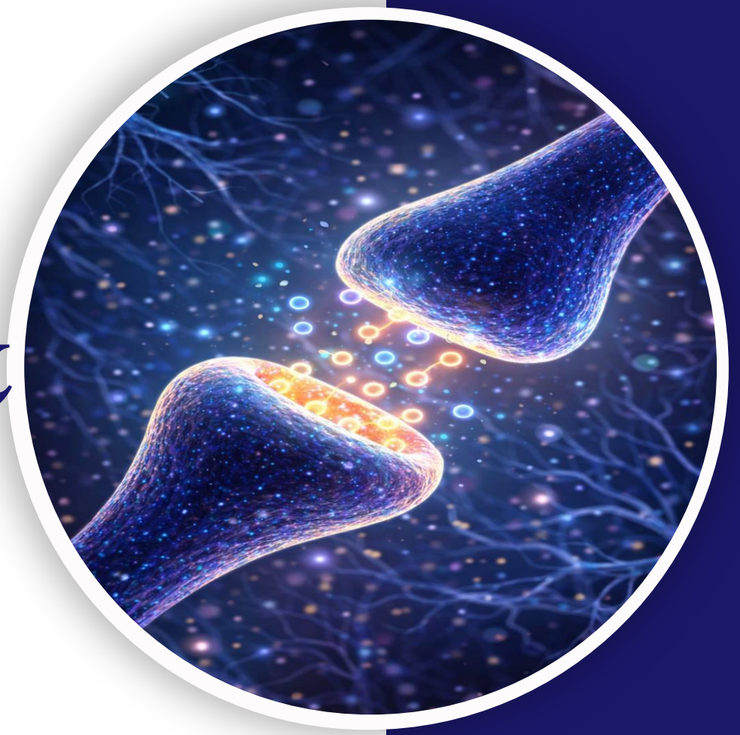
بسم الله الرحمـٰن الرحيم

(وَفَوْقَ كُلِّ ذِي عِلْمٍ عَلِيمٌ)

Endocrine Physiology | MID L4

Pituitary Hormones & their control Pt.2



Written by : Abdallah Hindash
Rzan Al-adhami

Pituitary Hormones and Their Control by the Hypothalamus

Remember :

1- Posterior Pituitary doesn't synthesis hormones, it only stores hypothalamus one's.

2- Anterior Pituitary synthesize & secretes hormones, this is controlled by releasing & inhibiting hormones produced by hypothalamus.

Anterior Lobe = Adenohypophysis

Posterior Lobe = Neurohypophysis

Each Hormone is produced within a specific, distinct cell type that shares a similar name with hormone itself

Example : (TSH = Thyrotropes)

Adenohypophyseal Cells & Hormones

A.A < 100 = peptides, we don't consider them a full protein

Cell	Hormone	Chemistry	Physiologic Actions
Corticotropes	Adrenocorticotropic hormone (cortico-tropin; ACTH)	Single chain of 39 amino acids **Peptide**	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) **Peptide**	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) **Peptide**	Stimulates development of ovarian follicles; regulates spermatogenesis in the testis
Gonadotropes	Lutenizing hormone (LH)	Glycoprotein having two sub-units, α (89aa) and ß (115aa) **Peptide**	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 because 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

1- Milk formation in mammary glands is Stimulated by prolactin (PRL)

2- Milk ejection is stimulated by oxytocin (OT)

Prolactin & GH are Proteins, why ? Because they have more than 100 A.A

Notice :

- TSH, FSH & LH they are glycoproteins with the same alpha subunit, while beta subunit is different.
- There is another glycoprotein hormone in the placenta called human chorionic Gonadotropin (hCG)

Examples of Peptide Hormone Families

Insulin Family

Insulin
Insulinlike growth factor I (IGF-1, somatomedin C)
Insulinlike growth factor II
Relaxin

Glycoprotein Family

Lutenizing hormone (LH)
Follicle-stimulating hormone (FSH)
Thyroid-stimulating hormone (TSH)
Chorionic gonadotropin (HCG),

Secreted from placenta, essence of pregnancy testing

POMC Family

Adrenocorticotropic hormone (ACTH)
Melanocyte-stimulating hormone (MSH)

Secretin-Glucagon Family

Secretin
Glucagon
Gastrointestinal polypeptide
Glicentin
Gastric inhibitory polypeptide (GIP)
Glucagon-like peptide 1 (GLP-1)

Growth Hormone Family

Growth hormone (GH)
Prolactin (PRL)
Chorionic somatomammotrophin (HCS)
Human placental lactogen (HPL)

HCS & HPL are secreted from placenta

Neurohypophyseal Family

Antidiuretic hormone (ADH)
Oxytocin

POMC (Pre-opiomelanocortin) :

- A parent protein that body uses and cleaves to produce various hormones and opioids.

Opioids :

- Substances that bind to opioid receptors in the body to produce pain-relieving effects. They come from 2 different main sources :

1- (Exogenous) / outside the body :

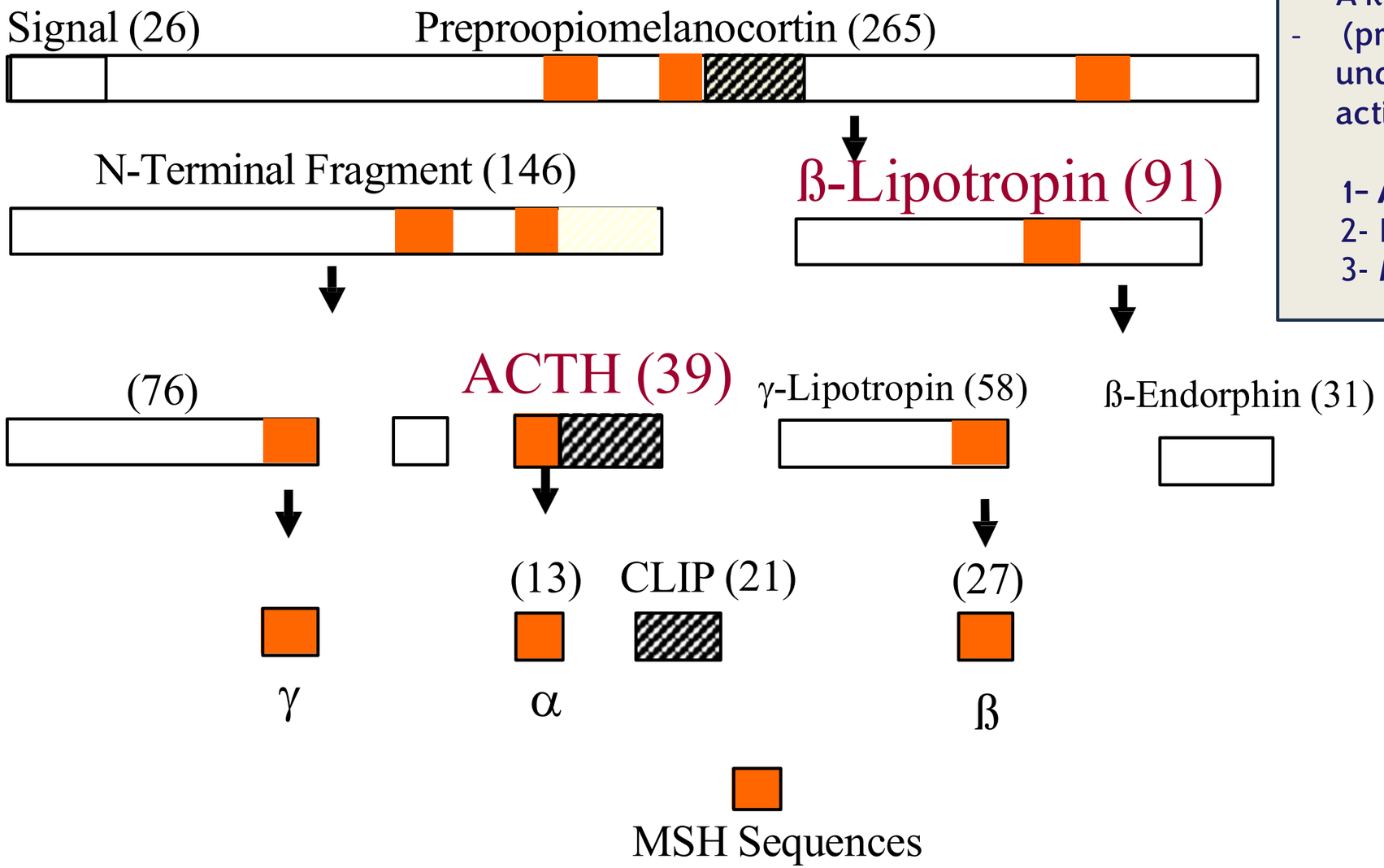
- They are plant-derived such as **morphine & pethidine (from opium plant)**

2- (Endogenous) Internal/Natural :

- **Substances synthesized naturally by the body, such as endorphins and enkephalins.**

Natural SOURCE explains why morphine & pethidine work as they mimic our body's own natural opioids binding perfectly into the receptors

Processing of Preproopiomelanocortin

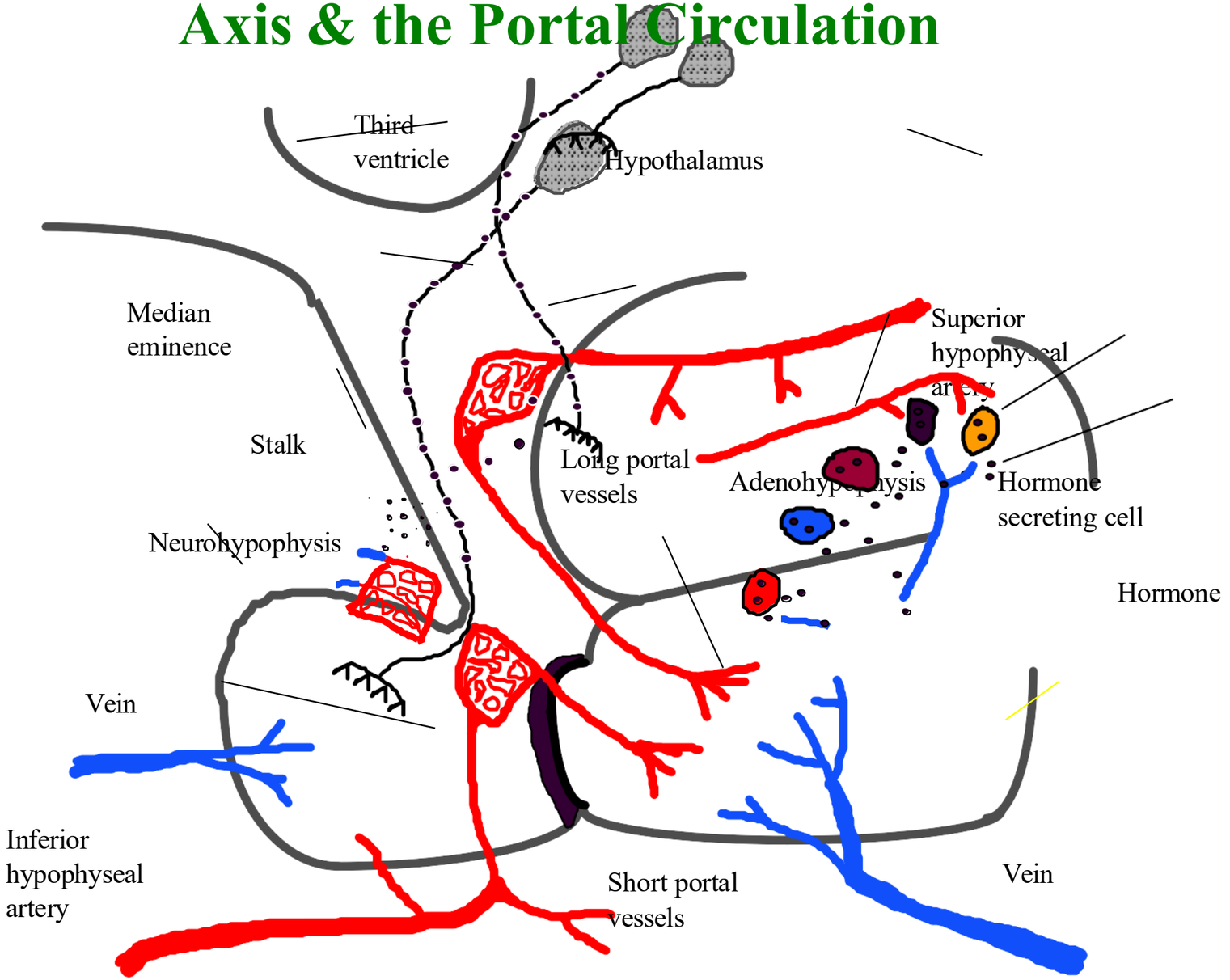


- Proteins (Peptides) hormones are initially synthesized as **large precursor peptides** in rough ER and then transported to Golgi Apparatus for post-translational modifications.

