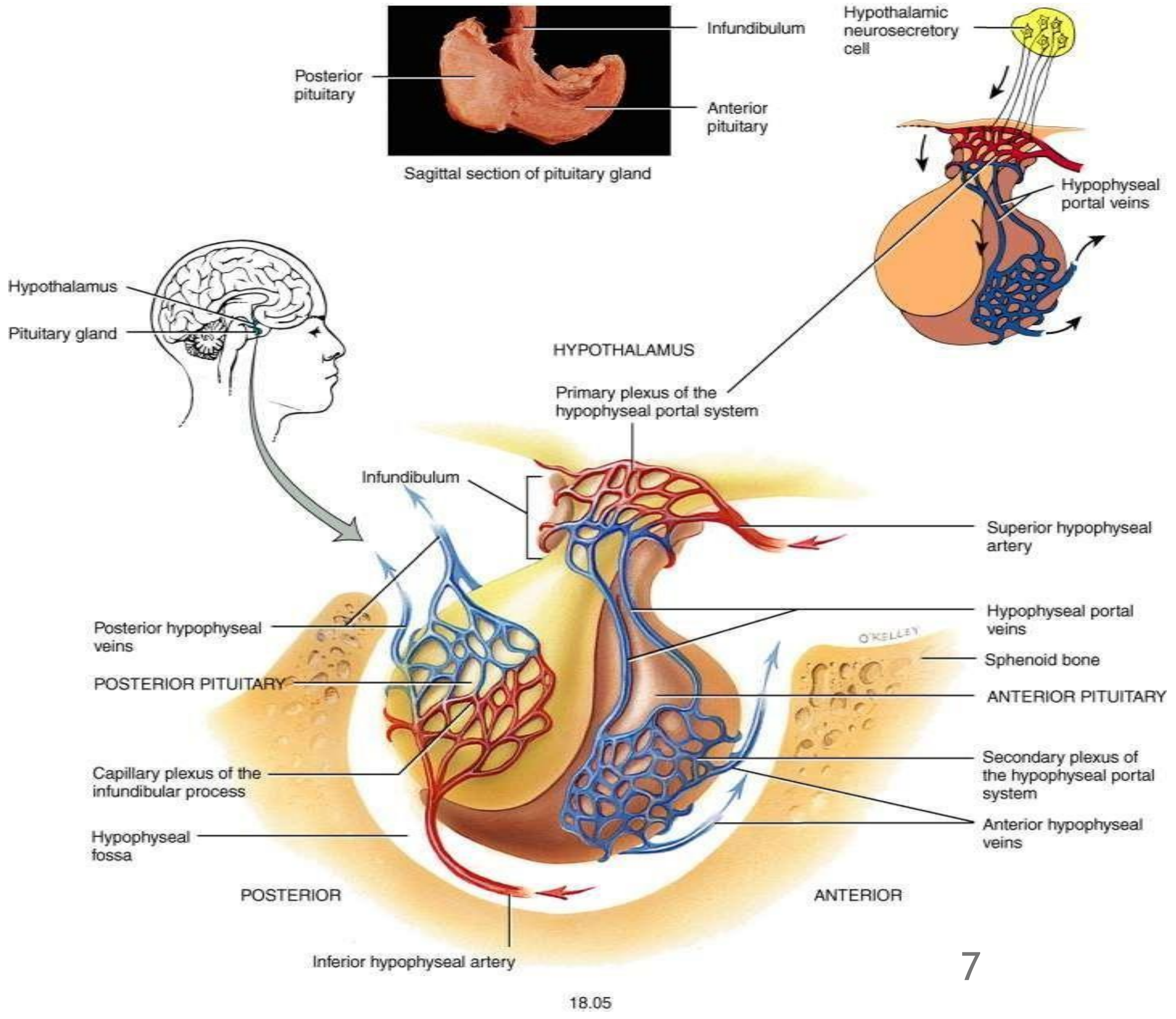
Hypothalamus and Pituitary Gland

Pituitary Stalk Lesion
The portal circulation is clinically important.
If there is damage or a cut in the pituitary stalk, the hypothalamic hormones can no longer reach the anterior pituitary directly.
Instead, they would have to enter the general circulation and eventually return to the anterior pituitary at very low concentrations, making them ineffective.
As a result, the anterior pituitary hormones will not be properly stimulated.

If the hypophyseal portal circulation was cut, the hormones won't be concentrated to the anterior pituitary, and thus hypopituitarism occurs. This could be a Pan-hypopituitarism = all anterior pituitary hormones are reduced.

Or a physiological cut might happen (a cut due to disease) damage for a woman's circulation after delivery "Sheehan's Syndrome", damage due to a hemorrhage, tumor, etc causing hypopituitarism.

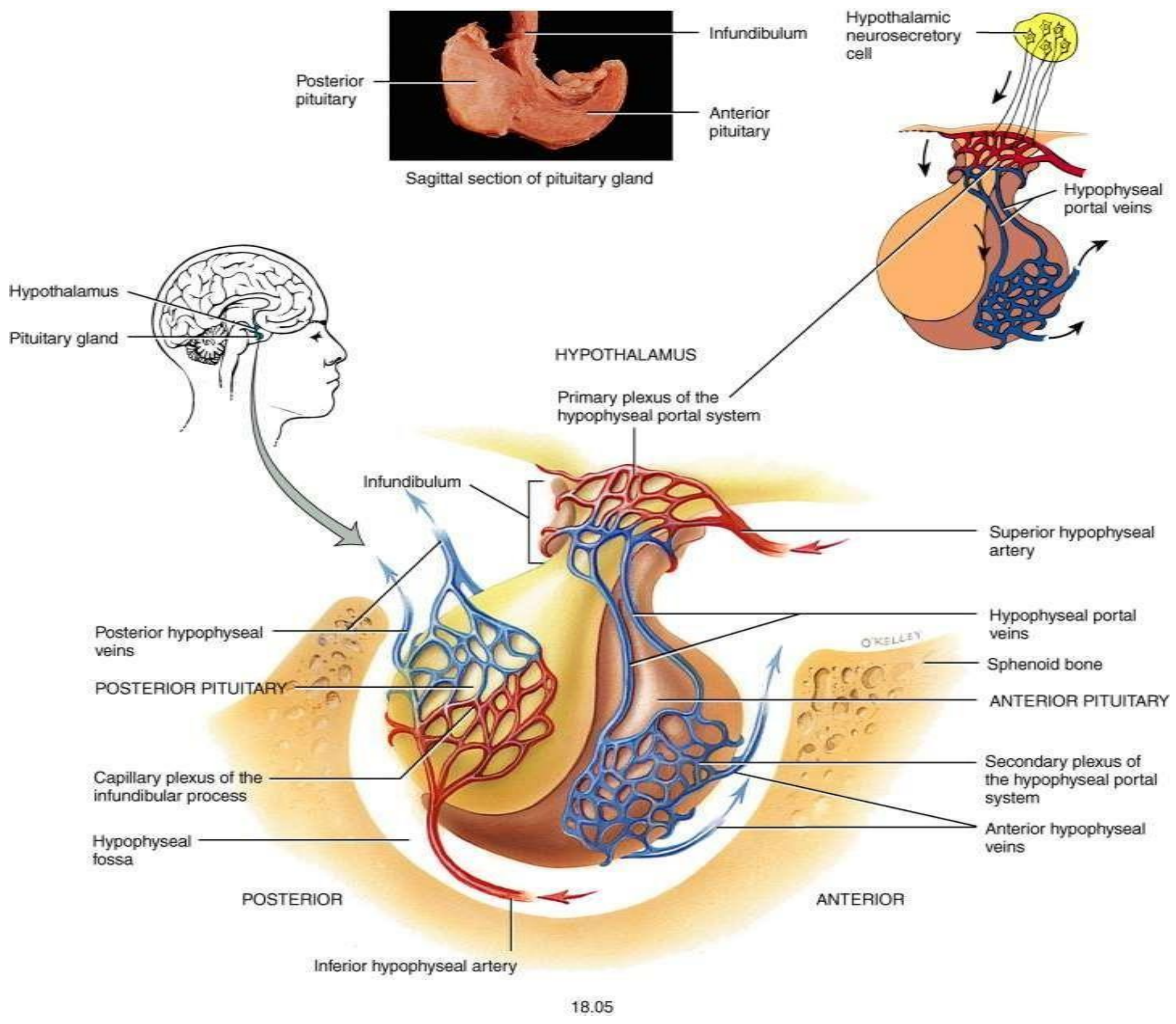
Remember that the anterior pituitary is glandular, derived from the ectoderm & the posterior pituitary is a neuronal, derived from ectoderm. This is similar to the adrenal medulla & adrenal cortex, the tongue's anterior 2/3 & posterior 1/3 (two distinct embryonical origins).



