Introduction to Endocrinology

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Hormone secretion and blood concentration

- Norepinephrine, epinephrine -secreted within **seconds** after the gland is stimulated and develop full action within another few **seconds to minutes**
- Thyroxine or growth hormone – require **months** to full effect
- **Rates of secretion**: µg – mg / day
- **Concentration in the blood:** pg - µg / ml of blood

Hormone release

- **Cyclical variation** influenced by seasonal changes, stages of development and aging, circadial cycle, sleep etc.
  - **STH** (growth hormone) – development, ↑ during early period of sleep, ↓ during later stages of sleep
  - **Gonadal hormones** - development and aging, seasonal changes, lunar cycles
  - **ACTH, glucocorticoids etc.** – circadial cycle
- **Reflex release** influenced by stress and new situations
  - **Stress hormones** – corticoids, renin-angiotensin-aldosterone system, prolactin

Episodic secretion of hormones

- The most prominent episodes of release occur with a frequency of about one hour—referred to as circhoral
- An episode of release longer than an hour, but less than 24 hours, the rhythm is referred to as ultradian
- If the periodicity is approximately 24 hours, the rhythm is referred to as circadian
  - ✓usually referred to as diurnal because the increase in secretory activity happens at a defined period of the day

Transport of hormones in the blood

- **Water-soluble hormones** (peptides and catecholamines) – dissolved in the plasma, diffusion from capillaries to the interstitial fluid and to target cells
- **Lipid soluble** (steroid hormones and thyroid hormones) – circulate in the blood mainly bound to plasma proteins (less then 10% as free hormones).
  - Thyroxine – more than 99% bound to plasma proteins.
  - Hormones bound to proteins are biologically inactive (reservoir) until they dissociate from plasma proteins

MCR of some hormones

Hormone	Half-life
Amines	2-3 min
Thyroid hormones: T4 T3	6.7 days 0.75 days
Polypeptides	4-40 min
Proteins	15-170 min
Steroids	4-120 min

Clearance" of hormones from the blood

Clearance = rate of disappearance from plasma / concentration in plasma (measuring by radioactive hormone)

Ways to clear hormones from plasma:

- Metabolic destruction by the tissue (enzymes)
- Binding with the tissue (some hormones may be recycled)
- Excretion by the liver into the bile (steroid hormones), long-time life period because they are bound to plasma proteins – half-life of thyroid hormones = 1-6 days
- Excretion by the kidneys into the urine (peptide hormones and catecholamines = water soluble – short-time life period)

Hormonal interactions

- The responsiveness of a target cell to a hormone depends on the hormone's concentration, the abundance of the target cell's hormone receptors, and influences exerted by other hormones.
- Three hormonal interactions are the
  - permissive effect
  - synergistic effect
  - antagonist effect

Permissive effect hormonal interactions

- A second hormone, strengthens the effects of the first
- Thyroid strengthens epinephrine’s effect upon lipolysis

Synergistic effect hormonal interactions

- Two hormones acting together for greater effect
- Estrogen & LH are both needed for oocyte production

Antagonistic effects hormonal interactions

- Two hormones with opposite effects
- Insulin promotes glycogen formation & glucagon stimulates glycogen breakdown

Agonist vs. Antagonist

- **Agonists** are molecules that bind the receptor and induce all the post-receptor events that lead to a biologic effect. In other words, they act like the "normal" hormone, although perhaps more or less potently
- **Antagonists** are molecules that bind the receptor and block binding of the agonist, but fail to trigger intracellular signaling events

Function of the endocrine system

- Water balance
- Uterine contractions & milk release
- Growth, metabolism, & tissue maturation
- Ion regulation
- Heart rate & blood pressure regulation
- Blood glucose control
- Immune system regulation
- Reproductive functions control

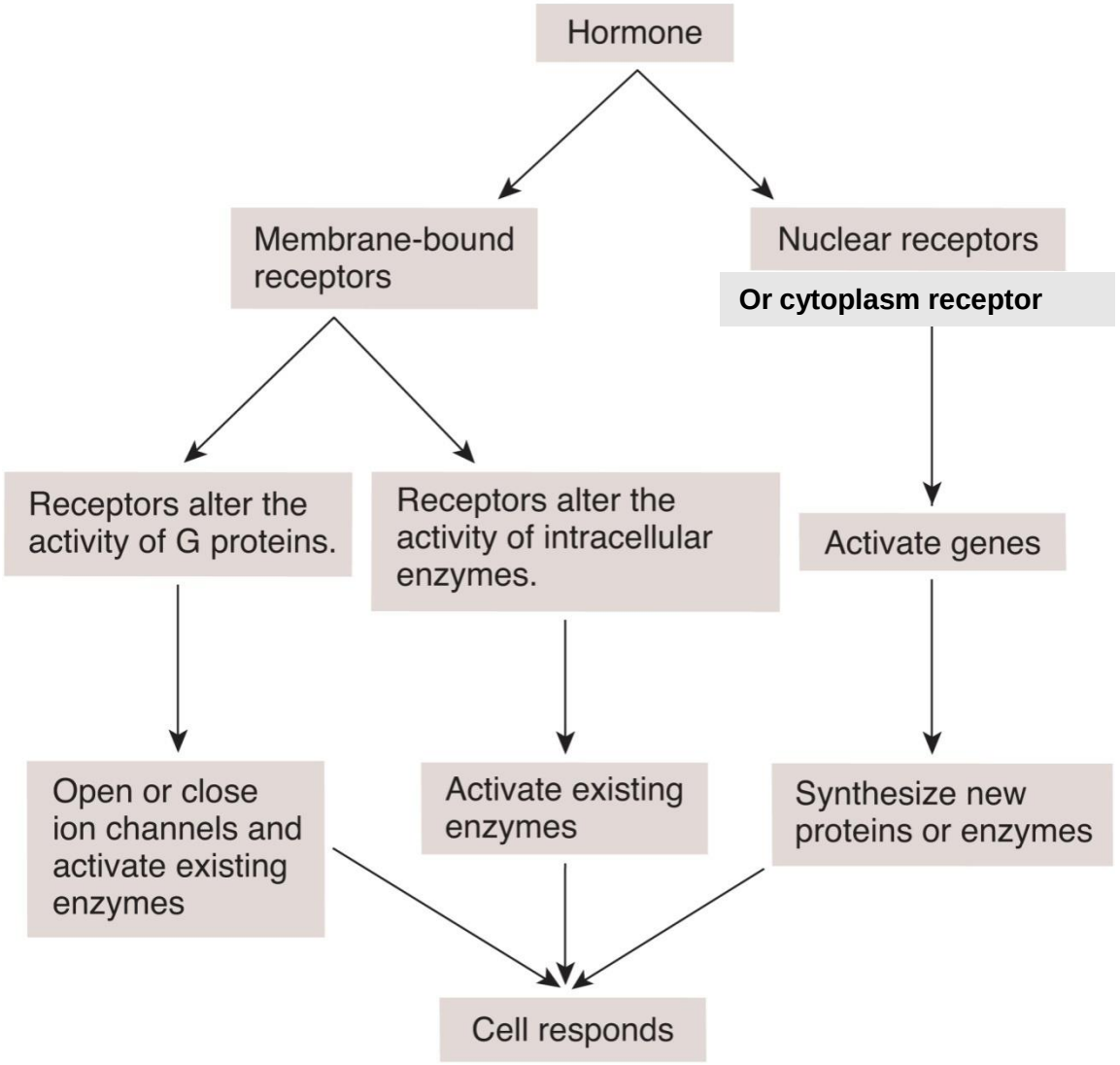
Control of hormone secretion

- Regulated by signals from nervous system, chemical changes in the blood or by other hormones
- Negative feedback control (most common)
  - decrease/increase in blood level is reversed
- Positive feedback control
  - the change produced by the hormone causes more hormone to be released
- Disorders involve either hyposecretion or hypersecretion of a hormone

Hormone receptors

- **Location:**
  - In or on the surface of the cell membrane – proteins, peptides, catecholamines
  - In the cell cytoplasm – steroid hormones
  - In the cell nucleus – Thyroid hormones
- Hormonal receptors are **large proteins**
- **Each cell** has 2 000 – 100 000 receptors
- Receptors are usually **highly specific** for single hormone

Hormone Receptors and Mechanisms of Action



Second Messengers Systems

- Some hormones exert their influence by increasing the synthesis of cAMP
  - ADH, TSH, ACTH, glucagon and epinephrine
- Some exert their influence by decreasing the level of cAMP
  - growth hormone inhibiting hormone
- Other substances can act as 2nd messengers
  - calcium ions
  - cGMP
- A hormone may use different 2nd messengers in different target cells

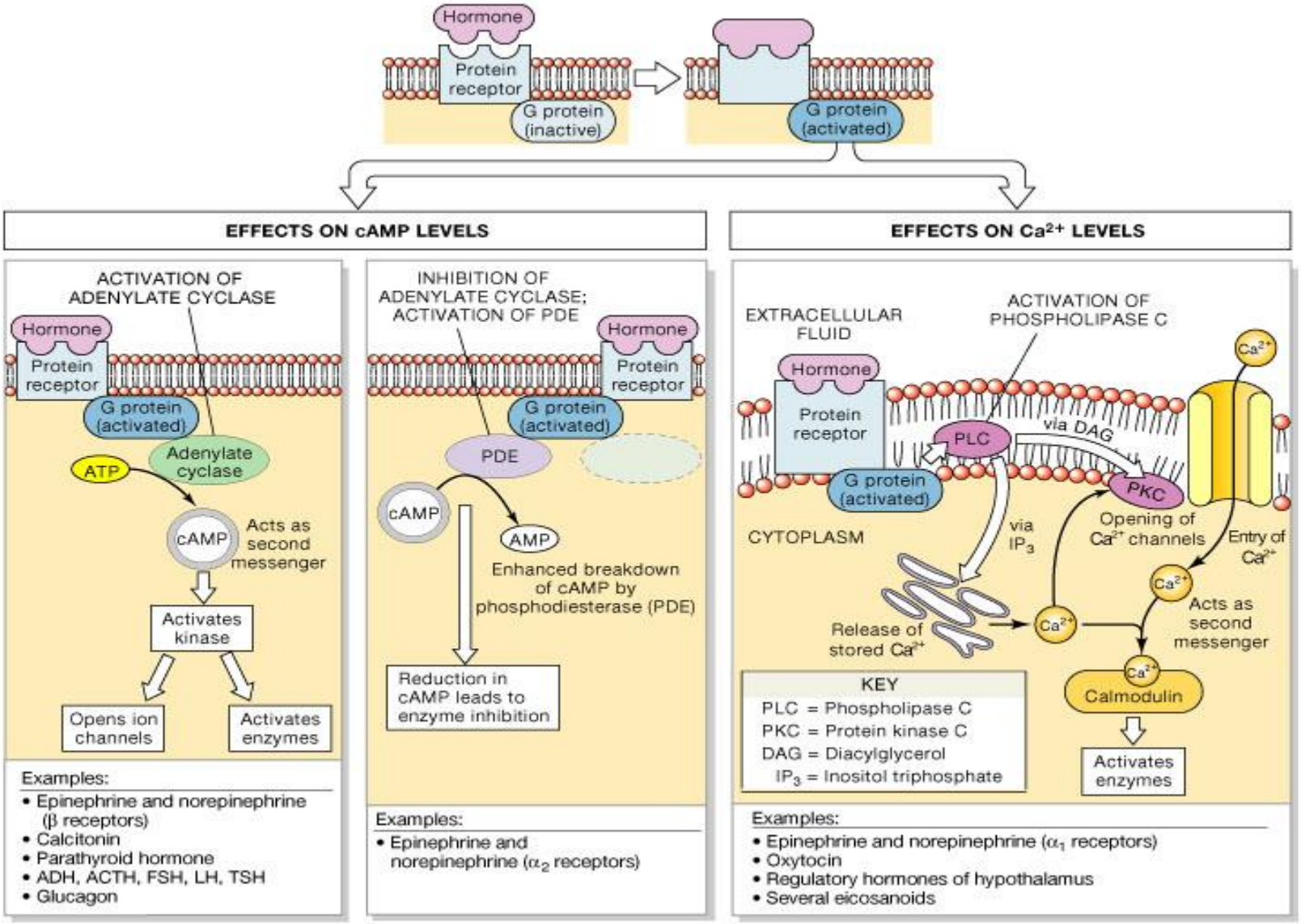
Second messengers for cell-surface receptors

- Second messenger systems include:
  - Adenylate cyclase which catalyzes the conversion of ATP to cyclic AMP;
  - Guanylate cyclase which catalyzes the conversion of GMP to cyclic GMP (cyclic AMP and cyclic GMP are known collectively as cyclic nucleotides);
  - Calcium and calmodulin; phospholipase C which catalyzes phosphoinositide turnover producing inositol phosphates and diacyl glycerol.

G proteins

- Are guanosine triphosphate (GTP)-binding proteins that couple hormone receptors to adjacent effector molecules
- Are used in the adenylate cyclase, Ca2+–calmodulin, and inositol 1,4,5-triphosphate (IP3) second messenger systems.
- Have intrinsic GTPase activity
- have three subunits: α, β, and γ.
- The ` subunit can bind either guanosine diphosphate (GDP) or GTP. When GDP is bound to the α subunit, the G protein is inactive. When GTP is bound, the G protein is active.
- G proteins can be either stimulatory (Gs) or inhibitory (Gi). Stimulatory or inhibitory activity resides in the α subunits, which are accordingly called αs and αi.

G Proteins and Hormone



The adenylyl cyclase – cAMP second messenger system

Hormones:

- **ACTH** (Adrenocorticotropic hormone)
- **Angiotensin II** (epithelial cells)
- **Calcitonin**
- **Catecholamines** (β receptors)
- **CRH** (Corticotropin-releasing hormone)
- **FSH** (Follicle-stimulating hormone)
- **Glucagon**
- HCG (Human chorionic gonadotropin)
- **LH** (Luteinizing hormone)
- **PTH** (Parathyroid hormone)
- **Secretin**
- **TSH** (Thyroid-stimulating hormone)
- **Vasopressin** (V2 receptor, epithelial cells)

The cell membrane phospholipids second messenger system

Hormones:

- **Angiotensin II** (vascular smooth muscles)
- **Catecholamines** (α receptor)
- **GRH** (gonadotropin-releasing hormone)
- **GHRH** (Growth hormone-releasing hormone)
- **Oxytocin**
- **TRH** (Thyroid-releasing hormone)
- **Vasopressin** (V1 receptor, vascular smooth muscle

Regulation of hormone receptors

- The number of receptors does not remain constant (from day to day, even from minute to minute). Receptors are inactivated or destroyed (down-regulation) and reactivated or produced new ones (up-regulation).
  - Down-regulation
  - excess hormone leads to a decrease in number of receptors
  - receptors undergo endocytosis and are degraded
  - decreases sensitivity of target cell to hormone
  - Up-regulation
  - deficiency of hormone leads to an increase in the number of receptors
  - target tissue becomes more sensitive to the hormone

General mechanisms of hormone action

- Hormone binds to cell surface or receptor inside target cell
- Cell may then
  - synthesize new molecules
  - change permeability of membrane
  - alter rates of reactions
- Each target cell responds to hormone differently

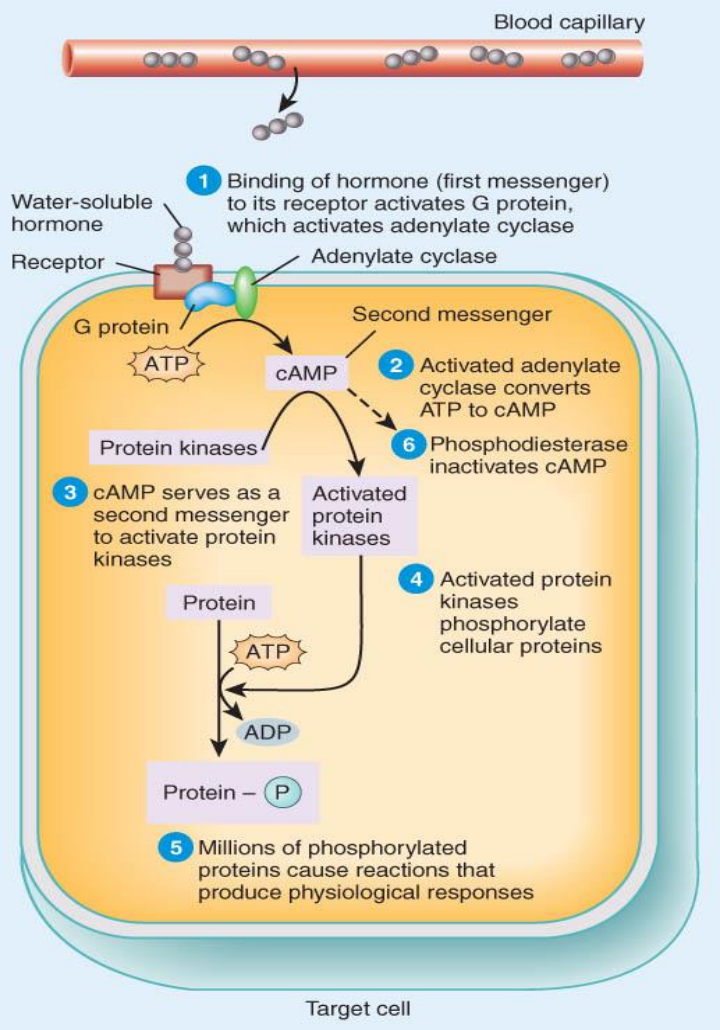
  At liver cells---insulin stimulates glycogen synthesis

  At adipocytes---insulin stimulates triglyceride synthesis

Action of water-soluble hormones

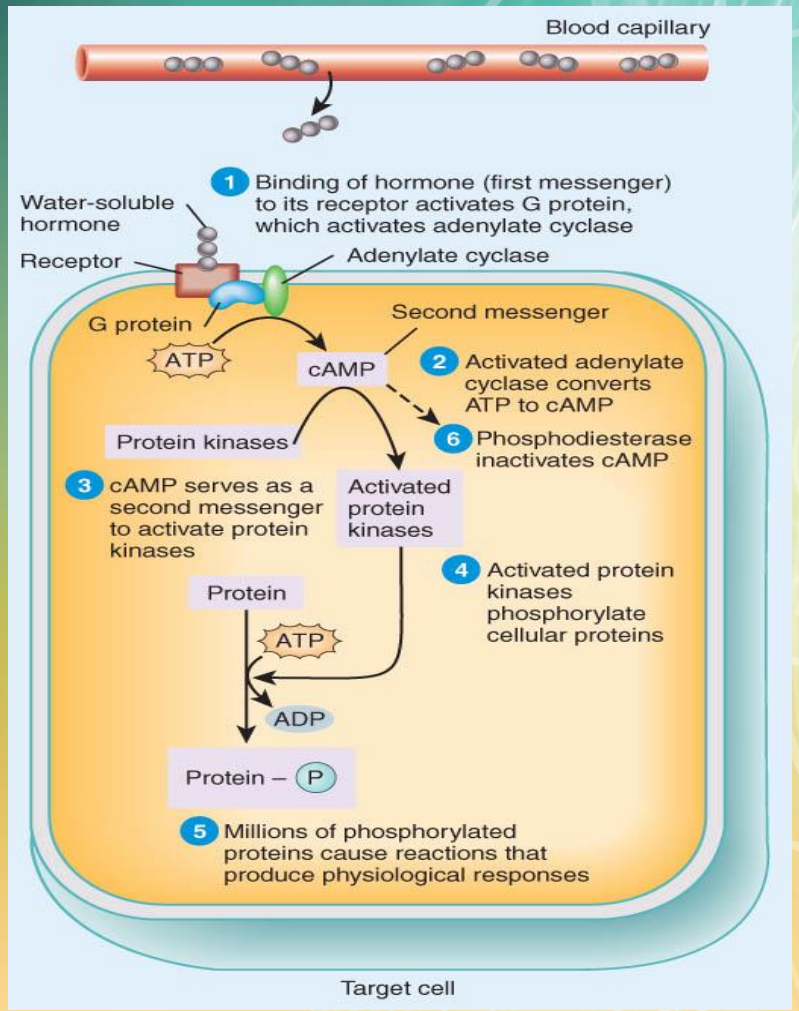
- Water-soluble hormones alter cell functions by activating plasma membrane receptors, which set off a cascade of events inside the cell.
  - The water-soluble hormone that binds to the cell membrane receptor is the first messenger.
  - A second messenger is released inside the cell where hormone stimulated response takes place.

Action of water-soluble hormones



- Can not diffuse through plasma membrane
- Hormone receptors are integral membrane proteins
  - act as first messenger
- The hormone binds to the membrane receptor.
- The activated receptor activates a membrane *G-protein* which turns on *adenylate cyclase*.
- Adenylate cyclase converts ATP into <u>cyclic AMP</u> which activates protein kinases.
- *Protein kinases* phosphorylate enzymes which catalyze reactions that produce the physiological response.

Action of water-soluble hormones

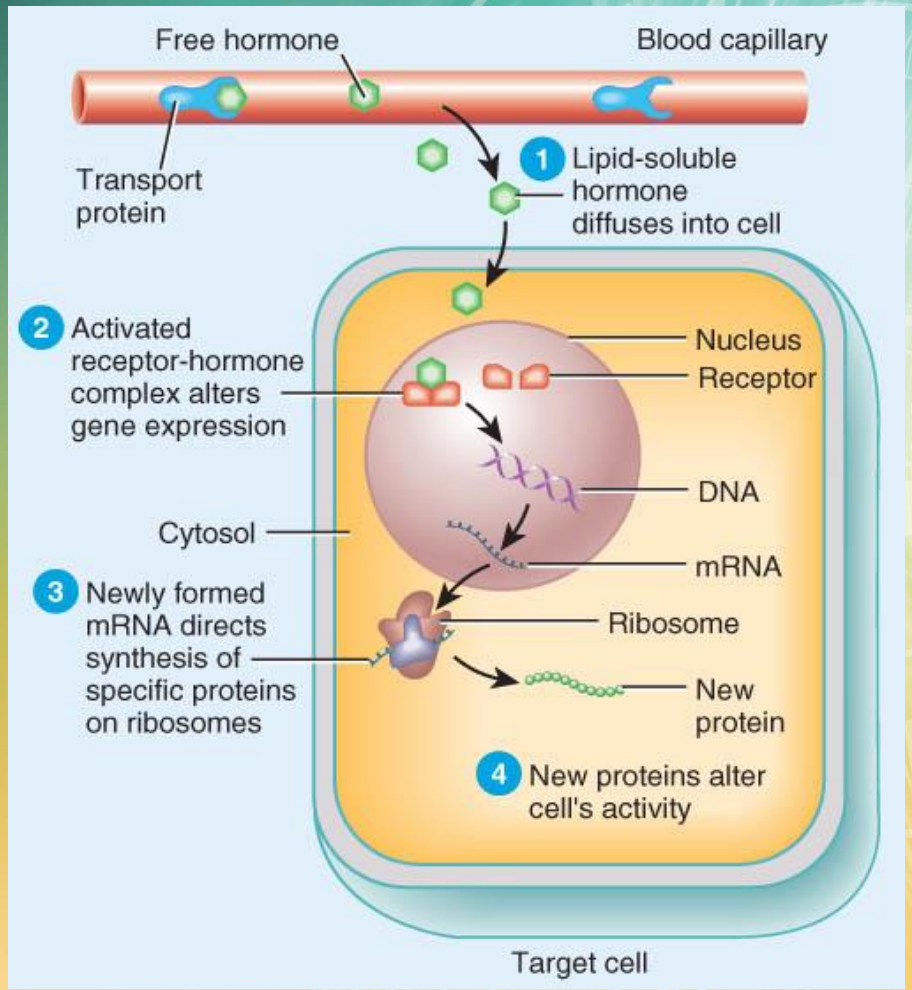


- Cyclic AMP is the 2nd messenger
  - kinases in the cytosol speed up/slow down physiological responses
- Phosphodiesterase inactivates cAMP quickly
- Cell response is turned off unless new hormone molecules arrive

Action of lipid-soluble hormone

- Lipid-soluble hormones bind to and activate receptors within cells
  - The activated receptors then alter gene expression which results in the formation of new proteins
  - The new proteins alter the cells activity and result in the physiological responses of those hormones

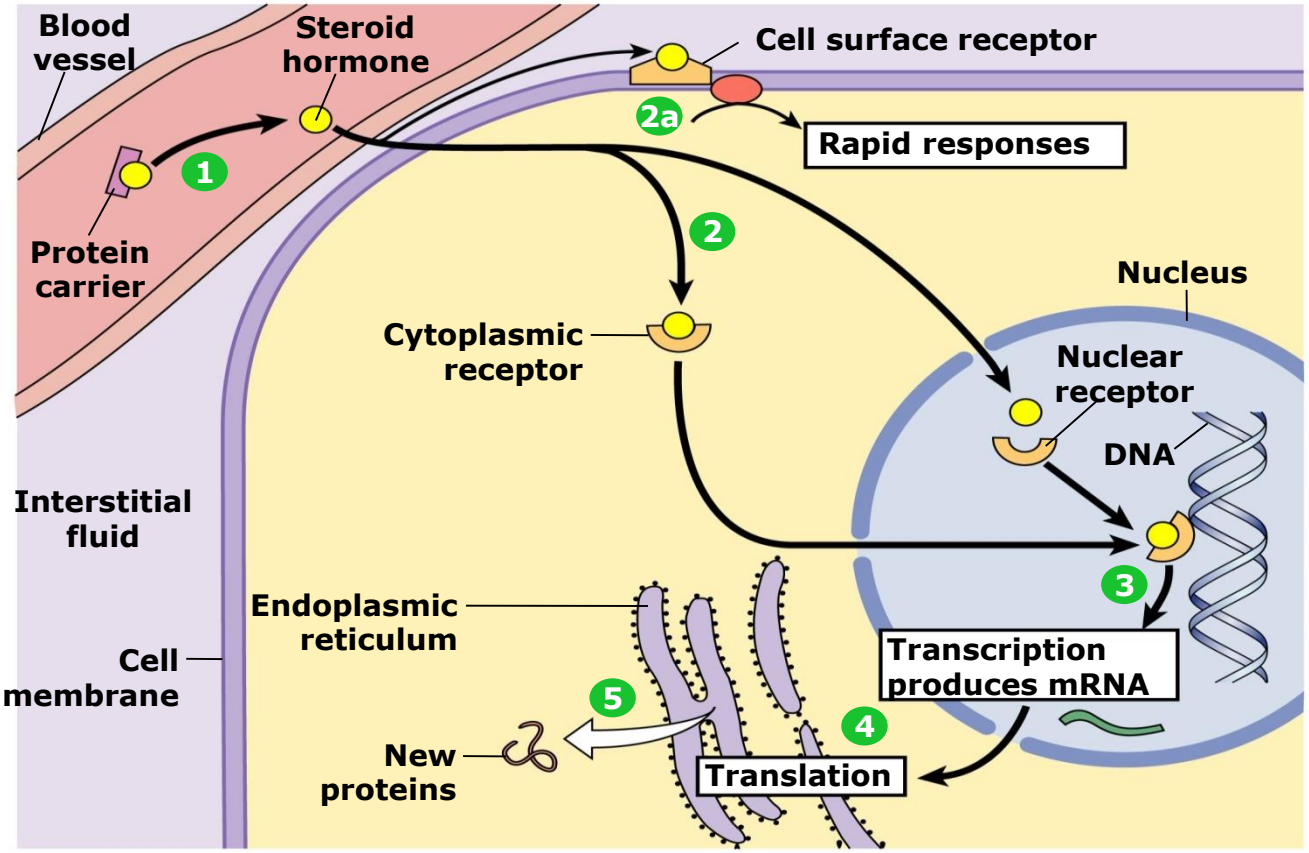
Action of lipid-soluble hormones



- Hormone diffuses through phospholipid bilayer & into cell
- Binds to receptor turning on/off specific genes
- New mRNA is formed & directs synthesis of new proteins
- New protein alters cell's activity

Steroid hormones: action

1. Most hydrophobic steroids are bound to plasma protein carriers. Only unbound hormones can diffuse into the target cell.
2. Steroid hormone receptors are typically in the cytoplasm or nucleus.
   - 2a Some steroid hormones also bind to membrane receptors that use second messenger systems to create rapid cellular responses.
3. The receptor-hormone complex binds to DNA and activates or represses one or more genes.



4. Activated genes create new mRNA that moves into the cytoplasm.
5. Translation produces new proteins for cell processes.

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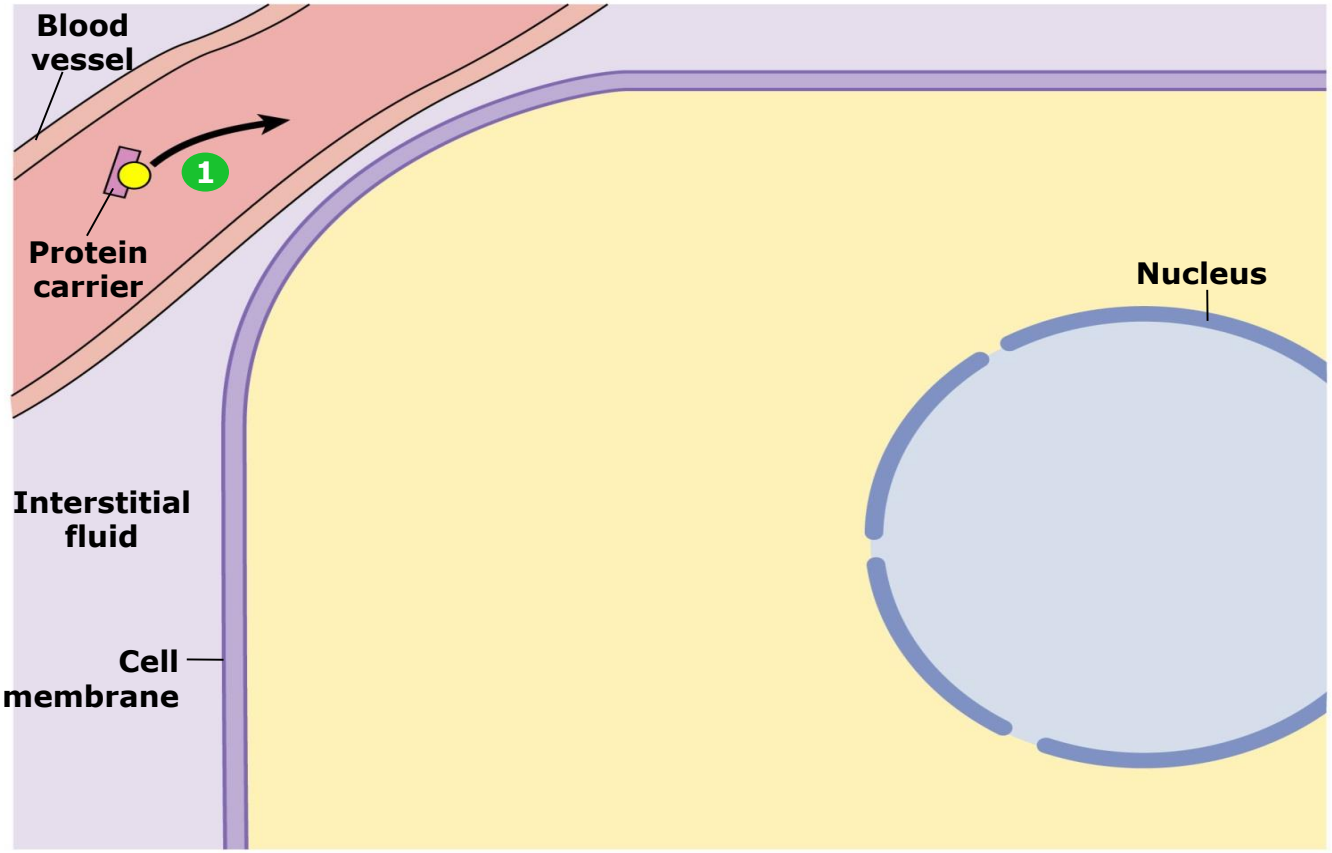

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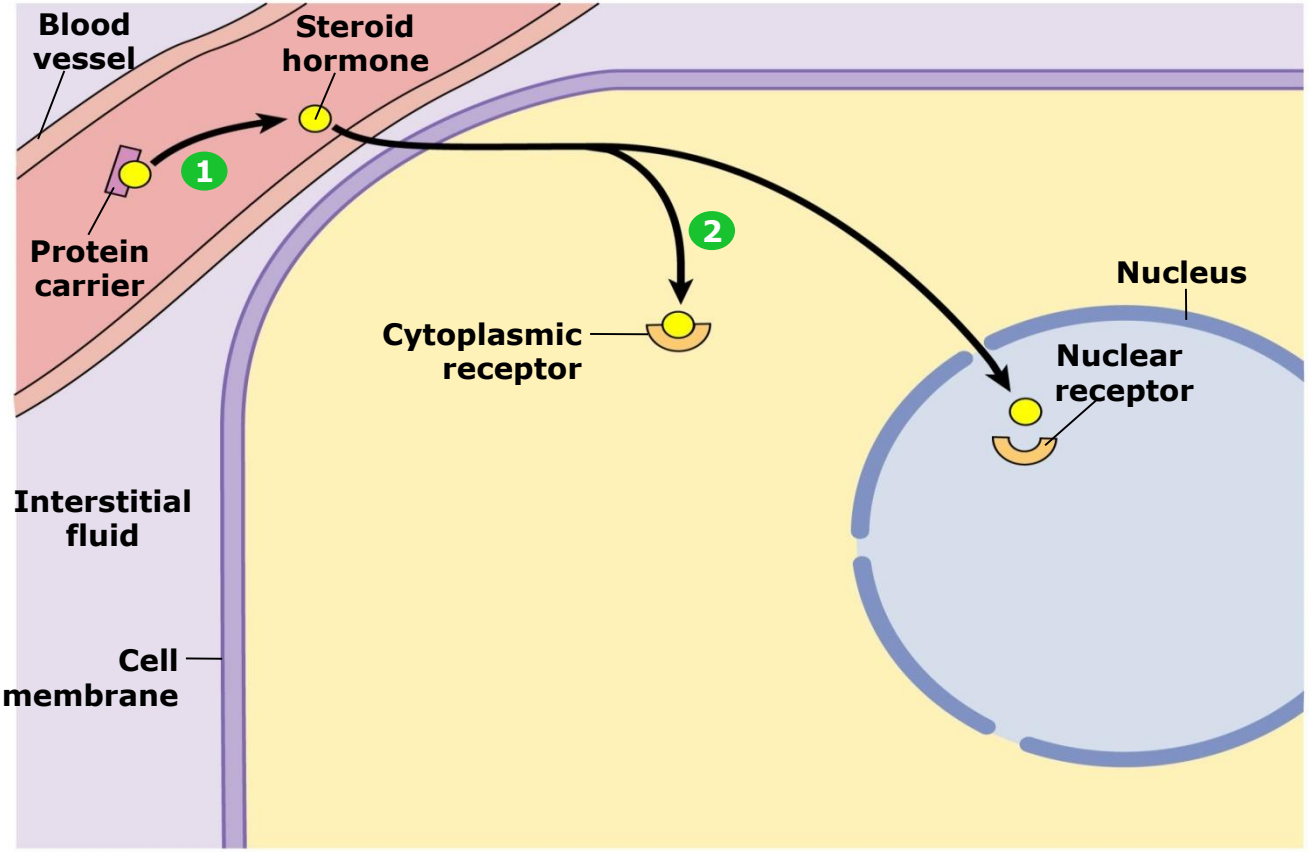

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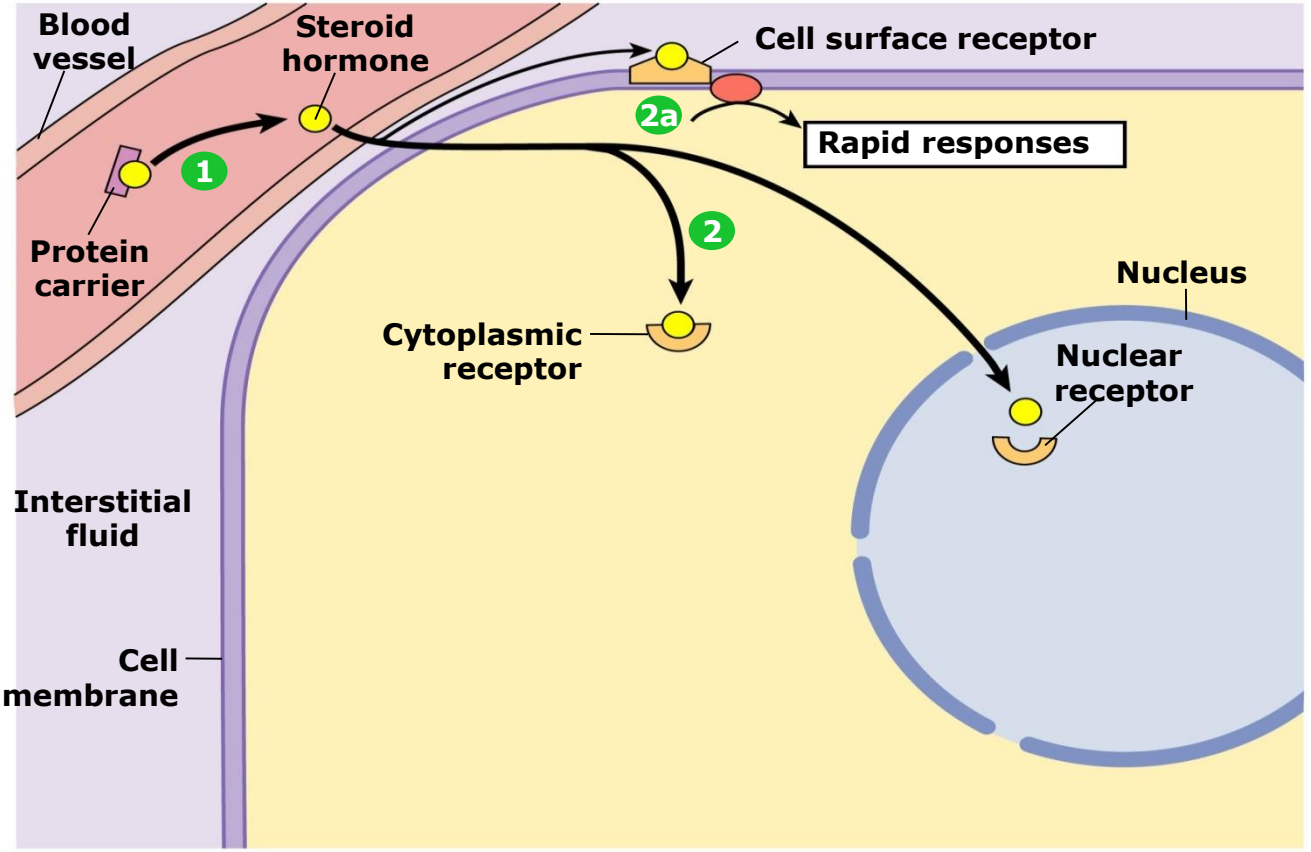