- A key example is **preproopiomelanocortin**
- (pre-POMC), a LARGE A.A sequence that undergo enzymatic cleavage to form several active hormones, including ;

1- **ACTH** (Adrenocorticotropic Hormone)
2- **Beta-endorphin** (endogenous opioid)
3- **MSH** (Melanocyte-Stimulating Hormone)

Endocrine Cells of the Hypothalamohypopyseal Axis & the Portal Circulation



Hypophysiotropic Hormones

- TRH **Thyroid**-Releasing Hormone
- GnRH **Gonadotropin**-Releasing Hormone
- CRH **Corticotropic**-Releasing Hormone
- GHRH **Growth Hormone** Releasing Hormone
- Somatostatin Which is : **Growth Hormone** Inhibiting Hormone (GHIH)
- Dopamine Which is ; **Prolactin** Inhibiting Hormone (PIH)

Hypophysiotropic Hormones

Hormone	Predominant hypothalamic	Structure	Actions on Anterior Pituitary
Thyrotropin-releasing hormone (TRH)	Paraventricular	Peptide consisting of 3 amino acids **Shortest (3 peptides)**	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

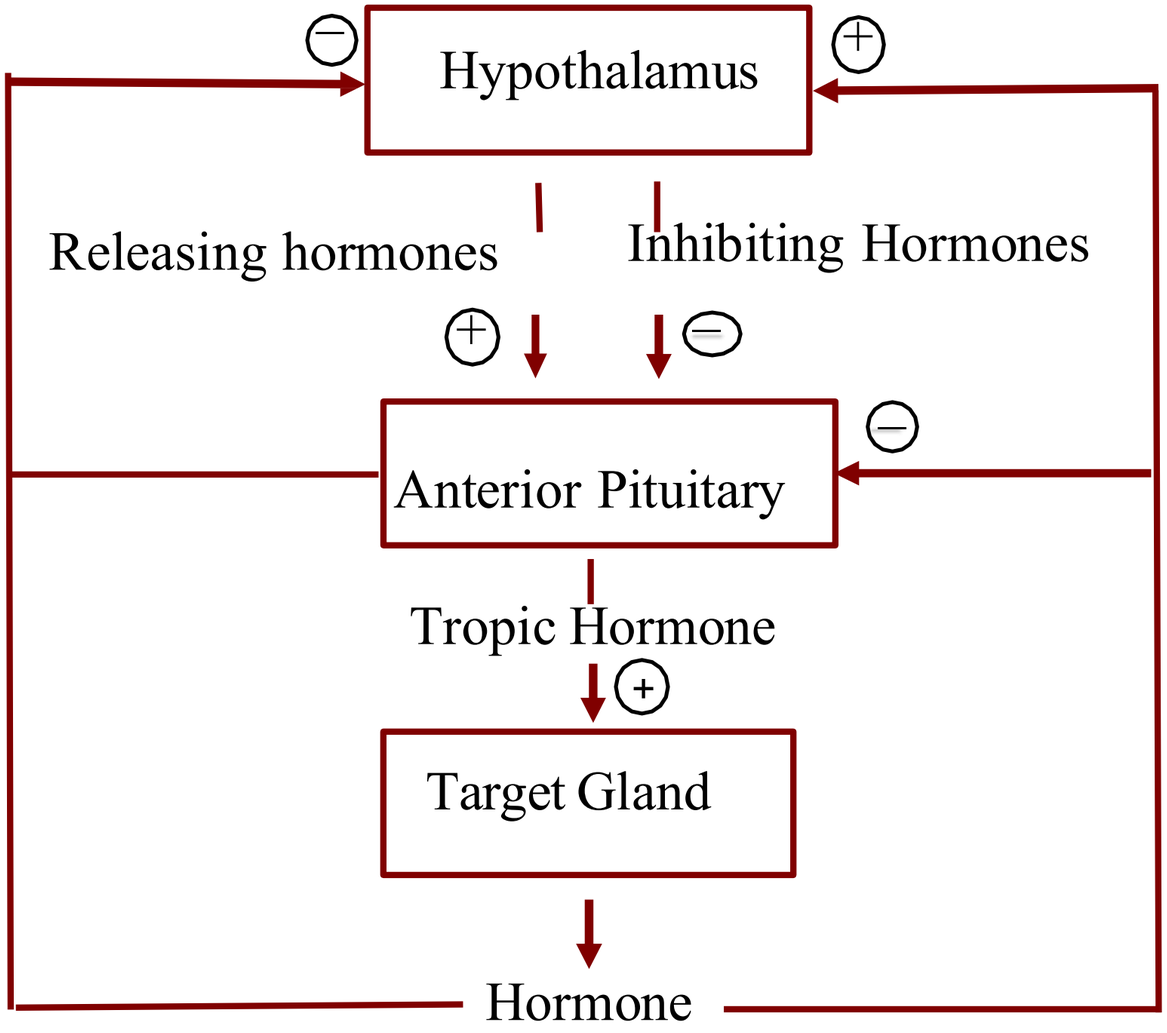
Hypothalamohypophyseal –Target Gland Axis

Extra Example to understand :

Hypothalamus produces TRH, which will enter hypophyseal portal to reach Anterior pituitary gland secreting TSH, then TSH will go to the thyroid gland to produce T3 & T4 and here there are :

Negative Feedback :

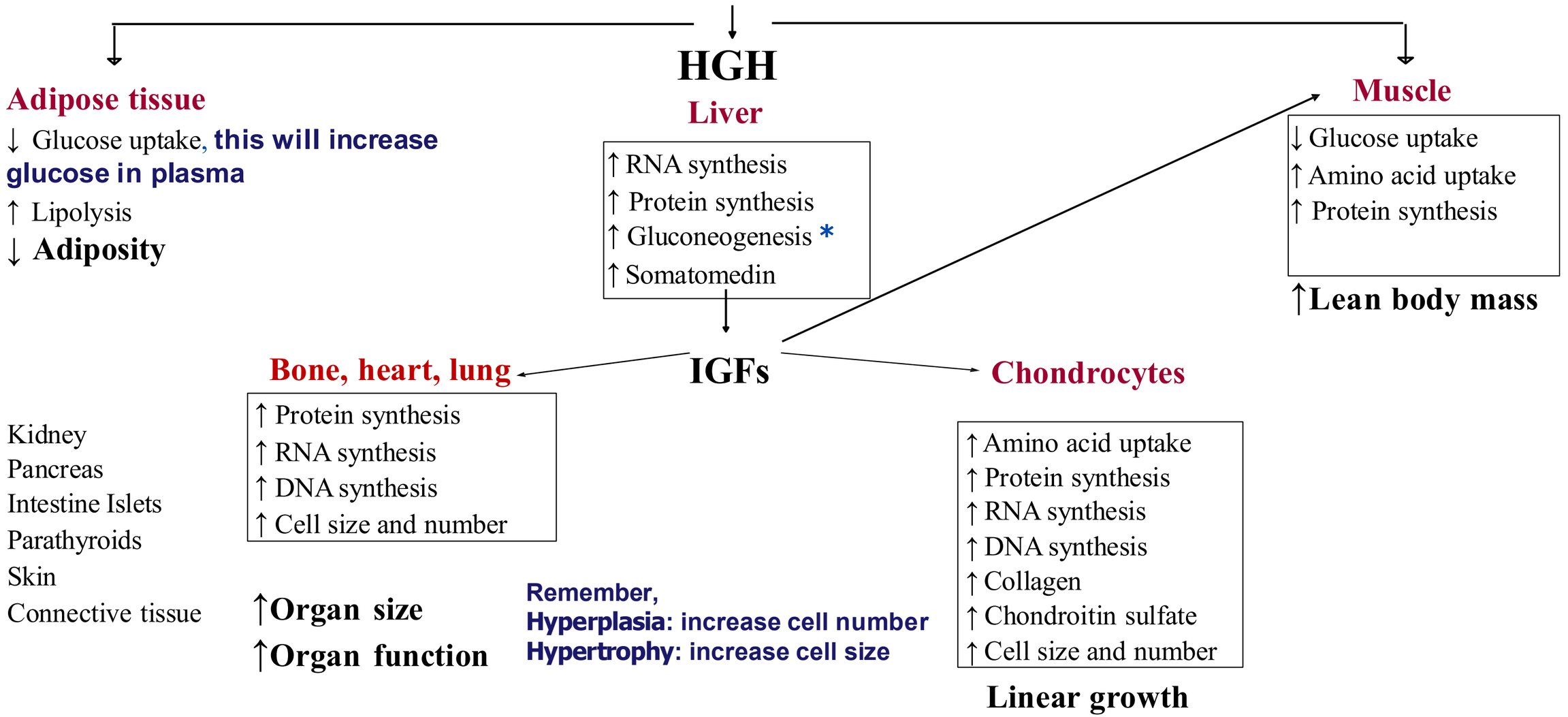
- If T3 & T4 increase in the blood this will inhibit hypothalamus from producing more TRH.



Adenohypophyseal Hormones

- ACTH
- TSH Thyroid-Stimulating Hormone
- FSH
- LH
- PRL
- **GH**

Biological Actions of Growth Hormone



Gluconeogenesis is the process of forming glucose from non-carbohydrate sources, primarily amino acids derived from proteins. It partially occurs from fats, as the glycerol component of triglycerides can be converted into glucose. However, most fatty acids cannot be used for gluconeogenesis because the conversion of glucose to acetyl-CoA is irreversible.

Growth Hormone

- There are two major **growth spurts** in childhood: one during **infancy** and another during **puberty**. In growing children, **growth hormone (GH)** stimulates **net protein synthesis**, contributing to body elongation and size increase.

- Although **weight gain** may accompany growth, it is not always a reliable indicator, as it can also result from **fat accumulation or fluid retention**.

- The first growth spurt occurs in the **first two years of life**, followed by a slower growth phase. The second growth spurt happens during **puberty**, when **sex hormones** (estrogen and testosterone) enhance **GH secretion**, promoting rapid growth.

- Sex hormones are sometimes called growth hormone like hormones.