Hypothalamus and Pituitary Gland

Development of the Pituitary Gland
The anterior and posterior pituitary originate from different embryological tissues.
Anterior pituitary (adenohypophysis): Oral ectoderm (Rathke's pouch)
Posterior pituitary (neurohypophysis): Neural ectoderm (down-growth from the diencephalon)
Although they arise from different embryological origins, both eventually occupy the sella turcica.

Comparison with the Adrenal Gland
The adrenal gland also develops from two different embryological origins. Adrenal cortex: Mesoderm
Adrenal medulla: Neural crest cells (ectoderm)



Anterior pituitary

- Release of hormones stimulated by releasing and inhibiting hormones from the hypothalamus -some hormones are controlled by both, and some are controlled by one of them - .
- Also regulated mostly by **negative feedback** ,but there are exceptions; for example LH is regulated also by positive feedback.
- Hypothalamic hormones made by neurosecretory cells transported by hypophyseal portal system >to concentrate the hormones.
- Anterior pituitary hormones that act on other endocrine systems called **tropic hormones.** E.g, Adrenocorticotropic hormone, somatotropic (Growth hormone), etc.

Hormones of the Anterior Pituitary

- **Human growth hormone (hGH) or somatotropin** (Bcz it causes growth of somatic tissue)
  - It has 2 actions:
  1. Metabolic: directly by the hormone itself.
  2. Growth: by intermediates (somato-mediators, IGFs) that are released from the liver under the effect of hGH.
  - hGH stimulates secretion of insulin-like growth factors (IGFs) that promote growth, protein synthesis.
  - hGH is a protein hormone, with 199 a.a's, so it has receptors on cell membranes. It is regulated by GHRH (growth hormone releasing hormone aka somatoliberin) and GHIH (growth hormone inhibiting hormone aka somatostatin) which are both released by the hypothalamus as peptide hormones, GHRH=41 a.a's, GHIH=14 a.a's.

Somatotropic hormone (Somatotropin). *(The doctor mentioned "Somato = skin (somatic tissue)." More accurately, "somato" refers to the* ***body*** *or* ***body tissues****, especially musculoskeletal tissues.)*

Growth Hormone Mechanism

Growth hormone is secreted by the anterior pituitary.

It does not produce most of its growth effects directly.

- Instead, it stimulates the liver to produce: Insulin-like Growth Factor-1 (IGF-1)
- Also called Somatomedin C

(The doctor mentioned the kidney, but physiologically the principal source is the liver.)

These somatomedins produce most of the effects on:

- Bone
- Muscle
- Connective tissue

They stimulate:

- Protein synthesis
- Cell growth

They also participate in regulating growth hormone secretion.

Why Are They Called "Insulin-like"?

They are called Insulin-like Growth Factors (IGFs) because they produce effects similar to insulin.

The doctor also reviewed insulin structure.

Insulin is a peptide hormone consisting of:

- 51 amino acids
- One **A chain (21 amino acids)**
- One **B chain (30 amino acids)**

The two chains are connected by **disulfide bonds**.

Hormones of the Anterior Pituitary - con.

- **Thyroid-stimulating hormone (TSH) or thyrotropin**

➢ Stimulates synthesis and secretion of thyroid hormones by thyroid

➢ TSH is a glycoprotein, all glycoproteins (TSH, FSH, LH, ...) in the body are composed of a common α unit & a specific β unit-due to β unit specificity ,hormone levels could be measured in serum *1 -.

➢ TSH is a glycoprotein hormone.

Glycoprotein hormones consist of:
- Alpha subunit
- Beta subunit

The alpha subunit is identical among: (TSH,LH,FSH,hCG)
The beta subunit gives each hormone its biological specificity

- TSH stimulates ALL the steps of the synthesis of thyroid hormones, and it induces the growth (increase of the size of the thyroid gland), which is referred to as goiter.

- Goiter could be because of Hyperthyroidism (More active = Hyperplasia) or Hypothyroidism (Less active = Atrophy) or Euthyroid (compensatory, as in the thyroid hormones are not secreted in sufficient quantities so the size of the gland increase, thus the amount of thyroxine secreted is increased which causes a normal amount of hormone to be secreted)

- TRH (thyroid releasing hormone) is a peptide hormone that is very small (only 3 a.a's) and is released by the hypothalamus.

Hyperthyroidism:

in the graves disease there are antibodies that stimulate the TSH receptor continuously, causing either hyperplasia or leading to goiter hypertrophy. Then hormone synthesis and secretion increases -> T3 and T4 increase so it causes hyperthyroidism.

In case of hypothyroidism:

like in case of iodine deficiency, the decrease of iodine decreases T3 and T4 -> so it causes a negative feedback; the negative feedback increases TRH and TSH , causing either hyperplasia leading to goiter, or hypertrophy

in case of Euthyroid (compensatory goiter):

Mild decrease in T3 and T4 causes increase NTSH so thyroid enlarges (hyperplasia) and the gland produces enough hormone to maintain normal. T3 and T4 and hormone levels become normal(Euthyroid).

Which lead to goiter, but normal hormone level.

Thyroid Hormone Synthesis
Thyroxine is synthesized from the amino acid tyrosine.
The first step is the transport of iodide from the plasma into the thyroid follicular cells.
This occurs by active transport through the sodium-iodide symporter (thyroid iodide pump).
TSH stimulates this pump.

Iodination (Organification)
After iodide enters the thyroid, it is oxidized and attached to tyrosine residues on thyroglobulin.
This process is called:
Iodination (Organification).
Tyrosine first becomes:
- MIT (Monoiodotyrosine)

Then:
- DIT (Diiodotyrosine)

TSH stimulates this process.

Coupling Reaction
Next comes the coupling reaction.
Examples:
DIT + DIT → T4 (Thyroxine, Tetraiodothyronine)
MIT + DIT → T3 (Triiodothyronine)
- The doctor emphasized that TSH stimulates the entire process, including: Iodide trapping
- Organification (iodination)
- Coupling
- Hormone synthesis
- Hormone release
- Growth of the thyroid gland

T4 and T3
T4 is considered the prohormone.
It is converted in peripheral tissues to T3, the biologically active hormone.
This conversion is called deiodination and is carried out by deiodinase enzymes.