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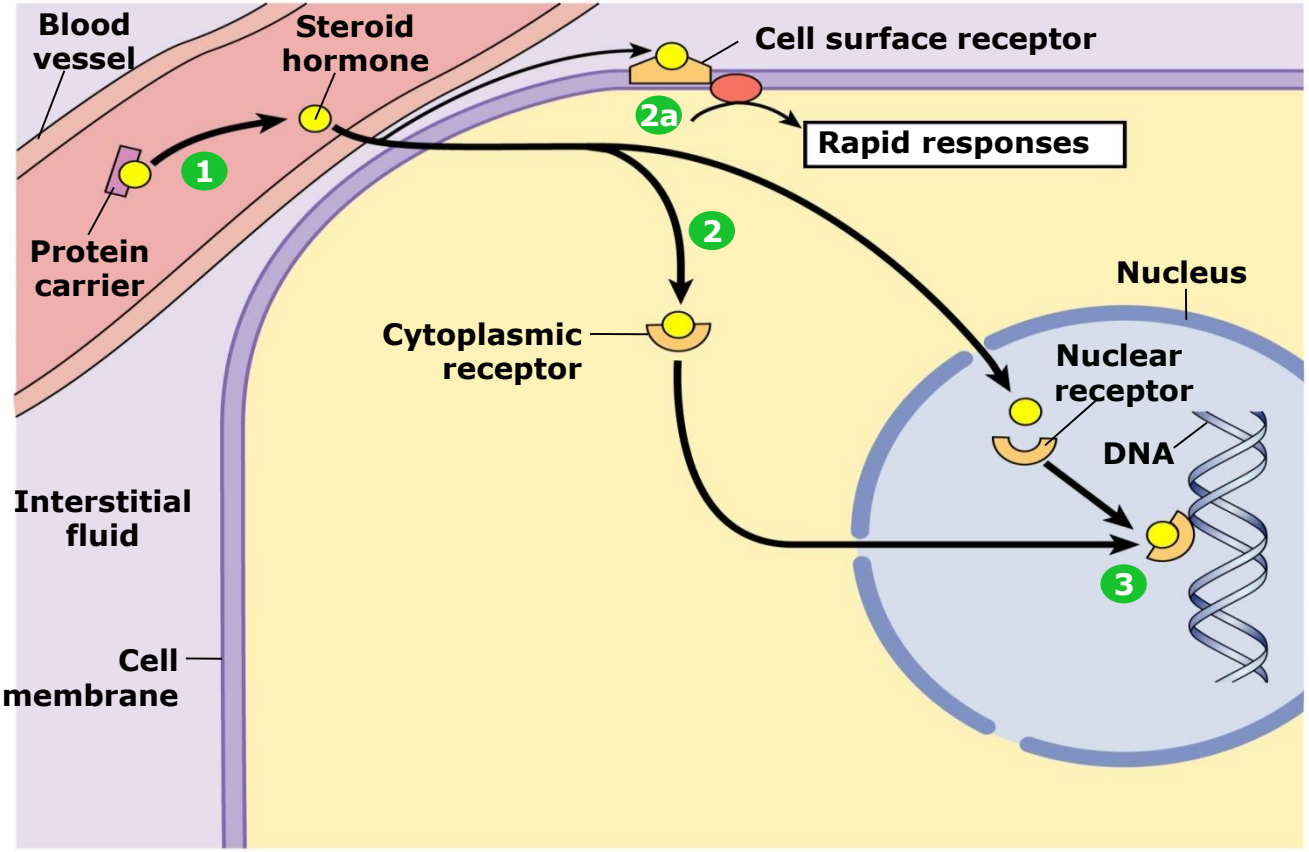

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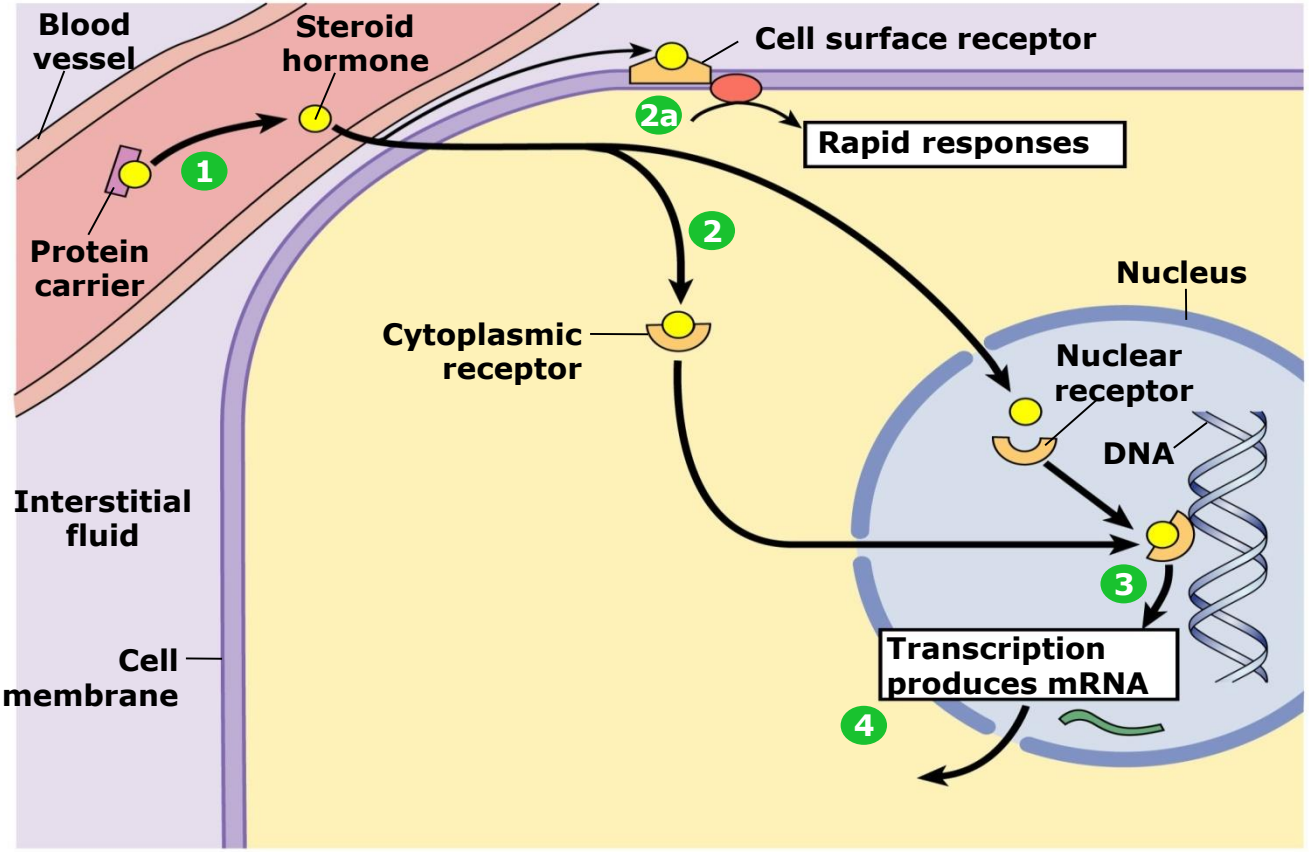

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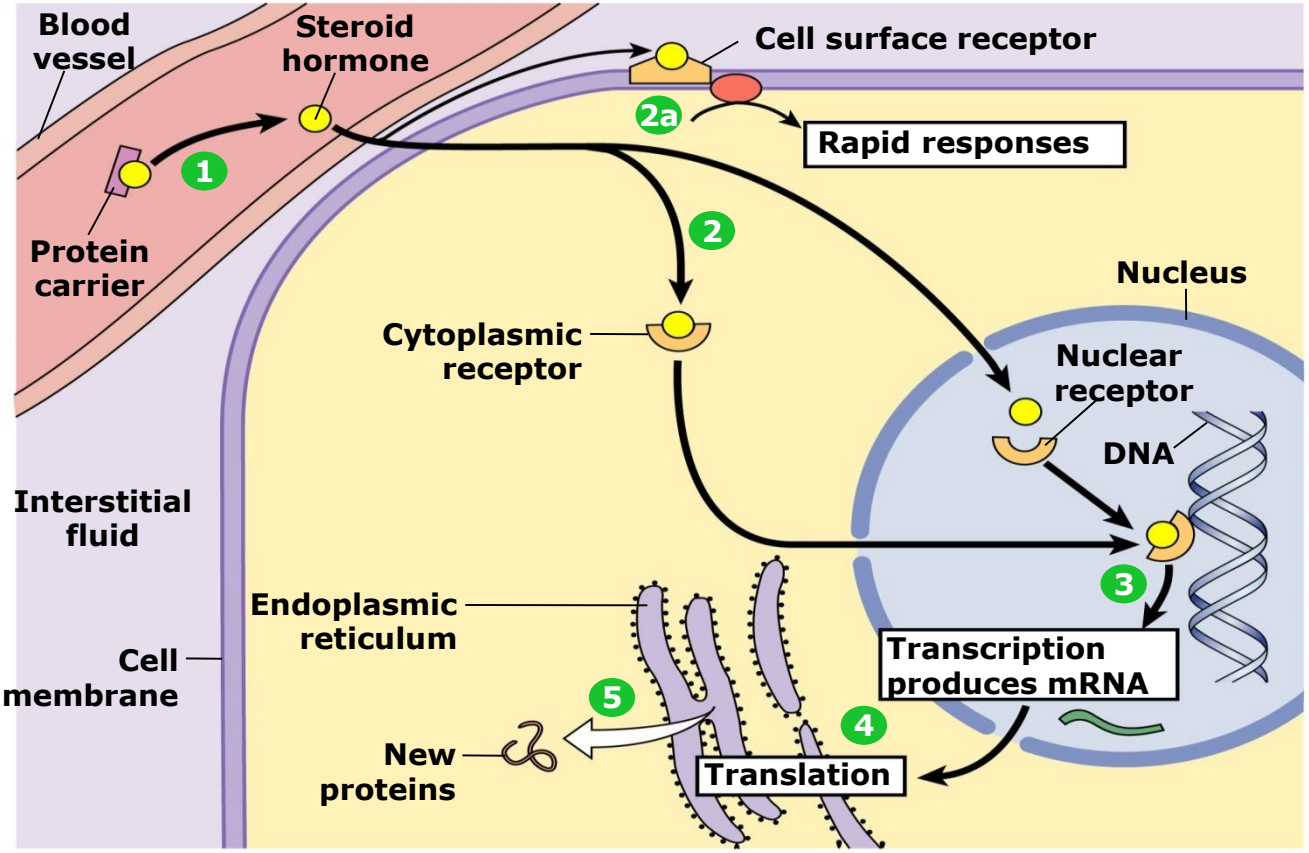

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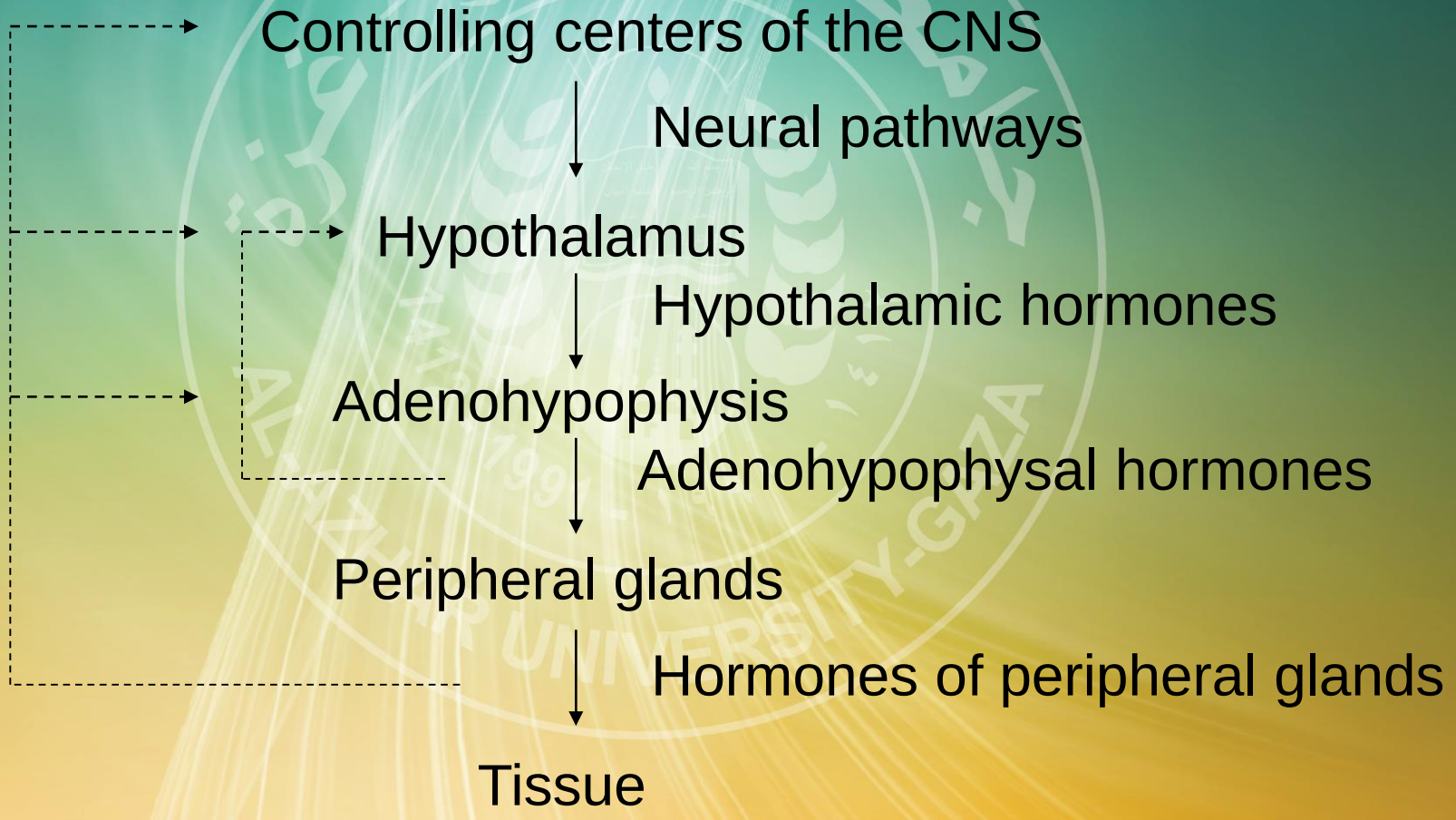
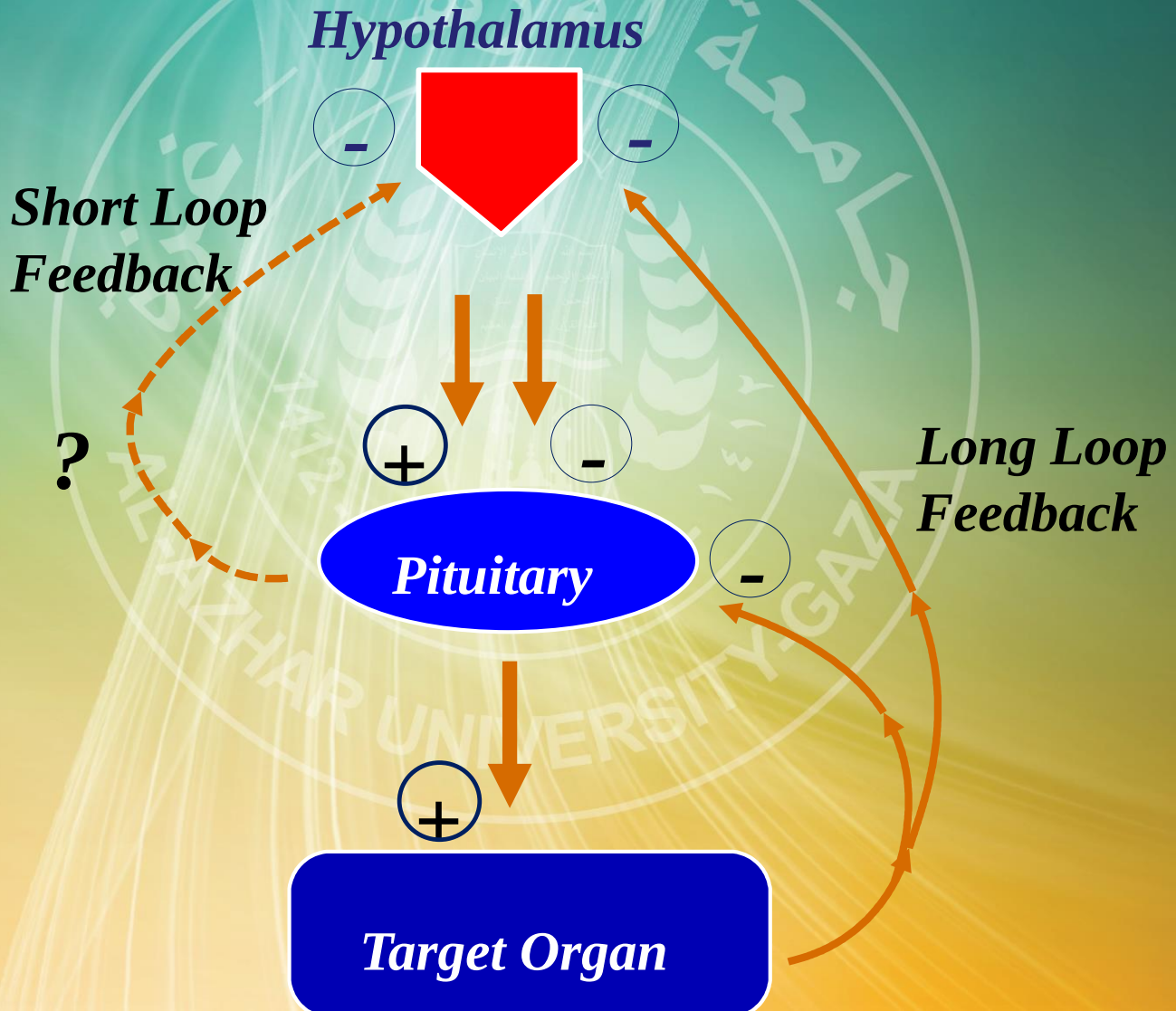
Feedback control of hormone secretion - negative feedback

- Prevents overactivity of hormone system
- The control variable is often not the secretory rate of the hormone itself but the degree of activity of the target tissue
- Feedback regulation of hormones can occur at all levels, including gene transcription and translation steps involved in processing the hormone or releasing the stored hormone
- HPA axis (hypothalamo-pituitary-adrenal axis) = **complex negative feedback**

Complex negative feedback

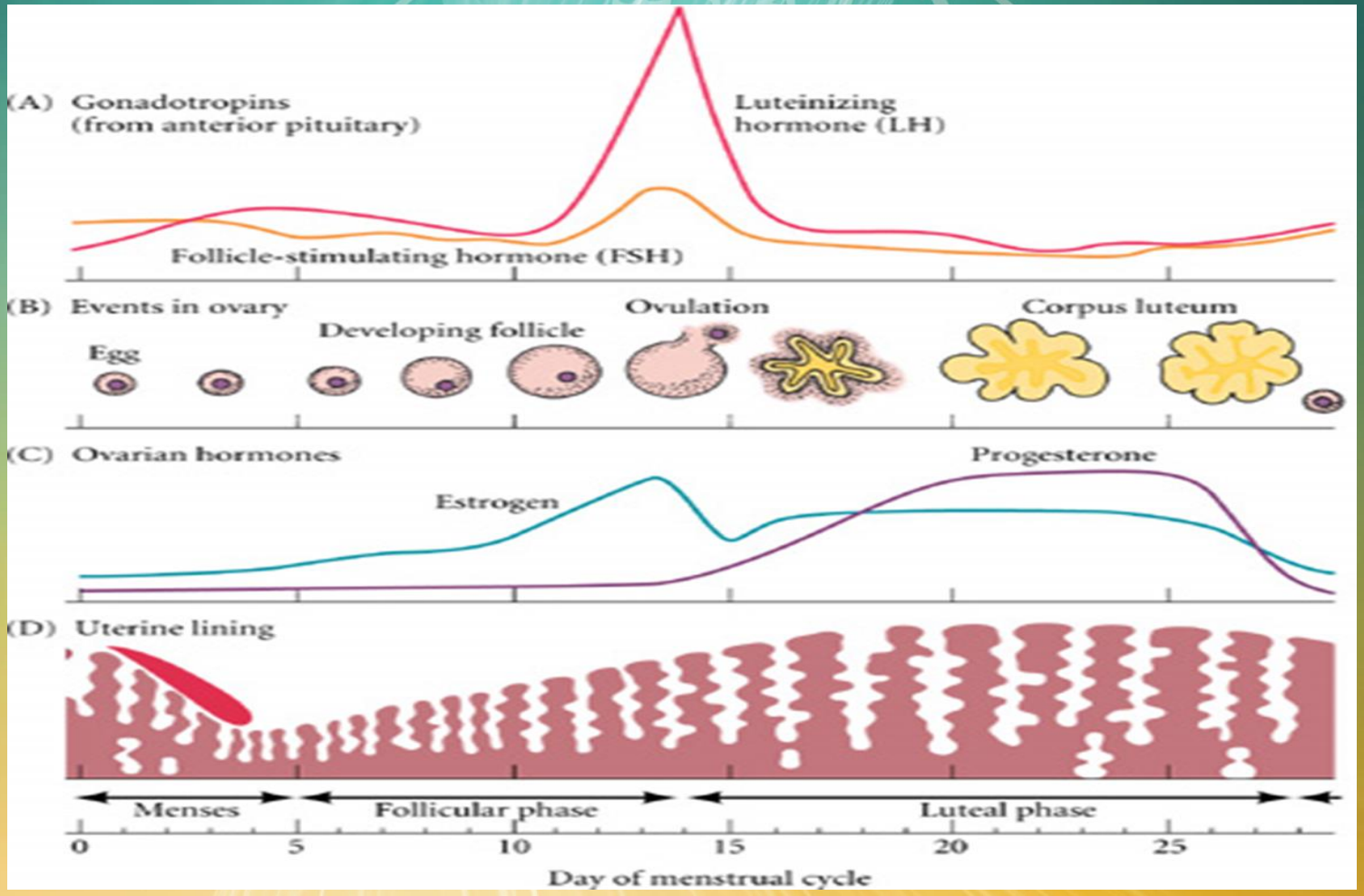


Feedback regulation of the anterior pituitary



Feedback control of hormone secretion - Positive feedback

- Positive feedback occurs when the biological action of the hormone causes additional secretion of the hormone
- Secretion of **LH** (luteinizing hormone) based of the stimulatory effect of **estrogen** before ovulation – LH stimulates ovaries to produce more estrogen and it stimulates again the pituitary gland to produce LH. When the LH reaches the appropriate concentration the negative feedback occurs


(A) Gonadotropins
(from anterior pituitary)
Luteinizing
hormone (LH)
Follicle-stimulating hormone (FSH)
(B) Events in ovary
Egg
Developing follicle
Ovulation
Corpus luteum
(C) Ovarian hormones
Estrogen
Progesterone
(D) Uterine lining
Menses
Follicular phase
Luteal phase
0
5
10
15
20
25
Day of menstrual cycle

No bad hormones – just too much or too little

Disorders of the endocrine system

- Excess of hormone
- Deficiency of hormone
- Resistance to hormone
- Administration of exogenous hormone or medication

Manifestation of endocrine disorders

- **Primary ... dysfunction of peripheral gland**
- **Secondary ... usually pituitary dysfunction projected to peripheral gland**
- **Tertially ... rarely used term for hypothalamic dysfunction**

Mechanisms of endocrine disease

- Deficiency usually is due to destructive process occurring at gland in which hormone is produced—infection, infarction, physical compression by tumor growth, autoimmune attack

Type 1 Diabetes

Mechanisms of endocrine disease

- Deficiency can also arise from genetic defects in hormone production—gene deletion or mutation, failure to cleave precursor, specific enzymatic defect (steroid or thyroid hormones)

Congenital Adrenal Hyperplasia

Mechanisms of endocrine disease

- Inactivating mutations of receptors can cause hormone deficiency

Testicular Feminization Syndrome

Mechanisms of endocrine disease

- Alterations in receptor number and function result in endocrine disorders
- Most commonly, an aberrant increase in the level of a specific hormone will cause a decrease in available receptors

Cushing's Syndrome

Approach to the patient with endocrine disease

- Function diagnosis
  - **History & physical examination**
  - **Laboratory studies**
  - **Screening for endocrine diseases**
- Pathology diagnosis
- Etiology diagnosis
  - **immunologic examination**
  - **genetic examination**
  - **Chemical examination**

Laboratory studies

Laboratory evaluations are critical both for making and confirming endocrine diagnose

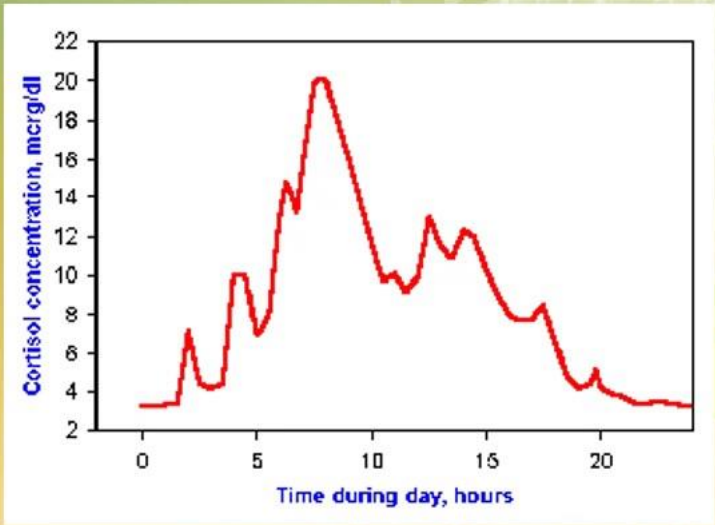
Hormones

- Examination approach
  - Basal hormonal concentrations
    - ✓ Basal plasma levels (one-time examination)
    - ✓ Diurnal dynamics of hormone concentrations (e.g. cortisol)
    - ✓ Other hormonal cycles (e.g. menstrual phase dynamics)
    - ✓ Urinary output
    - ✓ Hormonal metabolites – plasma, urine (e.g. C-peptide)
    - ✓ Evaluation – measurement of a metabolic response (ADH ... Diuresis, insulin … glycaemia etc.)
  - Functional tests
    1. Inhibitory tests
    2. Stimulatory tests

Hormones plasma levels and diurnal variability

- One-time blood sample collection is a sufficient procedure for a majority of hormones.

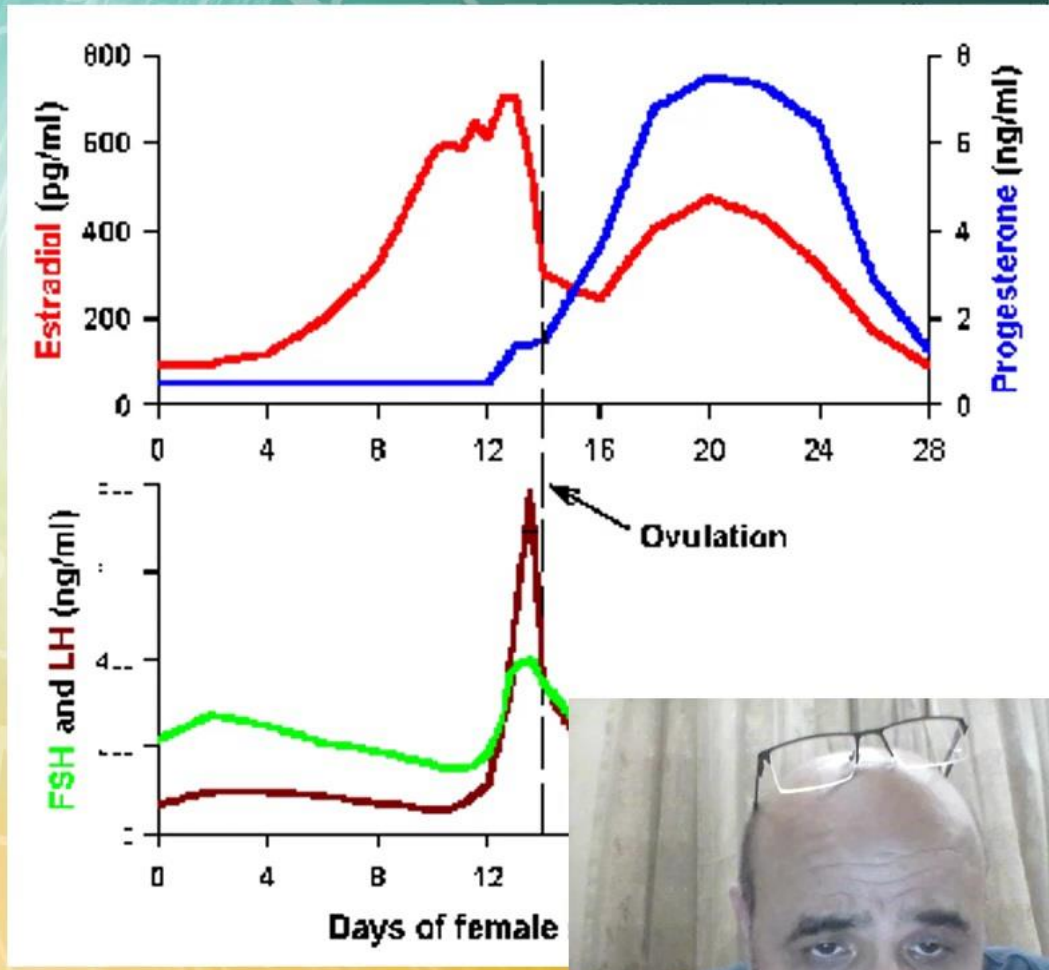
- Hormones with diurnal variability - e.g. cortisol, and growth hormone – several measurement during 24 h period needed (e.g. every 4 h or every 6 h)



P-cortisol: Physiological diu
with typical overnight decre

Hormones other hormonal cycles

- **Menstrual cycle is related to cyclic changes of LH, FSH, estrogens and progesteron.**
- **The measurement of these hormonal levels - timing of blood collection - must respect a phase of cycle.**



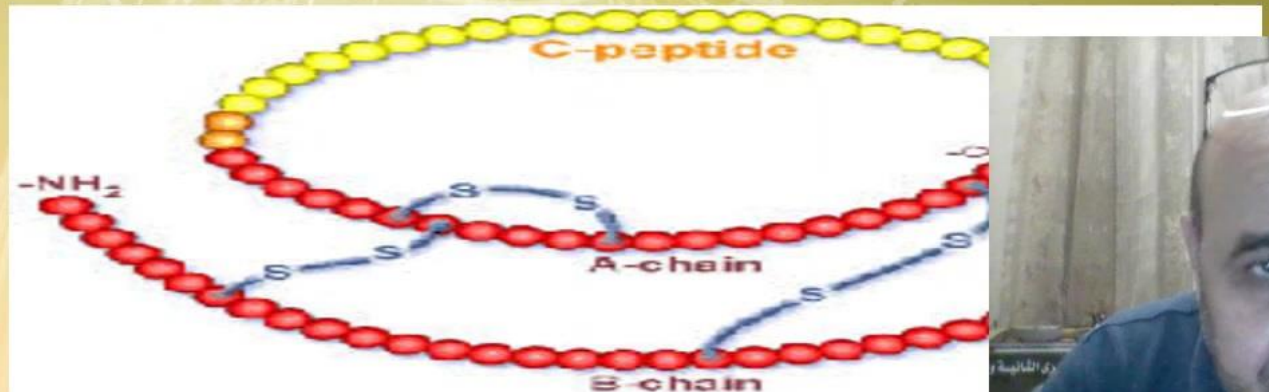
Hormones urinary concentrations

- **24-h collection of urine**

- **Alternative method for hormones with diurnal dynamics (cortisol, aldosterone) or pulsate secretion (catecholamines).**

Hormones plasma metabolites

- **C peptide**
- Co-product of insulin synthesis
  Plasma levels much higher than
  that of insulin due to longer half-life
- C peptide concentrations reflect insulin production and give in principle the same information as insulin levels.



Hormones plasma or urinary metabolites

5-HIAA (hydroxyindole acetic acid) Serotonin metabolite Urinary excretion measurement in patients with suspicious carcinoid

Functional tests

Basal hormonal concentration very often doesn´t allow to establish a diagnosis of hypo- or hyperfunction.

Suspect hypofunction → Stimulatory tests

= quantification of functional reserve of endocrine gland

Suspect hyperfunction → Inhibitory tests

= quantification of responsibility of endocrine gland to inhibitory factors

Principles:

negative feedback inhibition / stimulation

direct stimulation / inhibition

Stimulatory tests of pituitary function

Insulin hypoglycemia test (Insulin tolerance test)

- I.V insulin (O,1 IU/kg) to cause hypoglycaemia (2,2 mmol/L)
- Measure glucose, GH, cortisol at 30, 45, 60, 90 and 120 min
- stimulation of ACTH + GH secretion
- Normal response: GH > 7 ng/mL, P-cortisol > 18 μg / dL
- Contraind: diabetes mellitus

Stimulatory tests of pituitary function

- **Arginine infusion test**

  Physiol.: elevation of GH secretion in pituitary normal: GH > 7 ng/mL

- **TRH test**

  IV application of TRH rise TSH and PRL response

- **GnRH test**

  IV application of GnRH (LHRH) stimul elevation (+ slow FSH elevation)

Inhibitory tests of pituitary function

- **Dopaminergic drugs test**

  Dopamin = prolactin inhibitory factor

  Physiol. inhibition of PRL (+ GH) secretion

- **Dexamethazone test**

  ✓ Overnight dexamethasone suppression test 1 mg at 2300h

  ❖Plasma cortisol at 0800h: normal <2 µg/dl OR

  If abnormal:

  ✓Low dose dexamethasone suppr test

Local hormonal concentrations

Venous catheterization with selective blood sample collection

- Catheterization of sinus petrosus inferior

  inferior petrosal sinuses = venous drainage of pituitary gland

  Principle: Local concentration of ACTH (before and after stimulation with CRH) may distinguish pituitary and paraneoplastic Cushing syndrome)

- Catheterization of vena cava inferior

  Step by step blood sample collection from abdom. veins

  Principle: Localization of small (CT/MRI unde
  abdominal tumor (carcinoid, insulinoma etc.)
  local concentration of hormone

Tumor markers in endocrinology

- Thyroglobulin (Tg), anti-Tg antibodies

Markers of non-medullar thyroid carcinoma.

Useless as a screening markers (the only indication - systemic metastases of unknown origin)

Higher sensitivity after total thyroidectomy for cancer - for diagnostic of rest thyroid tissue or tumor relapses

- CEA (carcinoembryonic antigen)

Marker of non-medullar thyroid carcinoma (and anther malignancy – e.g. colorectal ca)

Diagnostic usage in combination with Tg and anti-Tg Ab

- Calcitonin, procalcitonin

Hormonal product and diagnostic marker of mec carcinoma (lower sensitivity that Tg for non-m ca)

Newborn screening

- Congenital hypothyroidism screening based on elevation of TSH
- Congenital adrenal hyperplasia (CAH) screening based on elevation of 17-OH-progesterone
- Phenylketonuria

Measurement of hormone concentration in the blood

Radioimmunoassay

- Hormone specific antibody is mixed with:
  - Animal fluid (serum) containing the hormone
  - Standard hormone marked by radioactivity
- Hormones (animal's and standard) compete for this antibody
- Result:
  - More radioactive hormone-antibody complex (after separation) = little animal's hormones
  - Less radioactive hormone-antibody complex (after separation) = lot of animal's hormones

Enzyme-Linked Immunosorbent Assay (ELISA)

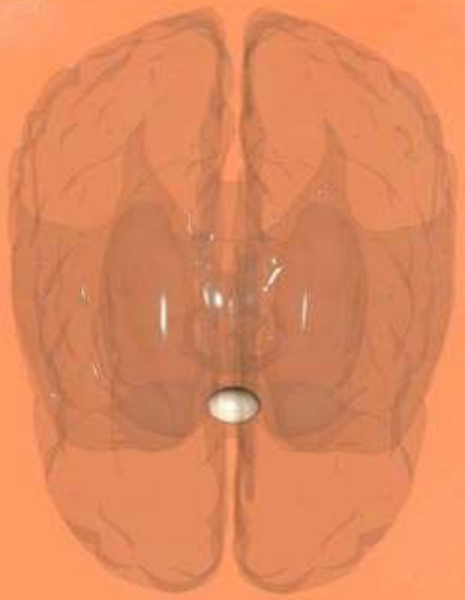
- ELISAs can be used to measure almost any protein, including hormones. This test combines the specificity of antibodies with the sensitivity of simple enzyme assays

Enzyme-Linked Immunosorbent Assay (ELISA)

The ELISA method has become widely used in clinical laboratories because

- It does not employ radioactive isotopes
- Much of the assay can be automated using 96-well plates
- It has proved to be a cost-effective and accurate method for assessing hormone levels

Pituitary and Hypothalamus Physiology



Dr. Mohammed R. Zughbur
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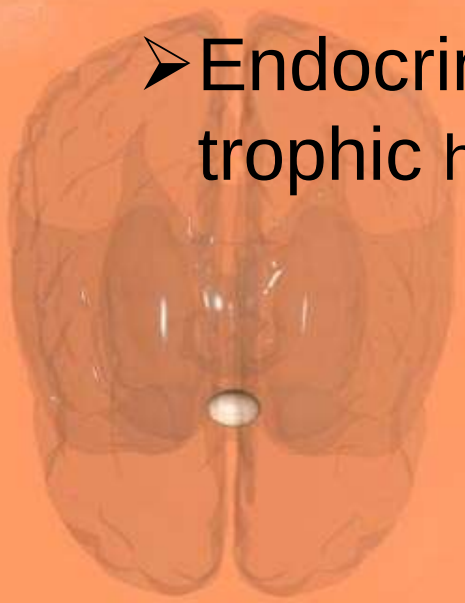
Al-Azhar University

2012

Endocrine Control: Three Levels of Integration

- Hypothalamic stimulation–from CNS
- Pituitary stimulation–from hypothalamic trophic hormones
- Endocrine gland stimulation–from pituitary trophic hormones



Functions of the Hypothalamus

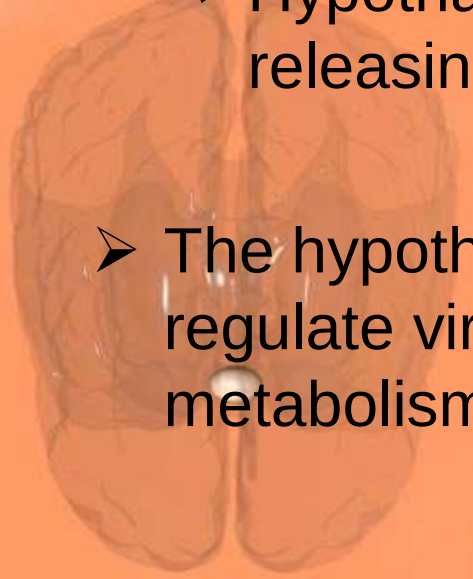
- Autonomic nervous system regulation
- Hormone production
- Endocrine regulation
- Circadian rhythm regulation
- Limbic system interaction
- Various
  - ✓ Temperature regulation
  - ✓ Feeding
    - Lateral n. induces eating
    - Ventromedial n. inhibits eating

Hypothalamu and Pituitary Gland

- The *hypothalamus* is the major integrating link between the nervous and endocrine systems.

  - ✓ Hypothalamus receives input from cortex, thalamus, limbic system & internal organs
  - ✓ Hypothalamus controls pituitary gland with 9 different releasing & inhibiting hormones

- The hypothalamus and the pituitary gland (hypophysis) regulate virtually all aspects of growth, development, metabolism, and homeostasis.