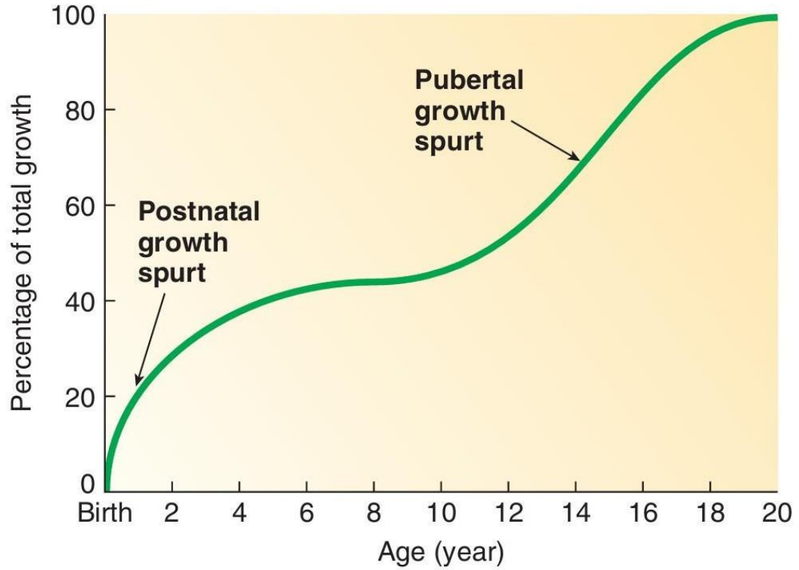
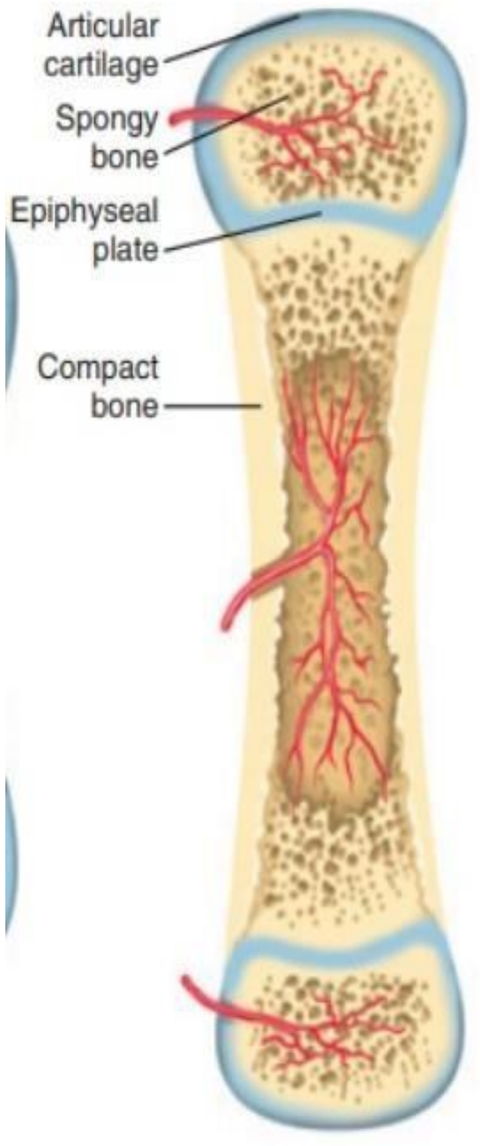
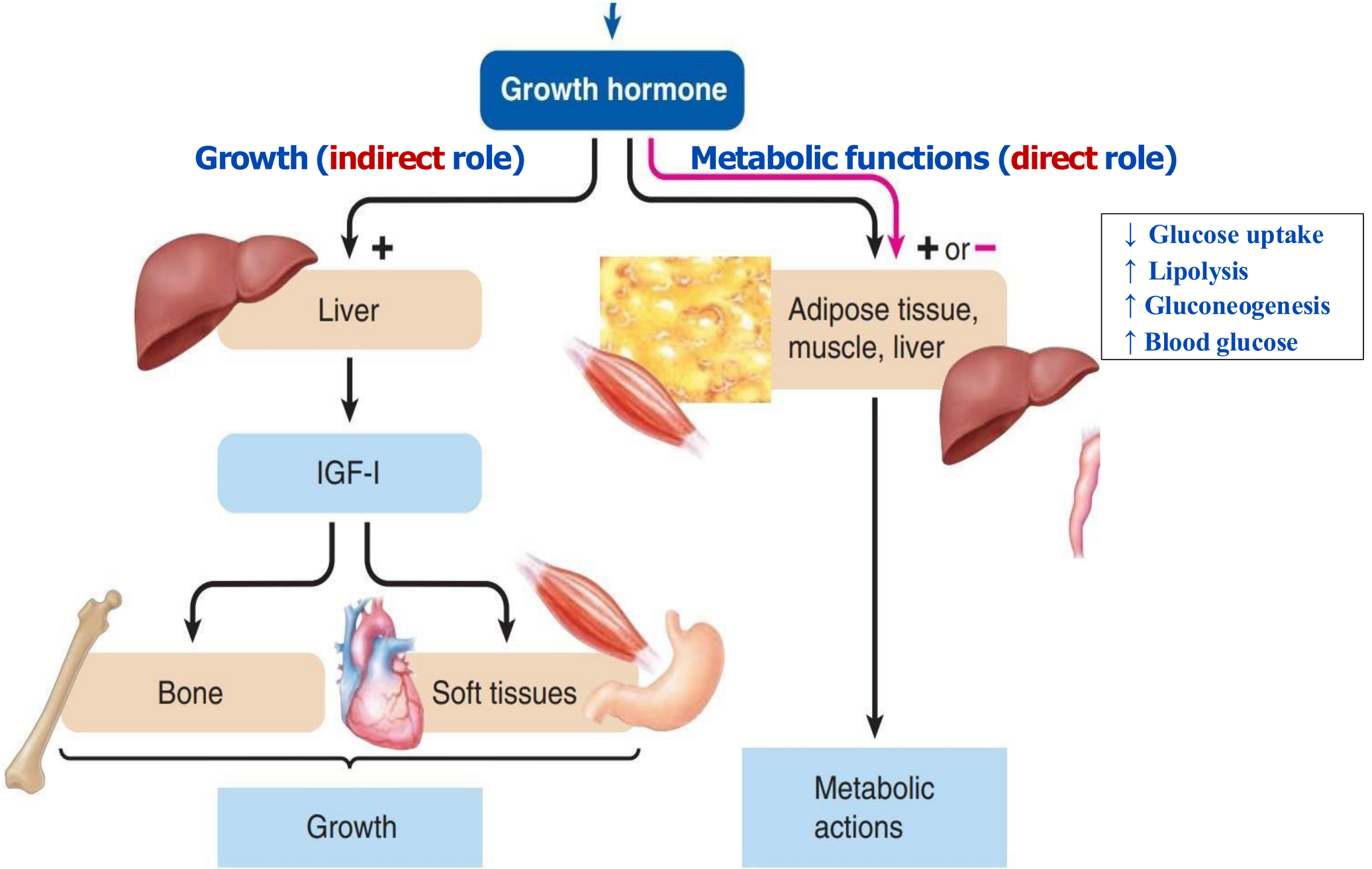


Figure 18-8 Normal growth curve.

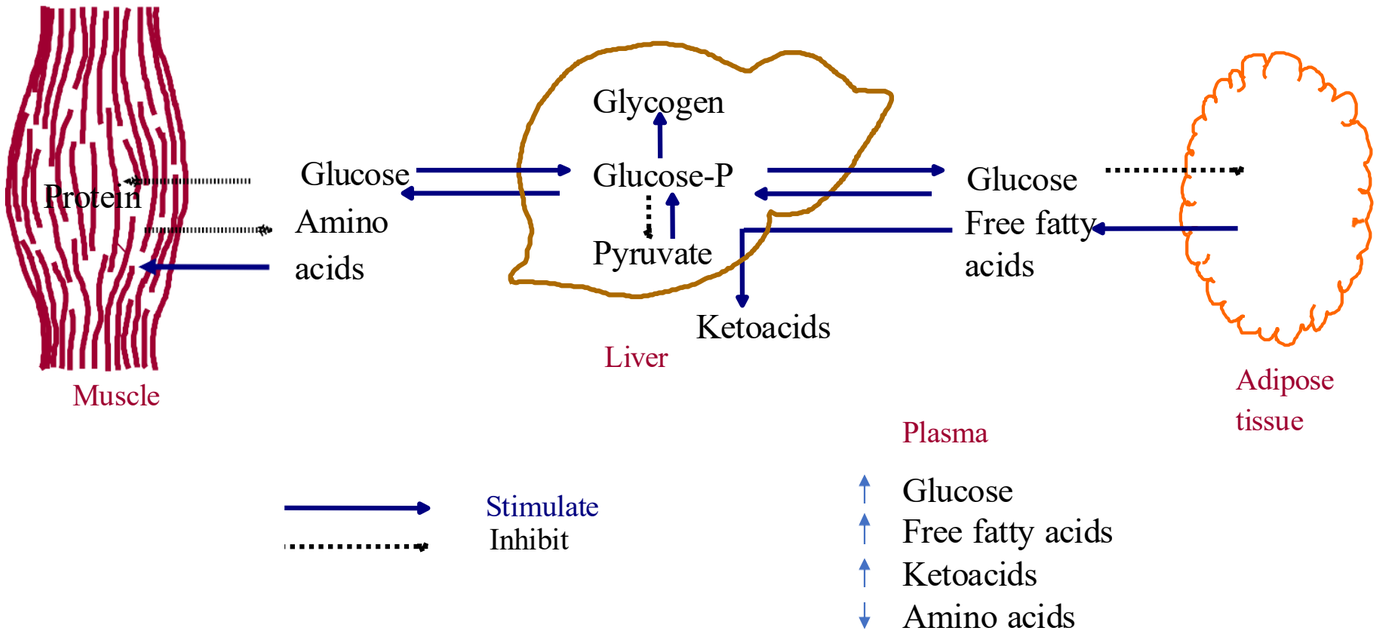
- Bone grows in **thickness** and in **length**, both stimulated by **GH**
- **Growth in thickness:**
  - **Osteoblast > Osteoclast** (Anabolic)

  The opposite, Osteoblast < Osteoclast is Catabolic
- **Growth in length (linear growth):**
  - **The epiphyseal plate remains active before puberty. During this period, chondrocytes proliferate within the plate, eventually becoming replaced by bone tissue through ossification, which leads to the elongation of bones.**
  - After puberty, the epiphyseal plate fuses and becomes **the epiphyseal line** under the **influence of sex hormones**, especially **estrogen**.