Skip if you want , these are information the dr mentioned about the next lecture in ahead of time

Hormones of the Anterior Pituitary- con.

- **Follicle-stimulating hormone (FSH)** a glycoprotein , it acts on both females & males
  - Ovaries initiates development of oocytes (oogenesis: formation of ovum) , testes stimulates testosterone production, (spermatogenesis: formation of sperm)
- **Luteinizing hormone (LH)**
  - Ovaries stimulates ovulation (the release of the ovum from the ovary to the fallopian tube) , testes stimulates testosterone production

- Testosterone is a steroid hormone produced by **Leydig cells** (interstitial cells)
- Bothare called gonadotropins since they act on the gonads, and both are glycoproteins. They controlled by the same GnRH (Gonadotropin-releasing hormone) from the hypothalamus which is a peptide hormone made up of 10a.a’s.
- They are secreted after puberty, because GnRH is released from the hypothalamus after it matures, inducing puberty, which induces the production of FSH & LH. So, the pituitary is active even before puberty, it just depends on the presence of GnRH to start it.
- Therefore, precocious puberty happens when the child has increased GnRH levels before the time of puberty.
- Another glycoprotein hormone is HCG (Human Chorionic Gonadotropin) it is also made of an alpha & beta subunits, so for pregnancy tests we measure the levels of the beta subunit – check slide 11 (*1).

Hormones of the Anterior Pituitary - con.

- **Prolactin (PRL)**
  - Promotes milk secretion by mammary glands
  - It's a 198a.a's protein hormone, It's regulated by prolactin inhibitory hormone, "DOPAMINE", which is synthesized in the hypothalamus.
  - It's VERY important to note that prolactin is normally inhibited by dopamine, and is induced when the pituitary stalk is damaged, which means all the other hormones will be inhibited but the prolactin will increase. This causes conditions like, Gynecomastia, and milk production for both males and females.
  - PRL does NOT causes ejection of milk, instead ANOTHER hormone causes that, it is oxytocin, which is stored in the posterior pituitary.
  - During pregnancy, the prolactin inhibiting hormones levels are reduced (less dopamine), causing the production of milk to start.

Hormones of the Anterior Pituitary - con.

- **Adrenocorticotropic hormone (ACTH) or corticotropin**
  - Stimulates glucocorticoid secretion by adrenal cortex especially cortisol.
  - Acts on the adrenal cortex. Is stimulated by CRH (Corticotropin-releasing hormones)
  - The adrenal cortex produces 3 types of hormones: Glucocorticoids (act on glucose metabolism), Mineralocorticoids (act on minerals; Na+/K+), & Androgens (male sex hormones)
- **Melanocyte-stimulating Hormone (MSH)**
  - Unknown role in humans. (Can cause pigmentation)

Hypophysiotropic Hormones

Hormone	Predominant hypothalamic localization	Structure	Actions on Anterior Pituitary
Thyrotropin-releasing hormone (TRH)	Paraventricular	Peptide consisting of 3 amino acids	Stimulates secretion of TSH by thyrotropes; stimulates expression of genes for α and ß subunits of TSH thyrotropes; stimulates synthesis of PRL by lactotropes
Gonadotropin-releasing hormone (GnRH)	Arcuate	Single chain of 10 amino acids	Stimulates secretion of FSH and LH by gonadotropes
Corticotropin-releasing hormone (CRH)	Paraventricular	Single chain of 41 amino acids	Stimulates secretion of ACTH by corticotropes; stimulates expression of gene for POMC in corticotropes
Growth hormone-releasing hormone (GHRH)	Arcuate	Single chain of 44 amino acids	Stimulates secretion of GH by somatotropes; stimulates expression of gene for GH in somatotropes
Growth hormone-inhibiting hormone (somatostatin)	Anterior periventricular	Single chain of 14 amino acids	Inhibits secretion of GH by somatotropes
Prolactin-inhibiting hormone (PIH)	Arcuate	Dopamine	Inhibits biosynthesis and secretion of PRL by lactotropes

- These hormones are produced from all areas in the hypothalamus, the second column just shows the most predominant one, professor said it's not important to know these areas!!

- TRH is the simplest known hormone ever

- The table is important!

Negative Feedback Regulation

(Example: ACTH)

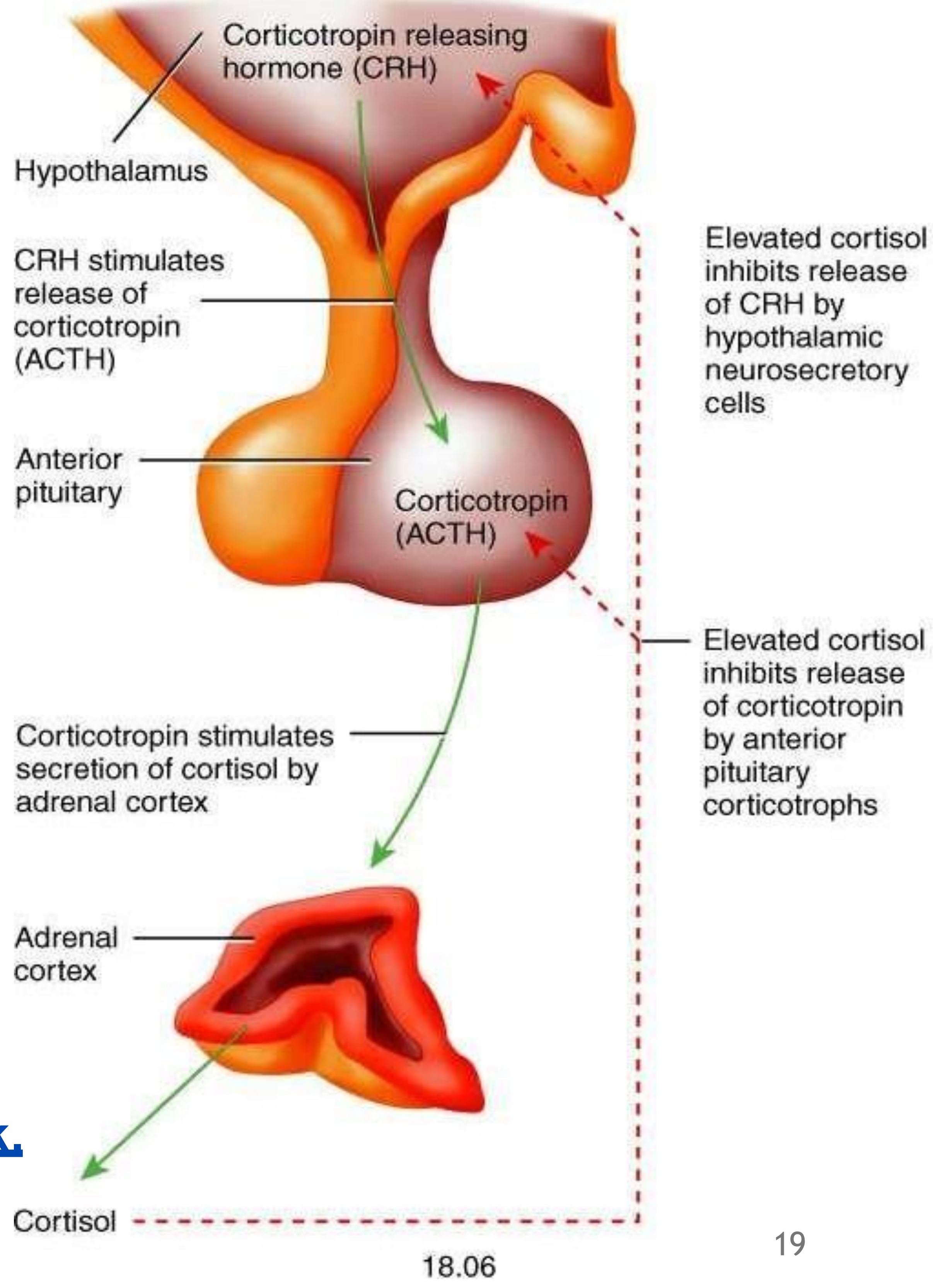
The secretion of ACTH (Adrenocorticotropic Hormone) from the anterior pituitary is regulated by CRH (Corticotropin-Releasing Hormone), which is a peptide hormone made of amino acids. CRH is released from the hypothalamus and is transported to the anterior pituitary via the hypophyseal portal system, where it stimulates the release of ACTH.