The Hypothalamus

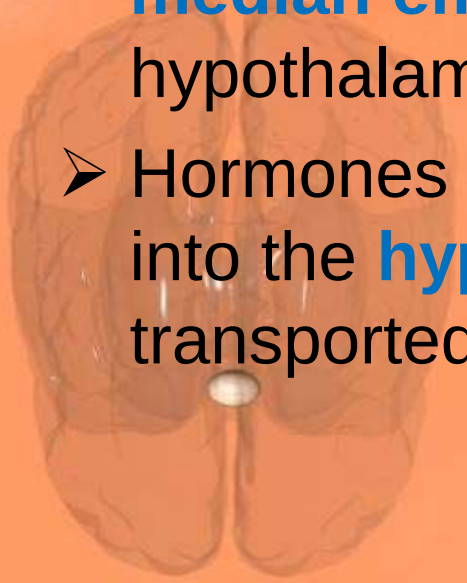
Hormonal (anterior portion) or nervous (posterior portion) control of the pituitary gland

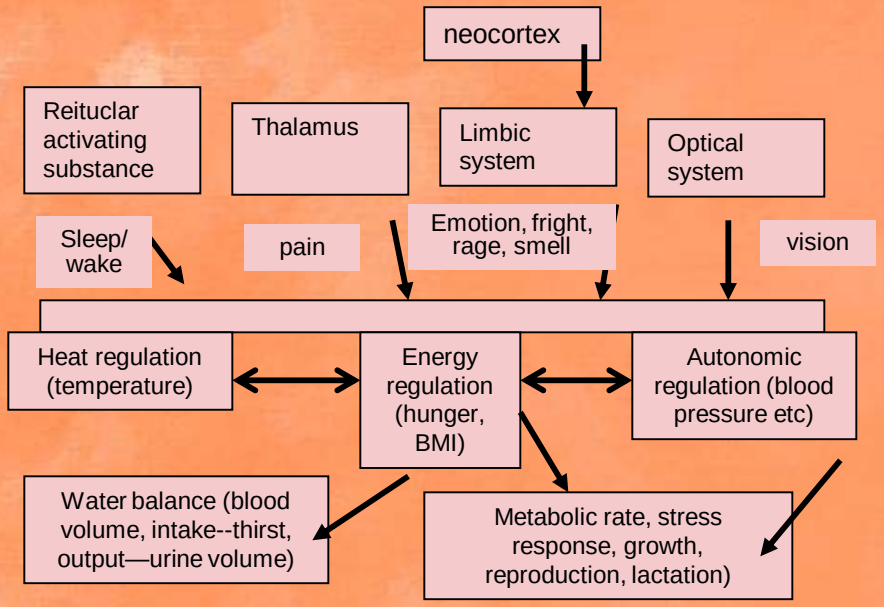
- **Hormones** – control secretion of hormones in the anterior pituitary
  - ✓ Releasing hormones (factors)
  - ✓ Inhibitory hormones (factors)

  Hormones secreted and transported to anterior pituitary through hypothalamic-hypophysial vessels to pituitary sinuses
- **Nerves** – Magnocellular neurons in the supraoptic and paraventricular nuclei of the hypothalamus – axoplasm transport of hormones from the hypothalamus to the posterior pituitary

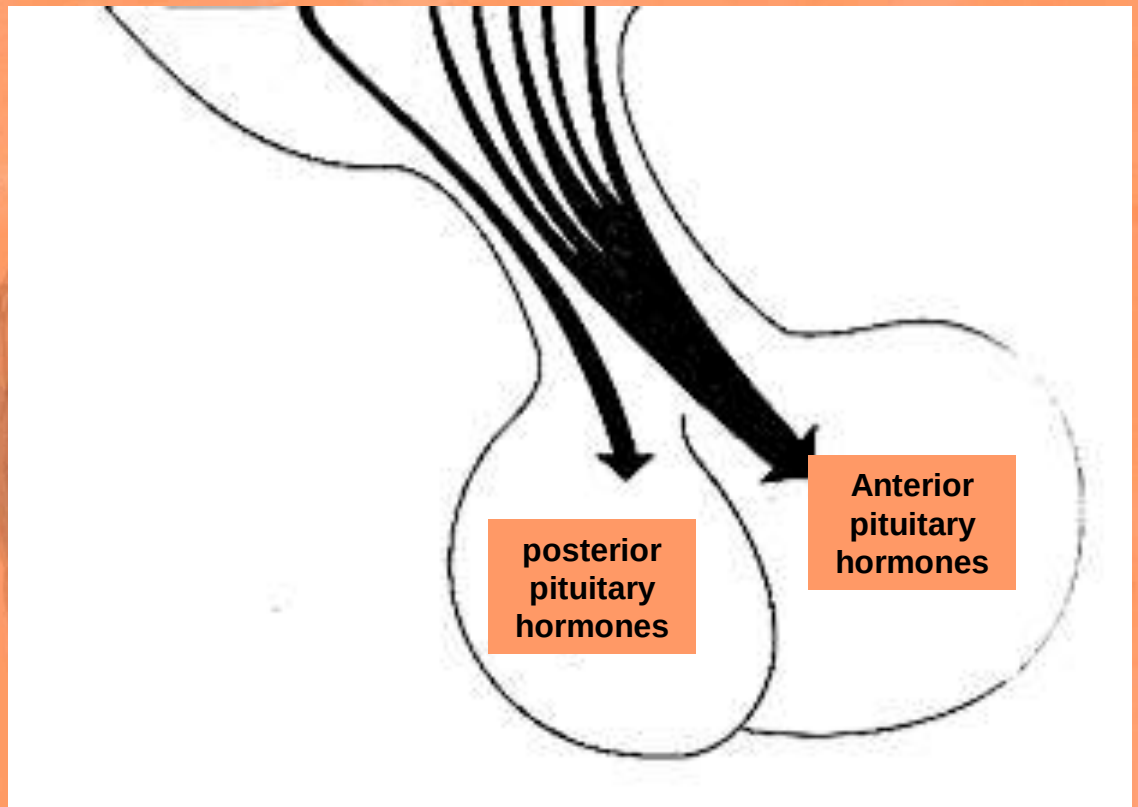
Hypothalamic-hypophysial portal system

- Special neurons in the hypothalamus synthesize and secrete the hypothalamic releasing and inhibitory hormones that control secretion of anterior pituitary
- These neurons originate in various parts of the hypothalamus and send their nerve fibers to the **median eminence** and **tuber cinerreum** (extension of hypothalamic tissue into the pituitary stalk)
- Hormones are secreted to the tissue fluids, absorbed into the **hypothalamic-hypophysial portal system** and transported to the sinuses of the anterior pituitary



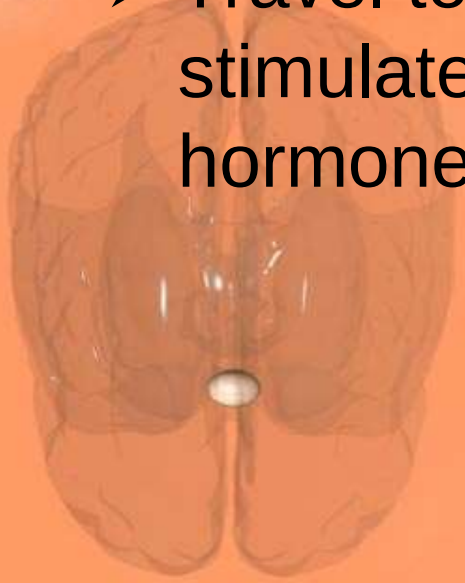


Regulation of Hypothalamus



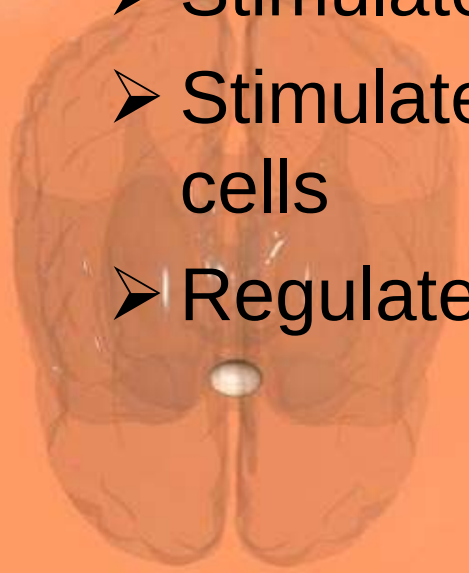
Hypothalamic releasing factors for anterior pituitary hormones

- Travel to adenohypophysis via hypophyseal-portal circulation
- Travel to specific cells in anterior pituitary to stimulate synthesis and secretion of trophic hormones



Characteristics of hypothalamic releasing hormones

- Secretion in pulses
- Act on specific membrane receptors
- Transduce signals via second messengers
- Stimulate release of stored pituitary hormones
- Stimulate synthesis of pituitary hormones
- Stimulates hyperplasia and hypertophy of target cells
- Regulates its own receptor



Hypothalamic hormones controlling anterior pituitary gland

- **Major hypothalamic releasing hormones:**
  - ✓**Thyreotropin-releasing hormone (TRH)** – causes release of thyroid stimulating hormone (TSH)
  - ✓**Corticotropin-releasing hormone (CRH)** – causes release of adrenocorticotropin hormone (ACTH)
  - ✓**Growth hormone releasing hormone (GHRH)** – causes release of growth hormone
  - ✓**Gonadotropin releasing hormone (GnRH)** – causes release of the 2 gonadotropic hormones (luteinizing and follicle-stimulating hormone)

Hypothalamic hormones controlling anterior pituitary gland

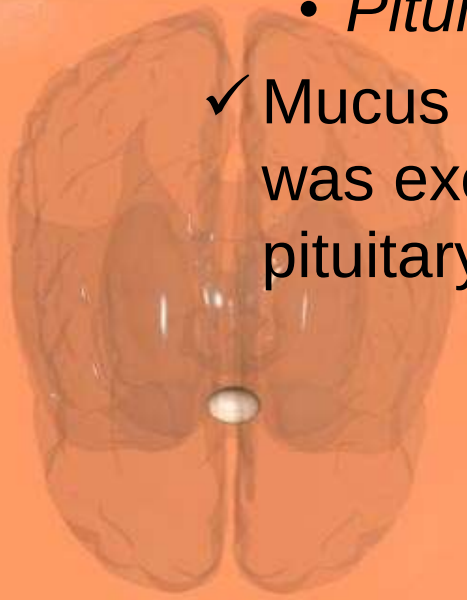
- **Major hypothalamic inhibitory hormones:**
  - ✓**Growth hormone inhibitory hormone (GHIH) = SOMATOSTATIN** – inhibits release of growth hormone
  - ✓**Prolactin inhibitory hormone (PIH)** – inhibits prolactin secretion

Hypothalamic releasing hormones

Hypothalamic releasing hormone	Effect on pituitary
Corticotropin releasing hormone (CRH)	Stimulates ACTH secretion
Thyrotropin releasing hormone (TRH)	Stimulates TSH and Prolactin secretion
Growth hormone releasing hormone (GHRH)	Stimulates GH secretion
Somatostatin	Inhibits GH (and other hormone) secretion
Gonadotropin releasing hormone (GnRH) a.k.a LHRH	Stimulates LH and FSH secretion
Prolactin releasing hormone (PRH)	Stimulates PRL secretion
Prolactin inhibiting hormone (dopamine)	Inhibits PRL secretion

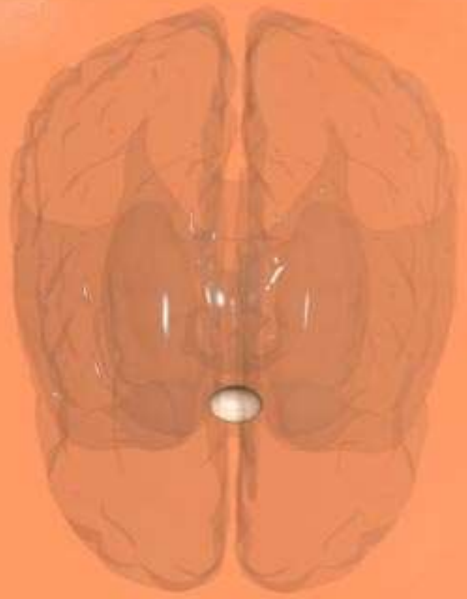
Nomenclature

- Pituitary
  - ✓ Greek
    - *ptuo* (to spit)
  - ✓ Latin
    - *Pituita* (mucus)
  - ✓ Mucus was produced by the brain and was excreted through the nose by the pituitary



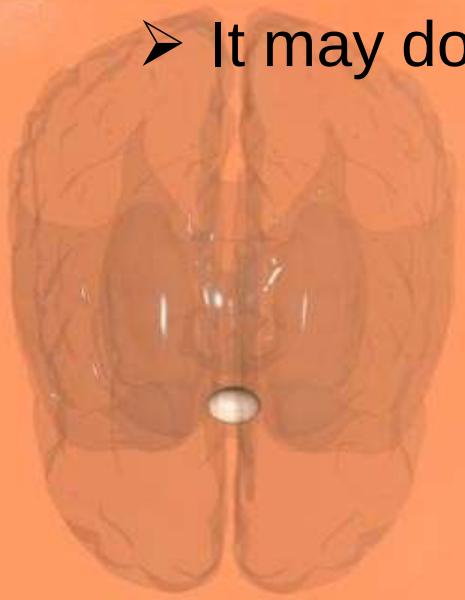
Anatomy of Pituitary Gland

- The pituitary gland is located in the sella turcica of the sphenoid bone and is differentiated into the anterior pituitary (adenohypophysis), the posterior pituitary (neurohypophysis), and pars intermedia (avascular zone in between)



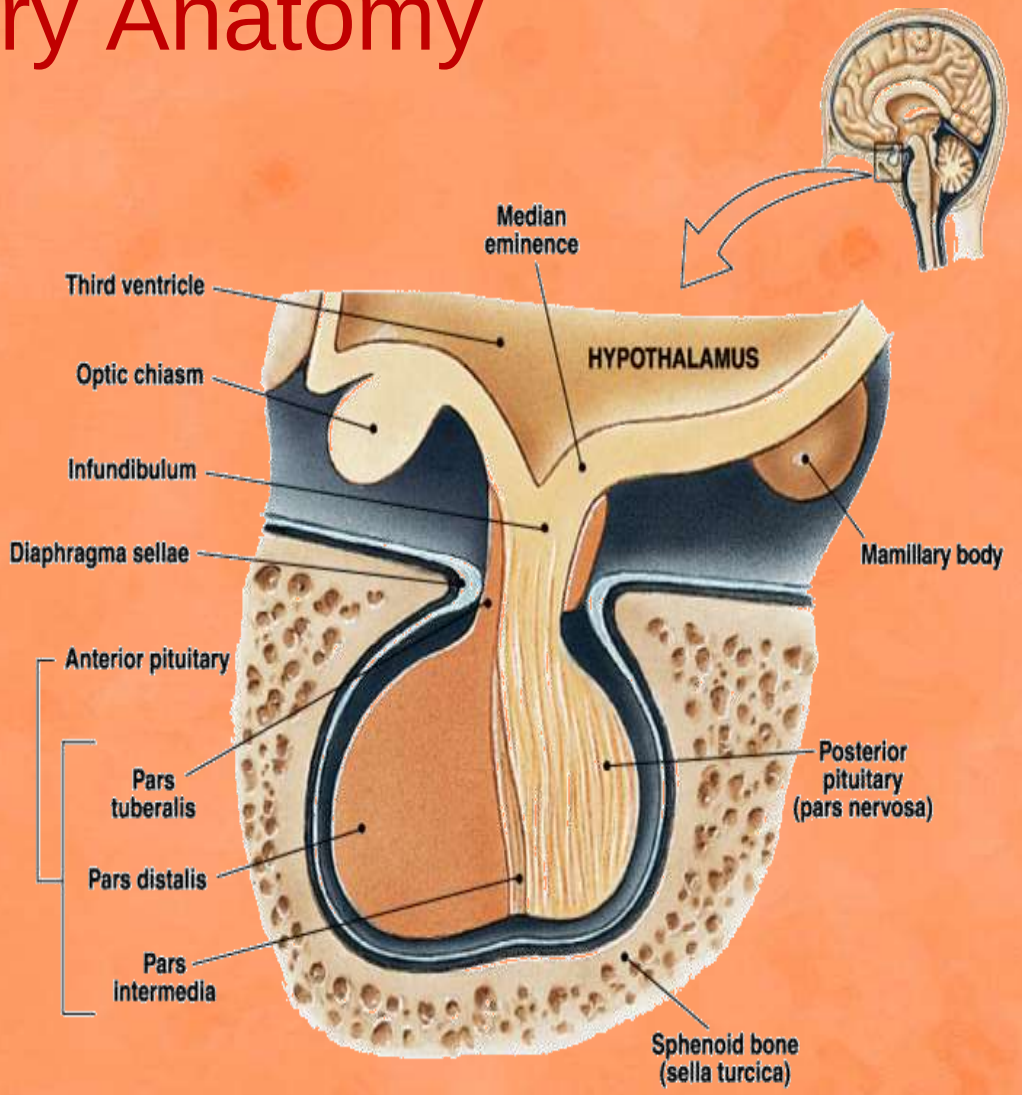
Anatomy of pituitary gland

- Pituitary gland lies in the base of the skull in a portion of sphenoid bone called sella turcica
- It consist of tow lobe anterior lobe (adenohypophysis),and posterior lobe (neurohypophysis)
- It may double in size during pregnancy

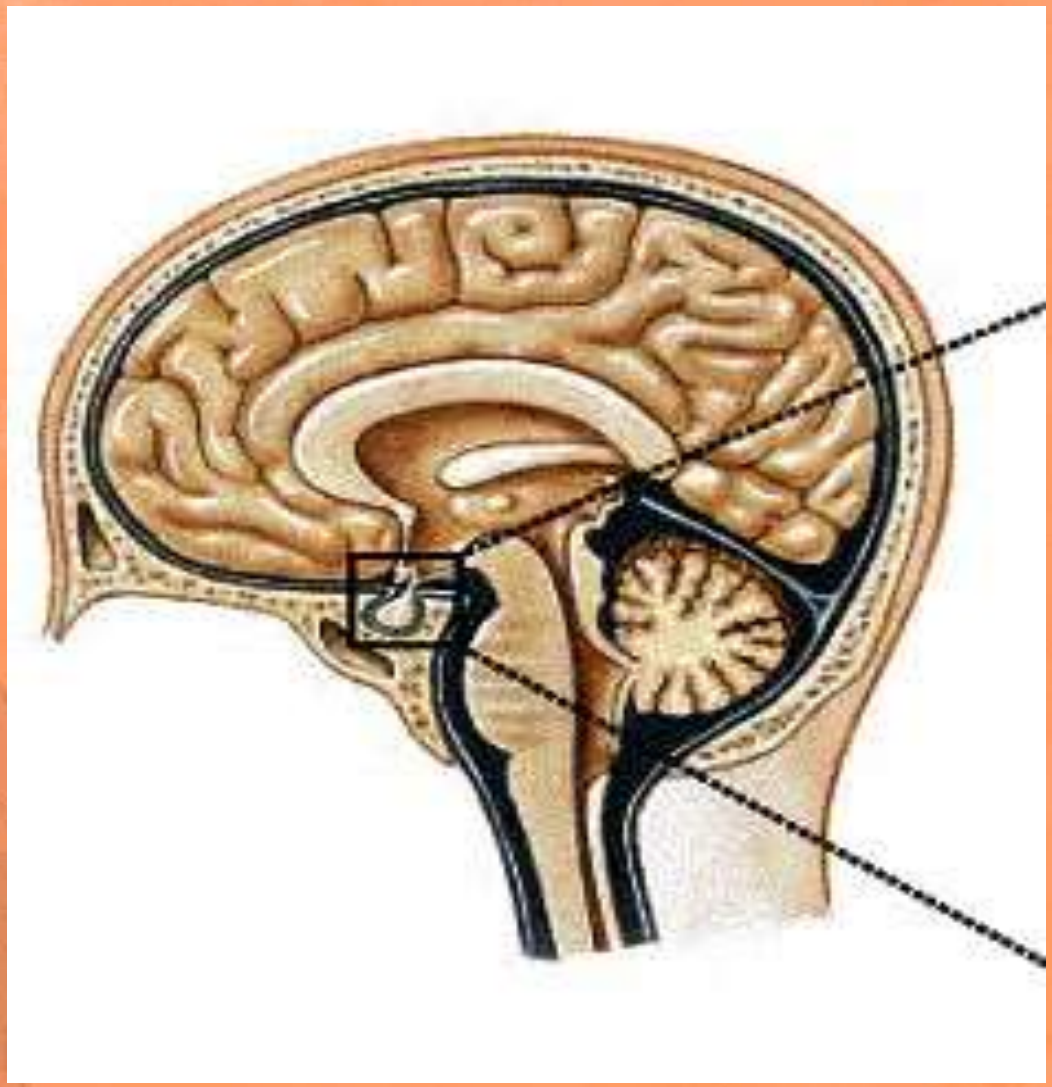


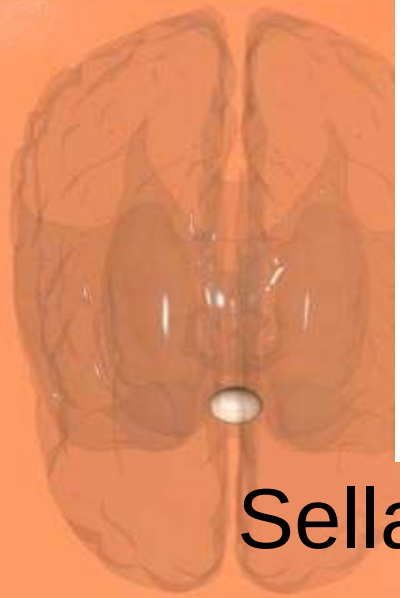
Pituitary Anatomy

- Sits in sella turcica
- Surrounded by dura
- Sphenoid
  - Lateral and inferior
- Lateral
  - Cavernous sinus
    - Internal carotid artery
    - CN III, IV, VI, V1 and V2



Location of the Pituitary

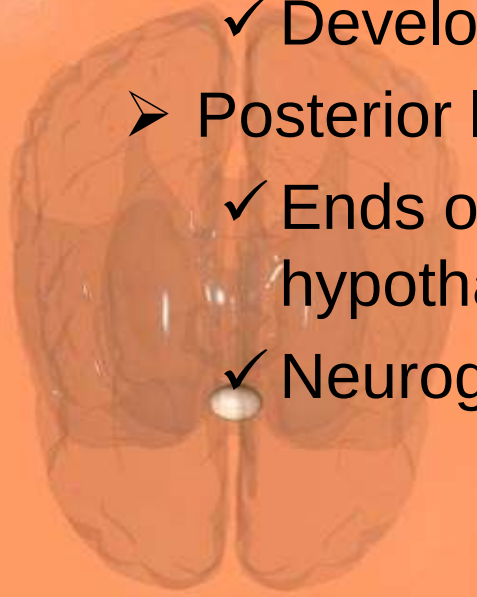




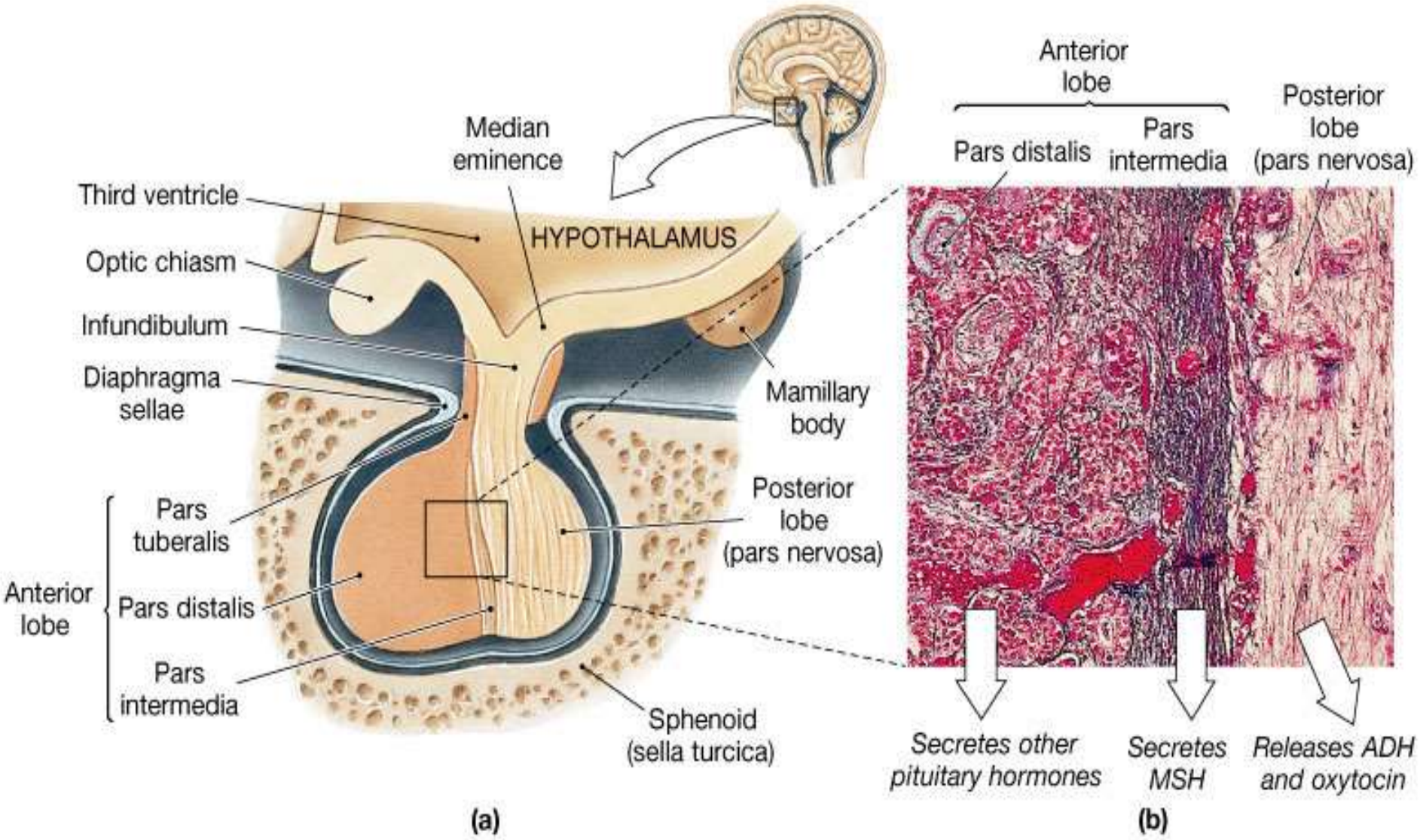
Sella turcica of the sphlenoid bone

Anatomy of Pituitary Gland

- Pea-shaped, 1/2 inch gland found in sella turcica of sphenoid
  - ✓ Infundibulum attaches it to brain
- Anterior lobe = 75 - 80%
  - ✓ Develops from roof of mouth
- Posterior lobe =20 - 25%
  - ✓ Ends of axons of 10,000 neurons found in hypothalamus
  - ✓ Neuroglial cells called pituicytes



The Anatomy and Orientation of the Pituitary Gland

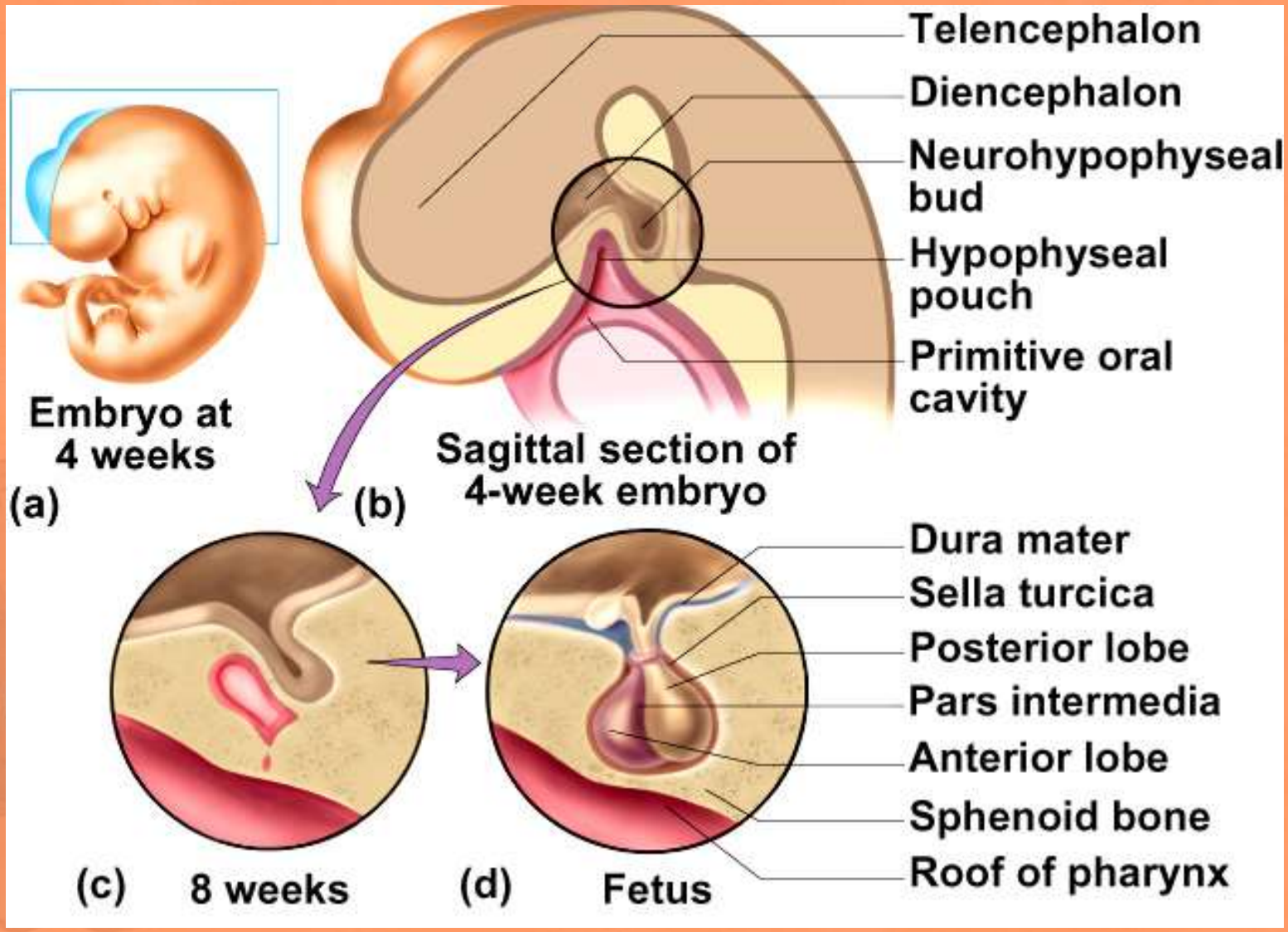


Embryology Pituitary Gland

- Anterior pituitary from *Rathke's pouch,* which is an embryonic invagination of the pharyngeal epithelium (roof of mouth, endoderm) from buccal cavity

- Posterior pituitary, Infundibulum and neural stalk from a neural tissue outgrowth from the hypothalamus(neural ectoderm) diencephalon
  - ✓Presence of large numbers of glial-type cells in this gland
- Development 3rd to the 15th week gestation

Embryonic Development of Pituitary



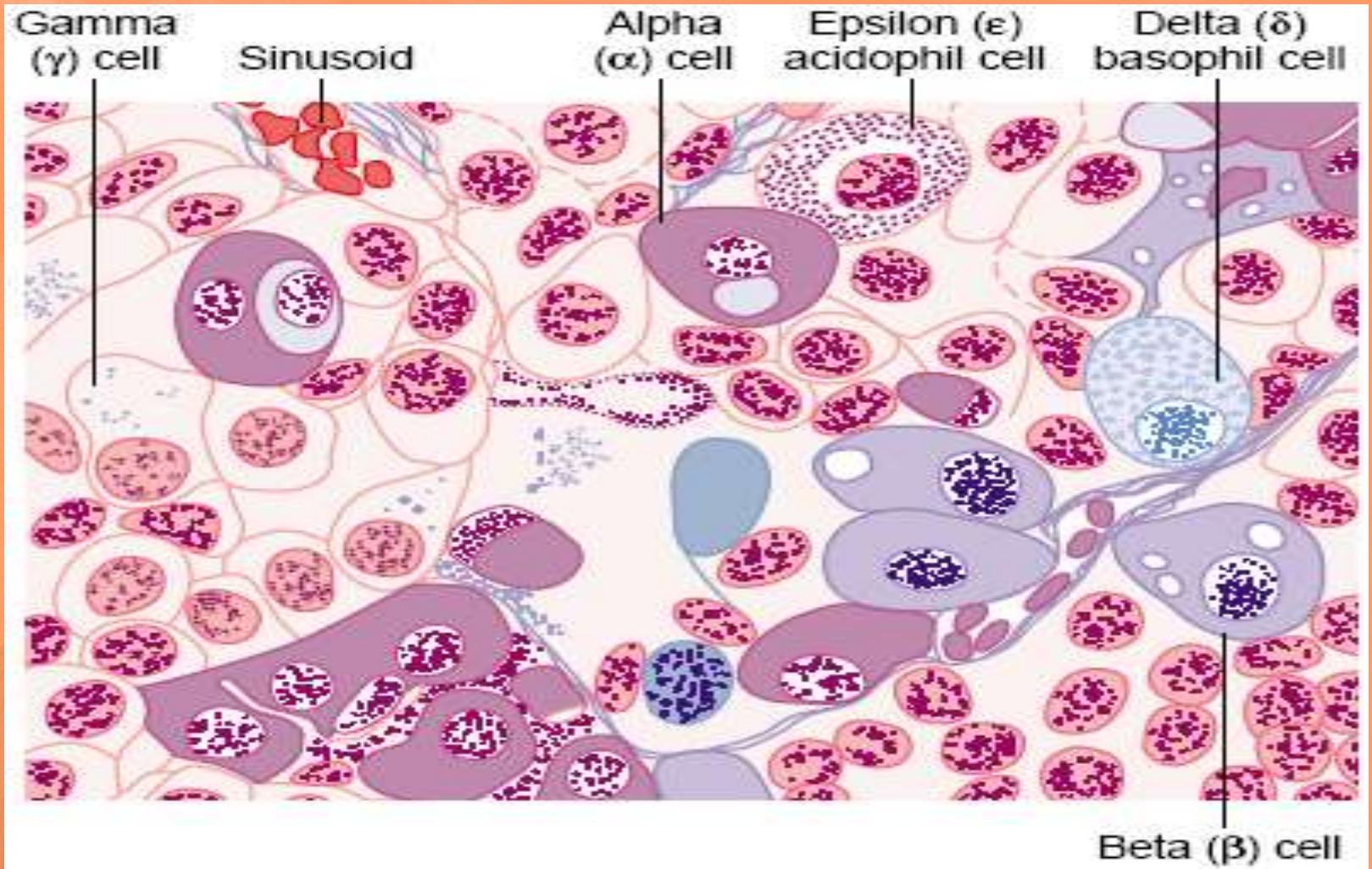
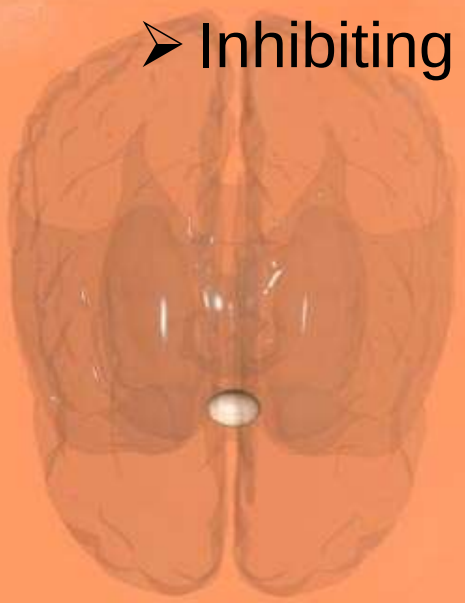


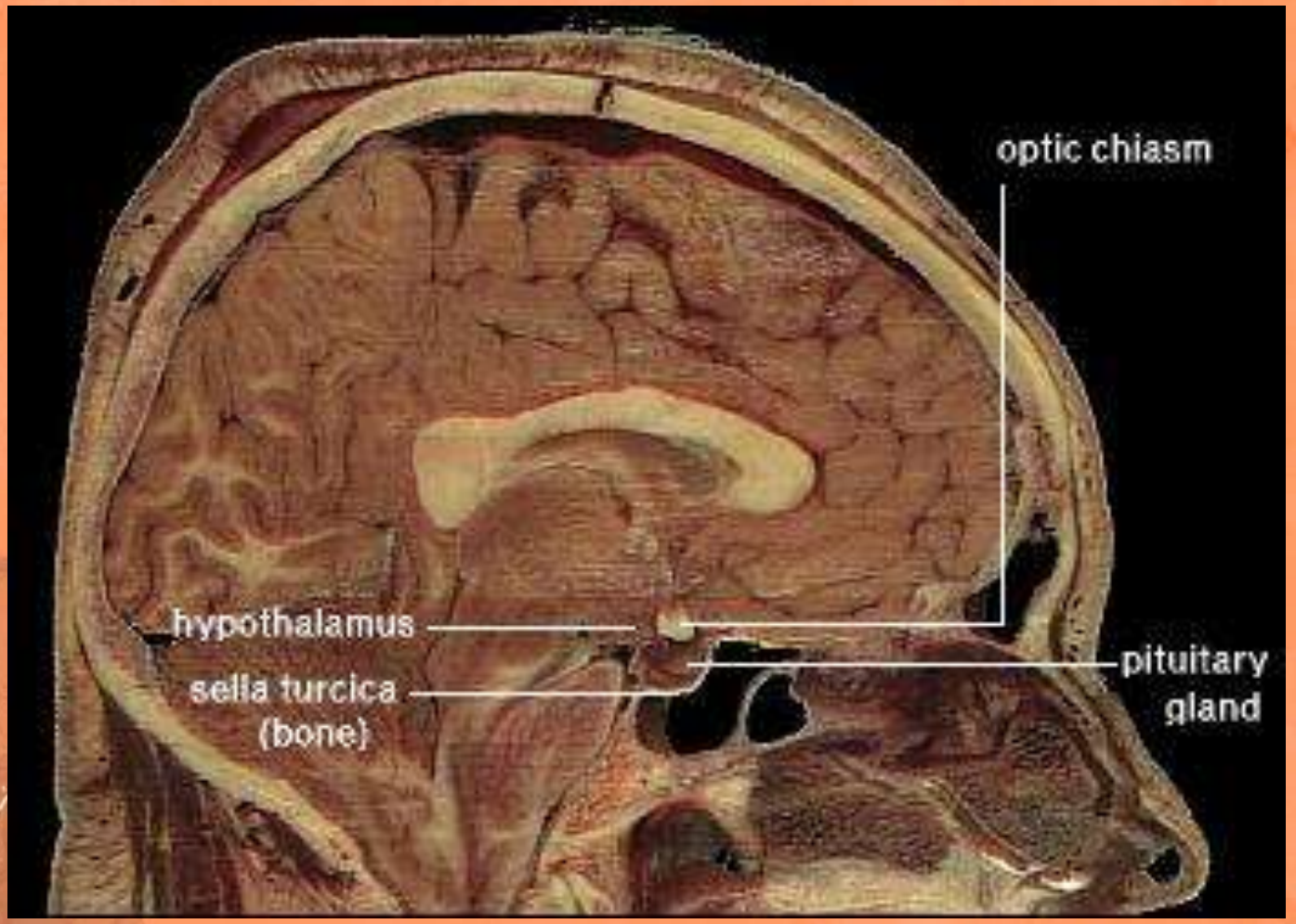
Figure 75–3

Cellular structure of the anterior pituitary gland. (Redrawn from Guyton AC: Physiology of the Human Body, 6th ed. Philadelphia: Saunders College Publishing, 1984.)