Growth hormone
Growth (indirect role)
Metabolic functions (direct role)
+
+ or −
Liver
Adipose tissue, muscle, liver
IGF-I
Bone
Soft tissues
Growth
Metabolic actions
↓ Glucose uptake
↑ Lipolysis
↑ Gluconeogenesis
↑ Blood glucose

Metabolic Effects of Growth Hormone

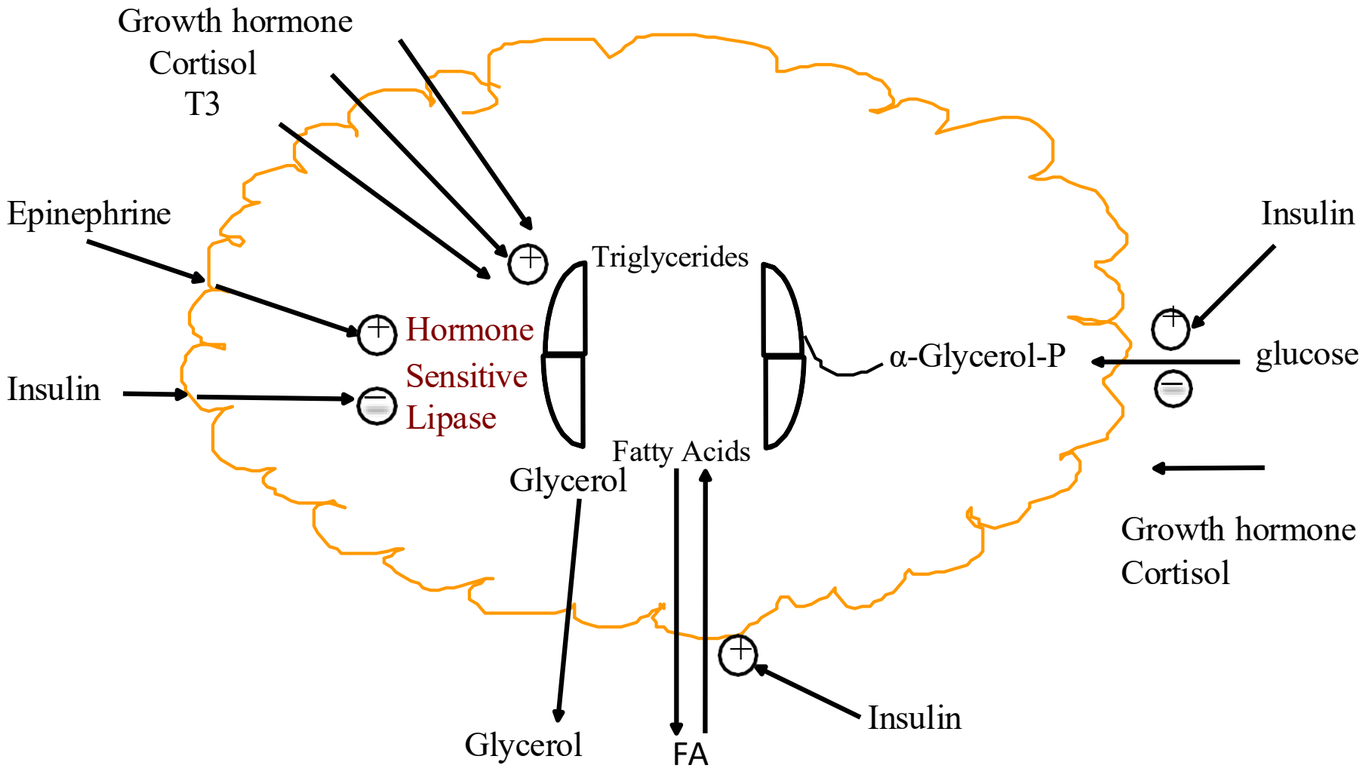


Metabolic Effects of Growth Hormone

- Growth hormone exerts its metabolic effects on multiple tissues in the body.
- In muscle, it **increases amino acid uptake**, enhancing protein synthesis, while **inhibiting glucose uptake**, resulting in a **glucose-sparing effect**. This promotes muscle growth while preserving glucose for other tissues.
- In the liver, growth hormone **stimulates gluconeogensis directly which will increase the glucose levels and as a result the hepatocyte will synthesize glycogen. (The growth hormone increases both glycogen synthesis and gluconeogensis but one of them directly and the other indirectly).**
- In adipose tissue, growth hormone **stimulates lipolysis**, releasing **free fatty acids**. These are transported to the liver, where they are metabolized into **ketone bodies**. A marked rise in ketone bodies, especially during prolonged GH activity, can contribute to **ketoacidosis**.
- In the blood, the net effects of growth hormone include:

  - an **increase in blood glucose**
  - a **decrease in glucose uptake by peripheral tissues**
  - a **reduction in plasma amino acid levels** due to increased uptake by muscle
  - a **significant rise in free fatty acids and ketone bodies**

Hormonal Effects on FFA Production in Adipose Tissue

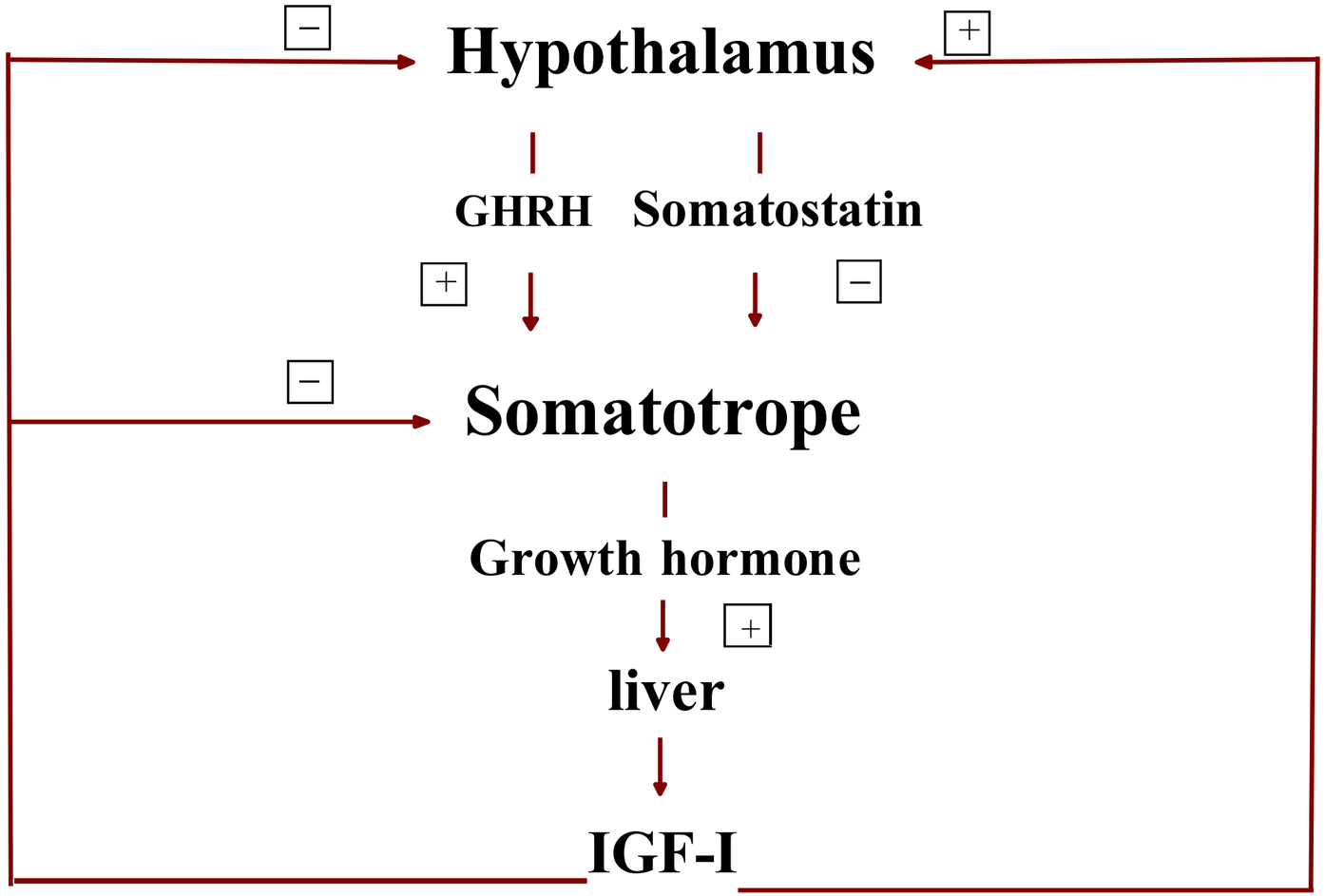


IGF-I (Somatomedin C)

- ❑ Circulating IGF-I produced **mainly** in the liver in response to GH
- ❑ Local production in tissues **(slightly)**
- ❑ **Before puberty** it stimulates chondrocytes → ↑ linear growth
- ❑ Structure & receptors ~ **similar** to those of insulin
- ❑ Inhibits GH secretion by **negative feedback**
- ❑ Highly bound to plasma proteins **(more than GH)**
- ❑ T1/2: IGF-I **>** GH (Remember, the greater the binding of a substance to plasma proteins, the longer its half-life)

- Insulin has a short half-life, primarily because it is rapidly degraded by **enzymes in the liver and kidneys**, and because it does not bind strongly to **plasma proteins** like albumin. This leads to its rapid clearance from the blood. As a result, **some diabetic patients require frequent insulin doses**. Fortunately, newer insulin formulations are designed to **prolong its half-life** by mechanisms such as **binding to carrier proteins such as albumin** or forming **slow-release complexes**, thereby reducing the need for repeated injections.

Hypothalamohypophyseal-GH Axis



Factors Affecting GH Secretion

Stimulation	Inhibition
Glucose decrease **(main stimulator)**	Somatostatin
Free fatty acid decrease	Glucose increase
Amino acid increase (arginine)	Free fatty acid increase
Fasting	Somatomedins
Prolonged caloric deprivation	Growth hormone
Stress	Senescence
Exercise	
Puberty	
Androgens and estrogens (sex hormones)	
Sleep	

Somatostatin is produced in multiple tissues, including the **hypothalamus** and the **pancreatic delta cells**. In the hypothalamus, it inhibits **growth hormone release** from the anterior pituitary. In the pancreas, it acts locally in a **paracrine** manner to inhibit the secretion of **both insulin and glucagon**. These functions give somatostatin both **neuroendocrine** and **local (paracrine) regulatory roles**.

Pathophysiology of Growth Hormone

- Abnormalities in growth hormone (GH) secretion can involve either excess or deficiency, each with distinct effects depending on the timing.
- In cases of **GH excess**, two major clinical scenarios are observed. If excess occurs **before puberty**, while the epiphyseal plates are still open, it leads to **gigantism**, characterized by excessive linear growth, with height potentially reaching **over 2.2 meters**. If excess occurs **after puberty**, when the epiphyseal plates have fused, the result is **acromegaly**, marked by **bone thickening** rather than height increase. This condition causes **enlargement of facial features, hands, and feet**. Although once thought to be more common in women due to self-observation, this view is now considered outdated.
- In contrast, **GH deficiency** also presents differently depending on age. When it occurs **before puberty**, it leads to **short stature and delayed growth**, a condition often referred to as **dwarfism**. If the deficiency develops **after puberty**, linear growth is unaffected, but individuals may experience **metabolic disturbances** such as **reduced energy levels, increased fat mass, and decreased muscle mass**, reflecting GH's role in maintaining metabolic function.

Clinical Features of Acromegaly

- Local tumor effects
- ↑ piuitary, visual field defects, headache
- Somatic systems
- Acral enlargement, prognathism, carpal tunnel syndrome
- CV system
- Ventricular hypertrophy, cardiomyopathy, HT, HF
- Pulmonary system
- Sleep disturbances, sleep apnea
- Visceromegaly
- Tongue, thyroid gland, liver, spleen, kidney, prostate
- Metabolic
- Insulin resistance, fasting hyperglycemia

- A pituitary tumor can grow large enough to **compress the optic chiasm**, typically resulting in **bitemporal hemianopia**, a visual field defect affecting the **temporal visual fields of both eyes**. It may also cause **headaches** due to **pressure on surrounding brain structures**.

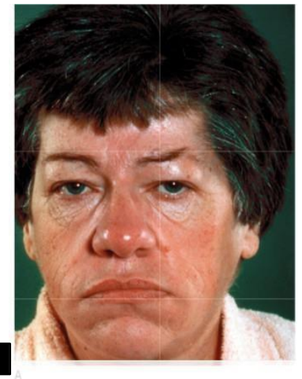
Therapies for Gigantism-Acromegly

- ❑ Hypophysectomy removal
- ❑ Radiation
- ❑ Somatostatin analogues (octreotide, lanreotide). Somatostatin like drugs
- ❑ GH antagonists (pegvisomant)

- When treating a pituitary tumor, the first step is to **determine its type and functional status**—whether it is **hormone-secreting** and how large it is. Although most pituitary tumors are **benign**, those that are malignant or large and compress surrounding structures may require **surgical removal**, typically via **transsphenoidal hypophysectomy**, or **radiation therapy** if surgery is not feasible. Additional treatments may include **medications to suppress excess hormone secretion** or **hormone replacement therapy** if normal pituitary function is impaired.