Once secreted, ACTH acts on the adrenal cortex, primarily stimulating the production of cortisol. Although ACTH affects cortisol secretion, mineralocorticoid secretion (such as aldosterone) is regulated by other mechanisms.

Cortisol, the main hormone regulated by ACTH, exerts negative feedback on both:

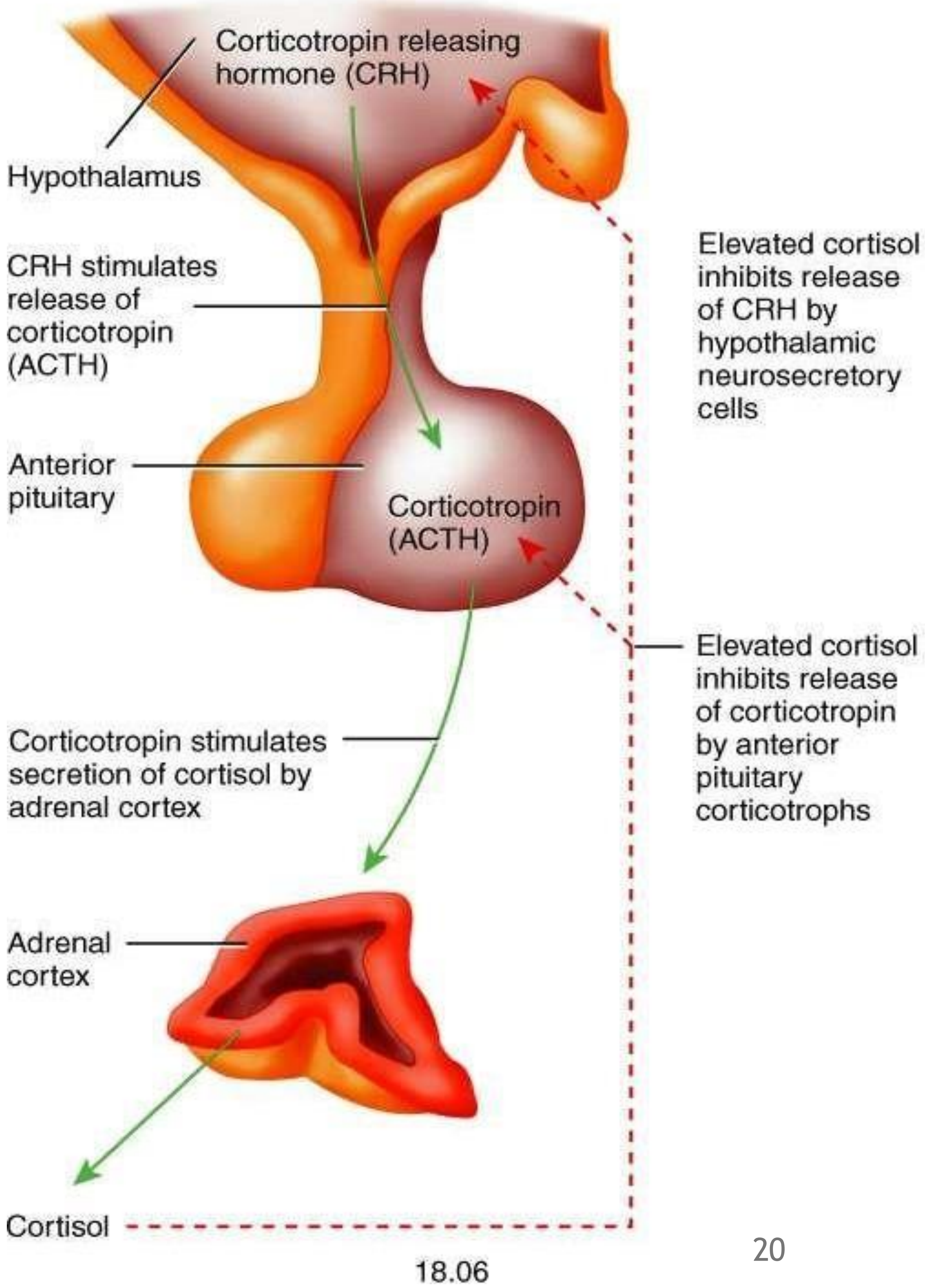
- The anterior pituitary, to inhibit further release of ACTH
- The hypothalamus, to inhibit the release of CRH

This feedback mechanism is known as the **long-loop negative feedback.**



Negative Feedback Regulation
(Example: ACTH)

Additionally, ACTH itself can inhibit CRH secretion at the level of the hypothalamus; a mechanism referred to as the short-loop negative feedback.