The anterior lobe (adenohypophysis)

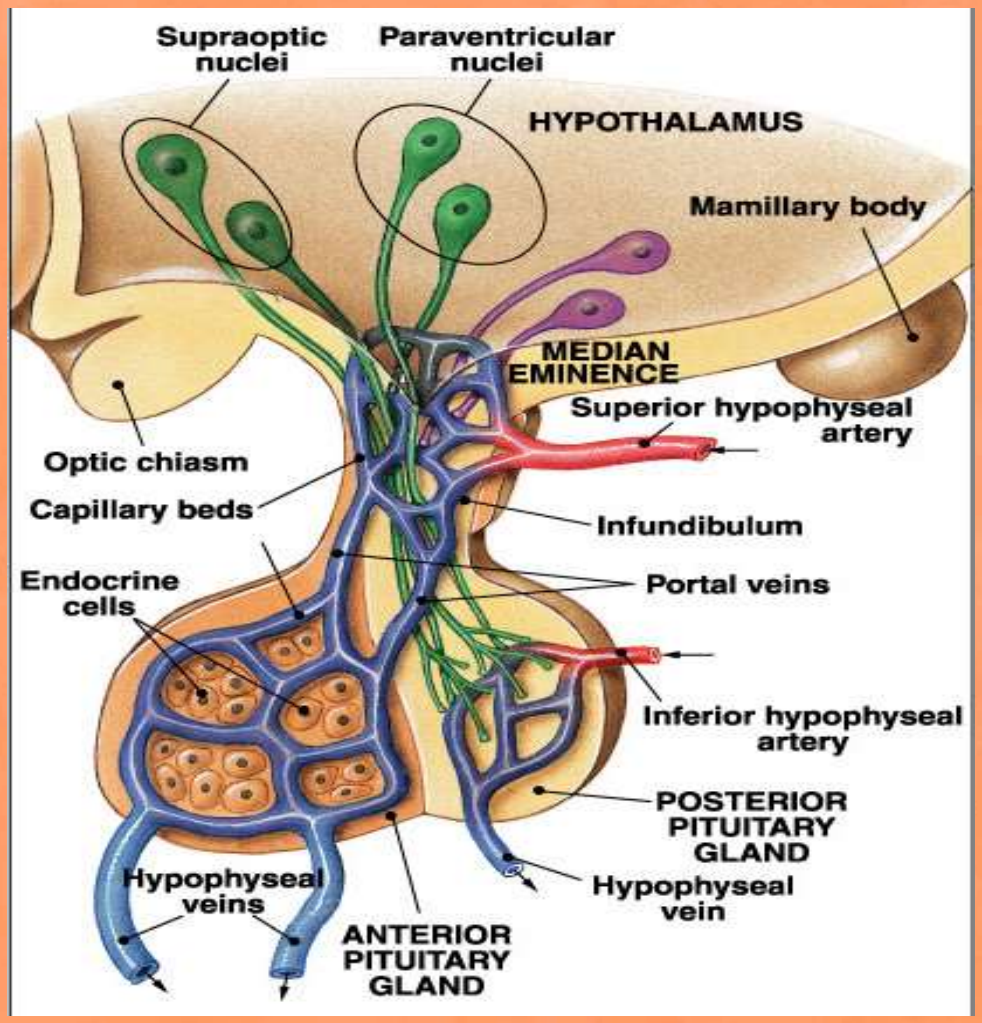
- Subdivided into the pars distalis, pars intermedia and pars tuberalis
- At the median eminence, neurons release regulatory factors through fenestrated capillaries
  - Releasing hormones
  - Inhibiting hormones



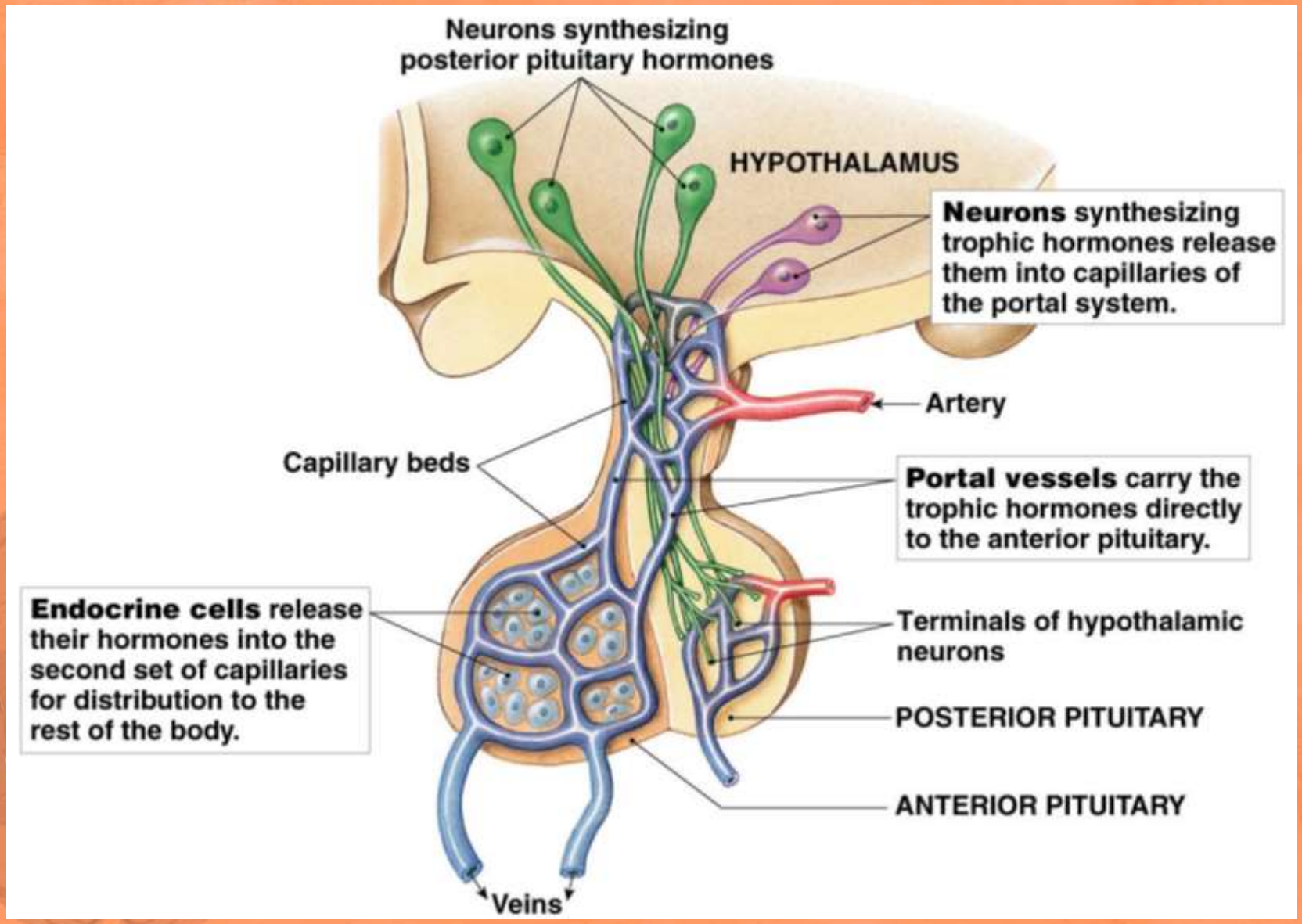

optic chiasm
hypothalamus
sella turcica
(bone)
pituitary
gland

Portal SystemPituitary

- Hypophyseal arteries
  - From carotid
  - Superior
    - ✓80-90% to adenophysis
  - Inferior
    - ✓Posterior pituitary
- Posterior lobe
  - ✓Rich nerve supply
  - ✓Unmyelinated nerves



The Hypothalamic-Hypophyseal Portal



Hypothalamic-Hypophysial Portal Blood Vessels of the Anterior Pituitary Gland

"**Superior hypophysial artery**"

↓

1st capillary network
(at the median eminence)

↓

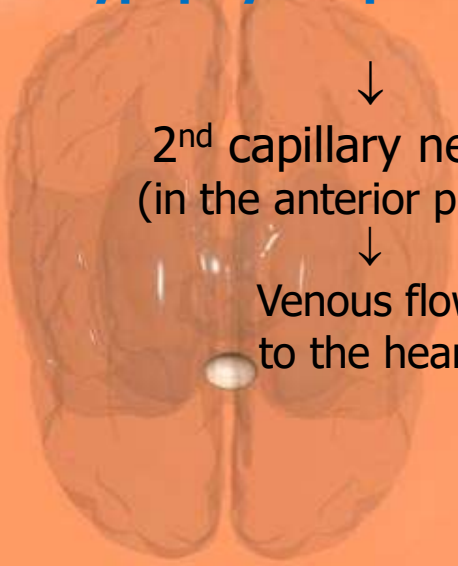
"**Hypophysial portal vessels**"

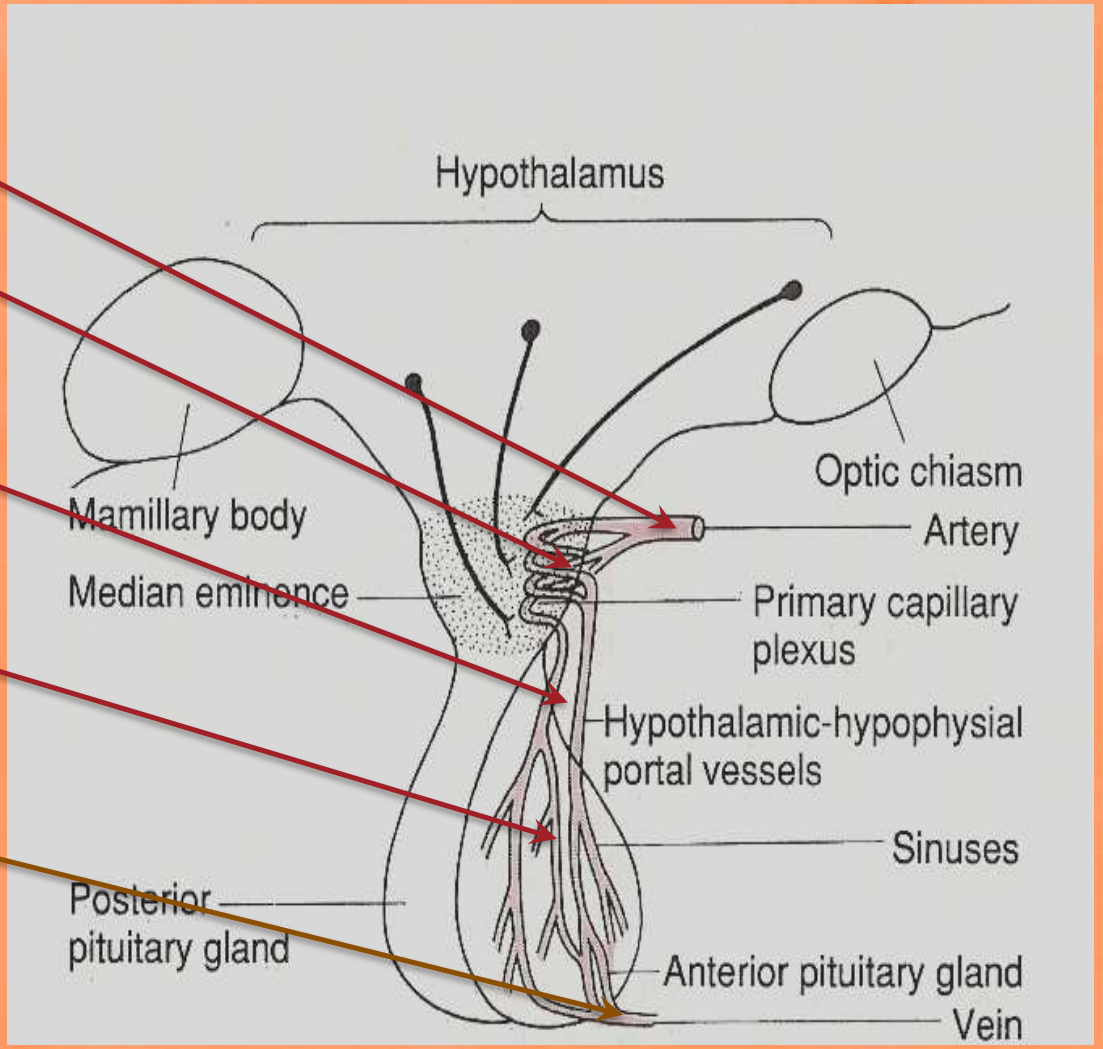
↓

2nd capillary network
(in the anterior pituitary)

↓

Venous flow
to the heart





Anterior Pituitary (adenohypophysis)

releasing vs inhibiting factors

hypophyseal portal system

↓

superior hypophyseal arteries

↓

primary plexus of capillaries

↓

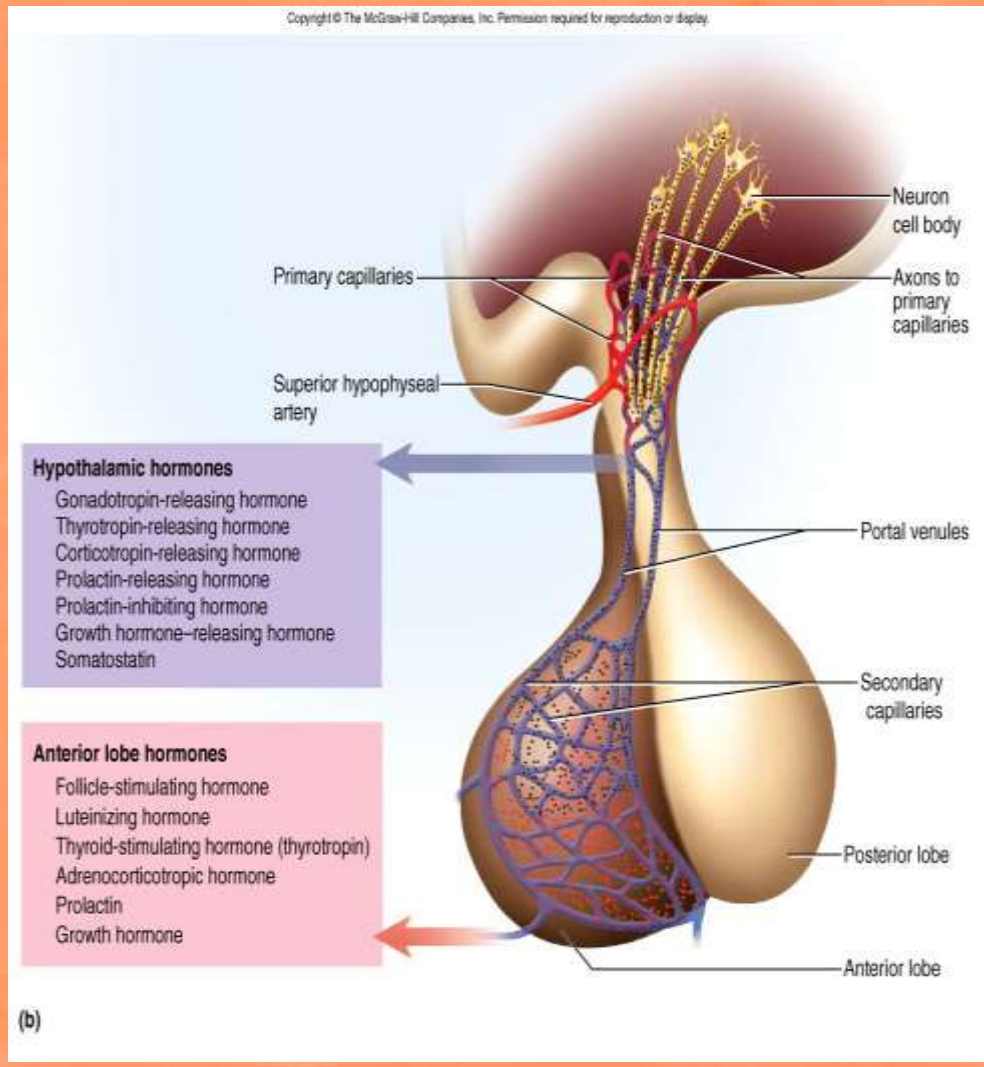
hypophyseal veins

↓

secondary plexus of capillaries

↓

anterior hypophyseal veins



Cell types in the anterior pituitary

- **Chromophobes** – mostly inactive cells with only few secretory granules
- **Chromophils** – active secretory cells
  - **Acidophils** (stained with acidic dyes)
  - **Basophils** (stained with basic dyes)

Cell type	Hormones secreted	% of total secretory cells	Stain affinity	Diameter of secretory granules (nm)
Somatotrope	hGH	40-50	Acidophilic	300-400
Lactotrope	Prolactin	10-30	Acidophilic	200
Corticotrope	ACTH	10	Basophilic	400-550
Thyrotrope	TSH	5	Basophilic	120-200
Gonadotrope	FSH, LH	20	Basophilic	250-400

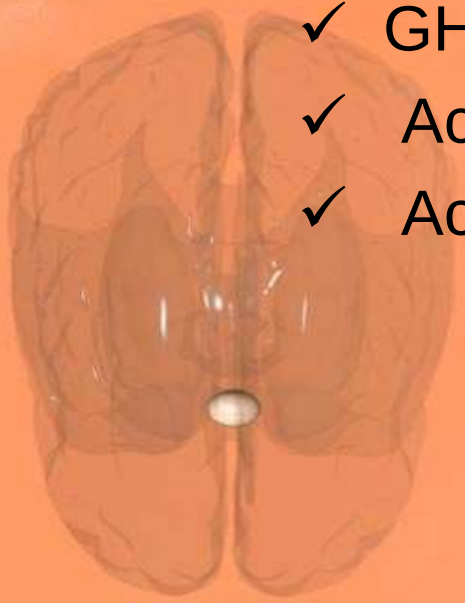
Hormone	Structure	Amino acids/Source	
Polypeptide/proteins			
ACTH	Polypeptide	39	Corticotroph
GH	Protein	191	Somatotroph
PRL	Protein	199	Lactotroph
Glycoproteins			
TSH	Alpha* / TSH-beta	110	Thyrotroph
LH	Alpha / LH-beta	115	Gonadotroph
FSH	Alpha / FSH-beta	115	Gonadotroph

* 92 amino acids

Histology of Pituitary Gland

Now with immunocytochemical and electron microscopic techniques,classified cells by their secretary products

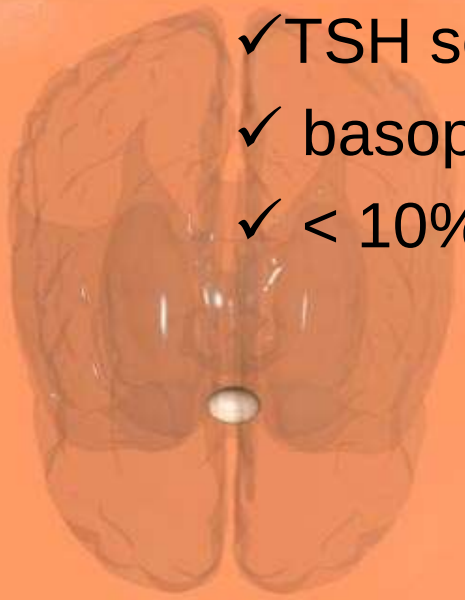
- Somatotrophs cells



  - ✓ GH secreting cells
  - ✓ Account about 40-50% of anterior pituitary gland
  - ✓ Acidophilic stained

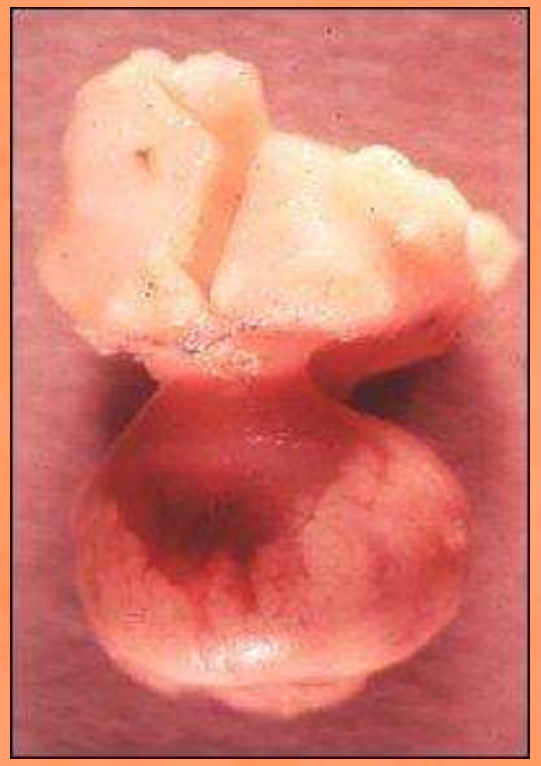
Histology of Pituitary Gland

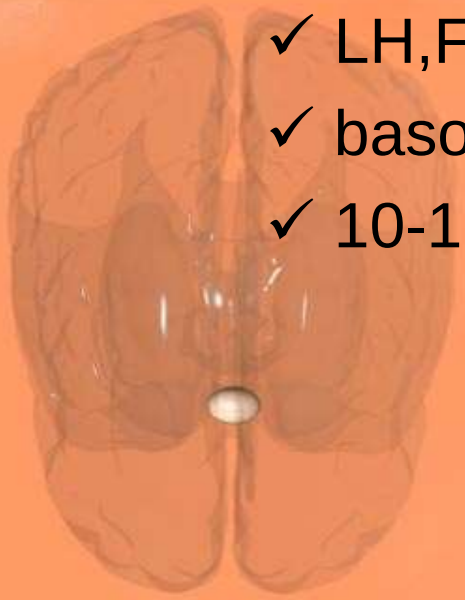
- Lactotrophic
  - ✓ Prolactin secreting cells
  - ✓ acidophilic stained
  - ✓ 10-15% of anterior pituitary gland
- Thyrotrophis
  - ✓TSH secreting cells
  - ✓ basophilic cells
  - ✓ < 10% of anterior pituitary gland



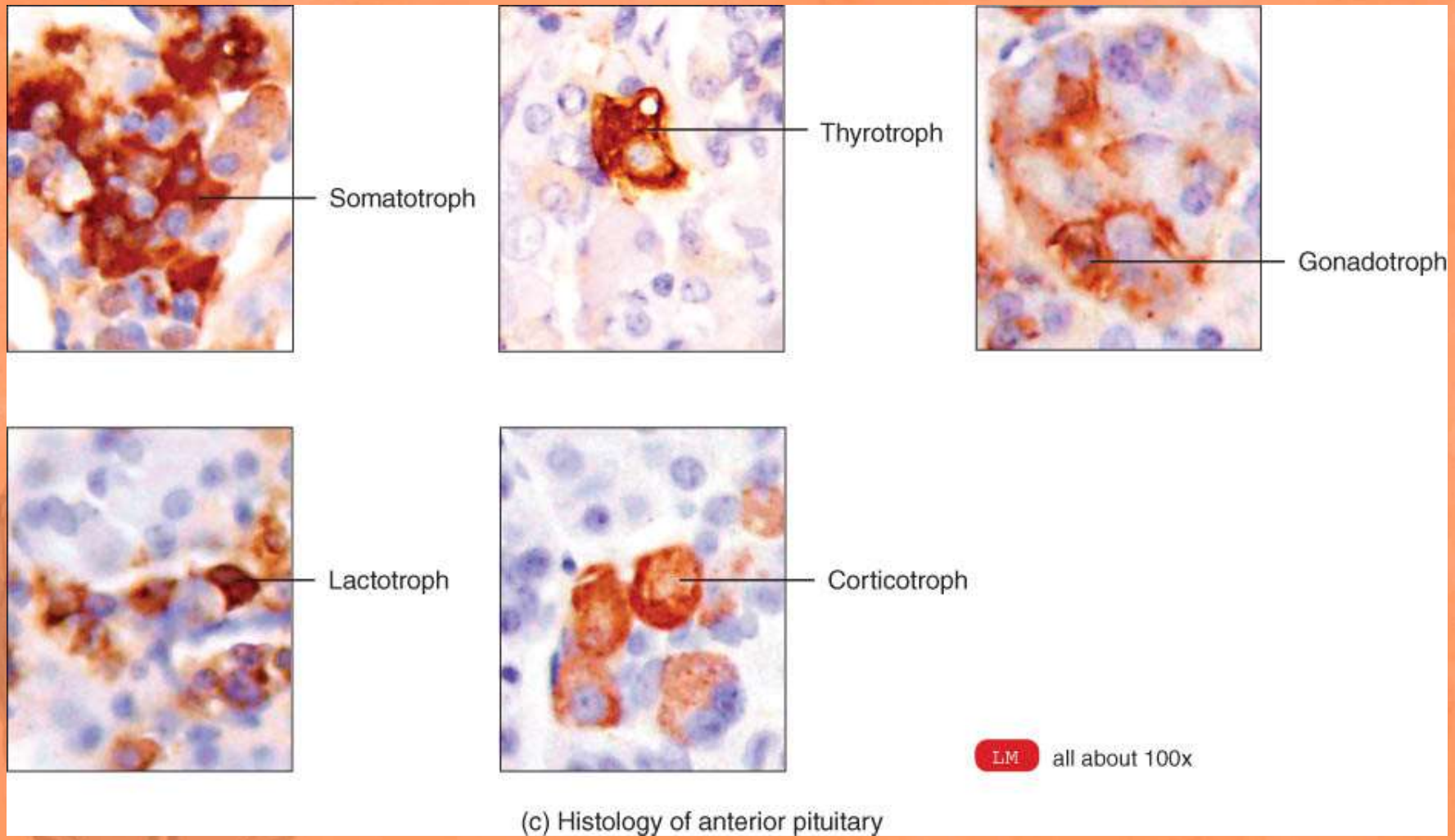
Histology of Pituitary Gland

- Corticotrophs
  - ✓ ACTH secretary cells
  - ✓ basophilic cells
  - ✓ 15-20% of anterior pituitary gland
- Gonadotrophs
  - ✓ LH,FSH secretary cells
  - ✓ basophilic staining
  - ✓ 10-15% of anterior pituitary gland





Anterior Pituitary



(c) Histology of anterior pituitary

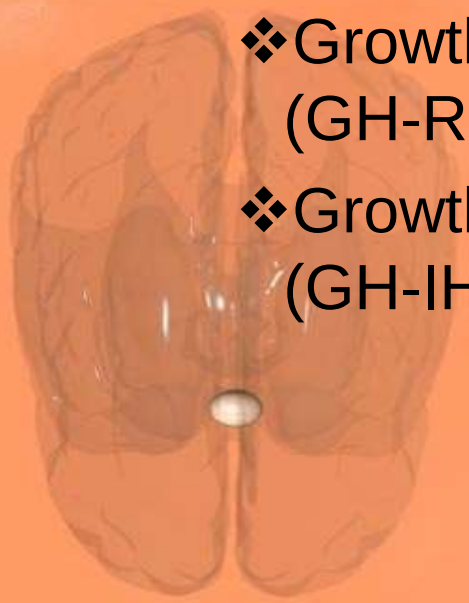
Anterior pituitary cells and hormones

Cell type	Pituitary population	Product	Target
Corticotroph	15-20%	ACTH β-lipotropin	Adrenal gland Adipocytes Melanocytes
Thyrotroph	3-5%	TSH	Thyroid gland
Gonadotroph	10-15%	LH, FSH	Gonads
Somatotroph	40-50%	GH	All tissues, liver
Lactotroph	10-15%	PRL	Breasts gonads

Cells	Hormone Produced	Target Tissues and Functions
Somatotrophs	Human growth hormone (hGH)	hGH stimulates general body growth and regulates metabolism
Thyrotrophs	Thyroid-stimulating hormone (TSH)	TSH stimulates thyroid gland to secrete its hormones
Gonadotrophs	Follicle-stimulating hormone (FSH)	FSH stimulates sperm production by testes FSH stimulates production of oocytes and secretion of estrogens by ovaries
	Luteinizing hormone (LH)	LH stimulates testosterone by testes LH stimulates secretion of estrogens by ovaries, ovulation, formation of corpus luteum, and secretion of progesterone by corpus luteum
Lactotrophs	Prolactin (PRL)	PRL initiates milk production in suitably prepared mammary glands
Corticotrophs	Adrenocorticotropic hormone (ACTH)	ACTH stimulates adrenal cortex to secrete glucocorticoids
	Melanocyte-stimulating hormone (MSH)	Excessive MSH increases skin pigmentation

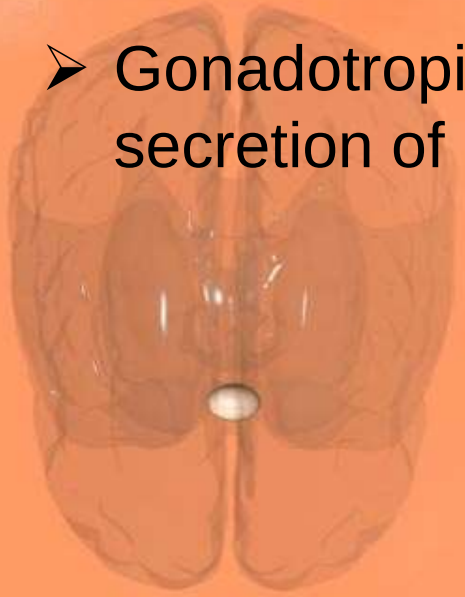
Hormones of the adenohypophysis

- Prolactin (PR)
  - ✓ Stimulates the development of mammary glands and milk production
- Growth hormone (GH or somatotropin)
  - ✓ Stimulates cell growth and replication through release of somatomedins or IGF
    - ❖ Growth-hormone releasing hormone (GH-RH)
    - ❖ Growth-hormone inhibiting hormone (GH-IH)



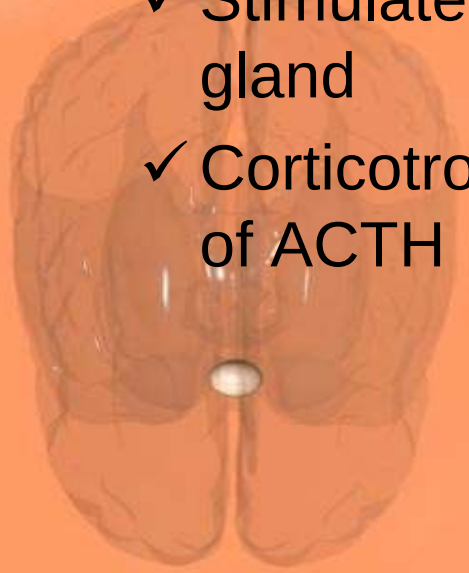
Hormones of the adenohypophysis

- Follicle stimulating hormone (FSH)
  - ✓ Stimulates follicle development and estrogen secretion in females and sperm production in males
- Leutinizing hormone (LH)
  - ✓ Causes ovulation and progestin production in females and androgen production in males
- Gonadotropin releasing hormone (GNRH) promotes the secretion of FSH and LH



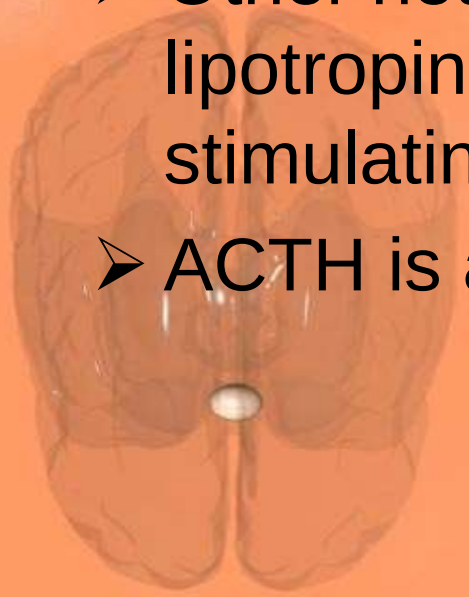
Hormones of the adenohypophysis

- Thyroid stimulating hormone (TSH)
  - ✓ Triggers the release of thyroid hormones
  - ✓ Thyrotropin releasing hormone promotes the release of TSH
- Adrenocorticotropic hormone (ACTH)
  - ✓ Stimulates the release of glucocorticoids by the adrenal gland
  - ✓ Corticotrophin releasing hormone causes the secretion of ACTH



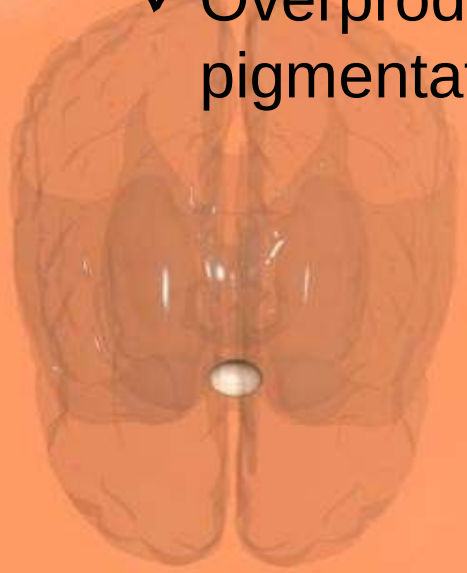
Adrenocorticotropic Hormone (ACTH) : synthesis and regulation of secretion

- Produced in corticotrophs
- ACTH is produced in the anterior pituitary by proteolytic processing of Prepro-opiomelanocortin (POMC).
- Other neuropeptide products include β and γ lipotropin, β-endorphin, and α-melanocyte-stimulating hormone (α-MSH).
- ACTH is a key regulator of the stress response



Adrenocorticotropic Hormone

- ACTH is made up of 39 amino acids
  - ✓ Regulates adrenal cortex and synthesis of adrenocorticosteroids
  - ✓ α-MSH resides in first 13 AA of ACTH
  - ✓ α-MSH stimulates melanocytes and can darken skin
  - ✓ Overproduction of ACTH may accompany increased pigmentation due to α-MSH.



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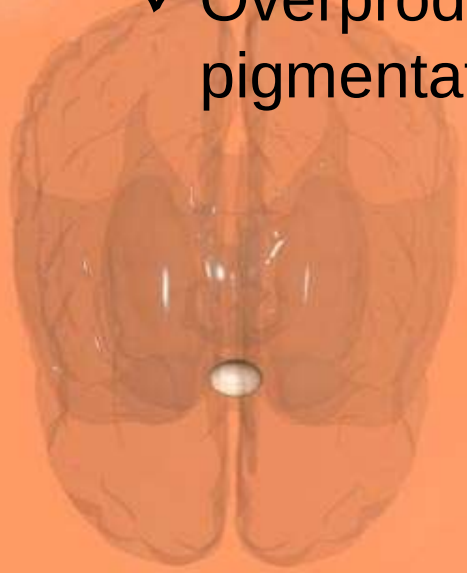
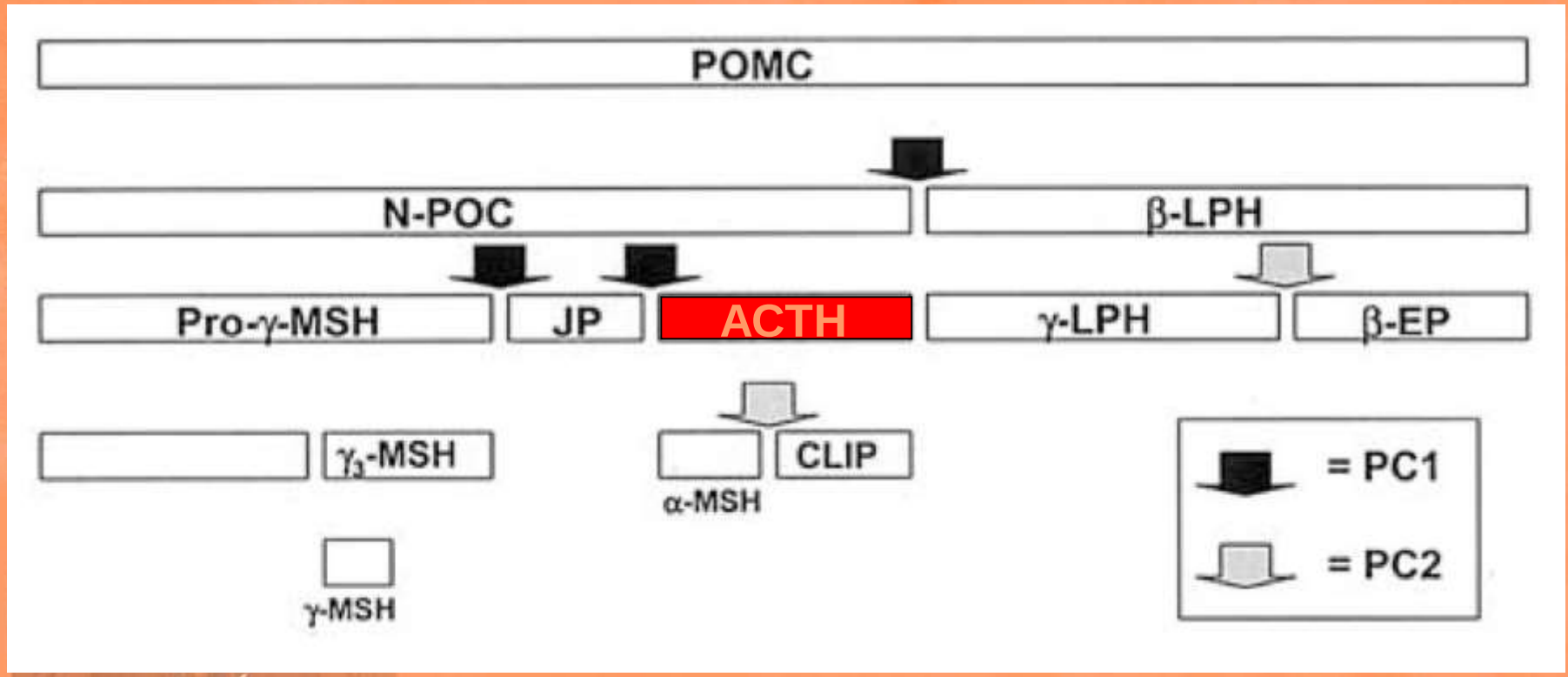


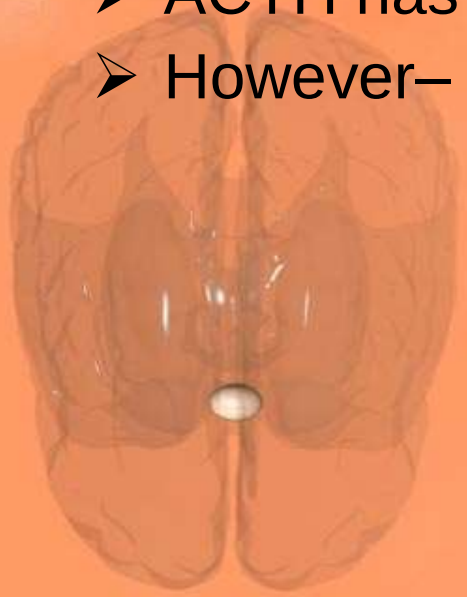
Adrenocorticotropic Hormone Synthesis



Processing and cleavage of pro-opiomelanocortin (POMC)

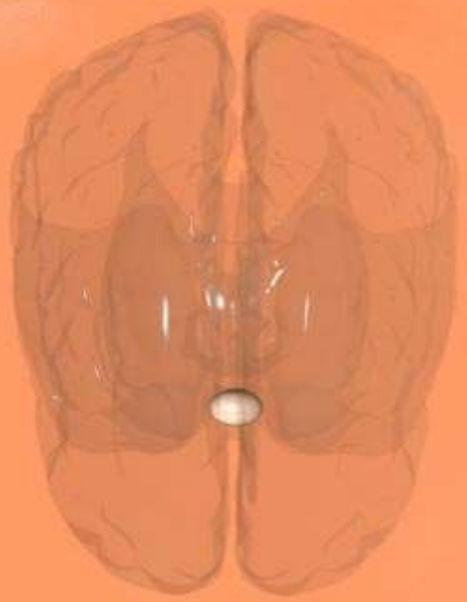
Melanocyte-stimulating hormone (MSH)

- MSH peptides derived by proteolytic cleavage of POMC
- α-MSH has antipyretic and anti-inflammatory effects
  - ✓ Also inhibits CRH and LHRH secretion
- Four MSH receptors identified
- May inhibit feeding behavior
- ACTH has MSH-like activity
- However– MSH has NO ACTH like activity



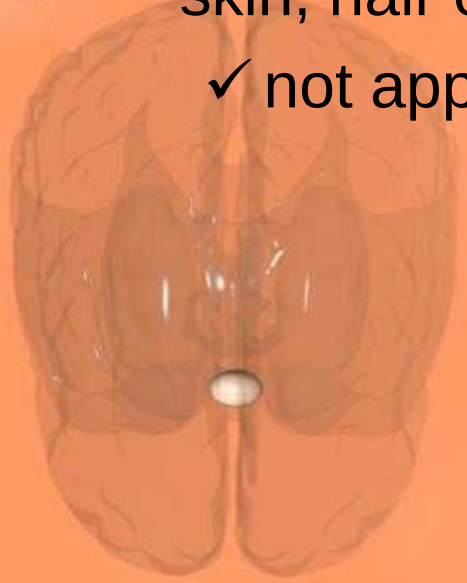
Melanocyte Stimulating Hormone (MSH)

- May be secreted by the pars intermedia during fetal development, early childhood, pregnancy or certain diseases
- Stimulates melanocytes to produce melanin



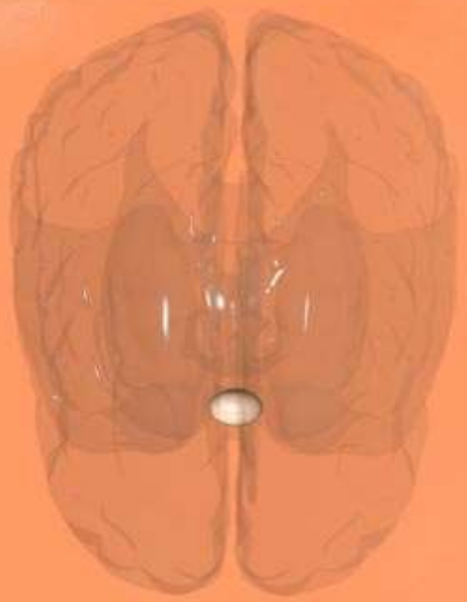
Pituitary Hormones - Pars Intermedia

- Absent from adult human although present in fetus
- Reminant cells
  - ✓ produce POMC (pro-opiomelanocortin) which is processed into ACTH and endorphins
- Produces MSH in animals influencing pigmentation of skin, hair or feathers
  - ✓ not apparently present/functioning in humans