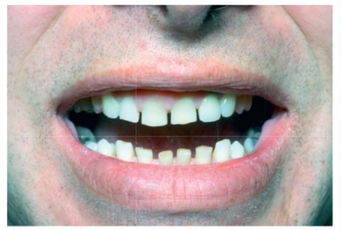
Gigantism & Acromegaly

Dwarfism is related to short stature (the one we talk about is pituitary dwarfism, the person is normal in terms of mental capacities BUT short) (thyroid dwarfism is one where they are short in stature with mental retardation)

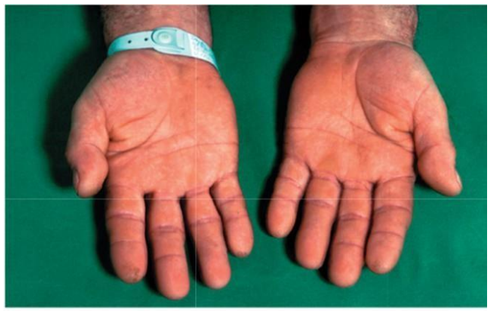


A: Typical facies.

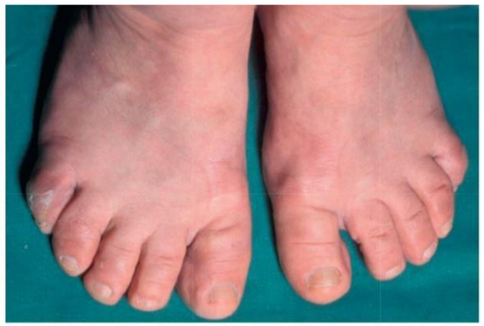
@Macleod's clinical examination



B: Separation of lower teeth.



C: Large fleshy hands.



D: Widening of the feet.

Pictures are hyperlinks.

Posterior Pituitary

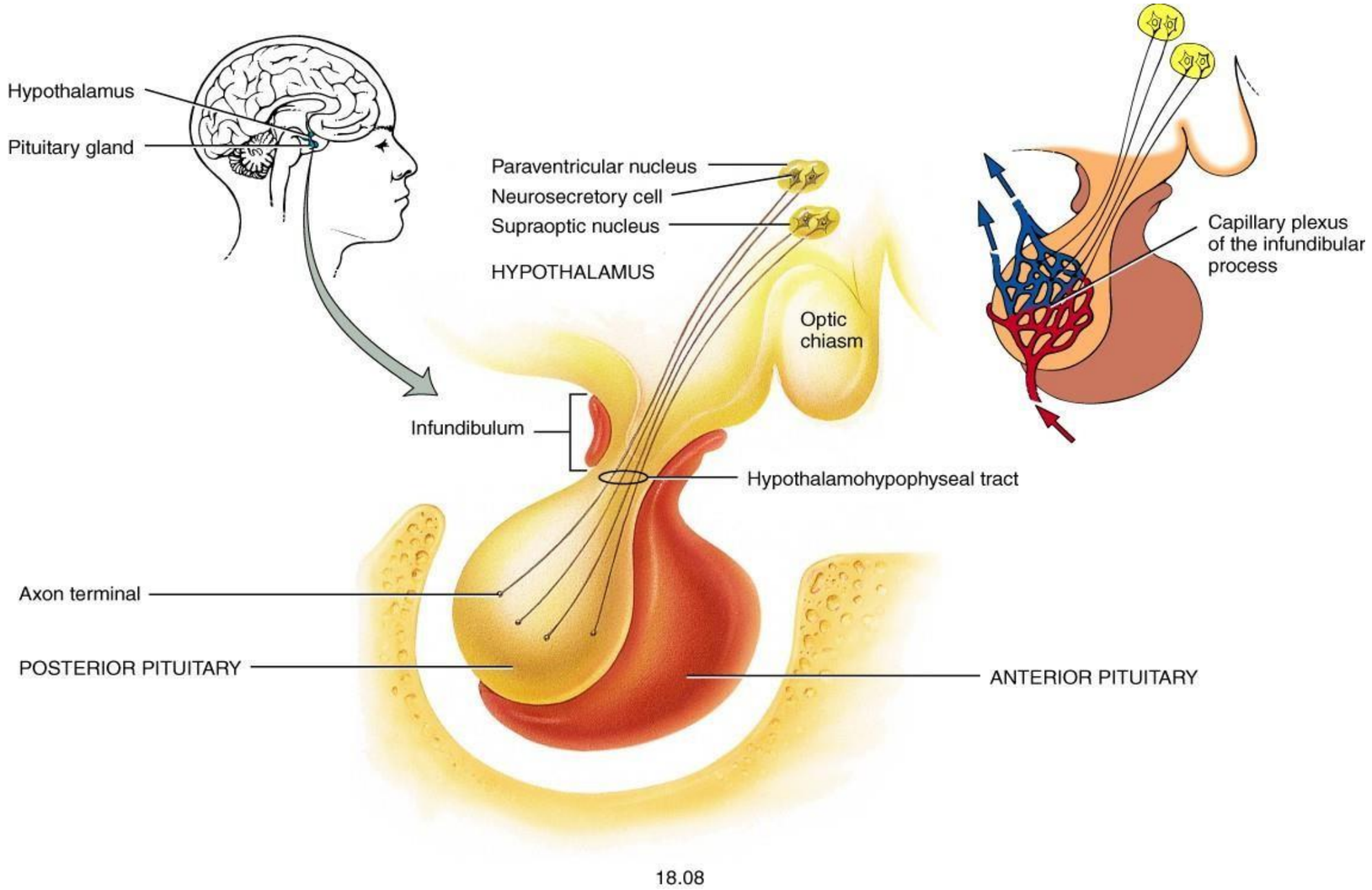
- Does not synthesize hormones
- Stores and releases hormones made by the hypothalamus, which are transported along hypothalamo-hypophyseal tract(neural tract)
- It releases:
  - Oxytocin (OT)
  - Antidiuretic hormone (ADH) or vasopressin two names cause ADH has two main actions
  - 1) ANTIDIURETIC (prevents urine production) by increasing reabsorption from distal part of nephron and collection duct
  - 2) vasoconstriction (vessel constriction)

Posterior Pituitary Hormones

- Also called neurohypophyseal hormones.
- The Posterior pituitary stores and releases 2 hormones that are produced in the hypothalamus:

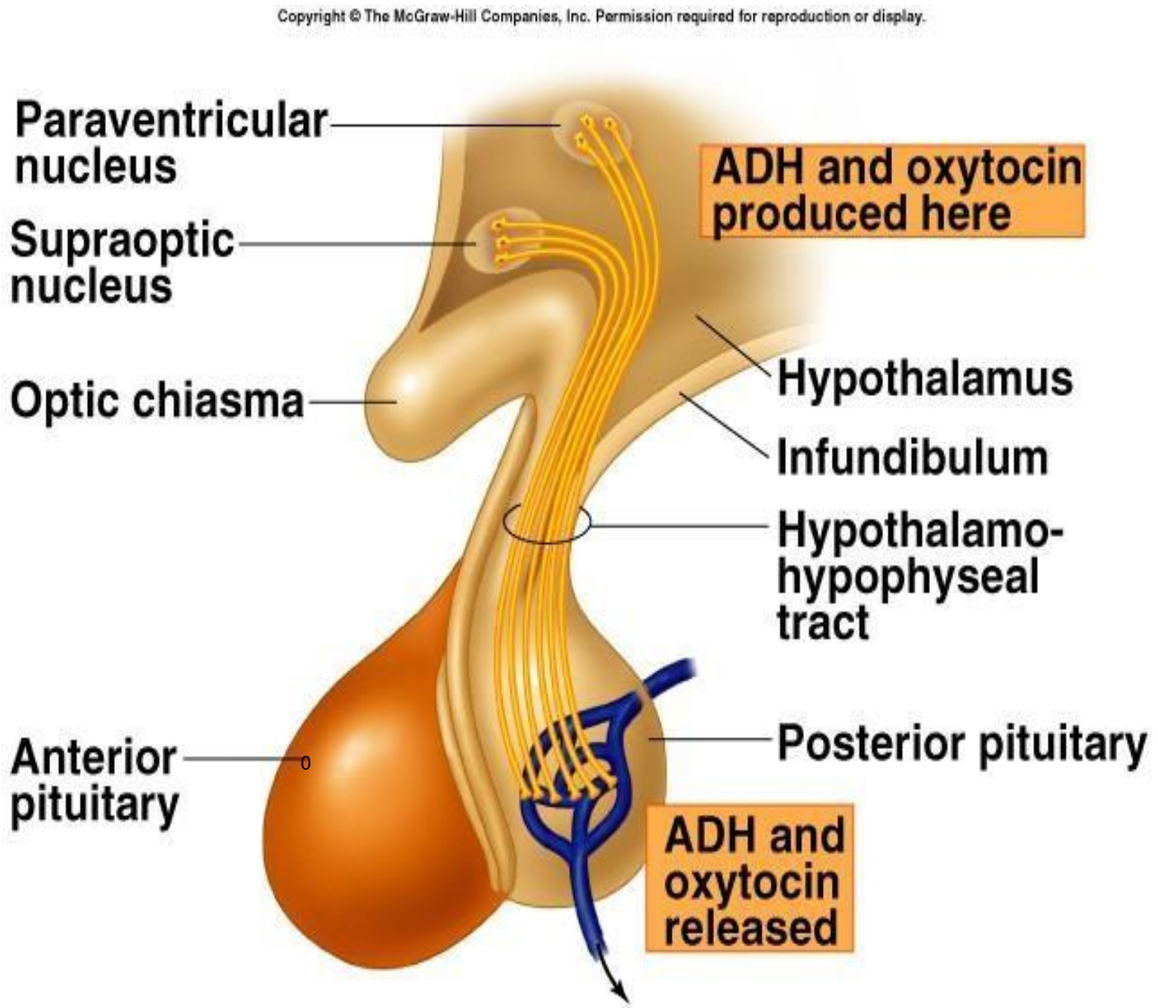
1. Antidiuretic hormone (ADH/vasopressin):
   - Promotes the retention (pulls water from kidneys) of H_2O by the kidneys, specifically in the collecting ducts. (Plasma is filtered in kidneys, how much filtered? 125 mL/min is the GFR, OR 180 liters per day))
   - Less H_2O is excreted in the urine. So more concentrated urine
2. Oxytocin:
   - Stimulates contractions of the uterus during parturition (during delivery).
   - Stimulates contractions of the mammary gland alveoli (Milk-ejection reflex).
     IF baby isn't breastfed/suckling oxytocin will not do milk ejection
   - POSTIVE feedback regulation

Hypothalamo-hypophyseal tract



Hypothalamic Control of Posterior Pituitary

- Hypothalamus neuron cell bodies synthesize:
  - ADH: **primarily in the** supraoptic nuclei.
  - Oxytocin: **primarily in the** paraventricular nuclei.
    - ❖ **Both nuclei contribute to the synthesis of both hormones, but each predominantly produces one.**
- Transported along the hypothalamo-hypophyseal tract.
- Stored in posterior pituitary.
- Release controlled by neuroendocrine reflexes.



Oxytocin (OT)

- During and after delivery of baby affects uterus and breasts:
  - ➢ Enhances smooth muscle contraction in the wall of the pregnant uterus.
  - ➢ Stimulates milk ejection from mammary glands; by enhancing myoepithelial contractions in the nipple.