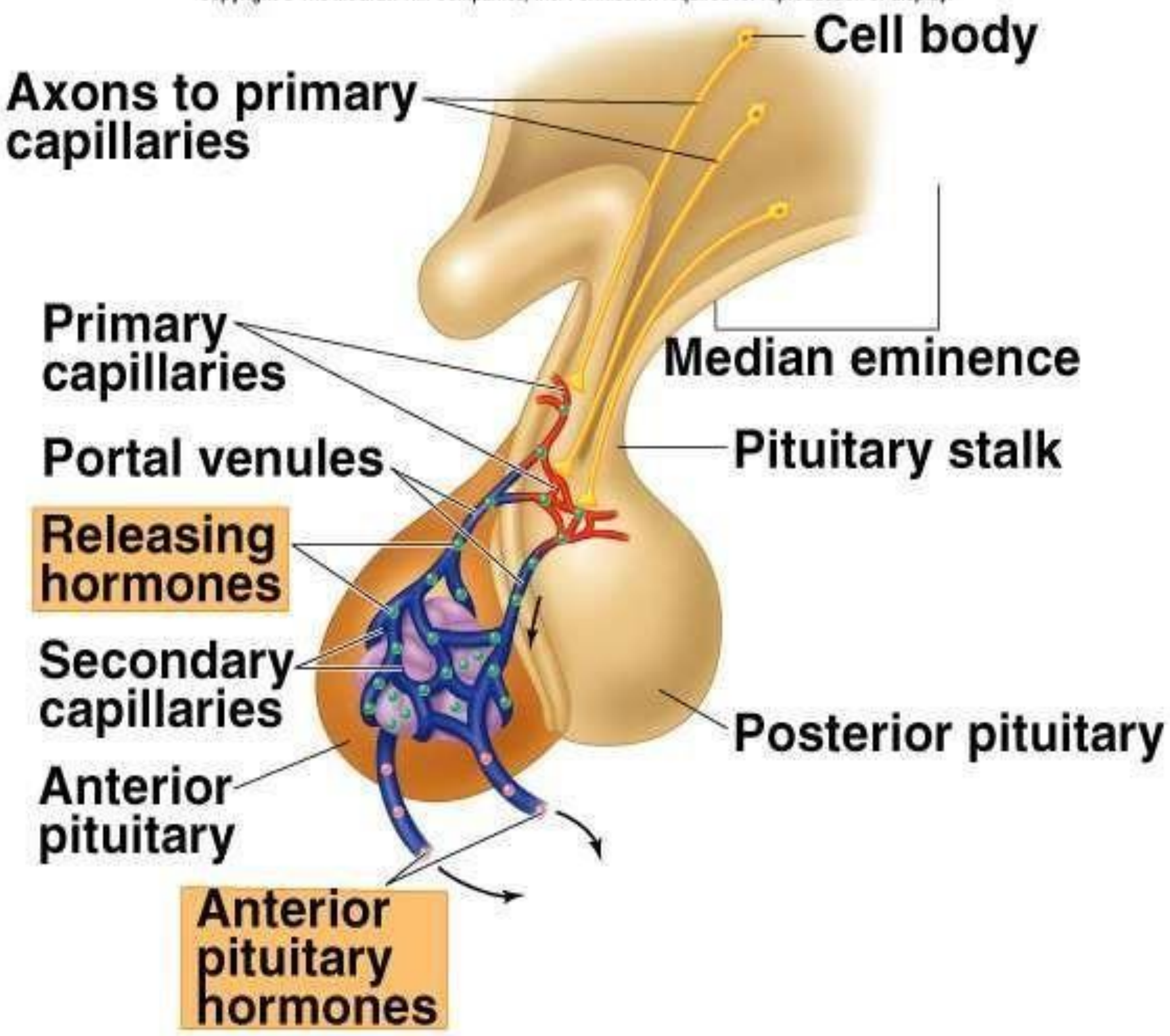
Hypothalamic Control of the Anterior Pituitary

- Hormonal control rather than neural.

- Hypothalamus neurons synthesize releasing and inhibiting hormones.

- Hormones are transported to axon endings of <u>median eminence</u> (very important in the hypothalamic-pituitary portal circulation) .

- Hormones secreted into the hypothalamo-hypophyseal portal system regulate the secretions of the anterior pituitary

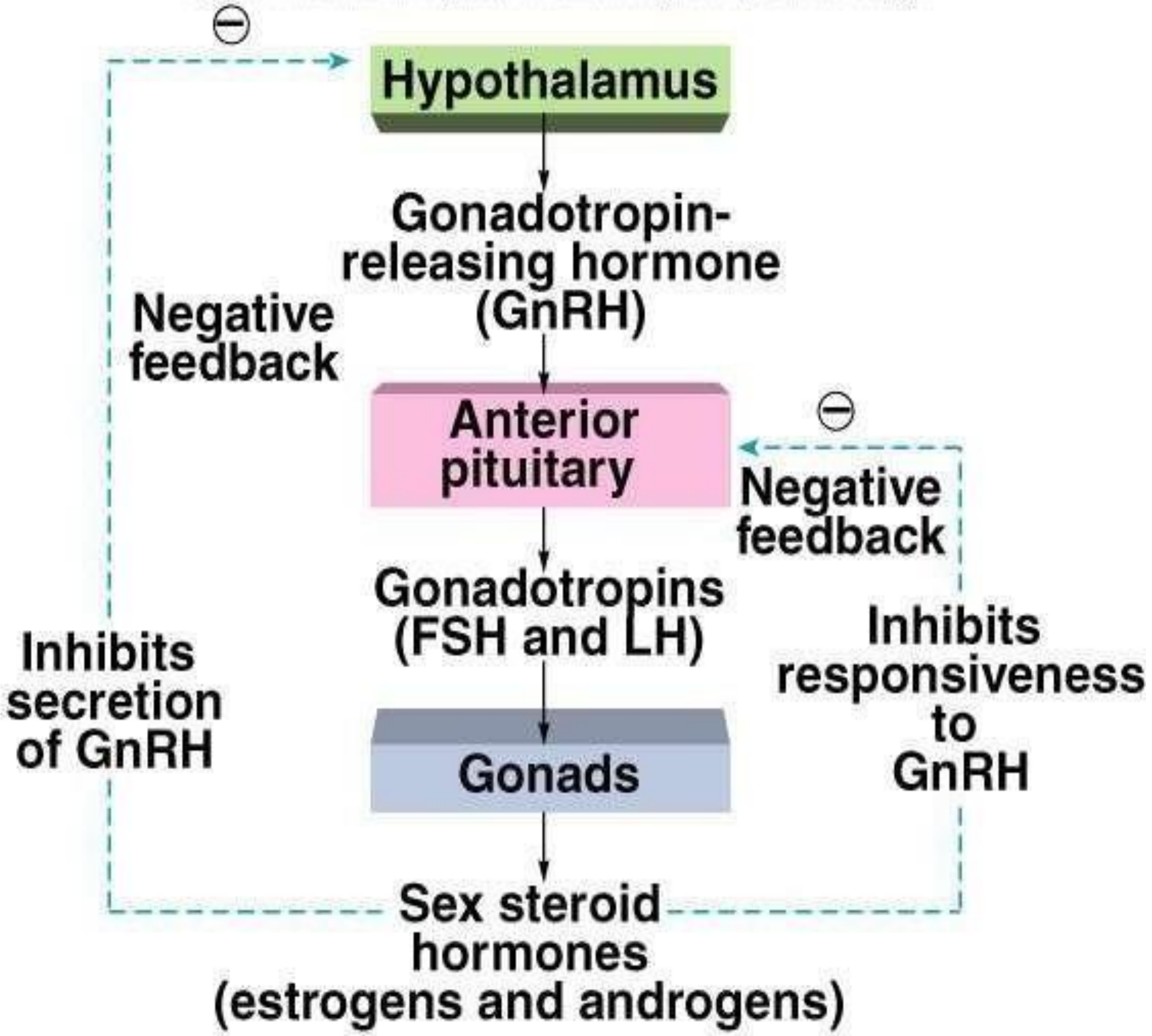


Feedback Control of the Anterior Pituitary

- Anterior pituitary and hypothalamic secretions are controlled by the target organs they regulate.
  - Secretions are controlled by negative feedback inhibition by target gland hormones.
- Negative feedback at 2 levels (long-loop)：
  - The target gland hormone can act on the hypothalamus and inhibit secretion of releasing hormones.
  - The target gland hormone can act on the anterior pituitary and inhibit response to the releasing hormone.

Feedback Control of the Anterior Pituitary (continued)

- Short feedback loop:
  - Retrograde transport of blood from anterior pituitary to the hypothalamus.
    - Hormone released by anterior pituitary inhibits secretion of releasing hormone.
    - E.g; (sex hormones): FSH and LH, secreted by the anterior pituitary, can directly inhibit GnRH secretion from the hypothalamus.
- Positive feedback effect:
  - During the menstrual cycle, estrogen stimulate "LH surge."