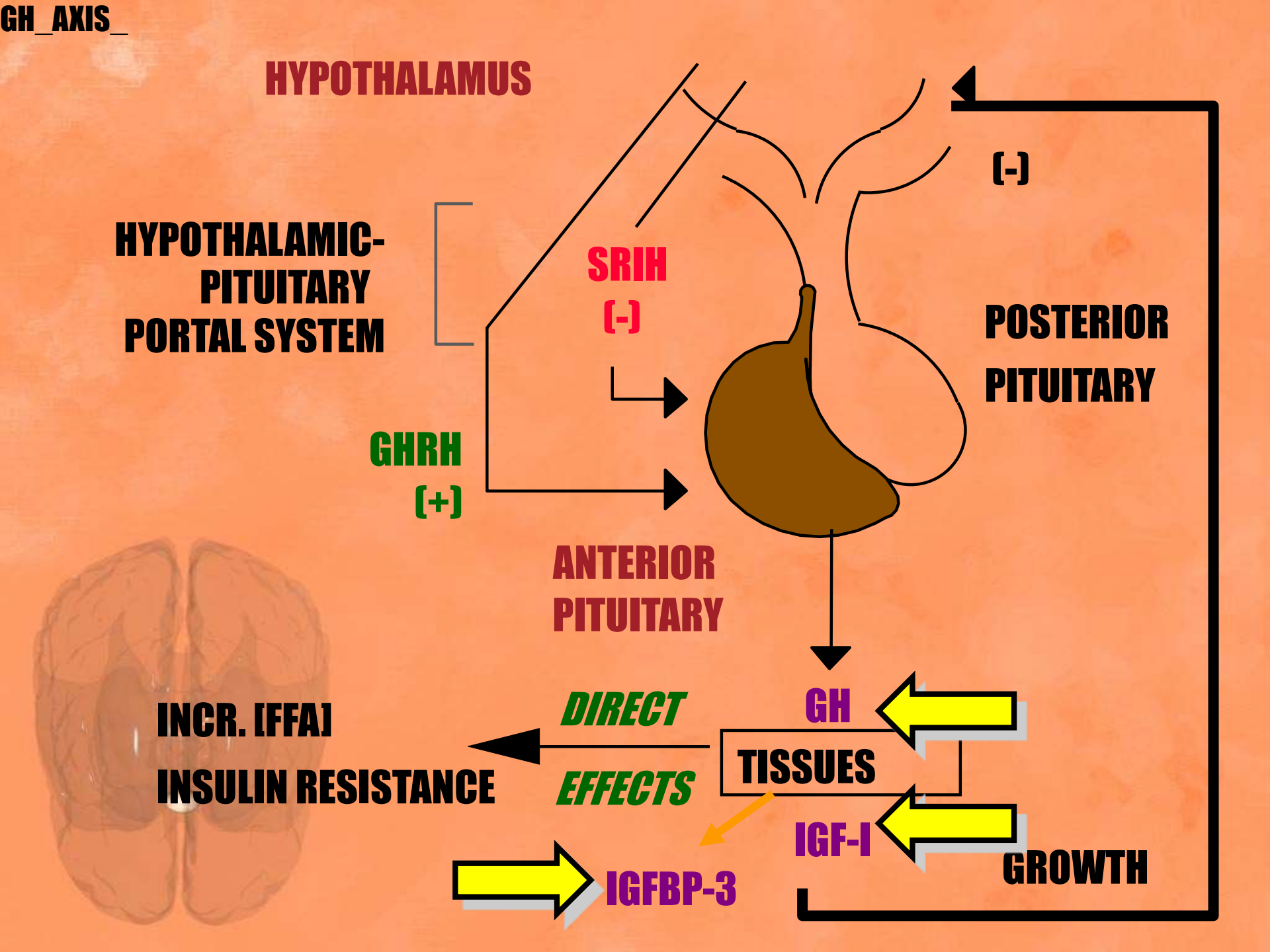


Feedback

- Secretion of anterior pituitary gland hormones is regulated by hypothalamic regulating hormones and by negative feedback mechanisms



GH_AXIS_


HYPOTHALAMUS
(-)
HYPOTHALAMIC-
PITUITARY
PORTAL SYSTEM
SRIH
(-)
POSTERIOR
PITUITARY
GHRH
(+)
ANTERIOR
PITUITARY
INCR. [FFA]
INSULIN RESISTANCE
DIRECT
EFFECTS
GH
TISSUES
IGF-I
GROWTH
IGFBP-3

HYPOTHALAMUS

(-)

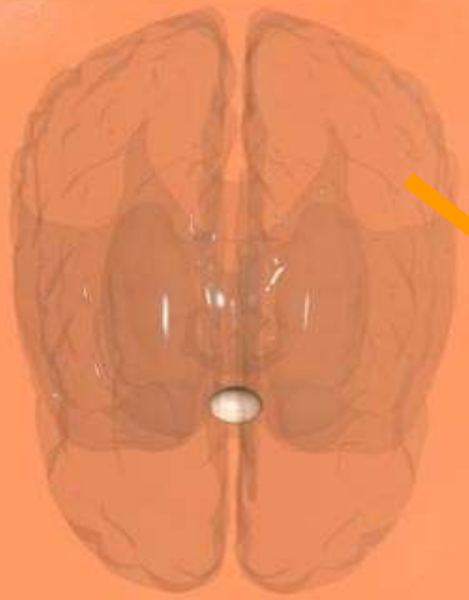
HYPOTHALAMIC-
PITUITARY
PORTAL SYSTEM

(-)

CRH
(+)

POSTERIOR
PITUITARY

ANTERIOR
PITUITARY



ACTH

ADRENAL Fasiculata

CORTISOL

HYPOTHALAMUS

HYPOTHALAMIC-
PITUITARY
PORTAL SYSTEM

(-)

(-)

TRH
(+)

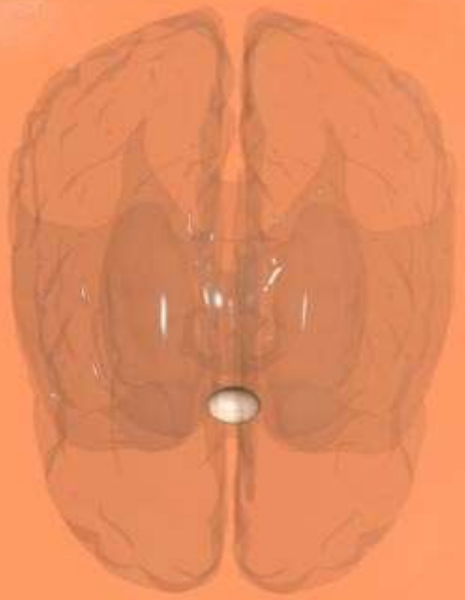
ANTERIOR
PITUITARY

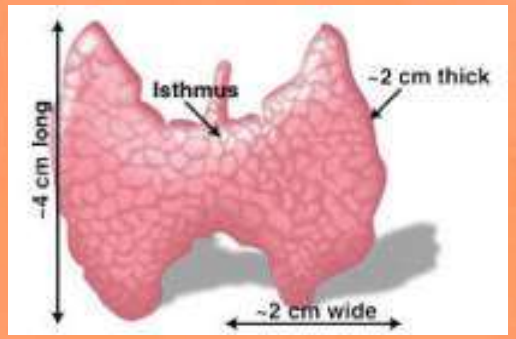
POSTERIOR
PITUITARY

TSH

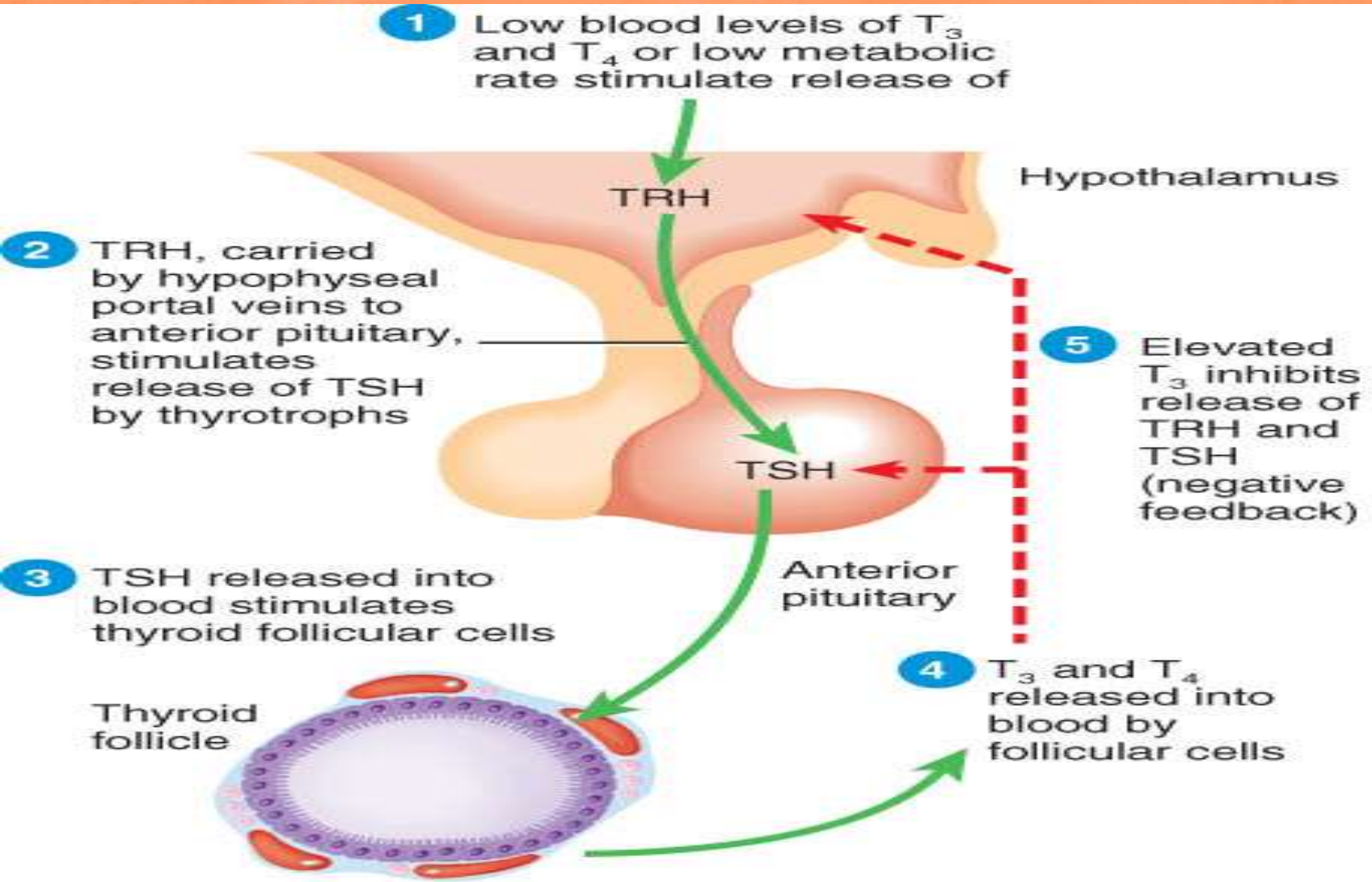
THYROID GLAND

T4, T3 (T4 --> T3)





Negative Feedback Systems



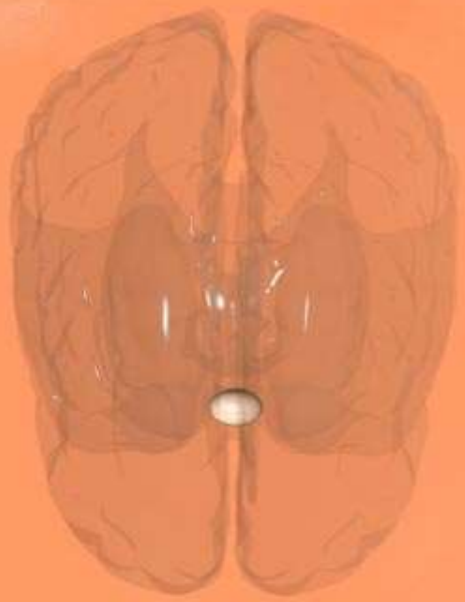
Actions of Thyroid Hormones:

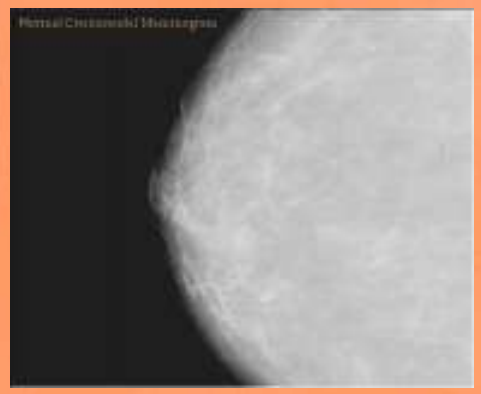
HYPOTHALAMUS

PRIH
(DOPAMINE)
(-)

ANTERIOR
PITUITARY

POSTERIOR
PITUITARY





PRL

BREAST

HYPOTHALAMUS

(-)

HYPOTHALAMIC-
PITUITARY
PORTAL SYSTEM

GnRH
(LHRH)
(+)

(-)

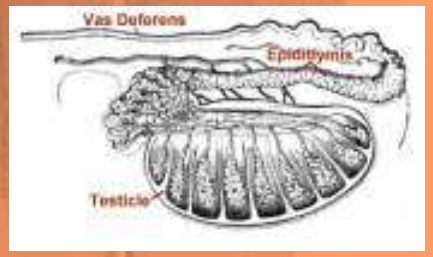
POSTERIOR
PITUITARY

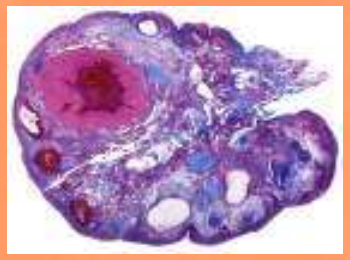
ANTERIOR
PITUITARY

LH, FSH

GONAD

SEX HORMONES, INHIBIN



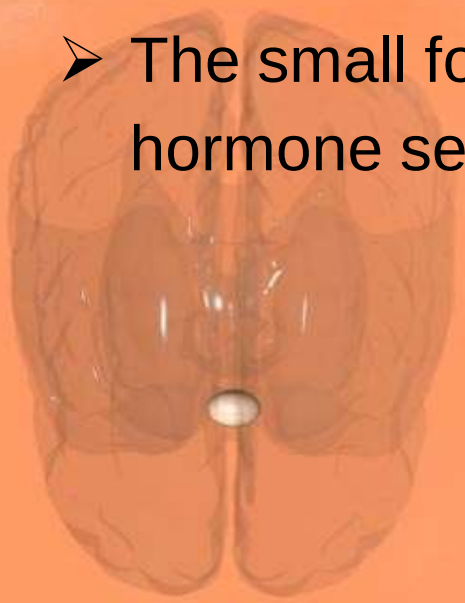


Lacotrophs

- Site of production of prolactin
- Lactogenesis (milk synthesis) requires prolactin
- Tonically inhibited
  - ✓ Of the anterior pituitary hormones, the only one
  - ✓ Multifactoral control, balance favors inhibition
- Dopamine inhibits prolactin
- Prolactin releasing hormone is TRH
  - ✓ Oxcytocin also stimulates prolactin release
  - ✓ Estradiol enhances prolactin synthesis

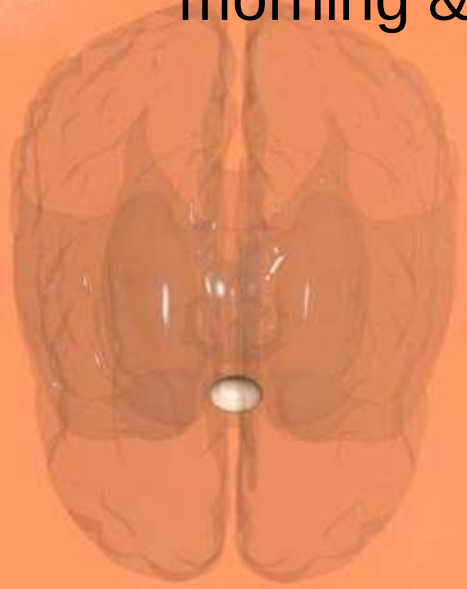
Prolactin

- Is a polypeptide hormone containing 198 amino acids and having a molecular weight of 22,000 daltons
- It circulates in different molecular sizes—a **(small)** form (mol wt 22,000), a **(big)** form (mol wt 50,000), and an even larger **(big-big)** form (mol wt >100,000)
- The small form is biologically active, and about 80% of the hormone secreted is in this form



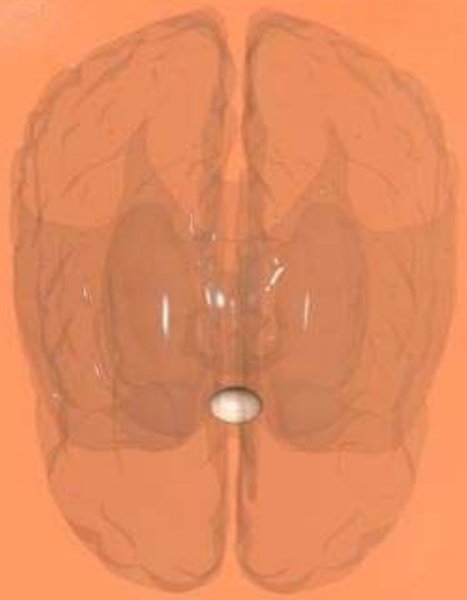
Prolactin

- Discovered by Sticker 1928 (Veterinarian)
- It is one of the stress hormones
- It has a short half-life (20 min)
- Sleep-related circadian rhythm , highest in the early morning & lower in the afternoon



Prolactin

- Stimulates breast development and lactogenesis
- May be involved in development of Leydig cells in pre-pubertal males
- Immunomodulatory effects– stimulates T cell functions
  - ✓ Prolactin receptors in thymus

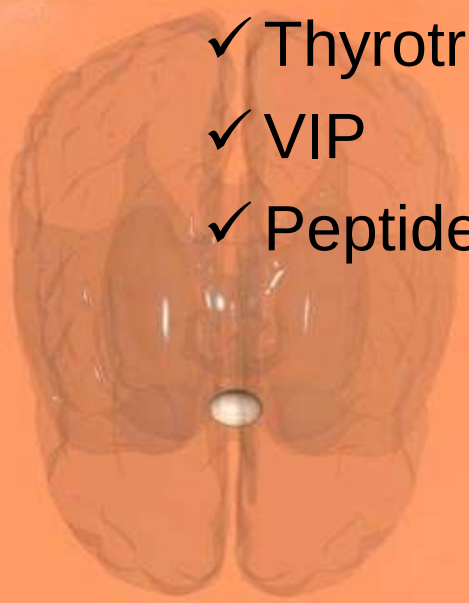


Prolactin

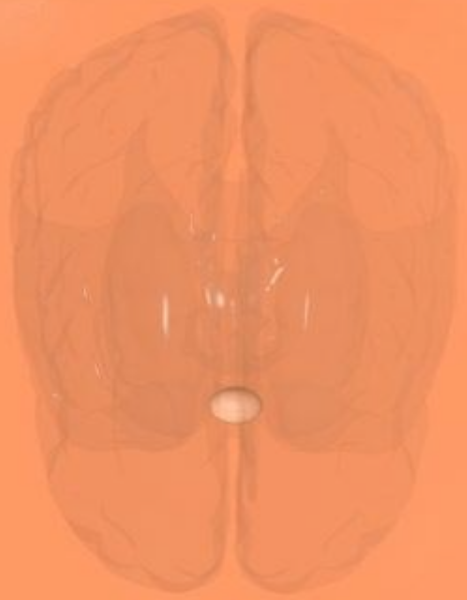
- Secreted in a pulsatile fashion
- Its primary function is to enhance breast development during pregnancy and to induce lactation
- However, prolactin also binds to specific receptors in the *gonads, lymphoid cells, and liver*

Neuroendocrine Regulation of Prolactin Secretion

- PIF
  - ✓ Dopamine
  - ✓ Gonadotropin-associated peptide (GAP)
  - ✓ Gamma aminobutyric acid (GABA)
- Prolactin releasing factors (PRF)
  - ✓ Thyrotropin releasing hormone
  - ✓ VIP
  - ✓ Peptide histidine methionine (PHM)



Growth hormone



Growth hormone

- Growth hormone, also called somatotropic hormone or somatotropin, is a small protein molecule that contains 191 amino acids in a **single chain** and has a molecular weight of 22,005. **It causes growth of almost all tissues of the body that are capable of growing.**
  - ✓It promotes increased sizes of the cells
  - ✓Increased mitosis, with development of greater numbers of cells
  - ✓Specific differentiation of certain types of cells such as bone growth cells and early muscle cells

Regulation of GH secretion

- The plasma concentration of GH changes with age. 5 – 20 years old, 6ng/ml; 20 – 40 years old, 3ng/ml; 40 –70 years old, 1.6ng/ml.
- Growth hormone is released in **pulsatile** fashion
- The change of GH concentration within one day.

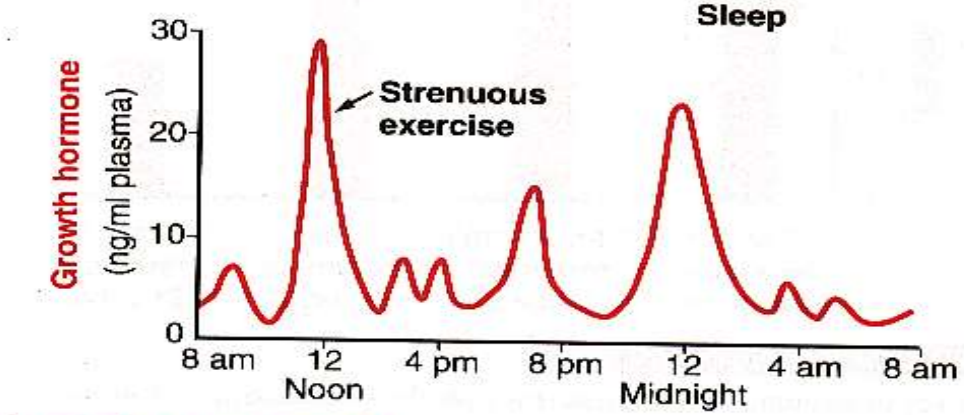


FIGURE 75 – 6

Typical variations in growth hormone secretion throughout the day, demonstrating the especially powerful effect of strenuous exercise and also the high rate of growth hormone secretion that occurs during the first few hours of deep sleep.

Functions of growth hormone

Promotion of growth

- ✓ ↑ cellular sizes & ↑ mitosis (no.).
- ✓ ↑ tissue growth & organ size.
- ✓ Does not act directly on bone & cartilage.

Depends on somatomedin C ('insulin– like growth factor I' [IGF-I] secreted by the liver, which is responsible for effect of GH on bone & cartilage growth.

GH → liver → produces peptides → bone & cartilage growth & development
(somatomedins)

Growth Hormone Has Metabolic Effects

- Growth hormone has multiple specific metabolic effects, including
  - ➢ Increased rate of protein synthesis in most cells of the body
  - ➢ Increased mobilization of fatty acids from adipose tissue, increased free fatty acids in the blood, and increased use of fatty acids for energy
  - ➢ Decreased rate of glucose utilization throughout the body
  - ✓ Growth hormone enhances body protein, uses up fat stores, and conserves carbohydrates

Functions of growth hormone

Short- term metabolic effects

1. **Protein metabolism:** Anabolic,
   ↑ rate of protein synthesis in all cells.

2. **Fat metabolism:** Catabolic,
   ↑ mobilization of FFAs from adipose tissue stores to provide energy.

3. **CHO metabolism:** Hyperglycemic,
   ↓ rate of glucose utilization throughout the body, & ↓ glucose uptake by cells.

Thus, GH enhances body protein, uses up fat stores, & conserves carbohydrates

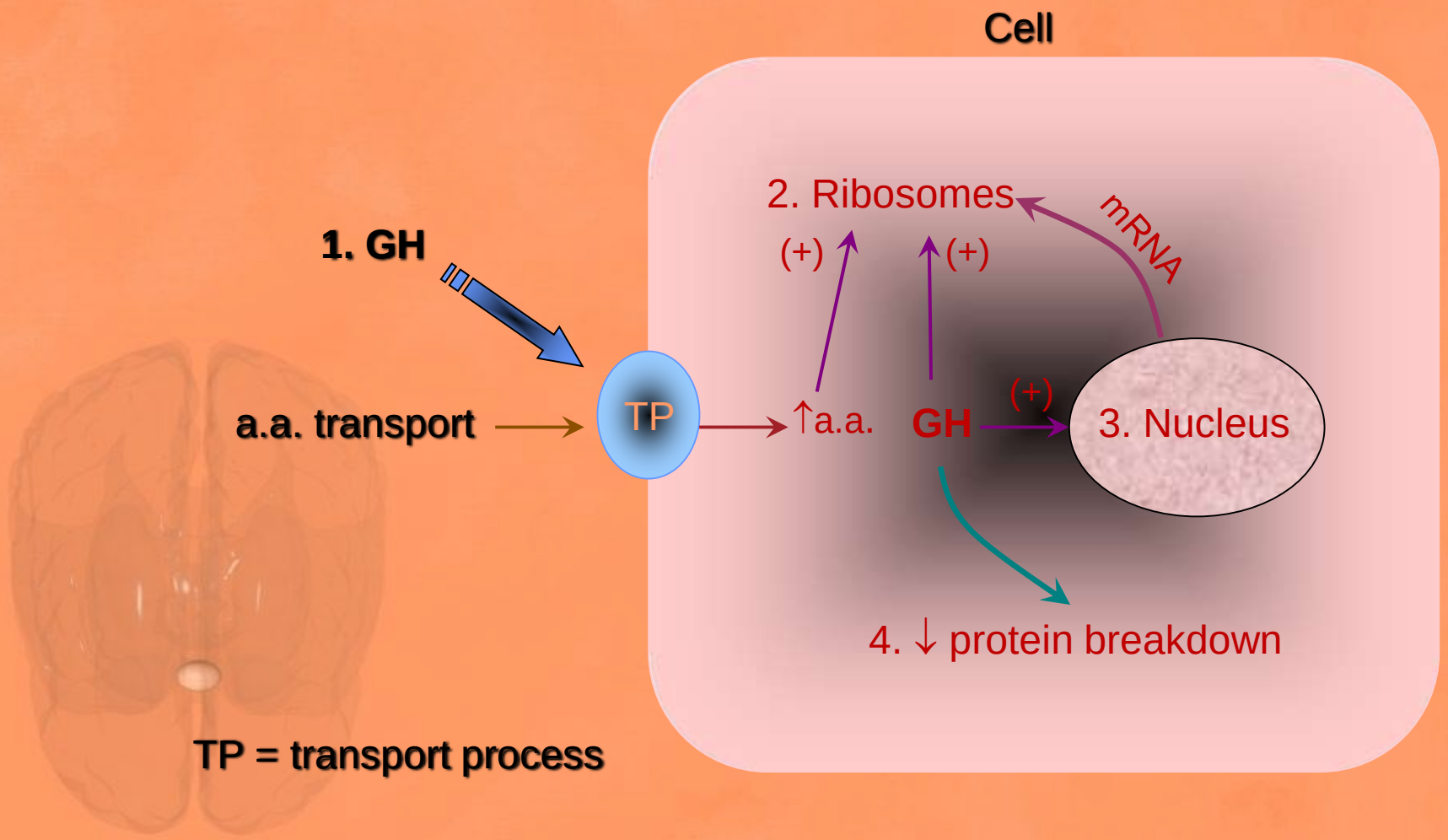
Role of GH in promoting protein synthesis

- **GH has 4 effects to ↑ rate of protein synthesis in all cells of the body:**

1. Enhancement of aa transport through cell membranes.
2. Enhancement of RNA translation to cause protein synthesis by the ribosomes.
3. ↑ nuclear transcription of DNA to form RNA.
4. ↓ catabolism of protein & aa.

The net result is more intracellular protein

Role Of GH In Promoting Protein Synthesis



Role of GH in Fat metabolism

GH enhances fat utilization for energy

- GH acts on fat cells (adipocytes) to release fatty acids from the triglycerides to the blood.
- GH produces several 2 carbon fragments (acetates).

Since fatty acid is a stearic acid ($C_{14}H_{35}COOH$). GH acts on stearic acid $\rightarrow$ several 2-carbon fargments (acetate CH_3COOH).

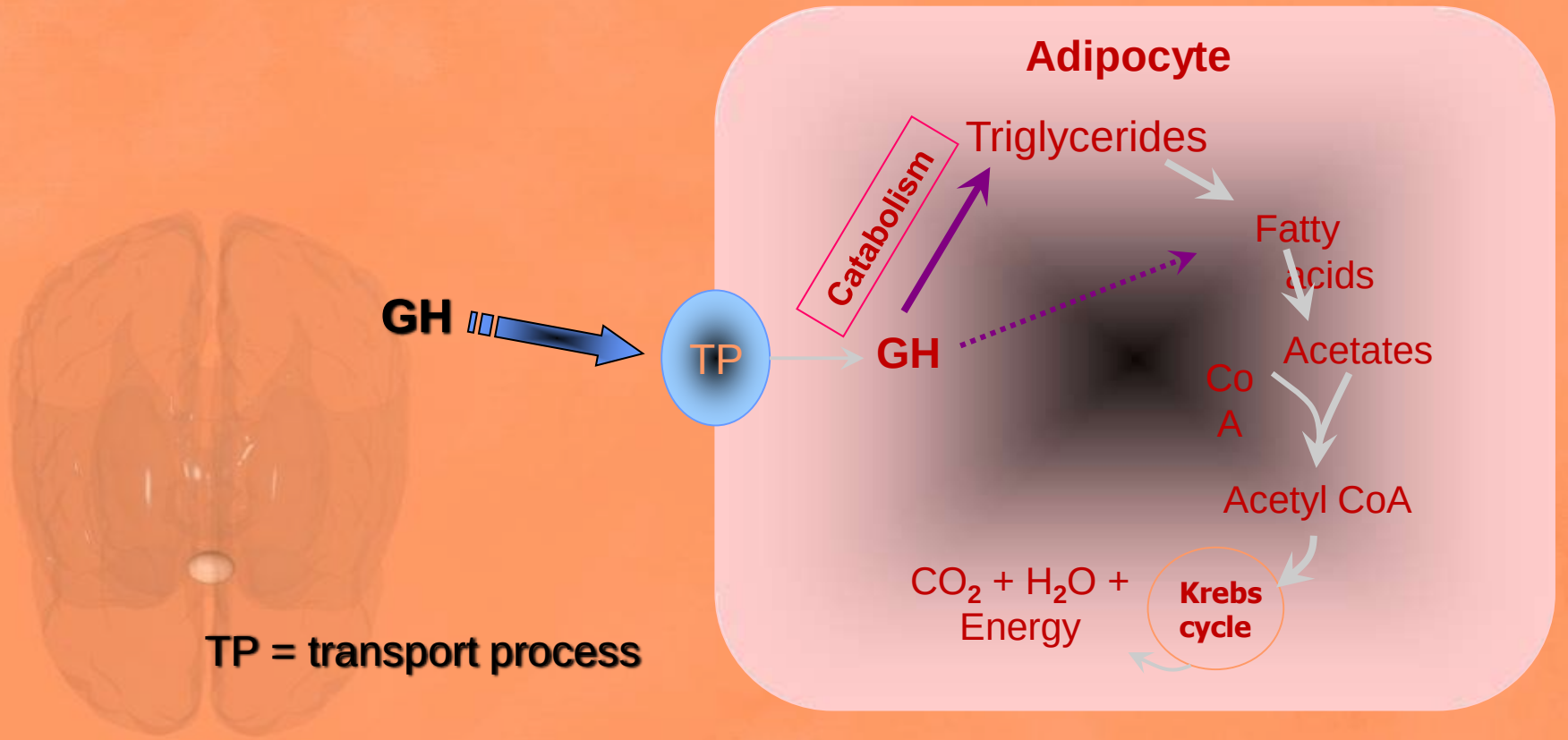
- Formation of acetyl- CoA.

[acetate + Co-enzyme A (Co-A) $\rightarrow$ acetyl-CoA].

- Acetyl-CoA enters Krebs cycle to produce CO_2 + H_2O + Energy.

Role of GH in Fat metabolism

- GH ↑ fat metabolism to provide more energy



Role of GH in Carbohydrate Metabolism

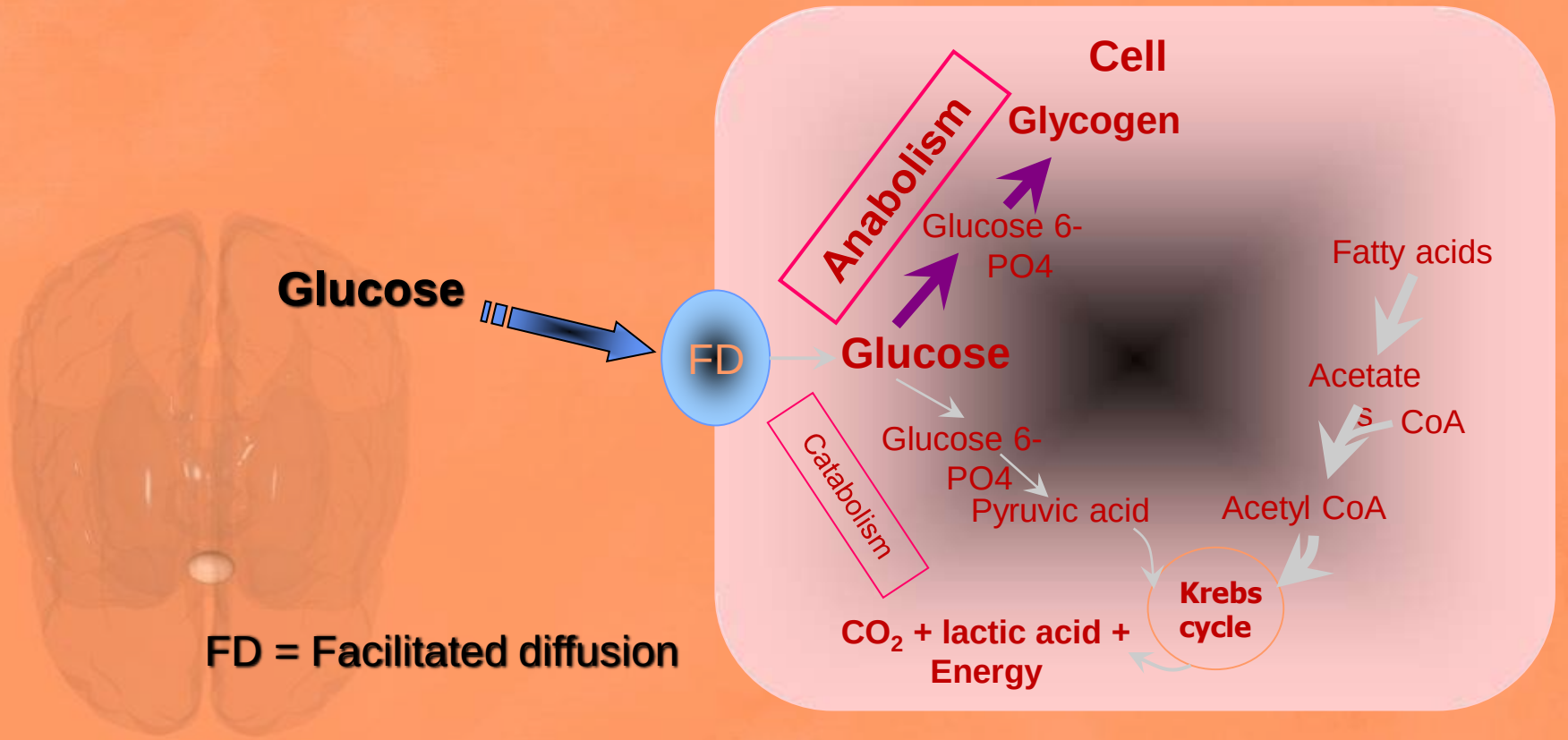
- **GH ↓ CHO utilization**

- ✓ Enhancement of glycogen deposition in the cell.
- ✓ Diminished uptake of glucose by the cells & ↑ blood glucose concentration – " **Pituitary Diabetes**".
- ✓ ↓ use of glucose for energy.
- ✓ ↑ secretion of insulin – Diabetogenic effect of growth hormone.

GH is diabetogenic

Role of GH in Carbohydrate metabolism

- GH ↓ CHO metabolism

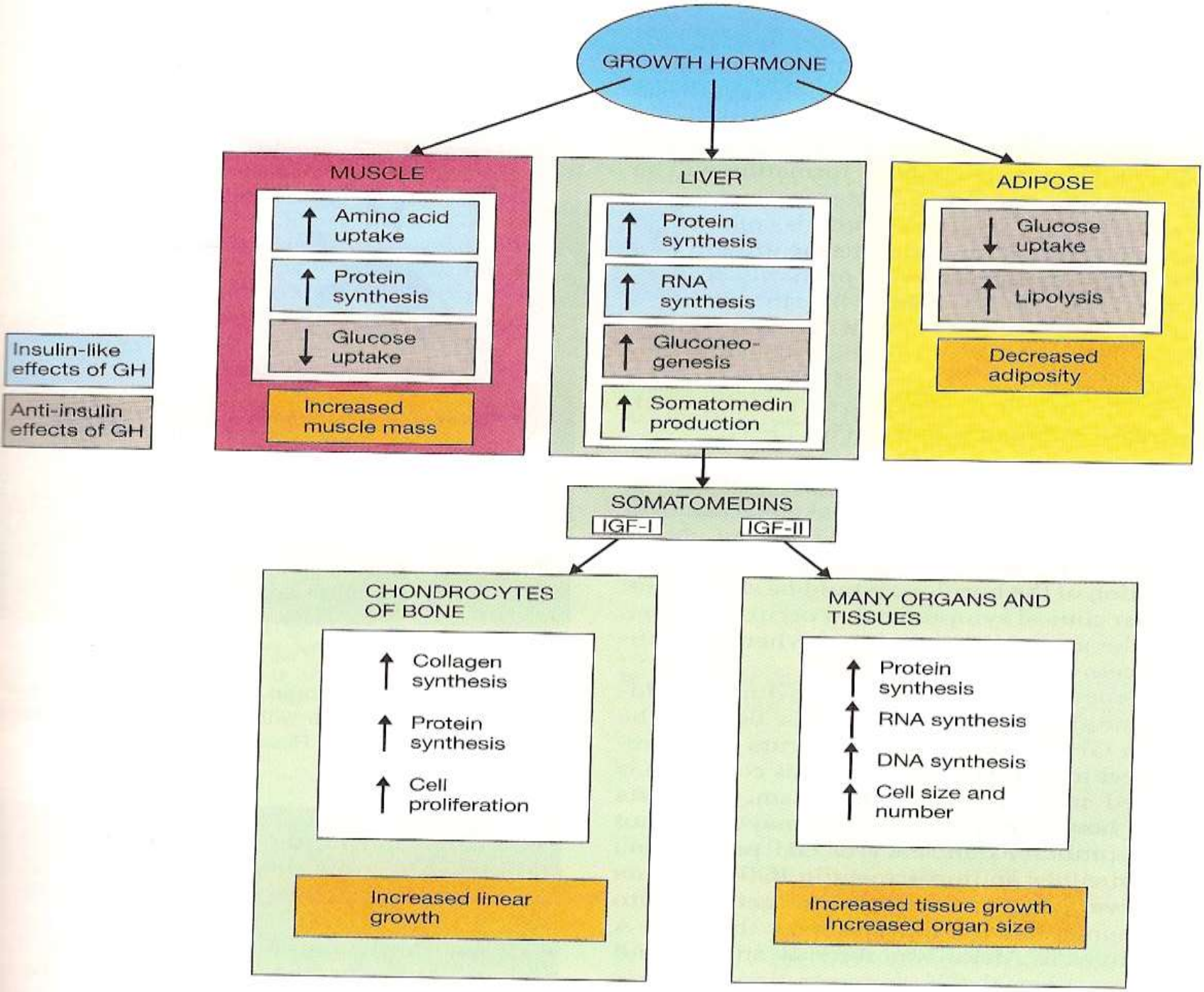


Role of GH in Carbohydrate metabolism

- GH ↓ CHO utilization

- ✓ Usage of fat by Kreb's cycle reduces glucose breakdown
- ✓ Cells build up glycogen up to certain limit
- ✓ Glucose concentration ↑ intracellularly until equilibrium with ECF
- ✓ This block glucose entry into the cell.
- ✓ Blood glucose will ↑ with next meal, which promotes insulin secretion till exhaustion of β cells of pancreas.