❖ Notes:

- While prolactin enhance milk formation, oxytocin enhances its ejection.
- Oxytocin has no known effects in male and non-pregnant/lactating female body. Do your own research
- Estrogen **primes oxytocin action by increasing the number of oxytocin receptors**, especially in the uterus and breast.
- Oxytocin is under **positive feedback control during labor: uterine contractions become more frequent and intense as childbirth approaches.**
- Breastfeeding **stimulates milk production through prolactin and milk ejection through oxytocin.**

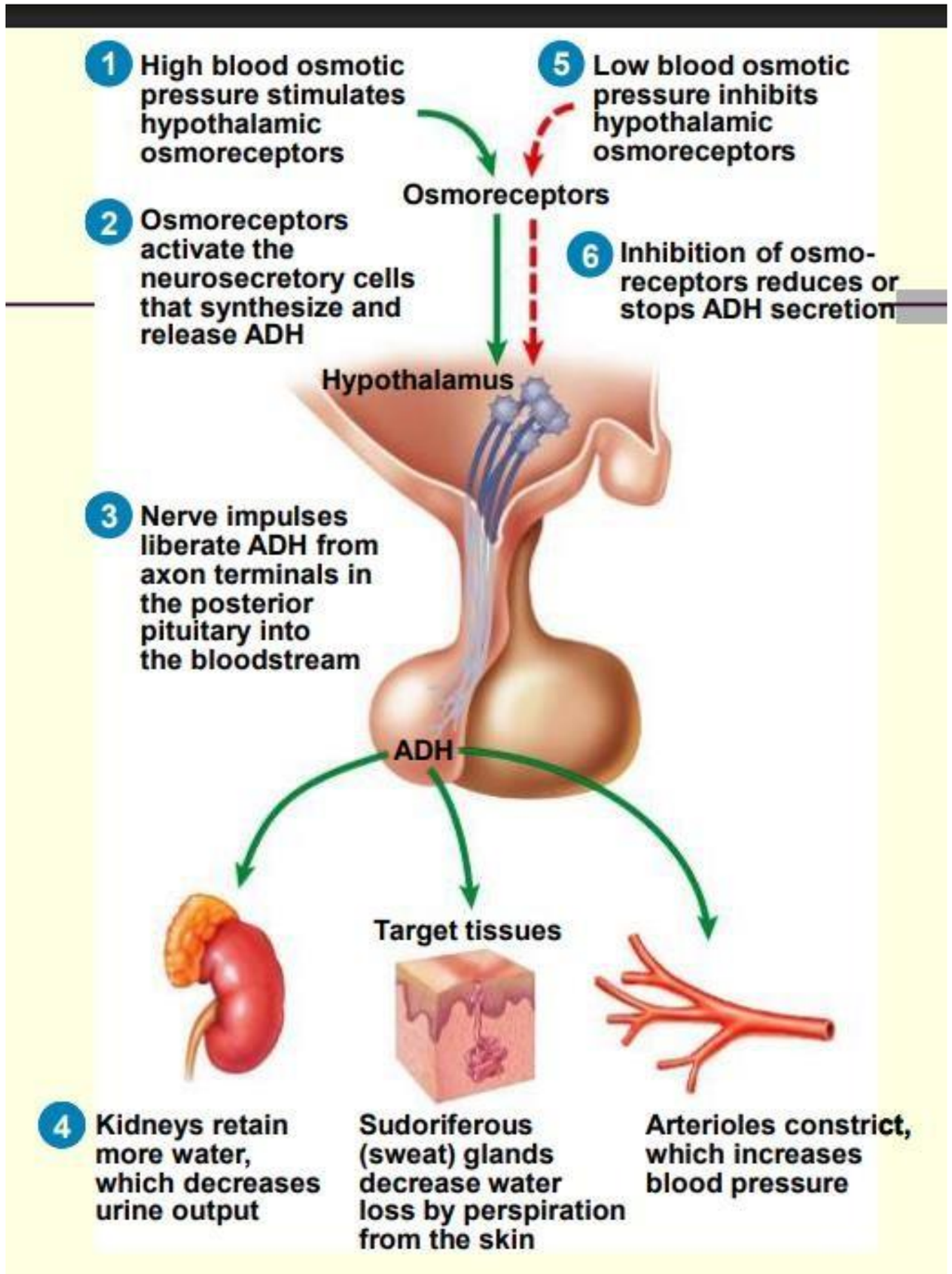
Antidiuretic Hormone (ADH)

- Decreases urine production cause increases water reabsorption by causing the kidneys to return more water to the blood through the collecting ducts in the nephrons, hence the name: Antidiuretic.
- Also decreases water lost through sweating and causes constriction of arterioles which increases blood pressure—hence the name **vasopressin**. It is also known as **arginine vasopressin (AVP)** because **arginine is part of its polypeptide chain**. Very impt controller of B.P

Examples on ADH's Mechanism of Action

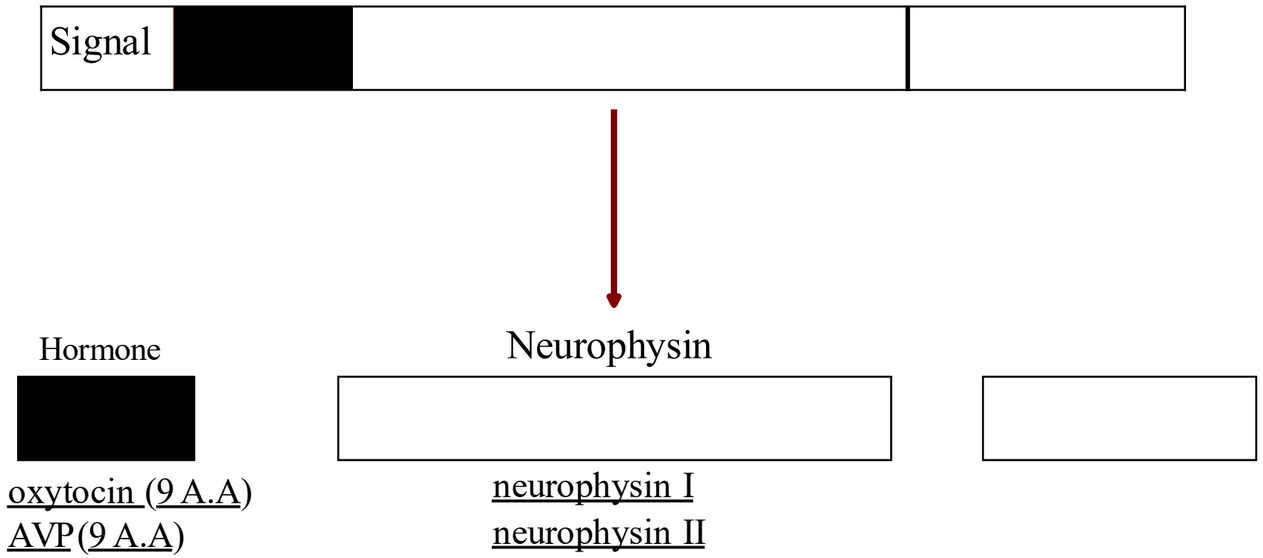
- In summer, **increased sweating causes water loss**, leading to **a rise in plasma osmolarity** (depends on number of molecules of plasma which depends on moles). This **stimulates osmoreceptors, initiating a sequence of events that leads to ADH release**, which promotes **water retention by the kidneys**. As a result, the urine becomes **more concentrated (dark yellow)** due to reduced water content.
- In contrast, during winter, **sweating is minimal**, so **plasma osmolarity remains more stable**, and **ADH secretion is lower**, leading to **reduced water reabsorption** and **lighter (dilute) urine**.
- Hemorrhages **lead to a decrease in blood volume**, which in turn **reduces blood pressure**. This **stimulates the secretion of ADH (vasopressin)**, which **constricts blood vessels to help raise blood pressure**, and also **increases water reabsorption in the kidneys to help restore plasma volume**.

1. High plasma osmotic pressure **(due to high solutes concentration)** stimulates hypothalamic osmoreceptors
2. Osmoreceptors activate the neurosecretory cells, **mainly in the supraoptic nucleus,** that synthesize and release ADH
3. Nerve impulses liberate ADH from axon terminals in the posterior pituitary into the bloodstream.
4. The following changes occur:
   A. Kidneys retain more water **by renal tubules**, decreasing water output.
   B. Sweat glands decrease loss by perspiration from the skin
   C. Arterioles constrict, increasing blood pressure
5. Low blood osmotic pressure inhibits hypothalamic osmoreceptors **(negative feedback)**
6. Inhibition of osmoreceptors reduces or stops ADH secretion **(negative feedback)**



- AVP (**arginine vasopressin**) and oxytocin(has **leucine**) come from large protein that is spliced and gives us oxytocin and ADH both are **nonapeptides (9 peptide)**
- ***Oxytocin*** is carried with **neurophysin 1.**
- ***AVP*** by **neurophysin 2.**
- Carried with proteins to prevent their degradation. BUT when it goes to circulation it stops carrying hormones in the blood circulation.

Processing of Prepro-oxyphysin & Prepropressophysin



❖ Recall from the first lecture that all peptide hormones are initially synthesized as preprohormones.

- Neurophysins are **carrier proteins that assist in the transport and stabilization** of the two hypothalamic hormones, **oxytocin and vasopressin**, during their axonal transport to the posterior pituitary.
- They **prevent premature diffusion or degradation** of these hormones during transit.
- Although **neurophysins can be detected in plasma**, their **concentrations are not physiologically significant.**

Structure-Activity Relationships for Neurohypophyseal Hormones

- Oxytocin **has mild vasopressor and antidiuretic effects**, similar to vasopressin, but **these effects are not significant under normal physiological conditions**.
- **Likewise, vasopressin has minor oxytocin-like actions**, such as smooth muscle contraction.
- **Oxytocin and vasopressin differ by only two amino acids** in their polypeptide chains, despite being functionally distinct, refer to the figure.
- **Desmopressin (dDAVP)** is a **synthetic analog of vasopressin** that selectively retains **antidiuretic effects with minimal vasopressor activity**, due in part to the presence of **D-arginine instead of L-arginine** in its structure.

Peptide	Oxytocic (O)	Milk Ejection (ME)	Vasopessor (P)	Antidiuretic (A)	Activity Ratios O/A	O/P	A/P
Oxytocin	520	475	4	4	130	130	----
Arginine Vasopressin (AVP)	14	70	370	320	----	----	1
Desmopressin (dDAVP)			0.5	955	----	----	2000