Unlike most hormonal pathways, estrogen can exert positive feedback on the hypothalamus and anterior pituitary during a brief period in the menstrual cycle. This surge in estrogen stimulates a sharp increase in LH secretion, triggering ovulation (release of the ovum from the ovary).

In long-loop negative feedback, hormones from the target glands (like estrogen or testosterone) inhibit both the anterior pituitary and the hypothalamus.

Higher Brain Function and Pituitary Secretion

- Axis:
  - Relationship between anterior pituitary and a particular target gland.
    - Pituitary-gonad axis.
    - Pituitary-adrenal axis....and so on.

- Hypothalamus receives input from higher brain centers.
  - Psychological stress affects (the limbic system):
    - Circadian rhythms. (Discussed in the next slide)
    - Menstrual cycle.

Circadian Rhythms

- The hypothalamus is part of the limbic system, which is heavily influenced by emotions. As a result, hypothalamic activity can be affected by psychological stress.
- Within the hypothalamus lies the suprachiasmatic nucleus (SCN), located above the optic chiasm. This region receives input from retinal fibers via the optic tract, allowing it to detect the presence or absence of light and distinguish between day and night.
- This light-based signaling helps the hypothalamus regulate the circadian rhythm, also known as the biological clock which is a system that controls the timing of various bodily functions, including hormone release.
- Hormone secretion follows a pulsatile pattern, not continuous. This pulsatility helps prevent excessive upregulation or downregulation of hormone receptors, maintaining effective control.
- Some hormones are secreted mainly during the day (e.g., cortisol), while others peak at night (e.g., growth hormone).
- Jet lag occurs when this internal clock is misaligned with the local time (e.g., traveling from the U.S. to another time zone). Recovery varies from person to person, it may take a few days to a few weeks.

Effects of hGH and IGFs

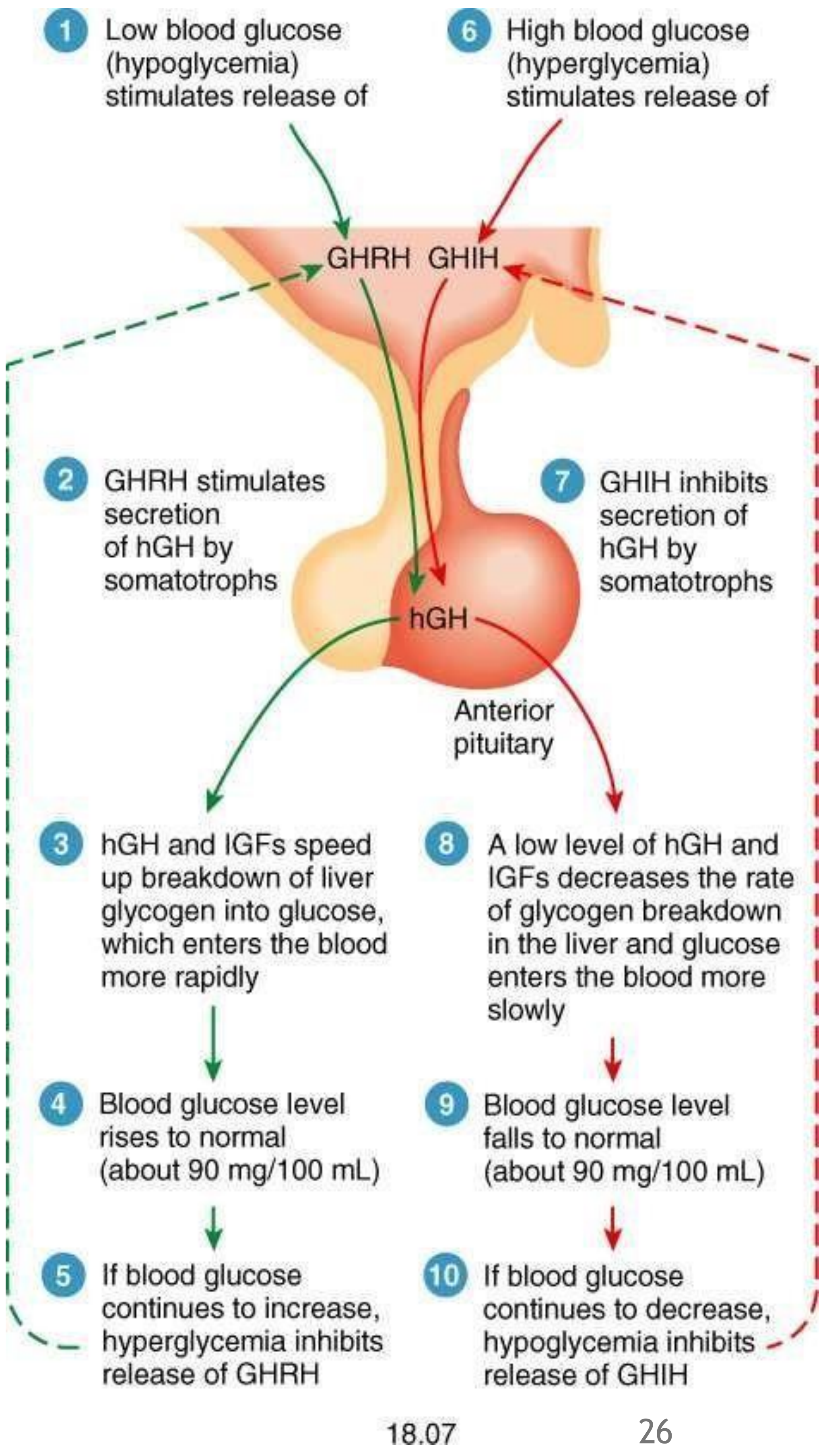
High levels of growth hormone (GH) cause excessive growth through stimulation of chondrocytes via IGFs (Insulin-like Growth Factors), on the other hand; sex hormones fuses the epiphyseal line preventing further chondrocytes growth (no further linear growth).

- High levels of GH before puberty causes Gigantism,

GH promotes linear bone growth; bcz the epiphyseal growth plates in long bones are still open, leading to proportionate increase in height and overall size (even on heart tissue, liver tissue, smooth muscle ..).

- After puberty causes Acromegaly

- Disproportionate growth and enlargement of body parts, but no increase in height. GH can no longer cause an increase in long bone length. Instead, it causes growth in flat bones and soft tissues (e.g., skull, jaw, hands, feet, sternum).