GH is diabetogenic


GROWTH HORMONE
MUSCLE
Amino acid uptake
Protein synthesis
Glucose uptake
Increased muscle mass
LIVER
Protein synthesis
RNA synthesis
Gluconeo-genesis
Somatomedin production
ADIPOSE
Glucose uptake
Lipolysis
Decreased adiposity
Insulin-like effects of GH
Anti-insulin effects of GH
SOMATOMEDINS
IGF-I
IGF-II
CHONDROCYTES OF BONE
Collagen synthesis
Protein synthesis
Cell proliferation
Increased linear growth
MANY ORGANS AND TISSUES
Protein synthesis
RNA synthesis
DNA synthesis
Cell size and number
Increased tissue growth
Increased organ size

- **Gluconeogenesis**

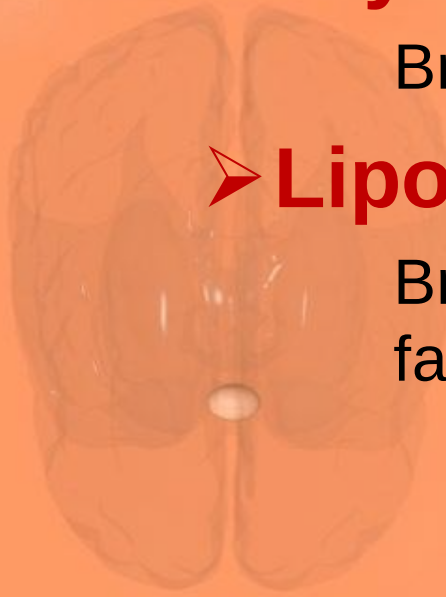
  Breakdown of proteins and lipids and conversion of amino acids and fatty acids into glucose

- **Glycogenolysis**

  Breakdown of liver glycogen into glucose

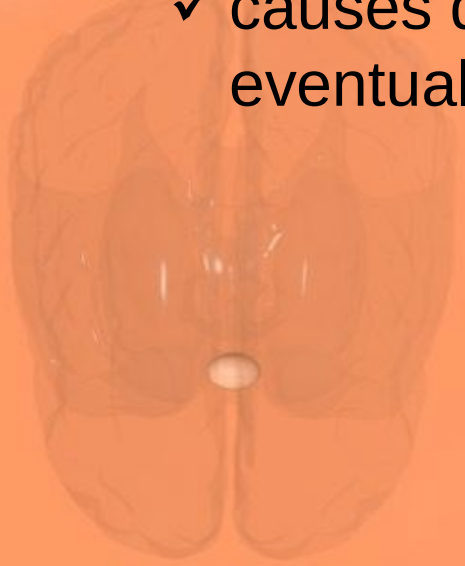
- **Lipolysis**

  Breakdown of adipose tissue into non-esterified fatty acids (NEFA)



Diabetogenic Effect of Human Growth Hormone

- Excess of growth hormone
  - ✓ raises blood glucose concentration
  - ✓ pancreas releases insulin continually
  - ✓ beta-cell burnout
- Diabetogenic effect
  - ✓ causes diabetes mellitis if no insulin activity can occur eventually



Role of GH in growth of bone & cartilage

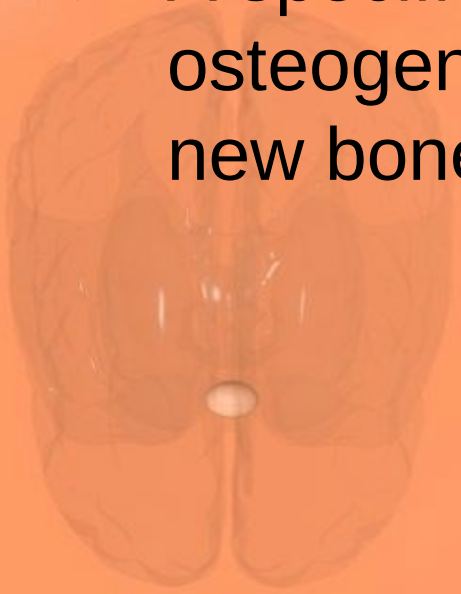
- **2 mechanisms of bone growth:**

1. Linear growth of long bones:
   - Long bones grow in length at epiphyseal cartilages, causing deposition of **New Cartilage** (↑collagen synthesis) followed by its conversion into bone.
   - When bony fusion occurs between shaft & epiphysis at each end, no further lengthening of long bone occur.

2. Deposition of **New Bone** (↑ cell proliferation) on surfaces of older bone & in some bone cavities, ↑ thickness of bone.
   - Occurs in membranous bones, e.g. jaw, & skull bones.

Growth Hormone Stimulates Cartilage and Bone Growth

- Increased deposition of protein by the chondrocytic and osteogenic cells that cause bone growth
- Increased rate of reproduction of these cells
- A specific effect of converting chondrocytes into osteogenic cells, thus causing deposition of new bone



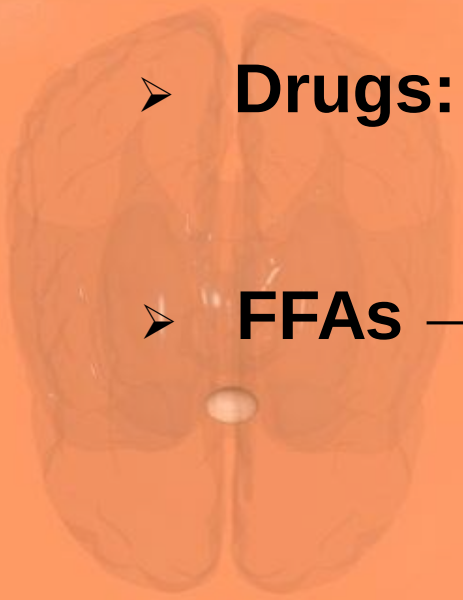
Control of GH secretion

- **The hypothalamus:**
  - ✓ GHRH → ↑ GH secretion.
  - ✓ GHIRH (somatostatin) → ↓ GH secretion.
  - ✓ Estrogens and androgens
- **Hypoglycemia** → ↑ GH secretion.

  (N.B. glucose intake → ↓ GH secretion).
- **Muscular exercise** → ↑ GH secretion.
- **Intake of protein or amino acids** → ↑ GH secretion.

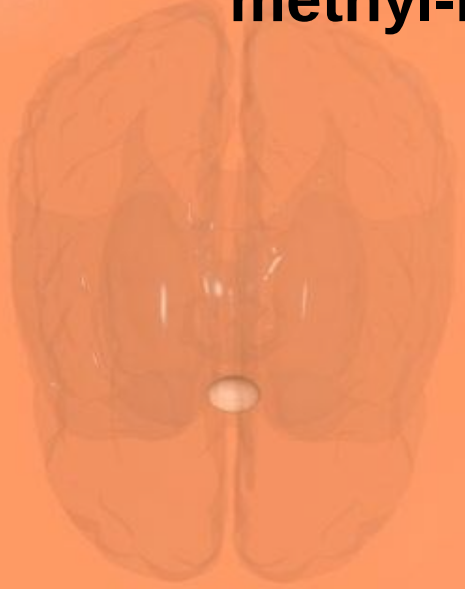
Control of GH secretion

- **During sleep** → ↑ more in children. The first 2 hrs of deep sleep (non-REM)
- **Stress conditions**, e.g. trauma or emotions → ↑ GH secretion.
- **Drugs:** glucagon, lysine-vasopressin & L-Dopa → ↑ GH secretion.
- **FFAs** → ↓ GH secretion.



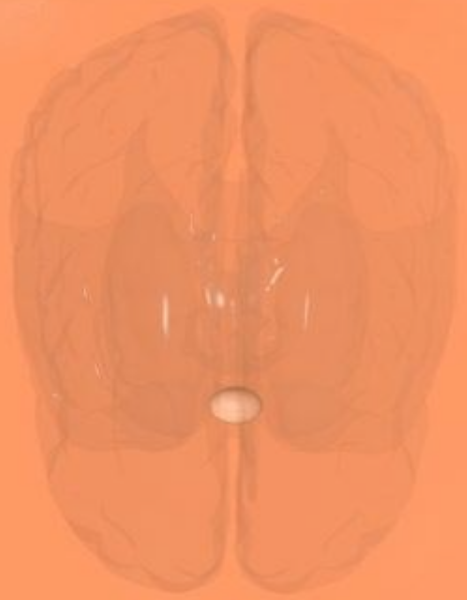
Regulation of Growth Hormone Secretion

- Neurotransmitter systems that stimulate GHRH and/or inhibit somatostatin
  - ✓ Catecholamines acting via α2-adrenergic receptors
  - ✓ Dopamine acting via D1 or D2 receptors
  - ✓ Excitatory amino acids acting via both NMDA (***N*-methyl-D-aspartate**) and non-NMDA receptors



Regulation of Growth Hormone Secretion

- β-adrenergic receptors stimulate somatostatin release and inhibit GH
- β-adrenergic receptors inhibit hypothalamic release of GHRH

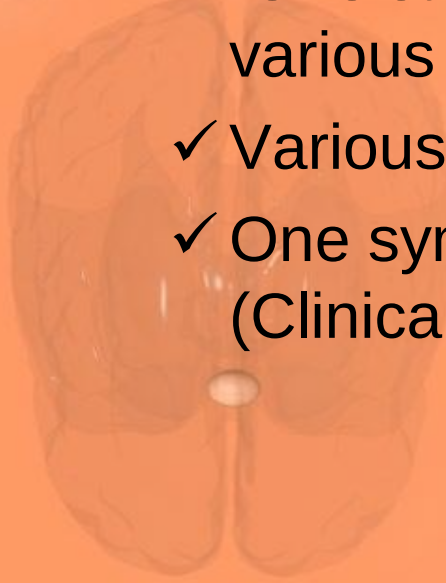


Regulation of hGH secretion (inhibition)

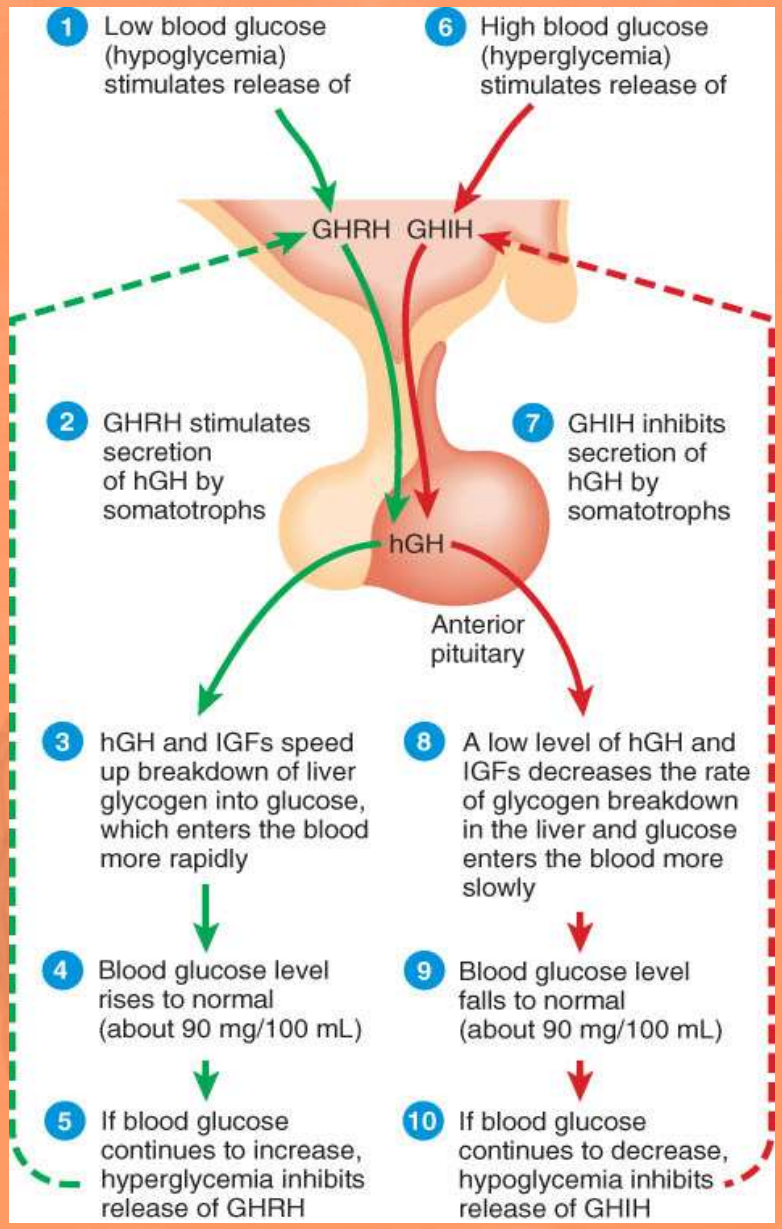
- **Factors inhibiting secretion:**
  - ✓ Hyperglycemia
  - ✓ High fatty acids in the blood
  - ✓ Aging
  - ✓ Obesity
- **REM sleep**
- **Hormones:**
  - ✓ GHIH = Growth hormone inhibitory hormone (Somatostatin)
  - ✓ Exogenous growth hormones
  - ✓ Somatomedins (IGF)

Human Growth Hormone and Insulin-like Growth Factors

- *Human growth hormone* (*hGH*) is the most plentiful anterior pituitary hormone.
- It acts indirectly on tissues by promoting the synthesis and secretion of small protein hormones called *insulin-like growth factors* (*IGFs*).
  - ✓ IGFs stimulate general body growth and regulate various aspects of metabolism.
  - ✓ Various stimuli promote and inhibit hGH production
  - ✓ One symptom of excess hGH is hyperglycemia. (Clinical Application)



Regulation of Human Growth Hormone



- Low blood sugar stimulates release of GHRH from hypothalamus
  - ✓ anterior pituitary releases more hGH, more glycogen broken down into glucose by liver cells
- High blood sugar stimulates release of GHIH from hypothalamus
  - ✓ less hGH from anterior pituitary, glycogen does not breakdown into glucose

Actions of growth hormone

- In the liver, growth hormone generates the production of **somatomedins [insulin-like growth factors (IGF)],** which serve as the intermediaries of several physiologic actions.
- The **IGF receptor** has **tyrosine kinase activity**

  similar to the insulin receptor.
- **Actions of growth hormone via IGF**

(a) ↑ protein synthesis in chondrocytes and ↑ linear growth (pubertal growth spurt)

(b) ↑ protein synthesis in muscle and ↑ lean body mass

(c) ↑ protein synthesis in most organs and ↑ organ size

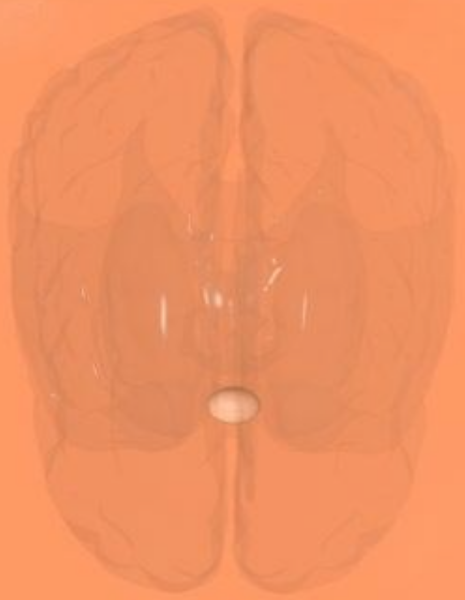
Abnormalities of hGH secretion (hypofunction)

- **Panhypopituitarism** = decrease of secretion of all anterior pituitary hormones
  - ✓ Congenital
  - ✓ Induced by tumor that destroys the gland
- **Dwarfism**
  - ✓ Decrease of all or more than 1 hormone of anterior pituitary (the person does not reach sexual maturation = missing gonadal hormones)
  - ✓ Decrease just in hGH – only smaller person, but can maturate
  - ✓ Missing somatomedins
- **Panhypopituitarism in the adulthood**
  - ✓ **Due to:** tumor or trombosis of the pituitary blood vessels
  - ✓ **Results in:** hypothyroidism, decrease in glucocorticoids, suppression of gonadotropic hormones

Abnormalities of hGH secretion (hyperfunction)

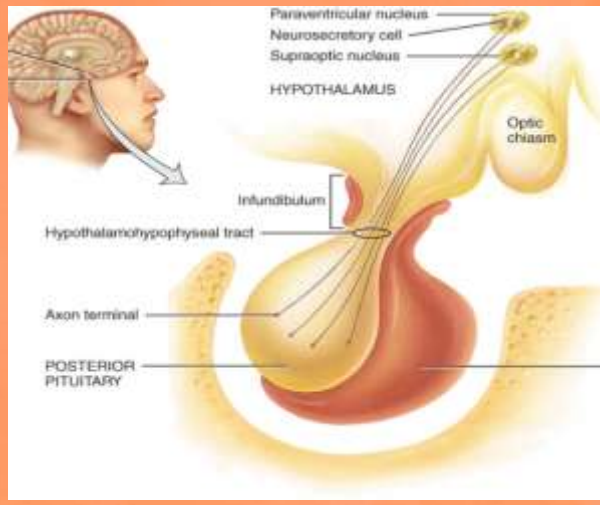
- **Gigantism** – increased growing (randomly) = giants
  - ✓ Due to: increased activity of somatotropes or tumor during development
- **Acromegaly** – increased growing of acral parts of the body
  - ✓ Due to: increased activity of somatotropes or tumor after puberty (after closure the epiphysal slits)
  - ✓ Bones grow only to thickness (enlargement of hands and feet, membranous bones such as cranium, nose, supraorbital ridges, chin etc.

Posterior Pituitary (neurohypophysis)



Posterior Pituitary Gland (Neurohypophysis)

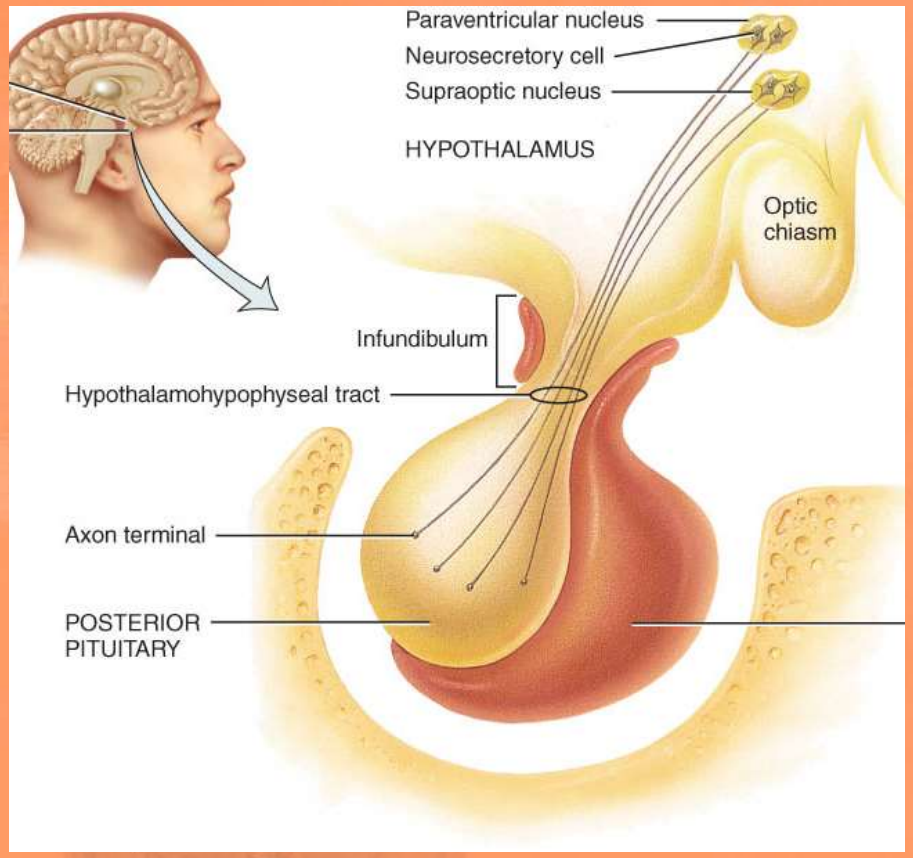
- Although the posterior pituitary gland does not synthesize hormones, it does store and release two hormones.
  - ✓ Hormones made by the hypothalamus and stored in the posterior pituitary are *oxytocin* (*OT*) and *antidiuretic hormone* (*ADH*)
  - ✓ The neural connection between the hypothalamus and the neurohypophysis is via the *hypothalamohypophyseal tract*
- paraventricular nucleus - oxytocin
- supraoptical nucleus - vasopresin



Hormones of the neurohypophysis

- ***Magnocellular neurons*** (long neurons) located in the **supraoptic** and **paraventricular nuclei** of the hypothalamus – axoplasm transport of hormones from the hypothalamus to the posterior pituitary
- **Hormones:** Polypeptides with 9 amino acids
  - ✓ **ADH (vasopressin)**: Cys-Tyr-**Phe**-Gln-Asn-Cys-Pro-**Arg**-GlyNH_2
  - ✓ **Oxytocin**: Cys-Tyr-**Ile**-Gln-Asn-Cys-Pro-**Leu**-GlyNH_2
  - Similar structure, similar action

Posterior Pituitary Gland (Neurohypophysis)

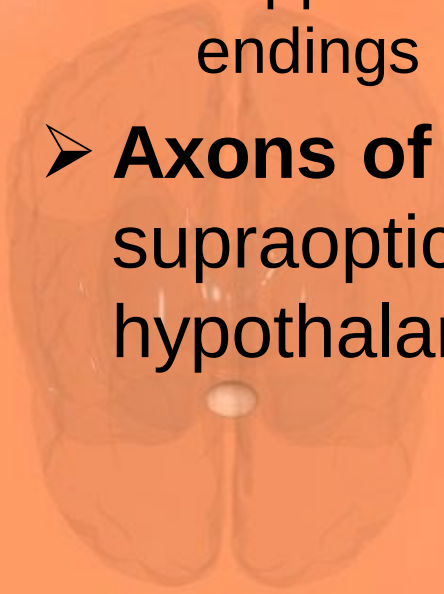


- Does not synthesize hormones
- Consists of axon terminals of hypothalamic neurons
- Neurons release two neurotransmitters into capillaries
  - antidiuretic hormone
  - oxytocin

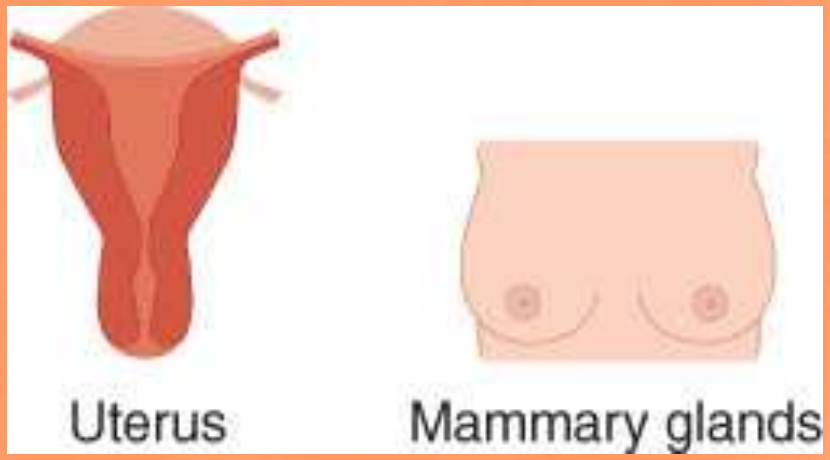
Cell types in the posterior pituitary

- Is synthesized as the precursor hormone: prepro-oxyphysin

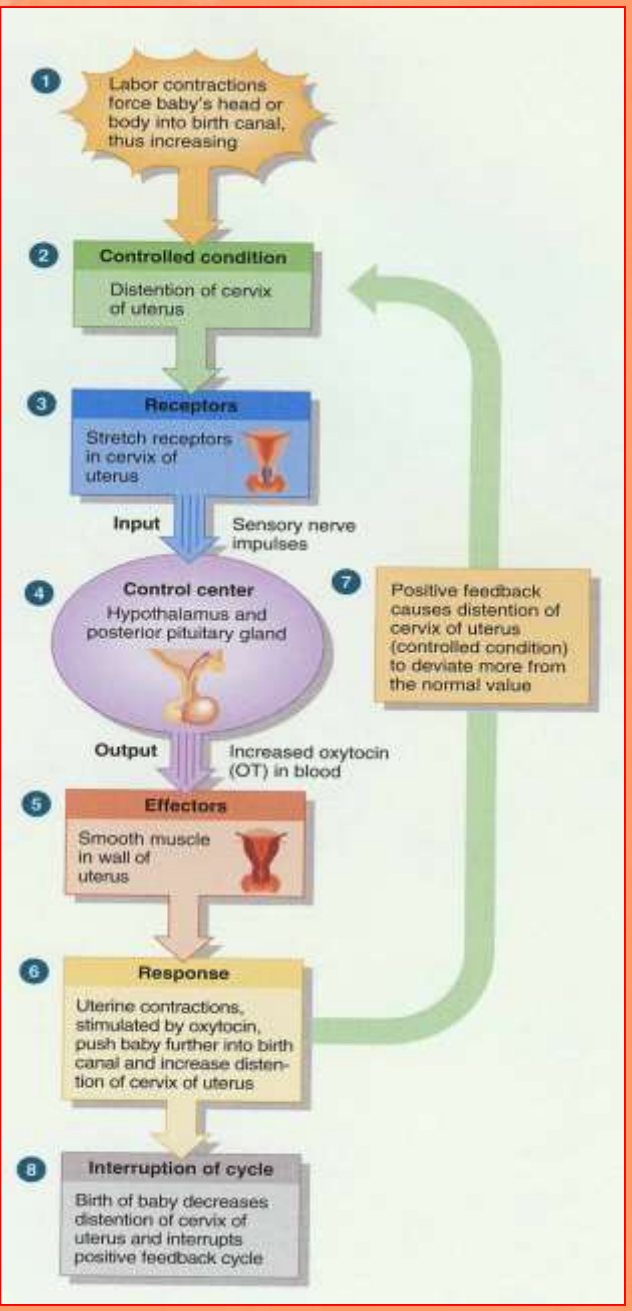
- **Pituicytes** = glial-like cells
  - ✓ no hormone secretion
  - ✓ supporting structure for terminal nerve fibers and endings
- **Axons of secretory neurons** located in the supraoptic and paraventricular nuclei of the hypothalamus



Physiologic effects of oxytocin



- Two target tissues both involved in neuroendocrine reflexes
- During delivery
  - ✓ baby's head stretches cervix
  - ✓ hormone release enhances uterine muscle contraction
  - ✓ baby & placenta are delivered
- After delivery
  - ✓ *Oxytocin* stimulates contraction of the uterus and ejection (let-down) of milk from the breasts.
    - ❖ Nursing a baby after delivery stimulates oxytocin release, promoting uterine contractions and the expulsion of the placenta (Clinical Application).
    - ❖ suckling & hearing baby's cry stimulates milk ejection

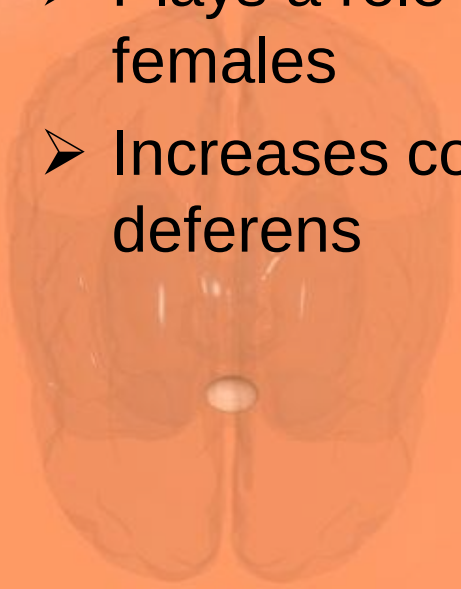


Oxytocin during Labor

- Stimulation of uterus by baby
- Hormone release from posterior pituitary
- Uterine smooth muscle contracts until birth of baby
- Baby pushed into cervix, increase hormone release
- More muscle contraction occurs
- When baby is born, positive feedback ceases

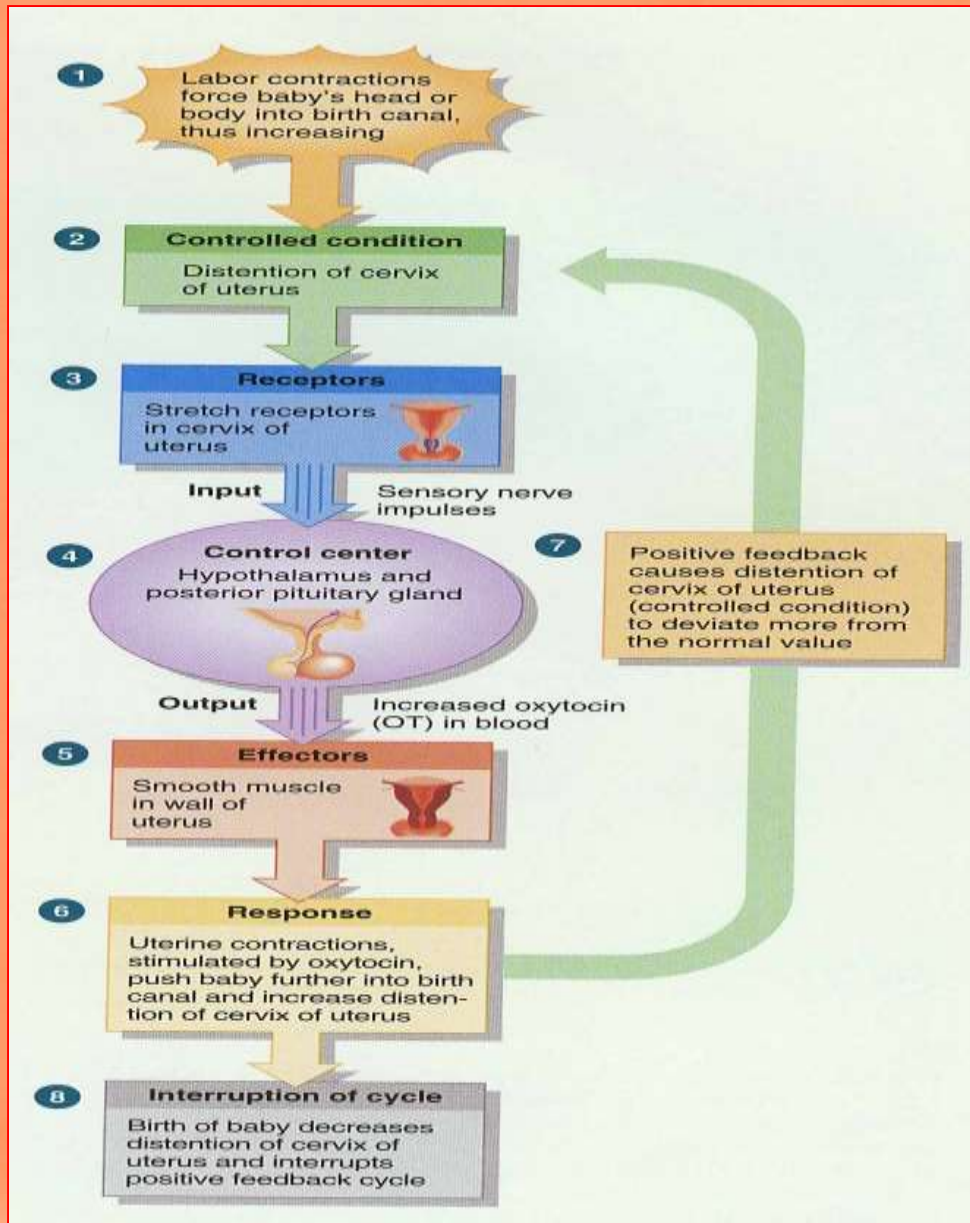
Physiologic effects of oxytocin

- Stimulates uterine contractions during childbirth by mobilizing Ca^{2+} through a PIP_2 (phosphatidylinositol 4,5-diphosphate) - Ca^{2+} second-messenger system
- Also triggers milk ejection (“letdown” reflex) in women producing milk
- Plays a role in sexual arousal and orgasm in males and females
- Increases contraction of smooth muscle of the vas deferens



Positive Feedback

- Oxytocin stimulates uterine contractions
- Uterine contractions stimulate oxytocin release

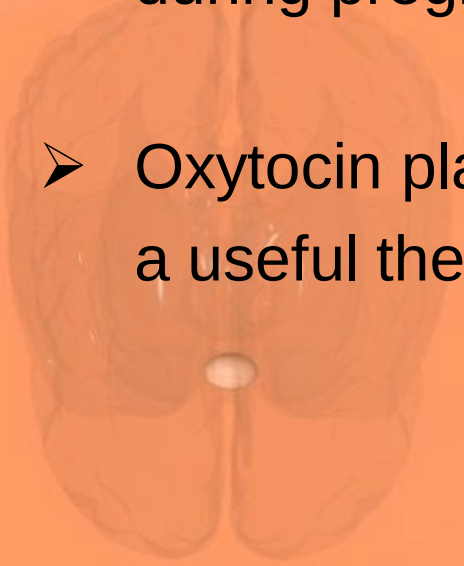


Physiologic effects of oxytocin

- Stimulates contraction of the smooth muscle (myometrium) of the lactating mammary gland **(milk ejection**) and myometrium of the uterus.

- The sensitivity of the myometrium to exogenous oxytocin during pregnancy increases as pregnancy advances.

- Oxytocin plays a role in **labor** and has been shown to be a useful therapeutic agent in the induction of labor.



Control of oxytocin secretion

Stimuli

- Stimulation of the “touch receptor” around the nipples
- Milk let-down or “milk ejection reflex” (latent period: 30-60 seconds)
- Genital tract stimulation

Inhibition

- Milk let-down can be inhibited by emotional stress and psychic factors such as fright
  - ✓ NE & Epi inhibit its secretion
  - ✓ Ethanol
  - ✓ enkephalins

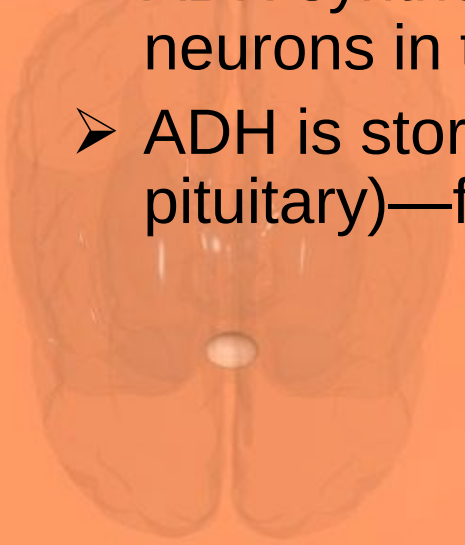
Vasopressin (ADH)

Is also known as antiduretic hormone (ADH)

Participates in body water regulation (Water is lost from lungs, sweat, feces and urine on a daily basis)

Synthesis of ADH

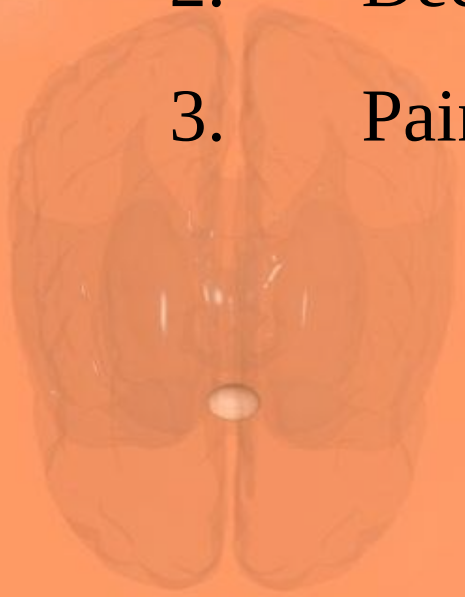
- It is synthesized as pre-prohormone and processed into a nonapeptide (nine amino acids).
  - ✓ Six of the amino acids form a ring structure, joined by disulfide bonds.
  - ✓ It is very similar in structure to oxytocin, differing only in amino acid (3 and 8).
- ADH synthesized in the cell bodies of hypothalamic neurons in the supraoptic nucleus
- ADH is stored in the neurohypophysis (posterior pituitary)—forms the most readily released ADH pool



Vasopressin (ADH) Secretion

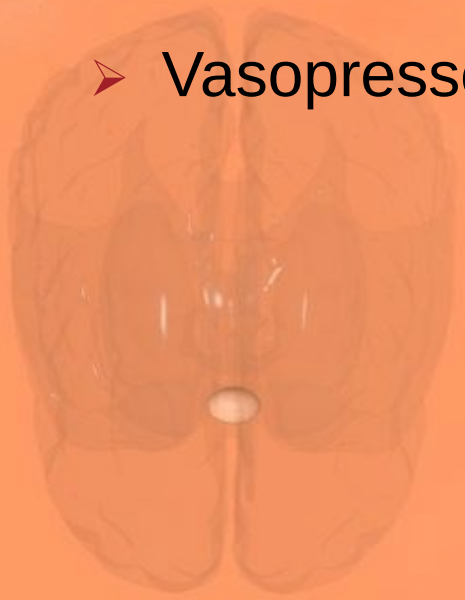
Secretion is Stimulated by:

1. Large decreases in blood volume
2. Decreases in blood pressure
3. Pain, fear, trauma, and stress



Vasopressin

- Antidiuretic hormone V_2-receptor:
  collecting duct and distal convoluted tubule
- Vasopressor hormone V_1-receptor:
  vascular smooth muscle
- Vasopressor hormone $V1_B$-receptor: anterior pituitary



Vasopressin

Decreases water excretion by kidneys (V_2 receptors)

Constricts blood vessels (V_1 receptors)- arteriolar smooth muscle

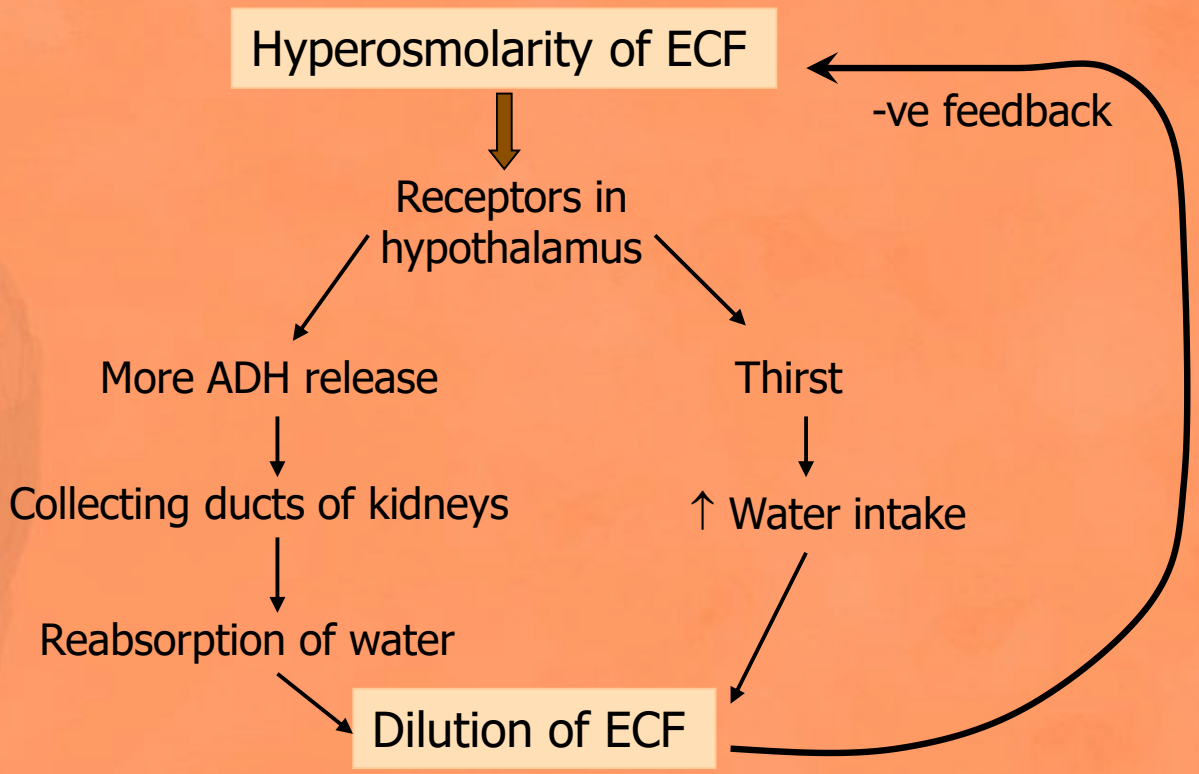
Increases adrenocorticortropin hormone (V_{1B} receptors) secretion from the anterior pituitary

ADH (vasopressin)

- Formed primarily in the **supraoptic nuclei**
- **Regulates water excretion by the kidneys**
  - ✓ Increases the permeability of collecting tubules and ducts to water - water reabsorption – concentrated urine
  - ✓ **Osmotic regulation** – osmoreceptors in the hypothalamus or somewhere near
- Causes vasoconstriction
  - ✓ Constrict arterioles throughout the entire body
  - ✓ **Blood volume** (activated when decreased blood volume)
    - ❖ Stretch (**volumoreceptors**) in right atrium of the heart
    - ❖ **Baroreceptors** in carotid, aortic and pulmonary regions

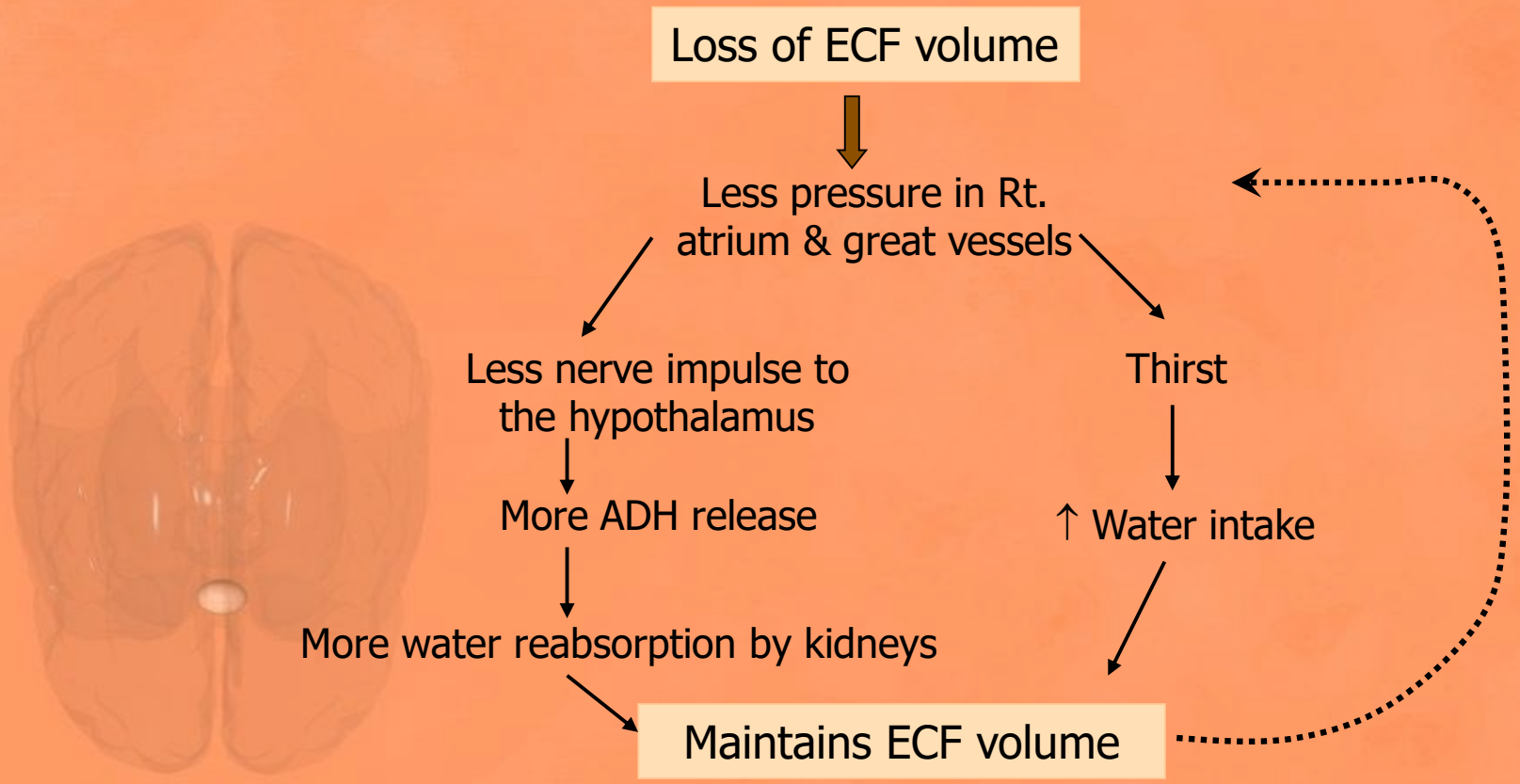
Control of ADH release

1. ↑ in osmotic pressure of the ECF (↑ in plasma osmolality), as in dehydration which will stimulate osmoreceptors in the hypothalamus → ↑ ADH.