Oxytocin

1 2 3 4 5 6 7 8 9
Cy-Tyr-Ile-Gln-Asn-Cy-Pro-Leu-Gly-NH2
S _____S

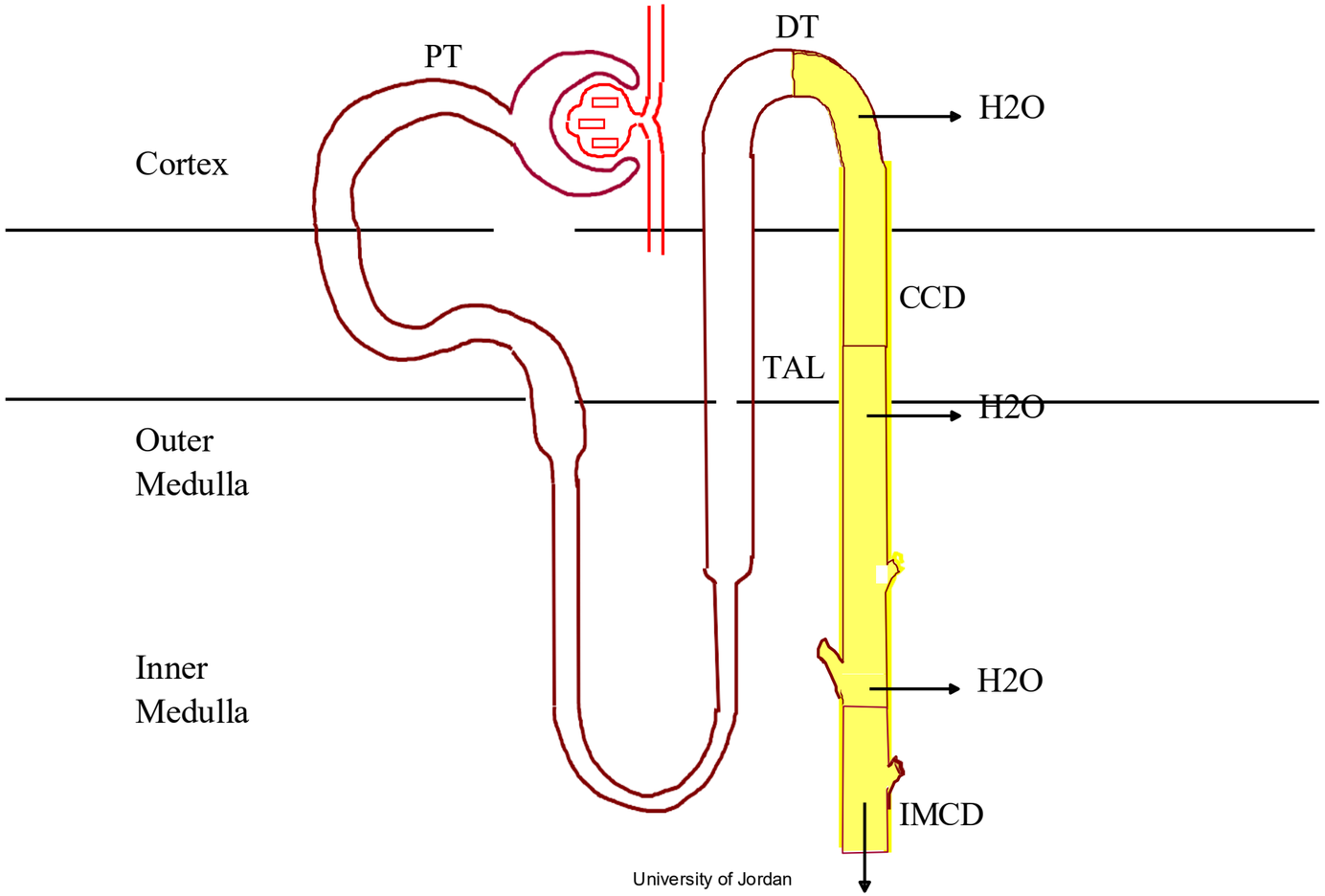
AVP

1 2 3 4 5 6 7 8 9
Cy-Tyr-Phe-Gln-Asn-Cy-Pro-L-Arg-Gly-NH2
S _____S

dDAVP

1 2 3 4 5 6 7 8 9
(CH2)2-CO-Tyr-Phe-Gln-Asn-Cy-Pro-D-Arg-Gly-NH2
S

Tubular Effects of AVP



Tubular Effects of AVP

- Each kidney **contains approximately 1 million nephrons**. Each nephron **receives an afferent arteriole,** which enters the **glomerulus, and an efferent arteriole exits it**.
- Both kidneys together receive **about 25% of the cardiac output**, which is approximately **1.2 liters of blood per minute**.
- Assuming plasma makes up **50% of blood**, this amounts to **600 mL of plasma per minute** delivered to the kidneys.
- About **125 mL/min of plasma is filtered through the glomeruli**, equivalent to **180 liters per day**.
- Roughly **65% of the filtrate is reabsorbed in the proximal tubule**, while the **distal tubule reabsorbs additional fluid**, making up about 25% of the filtrate, both under no control. So approximately 90% of what is filtered is reabsorped here and it requires **NO ADH.**
- Approximately **10% of the filtrate reaches the collecting ducts**, where **water reabsorption is regulated by ADH**.
    - In the absence of ADH, as seen in **diabetes insipidus**, up to **18 liters of urine may be excreted per day**. Which is too much!
    - In contrast, with normal ADH activity, only **about 1% of the filtrate (1-2 liters/day)** is excreted as urine.

Cellular Actions of AVP on Principal Cells of Collecting Duct

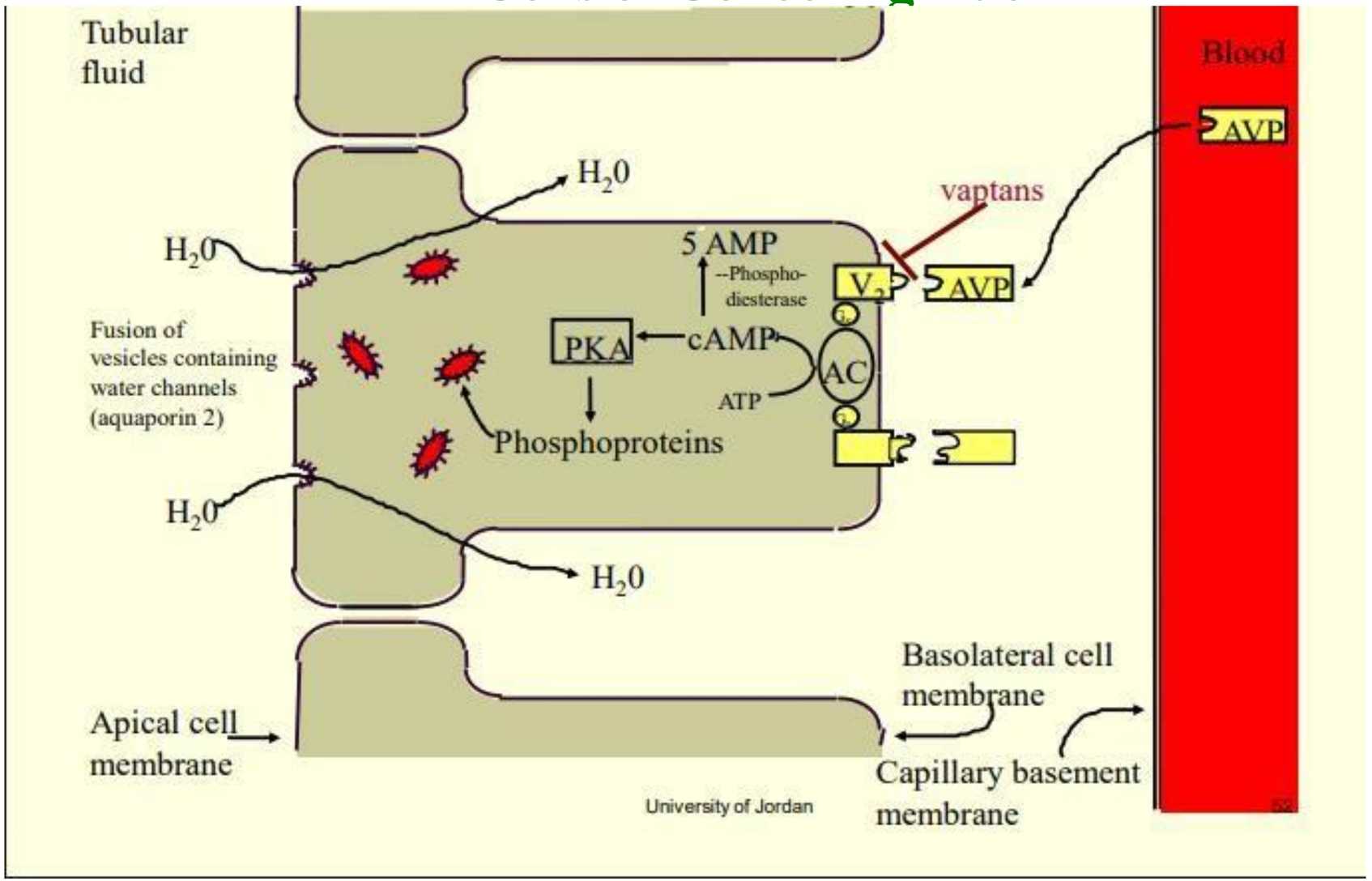
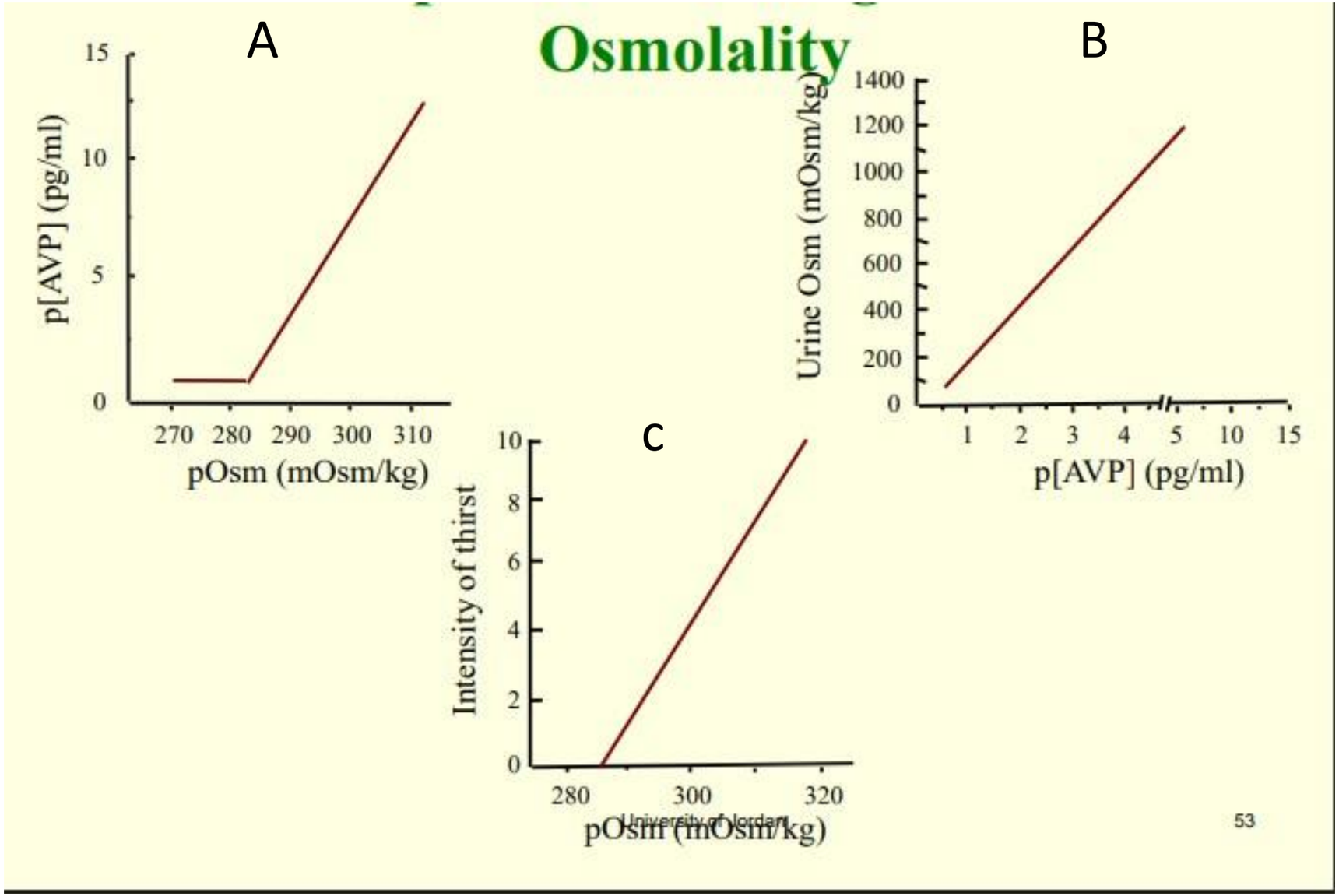


Image Interpretation

- Vasopressin **has effects on both blood vessels and kidney tubules**, acting on **V1 receptors in vascular smooth muscle** and **V2 receptors in the renal collecting ducts**.
- The **V2 receptor**, a **G protein-coupled receptor**, **initiates a signaling cascade** upon binding of vasopressin (AVP), using **cAMP as a second messenger**.
- **cAMP activates protein kinase A (PKA)**, which **phosphorylates specific target proteins**.
- These proteins then **stimulate the fusion of vesicles containing Aquaporin-2 (AQP2) channels** (water channel) with the apical membrane, thereby **promoting water reabsorption** in the kidney.
- **Protein kinase A (PKA)** → cAMP-dependent protein kinase.
- **Protein kinase B (PKB)** → calcium-calmodulin-dependent protein kinase.
- **Protein kinase C (PKC)** → calcium-phospholipid-dependent protein kinase.