Effects of hGH and IGFs

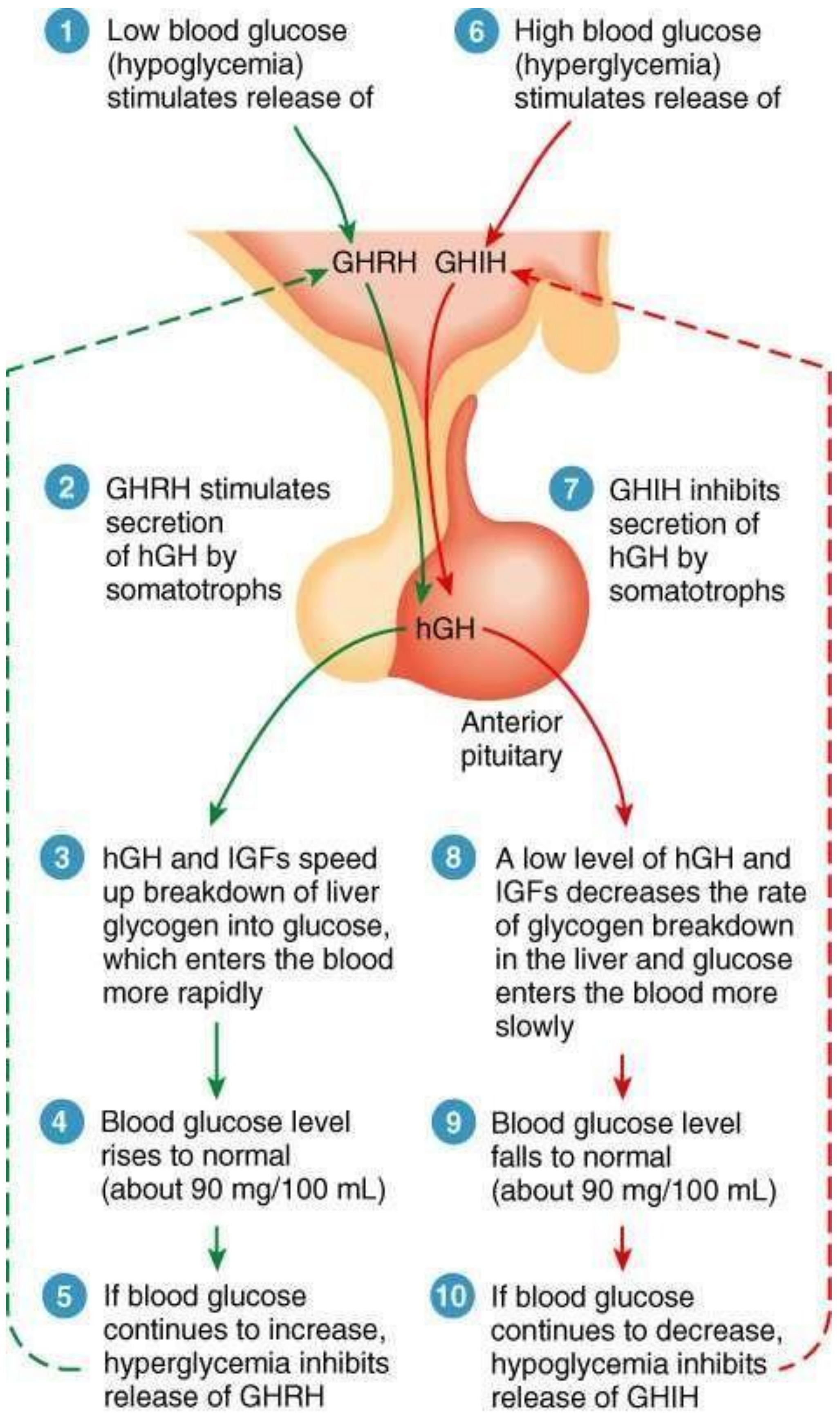
Effects of Hypopituitarism:

- Low levels of GH before puberty causes Dwarfism

The individual is shorter than average, but body proportions remain normal.

- After puberty leads to some Metabolic effects

Since the epiphyseal plates are already closed, GH deficiency does not affect height. However, it leads to metabolic disturbances.



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Growth hormone regulation

GH secretion from the anterior pituitary is regulated by:

- GHRH (Growth Hormone-Releasing Hormone) → stimulates GH release
- GHIH (Growth Hormone-Inhibiting Hormone / Somatostatin) → inhibits GH release

Main Regulator: Blood Glucose

Low blood glucose (hypoglycemia) stimulates:

- GHRH release from the hypothalamus
- Increased GH (hGH) secretion from the anterior pituitary

GH actions to raise blood glucose:

- Stimulates the liver to release IGFs (Insulin-like Growth Factors)
- Promotes glycogenolysis: breakdown of glycogen into glucose
- Stimulates gluconeogenesis: formation of glucose from non-carbohydrate sources

As a result, blood glucose levels rise back to normal.

Growth hormone regulation

If glucose continues to increase (hyperglycemia):

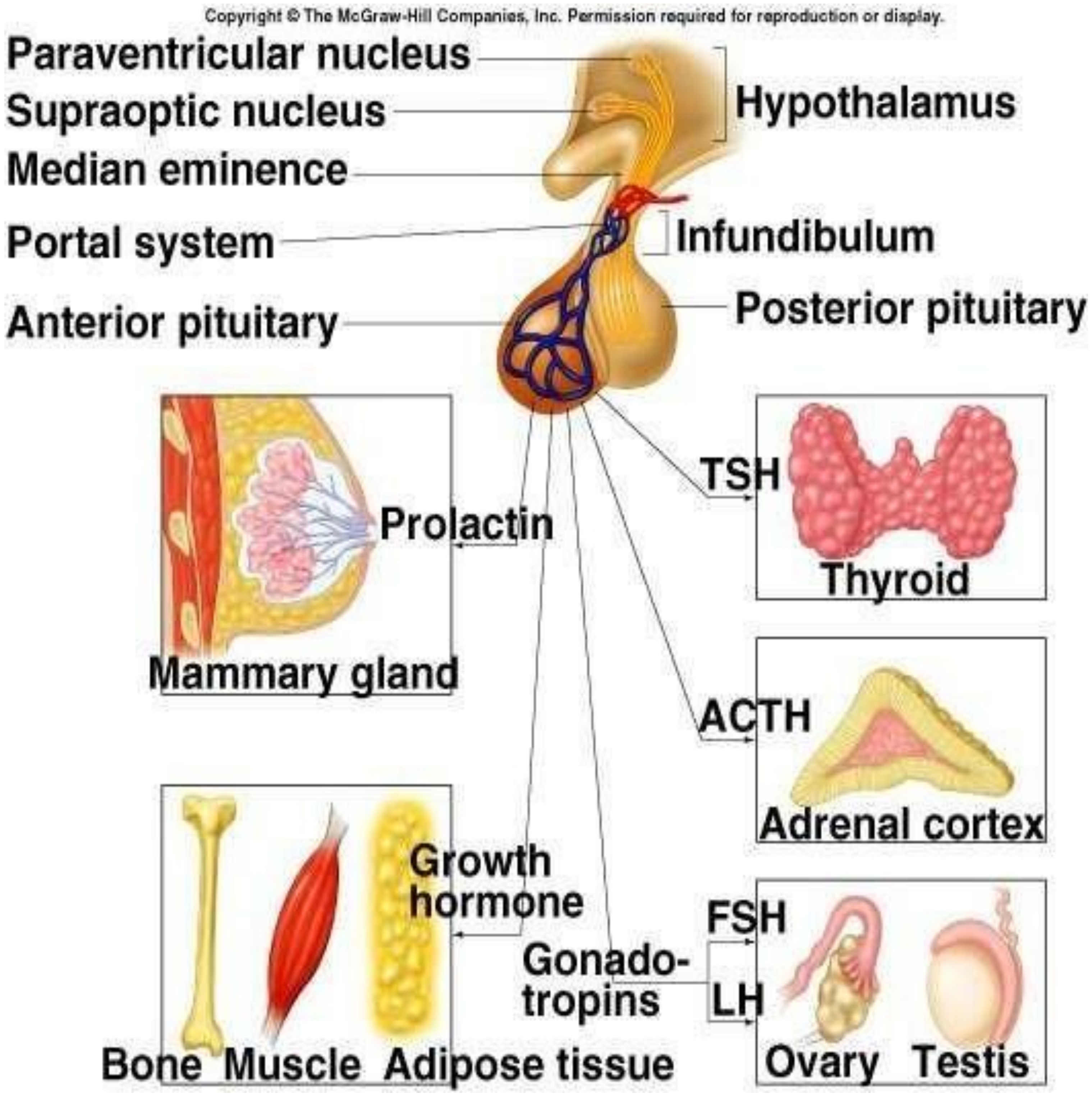
- Inhibits GHRH
- Stimulates GHIH (Somatostatin) secretion
- Leads to decreased GH release

To assess if the anterior pituitary is functioning properly, growth hormone (GH) levels can be measured before and after inducing hypoglycemia (by giving insulin).