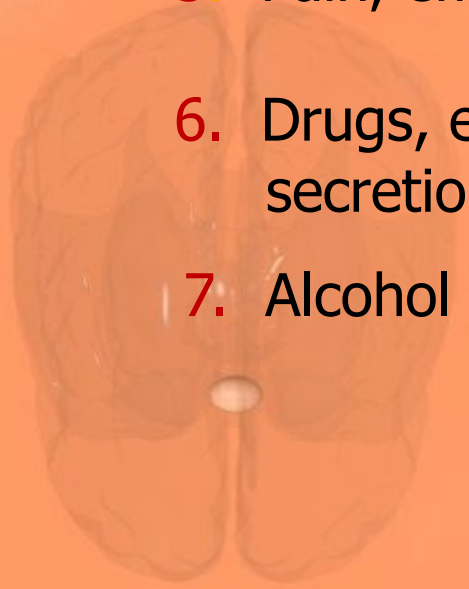
Control of ADH release

2. ↓ blood volume (≥ 10%) → stimulate mechanoreceptors in the great arteries (aorta & carotids) & right atrium → ↑ ADH.



Control of ADH release

3. ↓ arterial blood pressure, due to ↓ blood volume → ↑ ADH.
4. Age: → ↑ ADH secretion → water retention & hyponatremia.
5. Pain, emotional stress & physical trauma → ↑ ADH secretion.
6. Drugs, e.g. morphine, barbiturates, & nicotine → ↑ ADH secretion.
7. Alcohol → ↓ ADH secretion.



Action of ADH

ADH has 2 main effects:

- ↑ water re-absorption (retention) by distal tubules & collecting ducts of the kidneys → decrease osmotic pressure of the blood.

  * This effect is regulated by V_2 receptors, through the action of cAMP.

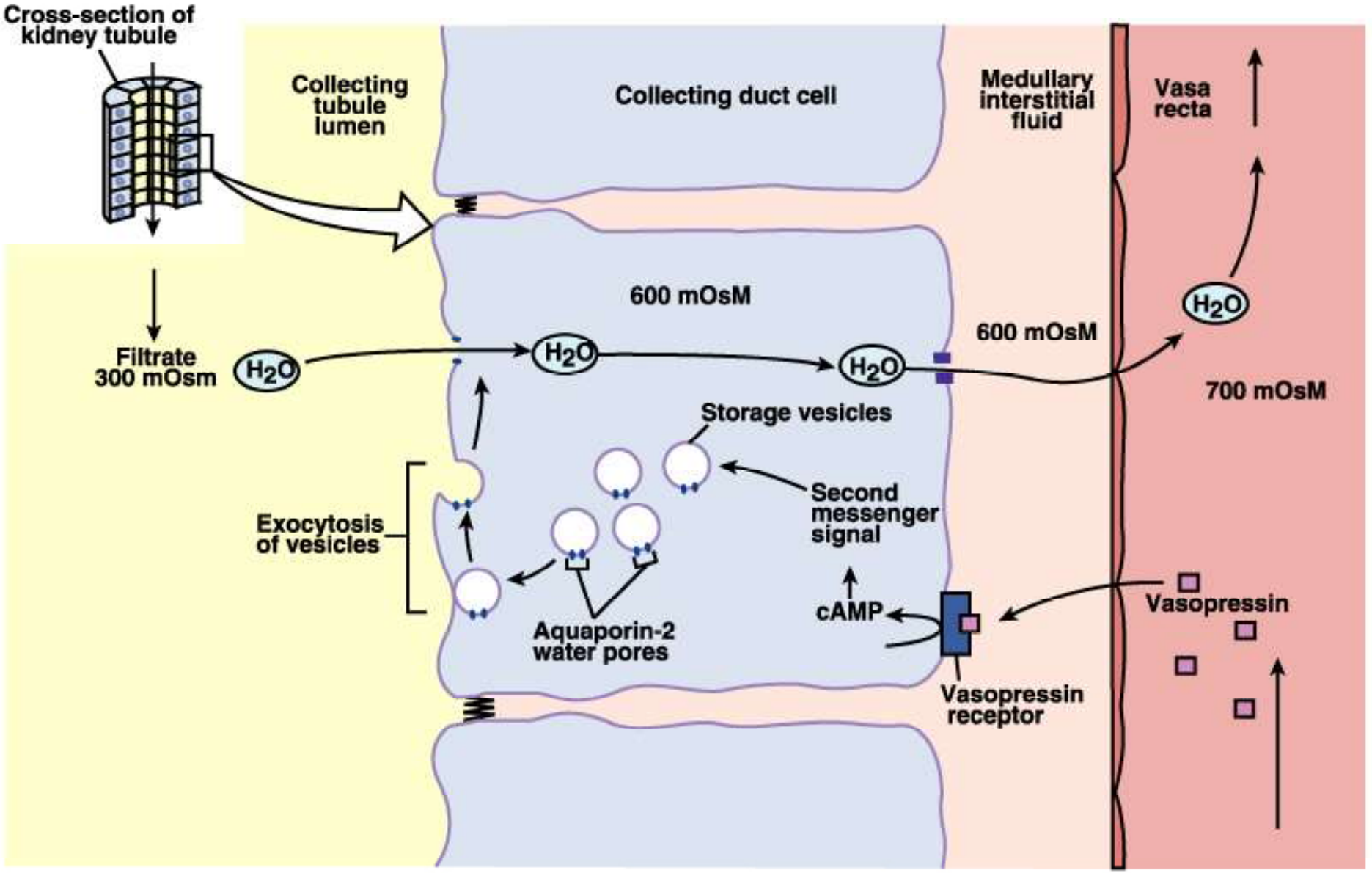
- Contraction of vascular smooth muscles → generalized vasoconstriction.

  * This effect is regulated by V_1 receptors, through the action of IP_3(inositol 1,4,5-triphosphate)/Ca^{2+}.

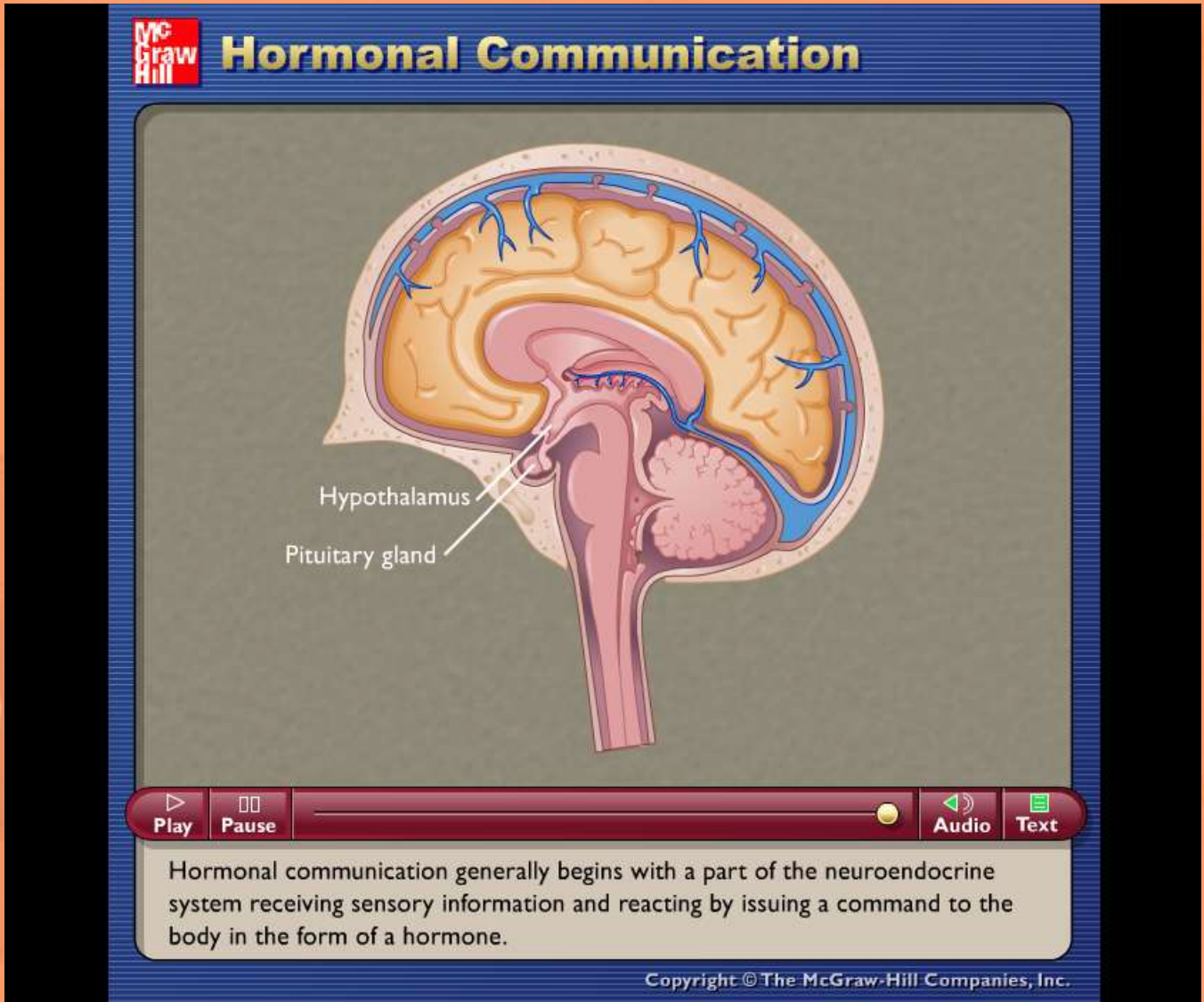
Actions of ADH

- ADH action in the kidney is mediated by its binding to V2 receptors, coupled to adenylate cyclase and cAMP production.
- cAMP activates protein kinase A which prompts the insertion of water channels into the apical membrane of the cell.
- When ADH is removed, the water channels withdraw from the membrane and the apical surface of the cell becomes impermeable to water once again.

Influence of ADH on the Collecting Ducts



ADH actions


Hormonal Communication
Hypothalamus
Pituitary gland
Play
Pause
Audio
Text
Hormonal communication generally begins with a part of the neuroendocrine system receiving sensory information and reacting by issuing a command to the body in the form of a hormone.
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Actions of ADH

- This mechanism of shuttling water channels into and out of the apical membrane provides a very rapid means to control water permeability
- The basolateral membrane of the ductal cells are freely permeable to water, so any water that enters via the apical membrane exits the cell across the basolateral membrane, resulting in the net absorption of water from the tubule lumen into the peritubular blood.

Regulation of ADH Secretion

- Response to osmolality of interstitial fluid:

  - Osmoreceptors in the brain detect changes in osmolality of the interstitial fluid or blood.

  - Increased osmolality results in increased [solutes] ADH release

    - increased water reabsorption

    - decreased osmolality of fluids

  - Decreased osmolality results in decreased ADH release = NEGATIVE FEEDBACK!

    - decreased water reabsorption

    - increased osmolality of fluids

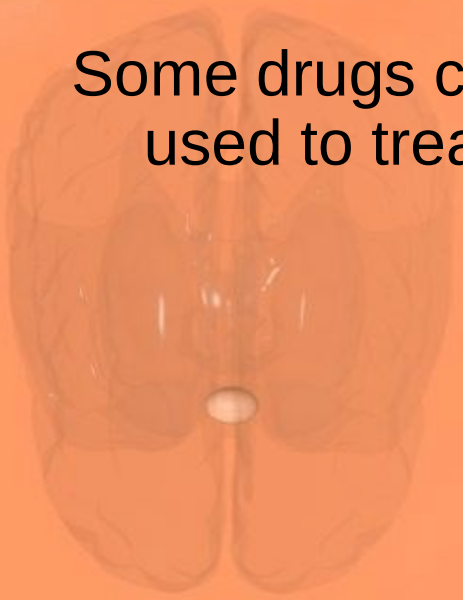
Regulation of ADH Secretion

- Response to changes in blood pressure:
  - ✓ Blood pressure receptors in heart, aortic arch, and carotid artery
  - ✓ Increased blood pressure results in <u>decreased</u> AVP release
    - ❖ decreased water reabsorption
    - ❖ decreased blood volume, blood pressure
  - ✓ Decreased blood pressure results in <u>increased</u> AVP release
    - ❖ increased water reabsorption
    - ❖ increased blood volume, pressure

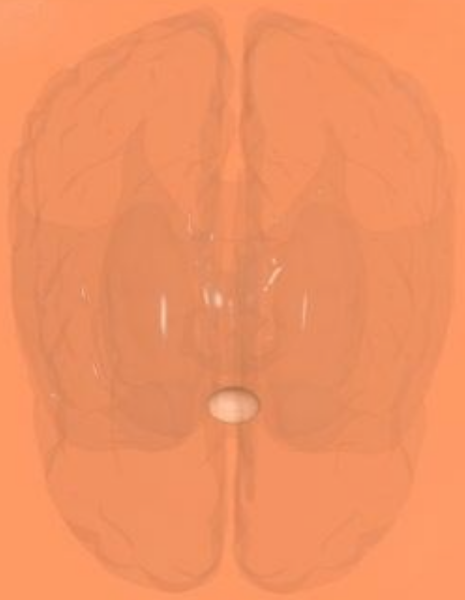
Regulation of ADH Secretion

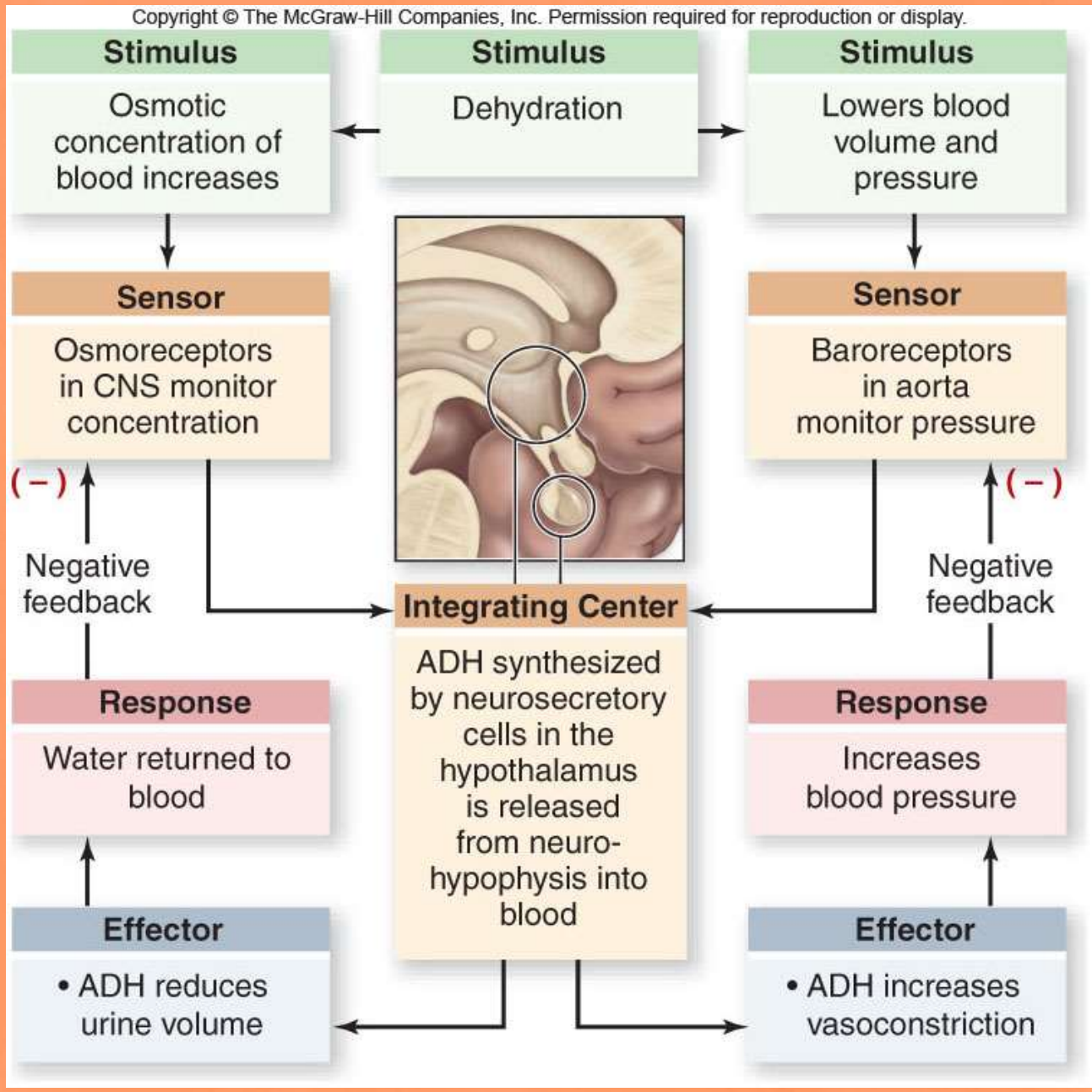
- ADH release is also inhibited by alcohol, caffeine (diuretics) – dehydrating effect “dry mouth” or intense thirst morning after → INCREASED urine output.
  - ✓ decreased water reabsorption
  - ✓ increased urinary volume
  - ✓ potential for dehydration

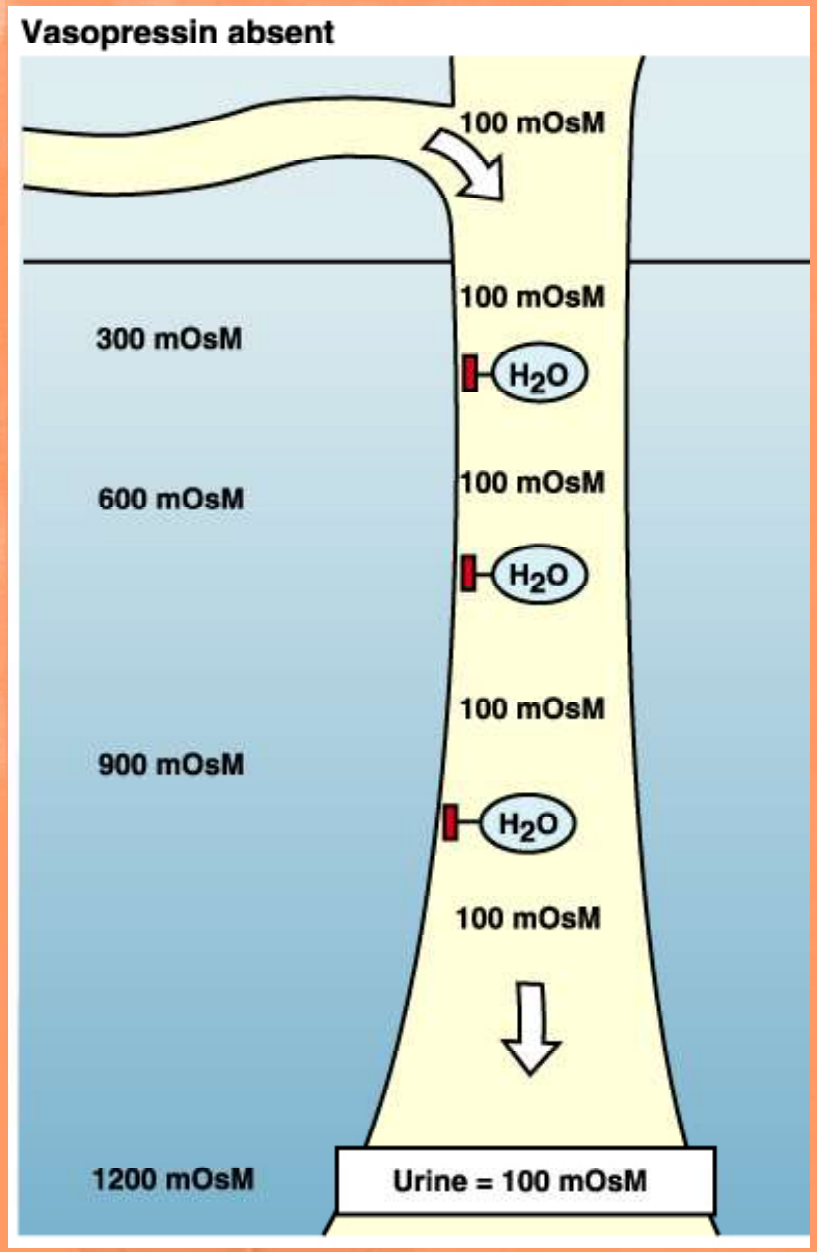
Some drugs can also antagonize ADH release: diuretics used to treat high BL Pr, edema, or CHF.

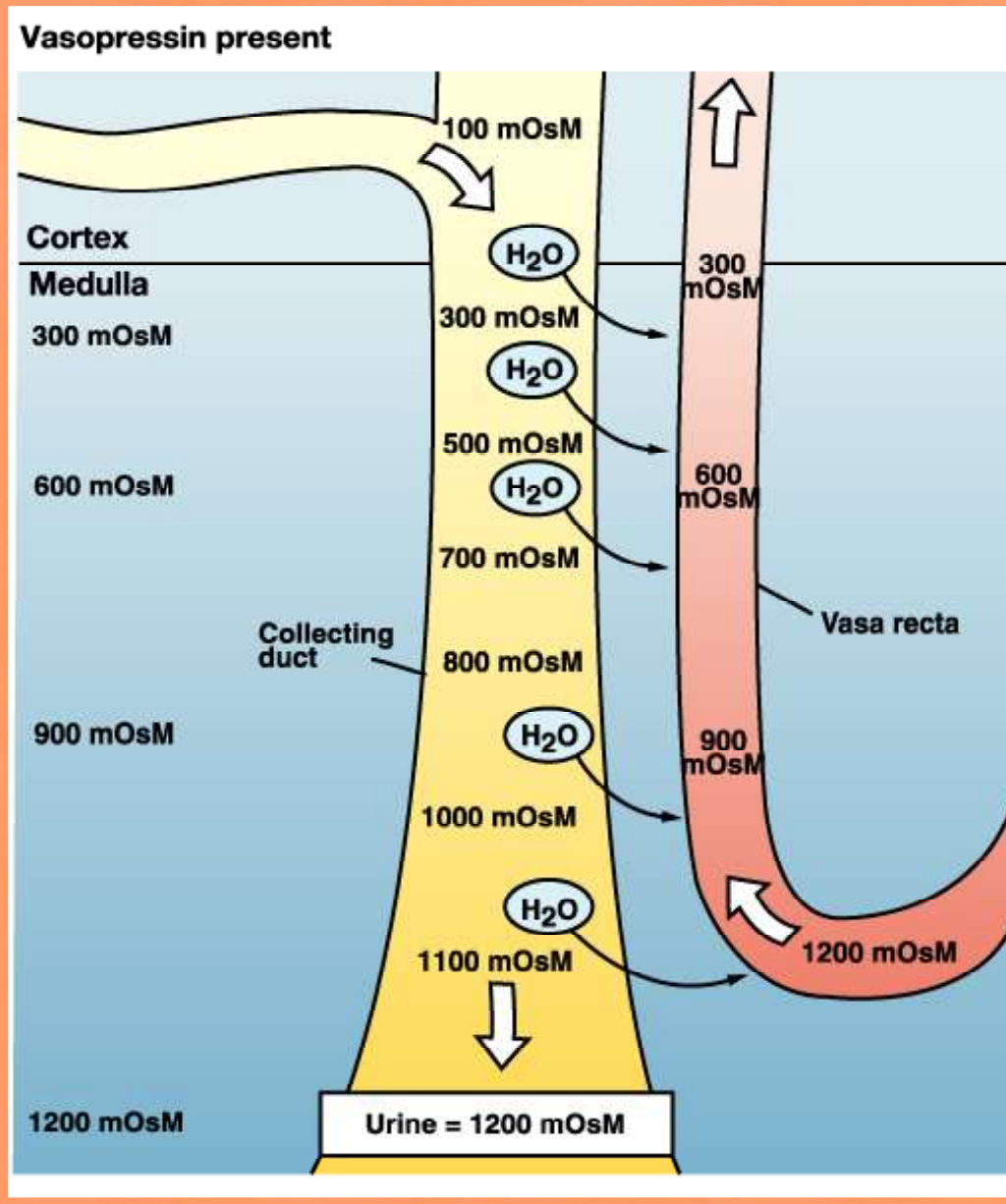


Feedback mechanisms in the control of blood osmotic pressure—the control of ADH.






Vasopressin absent
100 mOsM
100 mOsM
300 mOsM
H2O
100 mOsM
600 mOsM
H2O
100 mOsM
900 mOsM
H2O
100 mOsM
1200 mOsM
Urine = 100 mOsM


Vasopressin present
100 mOsM
Cortex
Medulla
H2O
300 mOsM
300 mOsM
300 mOsM
H2O
500 mOsM
600 mOsM
600 mOsM
H2O
700 mOsM
Vasa recta
Collecting duct
800 mOsM
900 mOsM
H2O
900 mOsM
1000 mOsM
H2O
1200 mOsM
1100 mOsM
1200 mOsM
Urine = 1200 mOsM

ADH and Water Balance

- The maintenance of water balance in the body is extremely important for proper functioning of cells.
- There are two main compartments of the body: intracellular and extracellular (includes interstitial space and plasma).
- Water moves freely between compartments depending upon osmotic gradients.

Osmolality

- Refers to the amount of solutes in a solution
- Loss or gain of water without solutes (free water gain or loss) changes the osmolality of ECF
- Must be regulated to maintain normal cell activity

$$sOsm = 2(Na) + Glu/18 + BUN/2.8$$

normal OSM = 285 – 295 mOSM/L

$$sOsm = 2(Na+K) + Glu/18 + BUN/2.8$$

normal OSM = 295 – 305 mOSM/L

Regulation of Osmolality

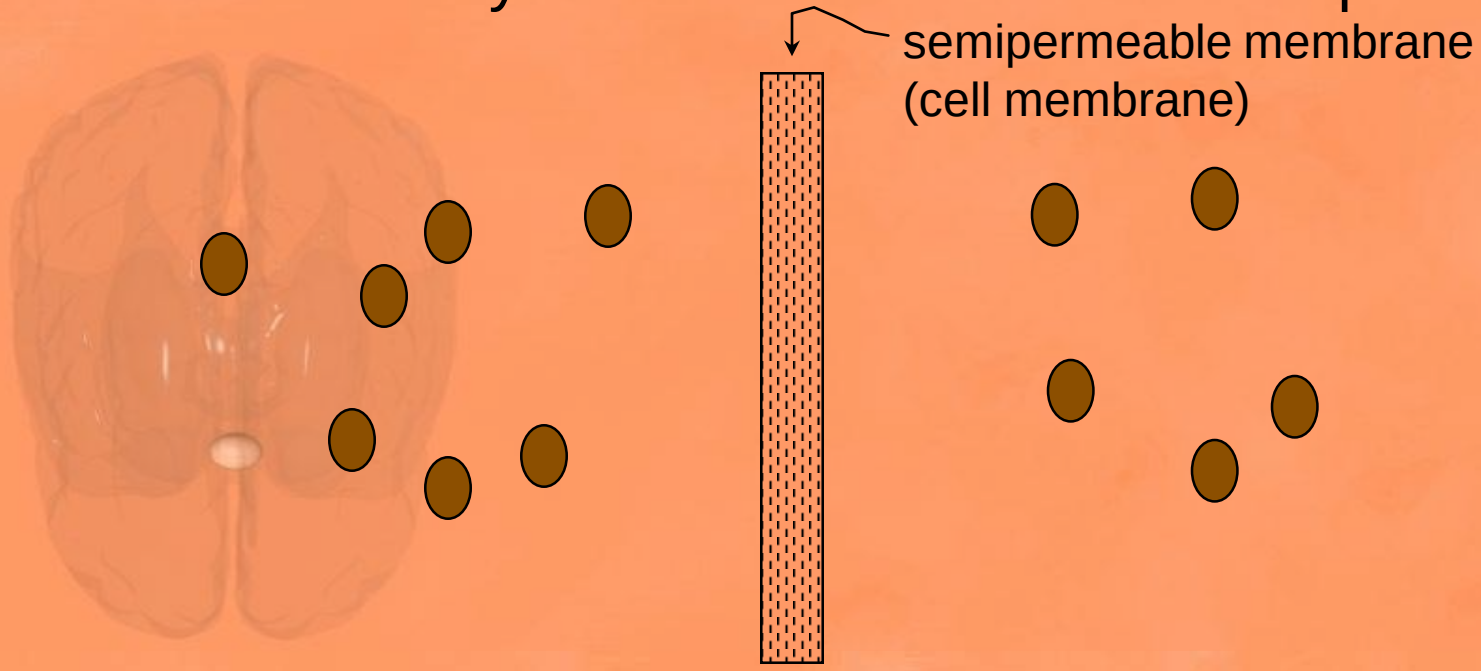
Plasma osmolality is monitored by osmoreceptors in the hypothalamus

Increases in plasma osmolality stimulates secretion of vasopressin

Small changes above the normal plasma osmotic pressure (285 mosm/kg) stimulate release of vasopressin

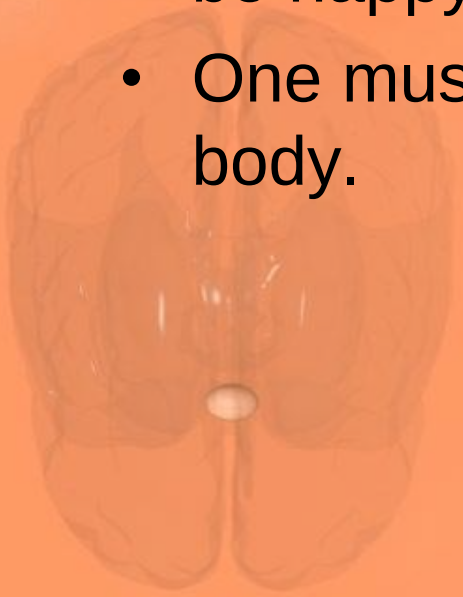
Osmolarity and Osmosis

- The osmolarity of a solution is determined by how much solute (such as salt) is present in a given amount of solvent (such as water).
- Water will move by osmosis from an area of lower osmolarity to one of higher osmolarity.
- Which way will water move in this example?



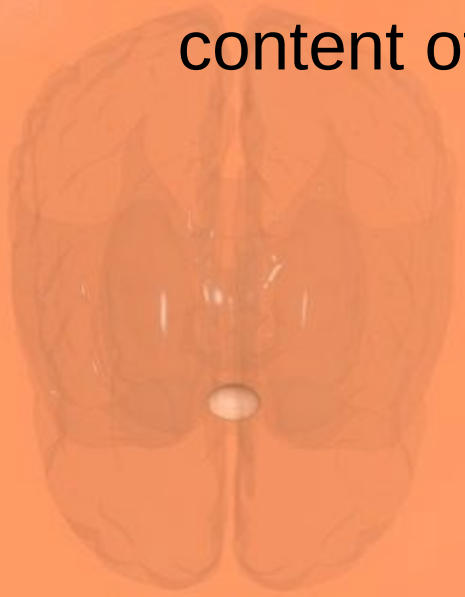
The Main Point....

- If there is insufficient fluid in the extracellular space, osmolarity increases, and water will begin to leave cells.
- This is a bad thing to have happen, cells will not be happy!
- One must regulate the amount of water in the body.



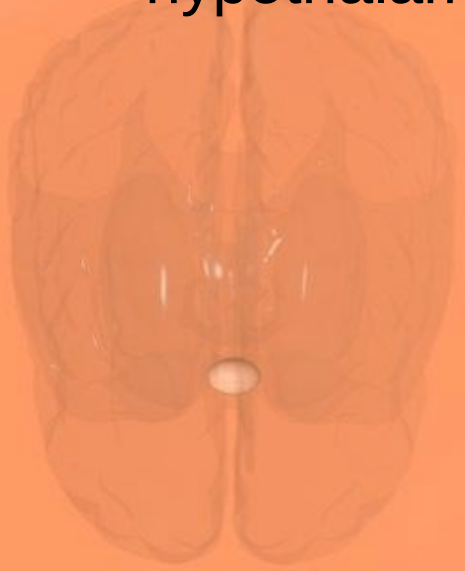
The Role of the Kidney in Water Balance

- The kidney removes about 170 liters/day of water from the blood.
- 99% of this water is reabsorbed from the urine back into the bloodstream.
- The kidney is an important site at which the water content of the body is regulated.



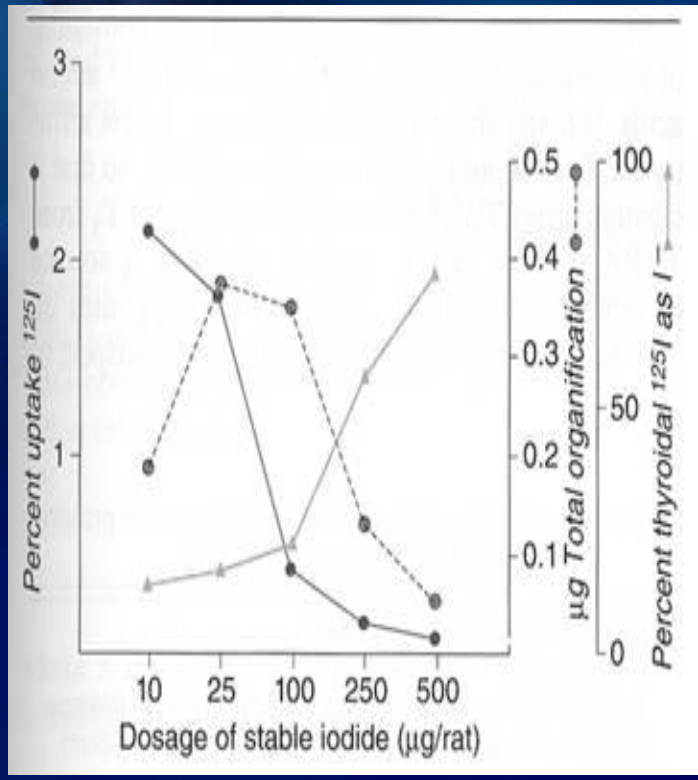
Diabetes Insipidus

- Insufficient ADH results in disease: diabetes insipidus (DI)
  - ✓ impaired water reabsorption from DCT, collecting ducts
  - ✓increase urine volume 10 times and intense thirst.
- DI can be caused by a blow to the head or other hypothalamic damage.