AVP Responses to Changes in Plasma



Normal osmolarity of plasma? 290-300 mOsm/kg
Increase in osmolarity=increase in thirst why? Caus ADH increase stimulate thirst centers (espc in hot days)

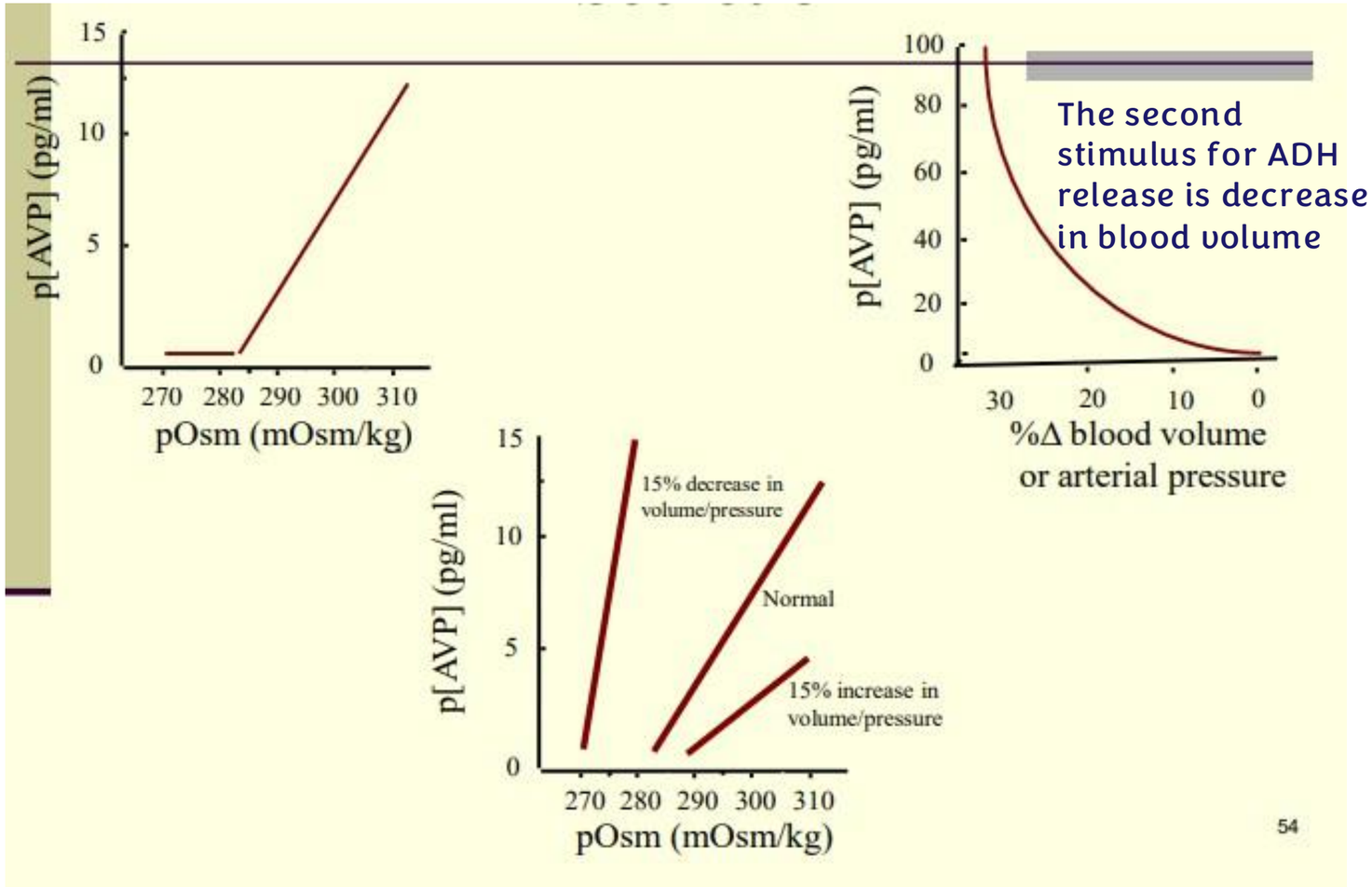
Image Interpretation

- **Image (A):**
  - This graph shows that **ADH (vasopressin) secretion increases sharply in response to rising plasma osmolality**. This helps maintain osmotic balance by promoting water retention in the kidneys.
- **Image (B):**
  - Urine osmolality is **directly proportional to plasma ADH concentration**.
  - Higher levels of ADH result in **more concentrated (hyperosmotic) urine**, which is typically observed as **darker-colored urine** due to reduced water excretion.
- **Image (C):**
  - Increased plasma osmolality not only stimulates ADH release but also **activates thirst centers in the hypothalamus**, increasing the urge to drink water.
  - Together, **water intake and renal water retention** contribute to the **restoration of osmotic homeostasis**.

Recommend it watch this part of the lecture!!!

Osmolar and Volume Control of AVP Secretion

- Notice that ADH secretion is also responsive to changes in blood volume and arterial pressure.
- **When blood volume decreases** (e.g., due to hemorrhage), **ADH levels increase significantly**. This compensates for the drop in blood pressure by **acting on V1 receptors in vascular smooth muscle**, causing **vasoconstriction**.
- **Conversely, when blood volume or arterial pressure increases, ADH secretion decreases markedly**, reducing both vasoconstriction and water retention.



Factors Affecting AVP Secretion

Stimulation	Inhibition
▪ Extracellular fluid osmolality increase ▪ Volume decrease ▪ Pressure decrease ▪ Pain ▪ Nausea and vomiting ▪ Stress ▪ Drugs: • Nicotine • Morphine • Barbituates	▪ Extracellular fluid osmolality decrease (no sweating) ▪ Volume increase ▪ Ethanol

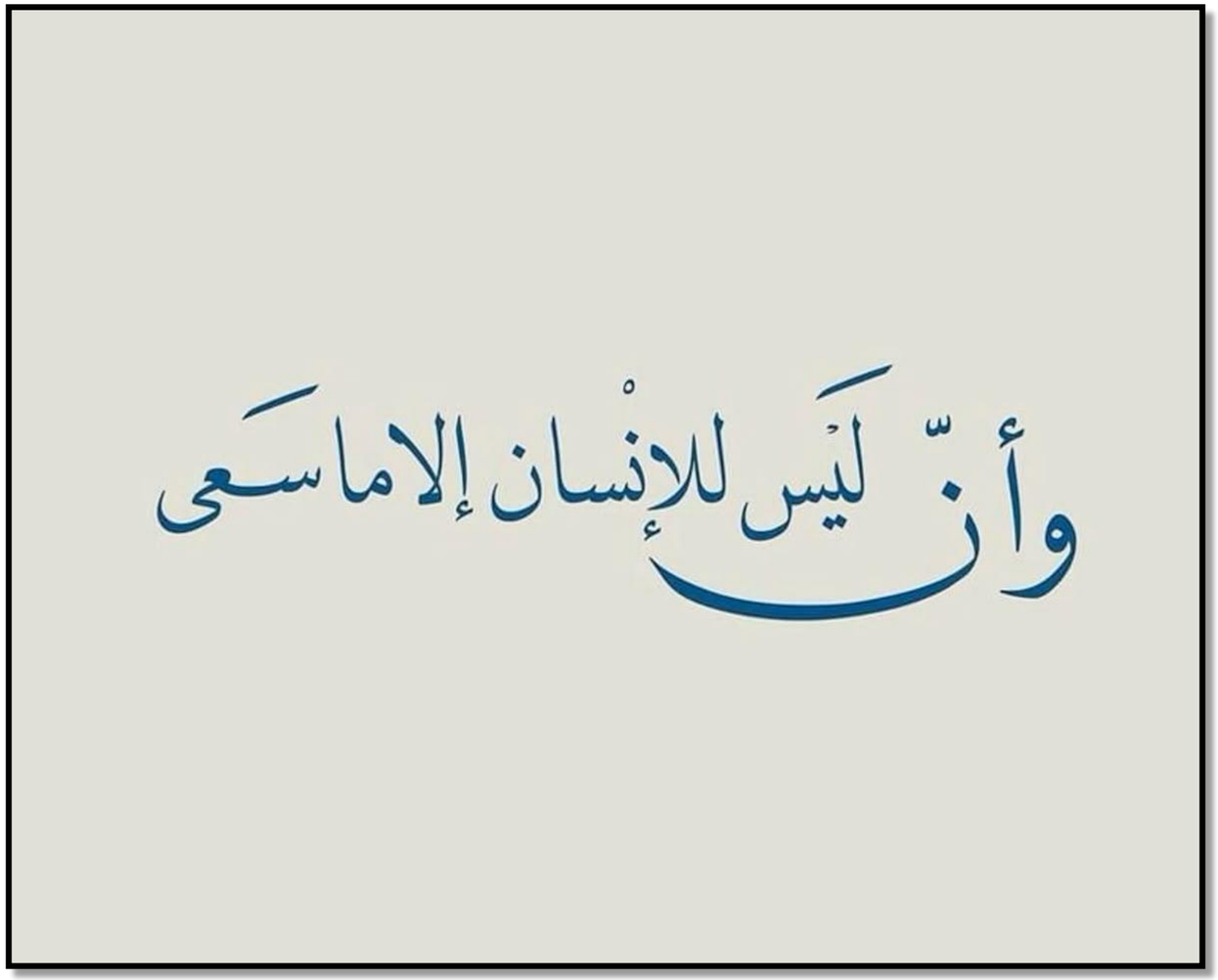
Pathophysiology of ADH

- **SIADH** (Syndrome of inappropriate ADH):
  - occurs when **ADH is secreted from ectopic sources**, such as **small cell lung carcinoma**.
  - This leads to **elevated levels of ADH**, causing **excessive water retention**.
  - As a result, **plasma sodium becomes diluted**, leading to **dilutional hyponatremia and occasionally hypokalemia**.
- Diabetes Insipidus:
  - **Central DI** occurs due to **impaired or absent ADH secretion** from the **hypothalamus or posterior pituitary** (no ADH so how much will urine volume be? 18 liters(remember the 10% we talked about that is under ADH regulation!!!), often due to trauma, tumors, or genetic defects.
  - **Nephrogenic DI** occurs when **ADH secretion is normal**, but the **kidneys are unresponsive** to it due to **defects in V_2 receptors or aquaporin-2 channels**.

Treatment of ADH Disorders: SIADH and Diabetes Insipidus

- Treatment of SIADH
  - Water restriction
  - Demeclocycline
  - Nonpeptide vasopressin antagonists (vaptans)
    - Conivaptan
    - Tolvaptan
- Treatment of Diabetes Insipidus
  - Central diabetes insipidus
    - dDAVP (desmopressin-(1-desamino-8-D-arginine vasopressin) (synthetic vasopressin)
  - Nephrogenic diabetes insipidus (more focused on symptom management and preventing dehydration, as the kidneys cannot respond to ADH)

رسالة من الفريق العلمي:



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			