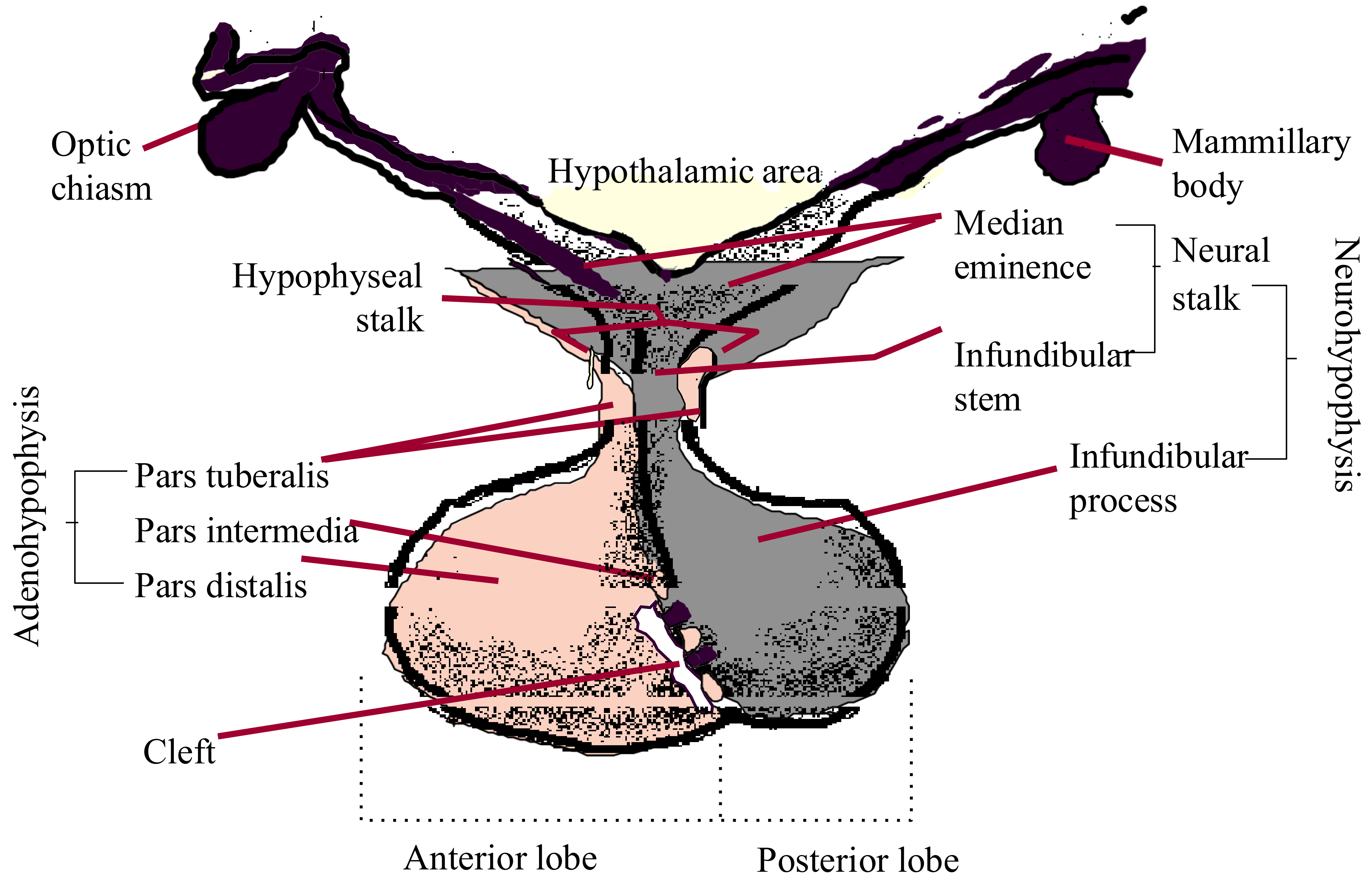
- Low blood glucose should naturally stimulate GH release.
- GH is measured before and after the drop in glucose.
- If GH levels rise after giving insulin (lowering glucose), it means the anterior pituitary is working well.
- If GH does not increase, it suggests pituitary dysfunction.

Pituitary Hormones

- Anterior Pituitary:
  - Trophic effects:
    - High blood [hormone] causes target organ to hypertrophy.
    - Low blood [hormone] causes target organ to atrophy.



Hypophysis



Optic chiasm
Hypothalamic area
Mammillary body
Median eminence
Neural stalk
Hypophyseal stalk
Infundibular stem
Neurohypophysis
Adenohypophysis
Pars tuberalis
Pars intermedia
Pars distalis
Infundibular process
Cleft
Anterior lobe
Posterior lobe

Adenohypophyseal Hormones

- ACTH
- TSH
- FSH
- LH
- PRL
- GH

Adenohypophyseal Cells & Hormones

Cell	Hormone	Chemistry	Physiologic Actions
Corticotropes	Adrenocorticotropic hormone (cortico-tropin; ACTH)	Single chain of 39 amino acids	Stimulates production of glucocorticoids and androgens by the adrenal cortex; maintains size of zona fasciculata and zona reticularis of cortex
Thyrotropes	Thyroid-stimulating hormone (thyro-tropin; TSH)	Glycoprotein having two subunits, α (89 amino acids) and ß (112 amino acids)	Stimulates production of thyroid hormones, T4 and T3, by thyroid follicular cells; maintains size of follicular cells
Gonadotropes	Follicle-stimulating hormone (FSH)	Glycoprotein having two sub-units, α (89aa) and ß (115aa)	Stimulates development of ovarian follicles; regulates spermatogenesis in the testis
Gonadotropes	Lutenizing hormone (LH)	Glycoprotein having two sub-units, α (89aa) and ß (115aa)	Causes ovulation and formation of corpus luteum in the ovary; stimulates production of estrogen and progesterone by the ovary; stimulates testosterone production by the testis
Mammotropes, Lactotropes	Prolactin (PRL)	Single chain of 198 amino acids	Essential for milk production by lactating mammary gland
Somatotropes (Called "somato" bcz it affects the somatic tissue)	Growth hormone (somatotropin; GH)	Single chain of 191 amino acids	Stimulates postnatal body growth; stimulates secretion of IGF-1; stimulates triglyceride lipolysis; inhibits actions of insulin on carbo-hydrate and lipid metabolism

Notice that: TSH, FSH, LH Glycoproteins with common alpha subunit, While beta is different

Physiology Quiz 3

رسالة من الفريق العلمي:

"اللّٰهُمَّ أجرنا من حر جهنم"

قالت جهنم:

{ اللّٰهُمَّ أجره من النار }

For any feedback, scan the code or click on it.

Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1			
V1 → V2			