Wolff-Chaikoff Effect

- Increasing doses of I I-increase hormone synthesis initially
- Higher doses cause cessation of hormone formation
- This effect is countered by the Iodide leak from normal thyroid tissue
- Patients with autoimmune thyroiditis may fail to adapt and become hypothyroid

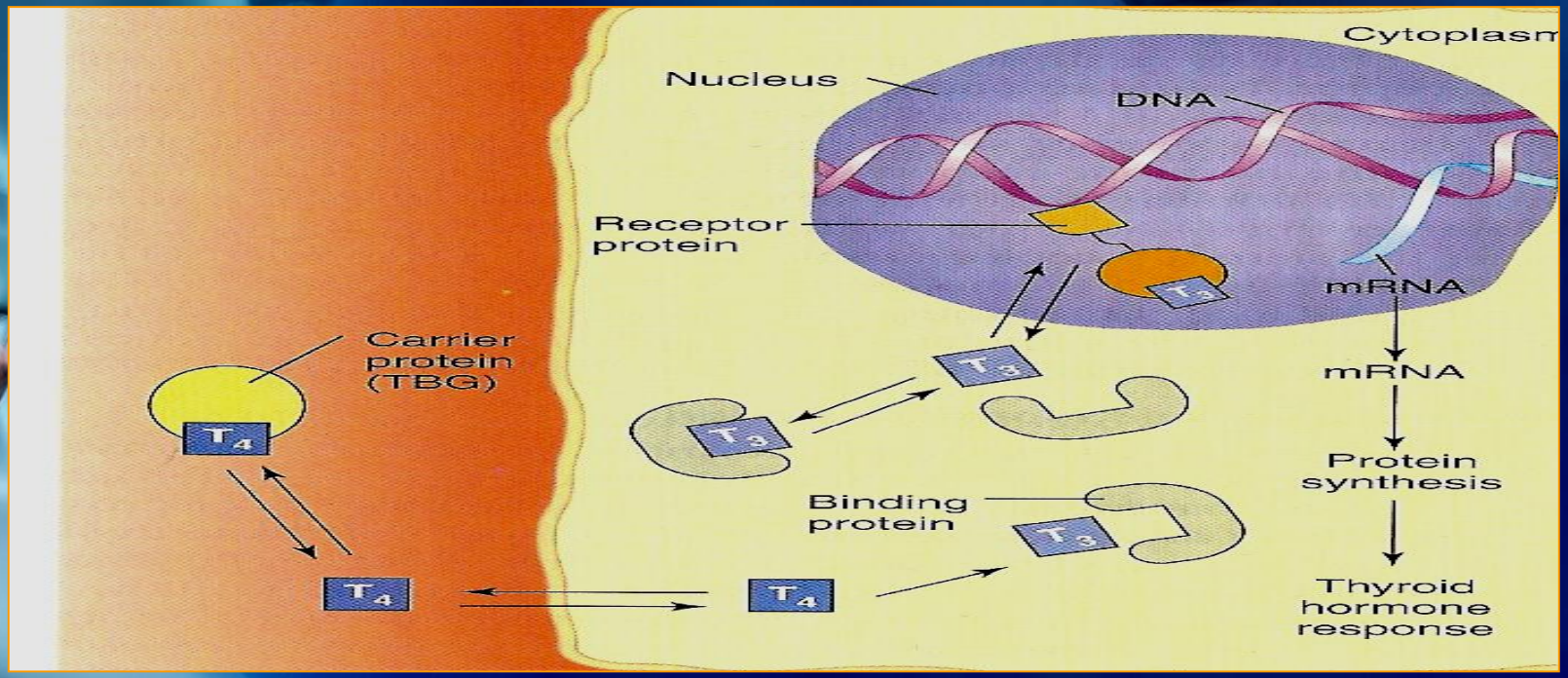


Jod-Basedow Effect

- Opposite of the Wolff Wolff-Chaikoff effect
- Excessive iodine loads induce hyperthyroidism
- Observed in hyperthyroid disease processes
  - ✓ Graves disease
  - ✓ Toxic multinodular goiter
  - ✓ Toxic adenoma
  - ✓ This effect may lead to symptomatic thyrotoxicosis in
- patients who receive large iodine doses from
  - ✓ Dietary changes
  - ✓ Contrast administration
  - ✓ Iodine containing medication (Amiodarone Amiodarone)

Mechanism of action of thyroid hormones

- THs are lipophilic amino acid derivative hormones.
- Their receptors are located within the nucleus of target cells




Thyroid Hormone Action

Metabolic effects of thyroid hormones

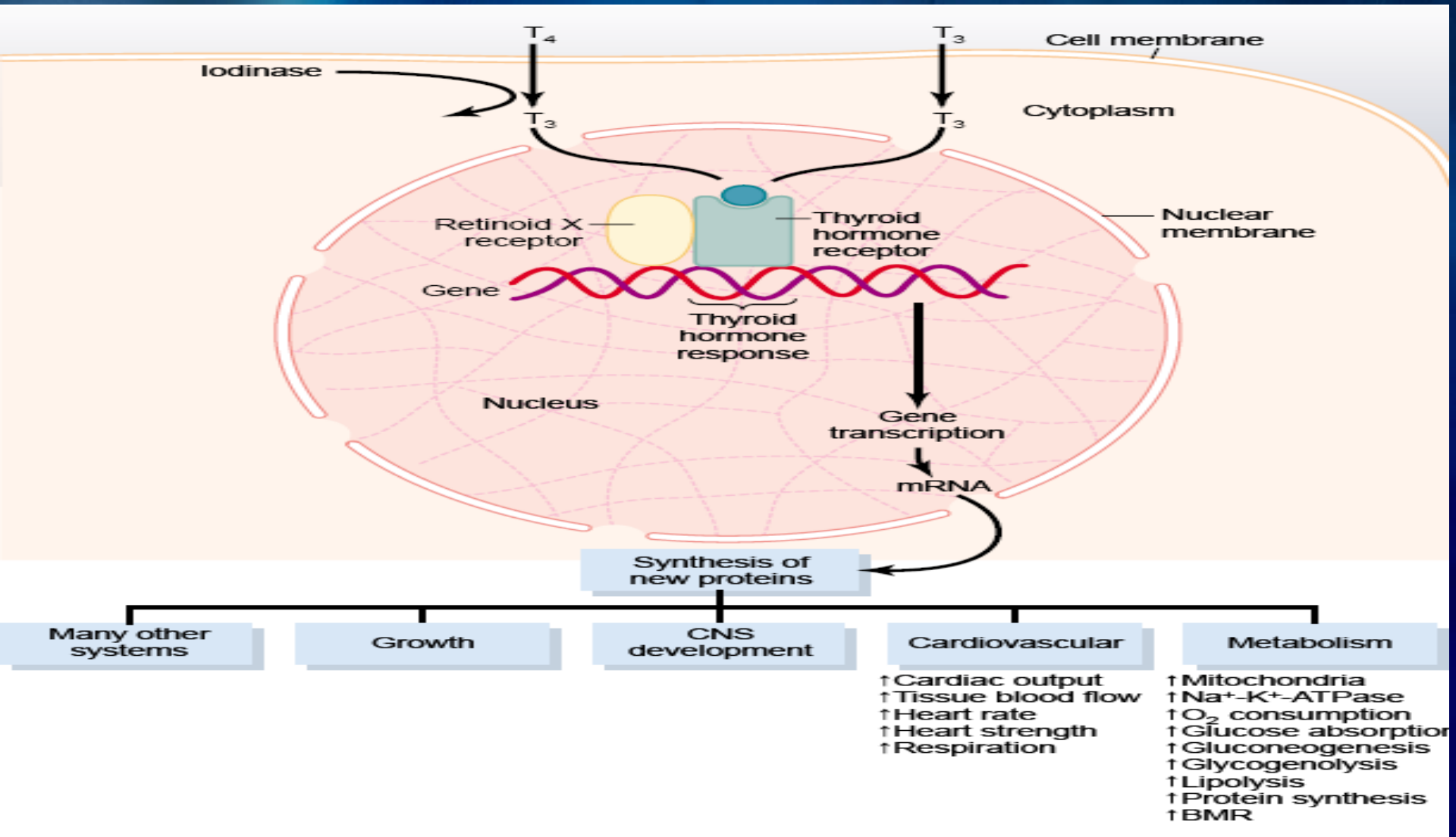
- Growth
- Central nervous system
- Cardiovascular system
- Reproductive system
- Lipid metabolism
- Carbohydrate metabolism
- Development (fetal and neonatal brain)
- Muscle metabolism
- Electrolyte balance
- Vitamin metabolism
- Hematopoietic system
- Gastrointestinal L system

Functions of thyroid hormones

Calorigenic action of thyroid hormones

- Thyroid hormones increase O2 consumption of most tissues in the body, increasing heat production and BMR
- ✓ Stimulates increased consumption of glucose, fatty acids and other molecules.
- ✓ Increases metabolic heat, by mitochondrial no & activity ATP
- ✓ Stimulates rate of cellular respiration by:
  - ❖ Production of uncoupling proteins.
  - ❖ Increase active transport by Na+/K+ pumps.
  - ❖ Stimulates O2 consumption of most of cells in the body.

Physiologic Functions of the Thyroid Hormones



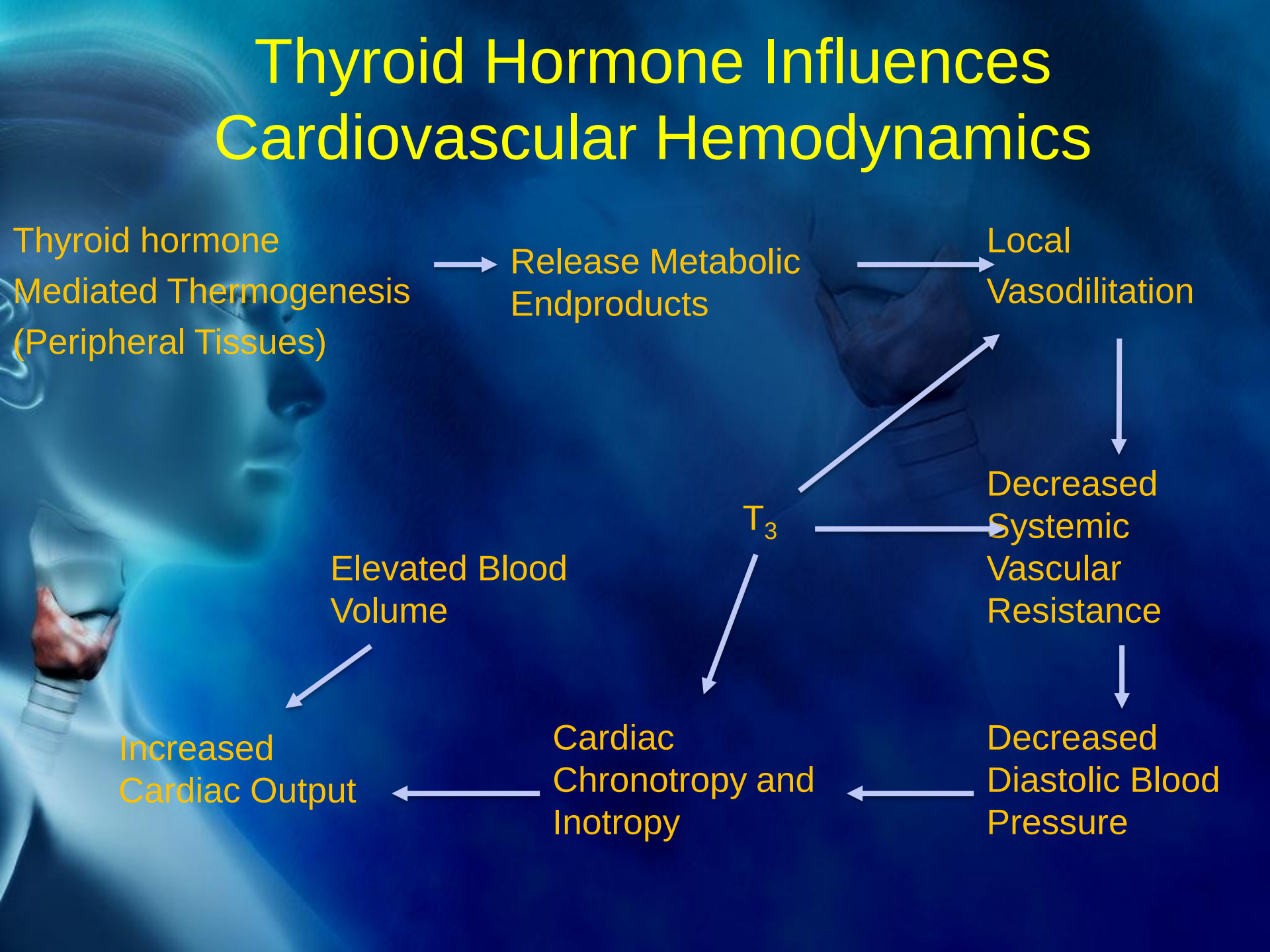
Thyroid Hormone Plays a Major Role in Growth and Development

- Thyroid hormone initiates or sustains differentiation and growth
  - ✓Stimulates formation of proteins, which exert trophic effects on tissues
  - ✓Is essential for normal brain development
- Essential for childhood growth
  - ✓Untreated congenital hypothyroidism or chronic hypothyroidism during childhood can result in incomplete development and mental retardation

Thyroid Hormones and the Central Nervous System (CNS)

- Thyroid hormones are essential for neural development and maturation and function of the CNS
- Decreased thyroid hormone concentrations may lead to alterations in cognitive function
  - ✓ Patients with hypothyroidism may develop impairment of attention, slowed motor function, and poor memory
  - ✓ Thyroid-replacement therapy may improve cognitive function when hypothyroidism is present

Thyroid Hormone Influences Cardiovascular Hemodynamics



Thyroid Hormone Influences the Female Reproductive System

- Normal thyroid hormone function is important for reproductive function
  - ✓Hypothyroidism may be associated with menstrual disorders, infertility, risk of miscarriage, and other complications of pregnancy

Thyroid Hormone is Critical for Normal Bone Growth and Development

- T_3 is an important regulator of skeletal maturation at the growth plate
  - ✓T_3 regulates the expression of factors and other contributors to linear growth directly in the growth plate
  - ✓T_3 also may participate in osteoblast differentiation and proliferation, and chondrocyte maturation leading to bone ossification

Thyroid Hormone Regulates Mitochondrial Activity

- Thyroid hormone is considered the major regulator of mitochondrial activity
  - ✓A potent T_3-dependent transcription factor of the mitochondrial genome induces early stimulation of transcription and increases transcription factor (TFA) expression
  - ✓T_3 stimulates oxygen consumption by the mitochondria

The Physiological Actions of Thyroid Hormones

Category	Specific Action
Development of CNS	Inhibit nerve cell replication Stimulate growth of nerve cell bodies Stimulate branching of dendrites Stimulate rate of axon myelinization
Body growth	Stimulate expression of gene for GH in somatotrophs Stimulate synthesis of many structural and enzymatic proteins Promote calcification of bones
Basal energy economy of the body	Regulate basal rates of oxidative phosphorylation, body heat production, and oxygen consumption (thermogenic effect)
Intermediary metabolism	Stimulate synthetic and degradative pathways of carbohydrate, lipid, and protein metabolism

Effects of Thyroid Hormone On (Carbohydrate Metabolism)

- Thyroid hormone stimulates almost all aspects of carbohydrate metabolism, including
  - ✓ Rapid uptake of glucose by the cells
  - ✓ Enhanced glycolysis
  - ✓ Enhanced gluconeogenesis
  - ✓ Increased rate of absorption from the gastro-intestinal tract
  - ✓ Increased insulin secretion with its resultant secondary effects on carbohydrate metabolism

Effects of Thyroid Hormone (Fat Metabolism)

- lipids are mobilized rapidly from the fat tissue
- Which decreases the fat stores of the body to a greater extent than almost any other tissue element
- This also increases the free fatty acid concentration in the plasma and greatly accelerates the oxidation of free fatty acids by the cells.

Effects of Thyroid Hormone (Fat Metabolism)

- Stimulates lipolysis and release of free fatty acids and glycerol
- Induces expression of lipogenic enzymes
- Effects cholesterol metabolism
- Stimulates metabolism of cholesterol to bile acids
- Facilitates rapid removal of LDL from plasma

The Physiological Actions of Thyroid Hormones (Protein Metabolism)

⇧ protein synthesis (normal level)

⬆ Na+-K+ pump, myosin ATPase activity, amount of calcium both in skeletal and heart muscle

⬇

Normal muscle function

⬆ High level of thyroid hormone

⬇

⬆ protein breakdown

Inhibit creatine kinase

The Physiological Actions of Thyroid Hormones (Protein Metabolism)

- Thyroid hormones act on nucleus receptor to activate DNA transcription and synthesis of mRNA, hence to promote the synthesis of proteins and enzymes.

Positive nitrogen balance

- ✓ Hyperthyroidism → Negative nitrogen balance.
- ✓ Hypothyroidism →mucoprotein↑→myxedema

Effects of Thyroid Hormone on (gastrointestinal tract)

- Thyroid hormones increase the appetite and food intake by metabolic rate increased
- Thyroid hormones increase both the rate of secretion of the digestive juices and the motility of the gastrointestinal tract
- Lack of thyroid hormone can cause constipation.

The Physiological Actions of Thyroid Hormones

- Increased milk production in lactation
- Calcium mobilization from bone
- Increase heart rate and contractility
  - ✓At least partly due to increased sensitivity to catecholamines
- Necessary for normal menstrual cycles and fertility


Abnormal thyroid hormones secretions

Hyperthyroidism (thyrotoxicosis)

- Hyperthyroidism → ↑ THs.
- <u>Could be</u>

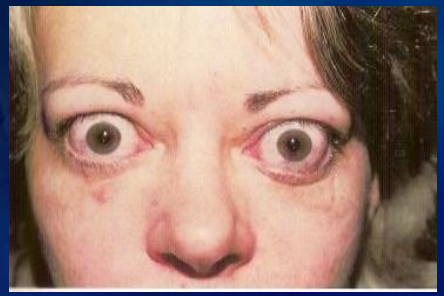
1ry hyperthyroidism … (diseases is in the gland),
e.g. Grave's disease
Exerts TSH-like effects on thyroid.
Not affected by negative feedback.
↑ T_3 & T_4 → reflex ↓ **TSH**.

2ry hyperthyroidism … (disease is higher up)
↑ **TRH** → ↑ **TSH** → ↑ T_3 & T_4.

- Follicular cells become overactive
- Females > males (4:1)

Hyperthyroidism … 'Grave's disease'

- 50% of hyperthyoidism is due to "Grave's disease"
- GD is an autoimmune disease → ↑ thyroid stimulating antibodies IgG



- **Symptoms of GD**
  - ✓ Exophthalmous, due to retro-orbital oedema (irreversible)
  - ✓ Lid lag, due to weakness of extraoccular muscles (reversible)
  - ✓ Anxiety & restlessness
  - ✓ Sleeplessness
  - ✓ ↑ appetite, ↓ weight & diarrhea
  - ✓ Intolerance to heat.
- **Treatment:**
  - ✓ drugs to ↓ iodination process, such as PTU 'Propylthiouracil'; MMI 'methylmercaptoimidazole'.

Hypothyroidism
Adult (Myxedema)

- Hypothyroidism in adults → ↓ THs.
- <u>Could be</u>:

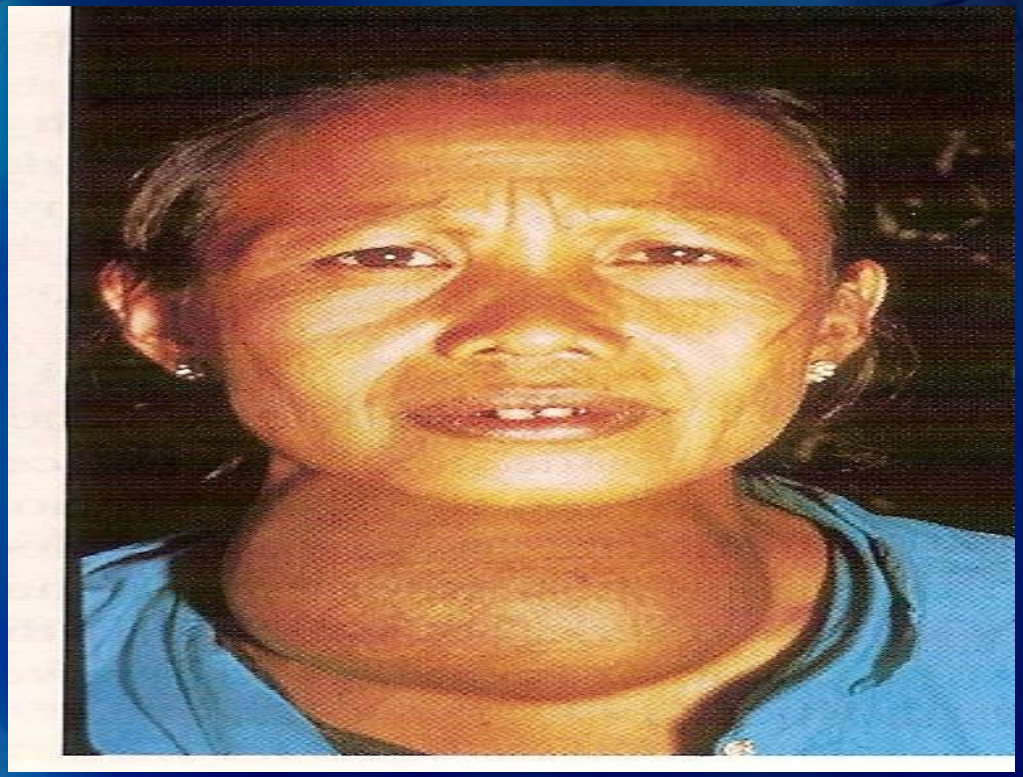
  1ry hypothyroidism … (diseases is in the gland)
  - autoimmune disease such as "Hashimoto's throiditis".
  - lack of iodine.
  - absence of deiodination enzyme.

  ↓ **T_3** & **T_4** → reflex ↑ **TSH**.

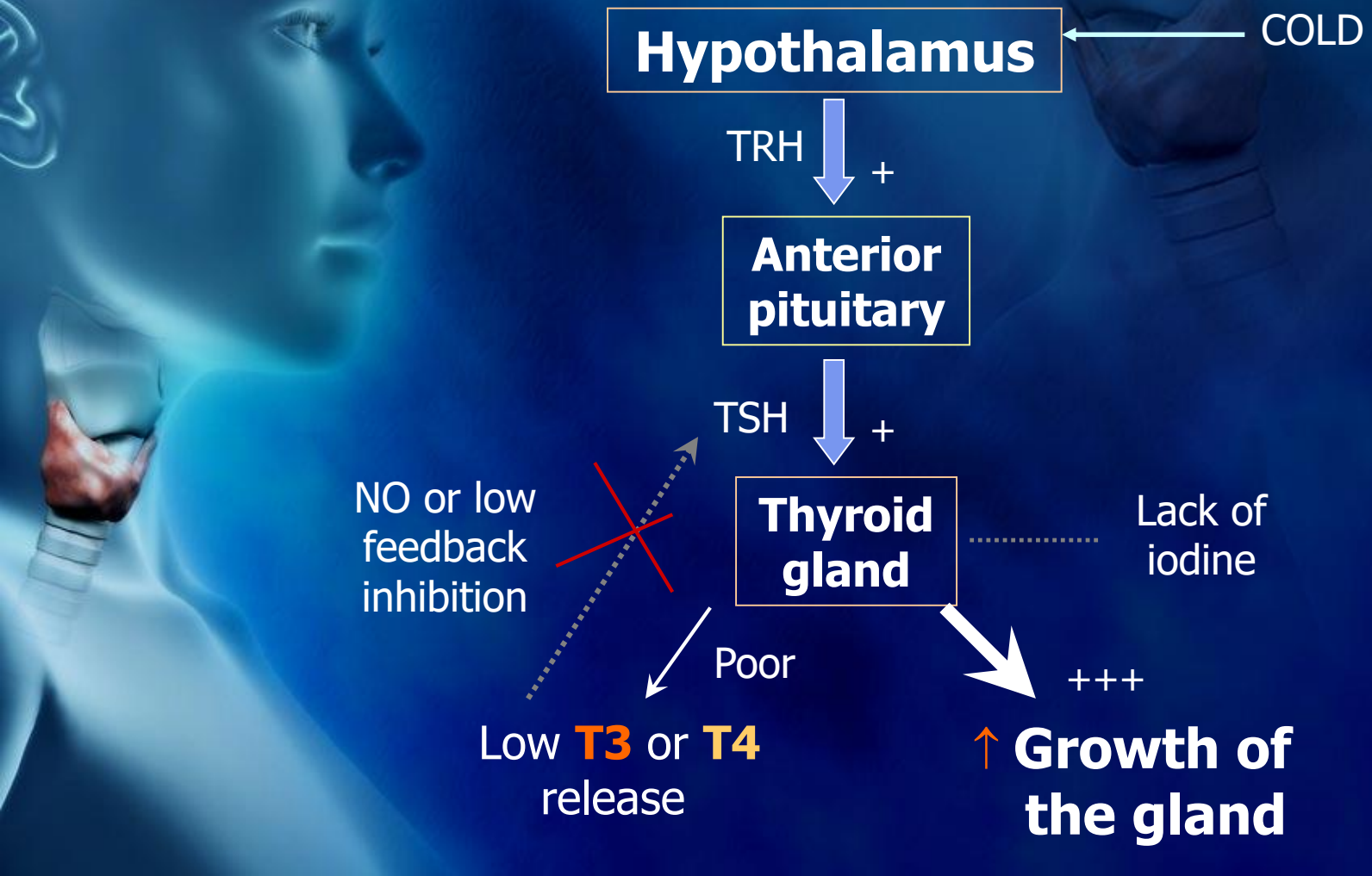
  2ry hypothyroidism … (disease is higher up)
  ↓ **TRH** → ↓ **TSH** → ↓ **T_3** & **T_4**.
- Follicular cells become less active.

Hypothyroidism (myxedema)

- If **No Iodine** → ↓ **T_3** & **T_4** → ↑ **TRH** → ↑ **TSH** → ↑ growth (size) of the gland → **simple goiter**.



How goiter ‘swollen neck’ is formed? With lack of iodine …



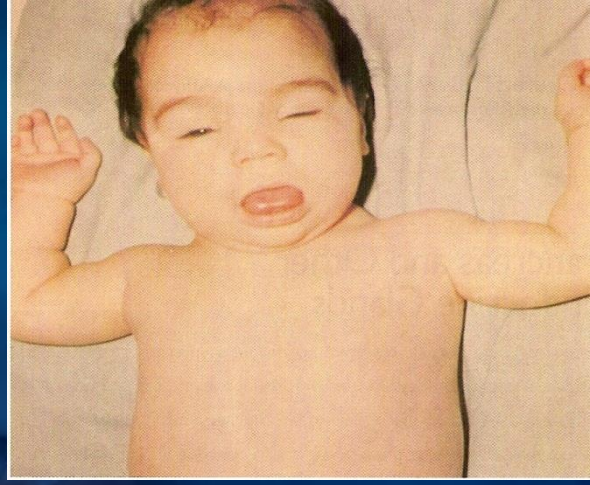
Hypothyroidism (myxedema)

- If there is **absence of deionization enzyme** → NO recycle synthesis of **DIT** & **MIT** → accumulate.
- **DIT** & **MIT** will not be used for new THs formation → ↓ **THs**.

Hypothyroidism (myxedema)

- Symptoms of Hypothyroidism
  - ✓ Decreased metabolic rate.
  - ✓ Slow heart rate & pulse.
  - ✓ Slow muscle contractions
  - ✓ ↓ appetite, ↑ weight gain, & constipation.
  - ✓ Prolonged sleep, & dizziness.
  - ✓ Coarse skin.
  - ✓ Slow thinking, lethargy, & mask face.
  - ✓ Intolerence to cold (↓ ability to adapt cold).
  - ✓ Myxoedema → swollen & puffy appearance of body,
  - ✓ due to deposition of protein-carbohydrate complexes
  - ✓ 'mucopolysaccharides' & fluid in subcutaneous tissue.

Hypothyroidism Children (Cretinism)



- Hypothyroidism in children→ ↓ THs
  - ✓ Hypothyroid from end of 1st trimester to 6 months postnatally, or in the 1st few years of life

    ↓ T_3 & T_4 → reflex ↑ **TSH**
- **Additional Signs & Symptoms:**
  - ✓ Short stature (due to ↓ growth of bones, muscle, & brain)
  - ✓ Severe mental retardation
- **Treatment:** Thyroxine.

Figure 5: Cretin in China J Dunn, 1991

Cretinism

Severe mental retardation

Severe growth deficit

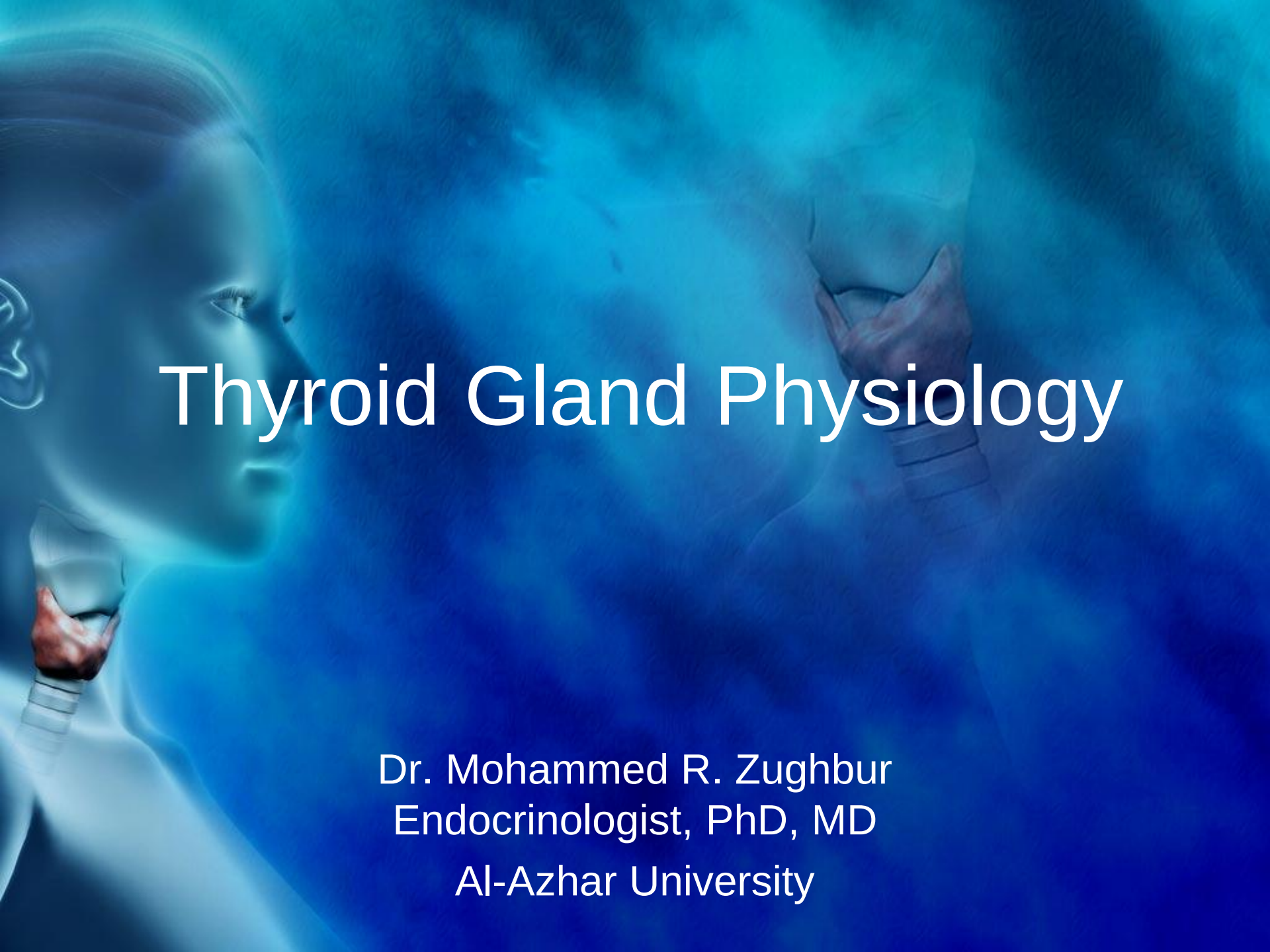
Paraplegia (lower limb paralysis)

Rigidity

Deaf-mutism

Facial disturbances

The type and severity of brain, neural and musculoskeletal defects arise from timing, severity and duration of deficiency.



Thyroid Gland Physiology

Dr. Mohammed R. Zughbur
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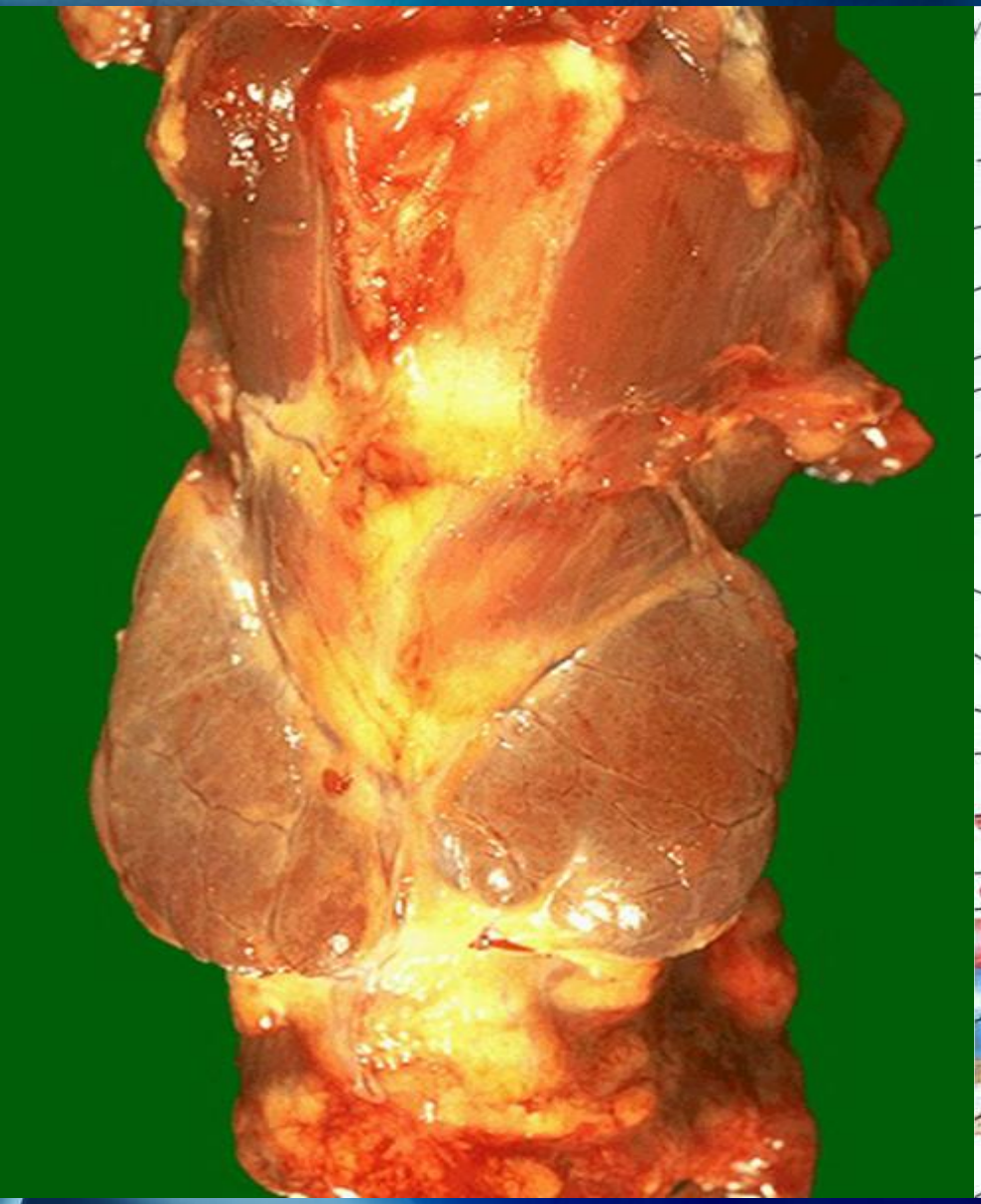
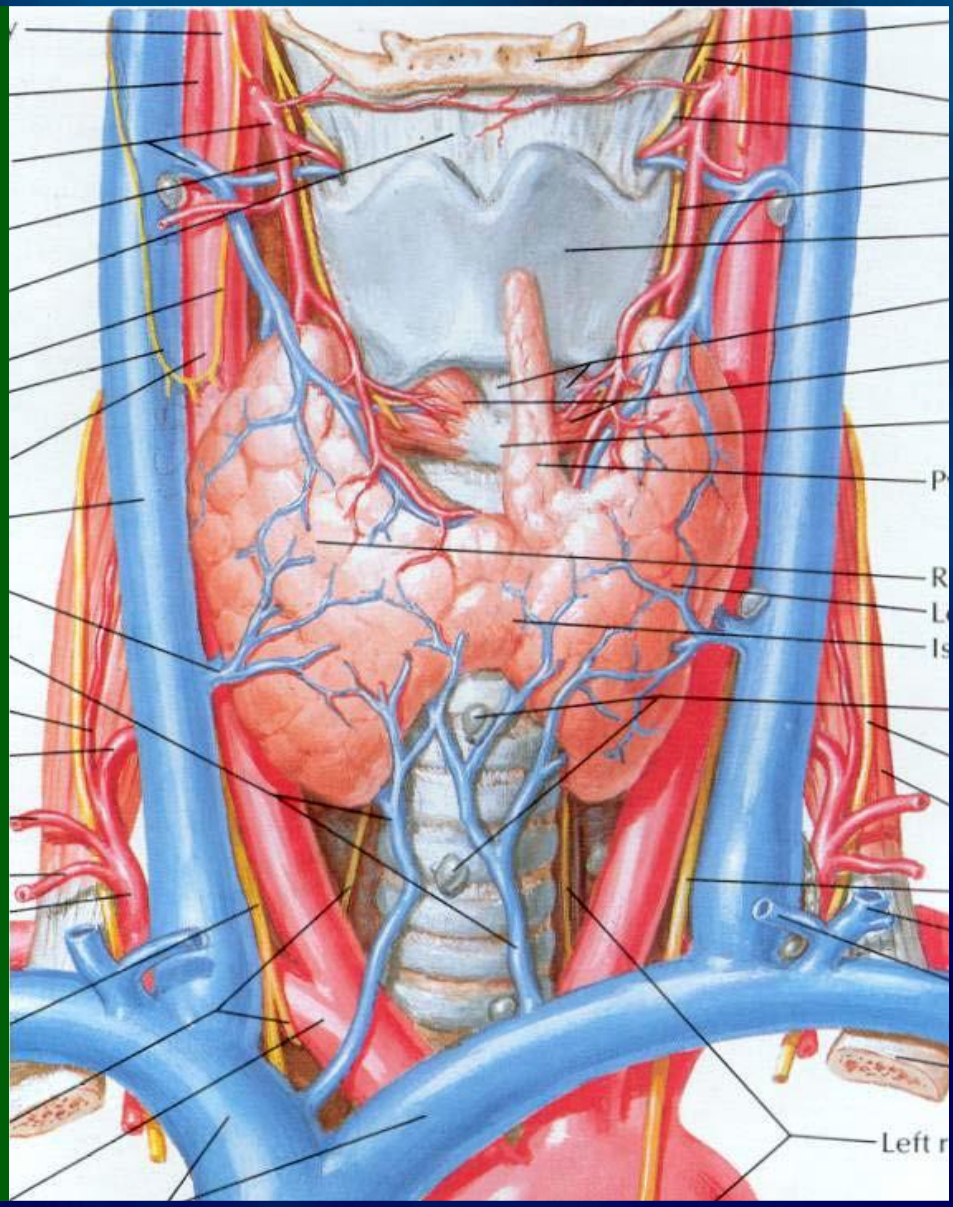
Aims

- Functional anatomy of thyroid gland
- Synthesis, secretion and metabolism of the thyroid hormones
- The mechanism of thyroid hormone action
- Role of thyroid hormone in development , growth and metabolism
- Thyroid hormone deficiency and excess in adult

Thyroid Anatomy

- One of the largest of the endocrine glands
- Normally weighing 15 to 20 grams in adults
- Brownish-red and soft during life
- The thyroid gland, located immediately below the larynx on each side of and anterior to the trachea
- Right and left lobes united by a narrow isthmus
- Some people a third “pyramidal lobe” exists, ascending from the isthmus towards hyoid bone





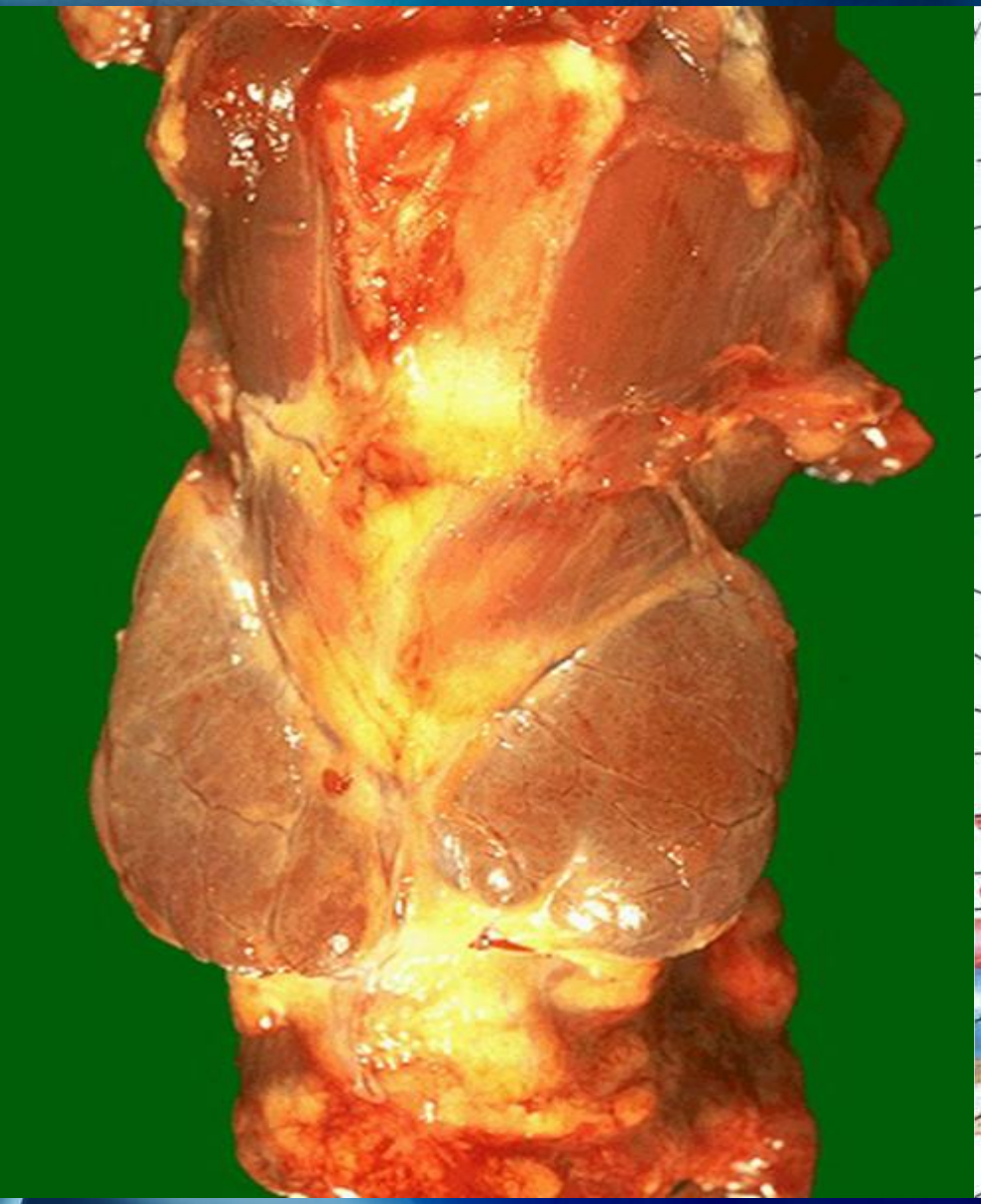
Anterior view

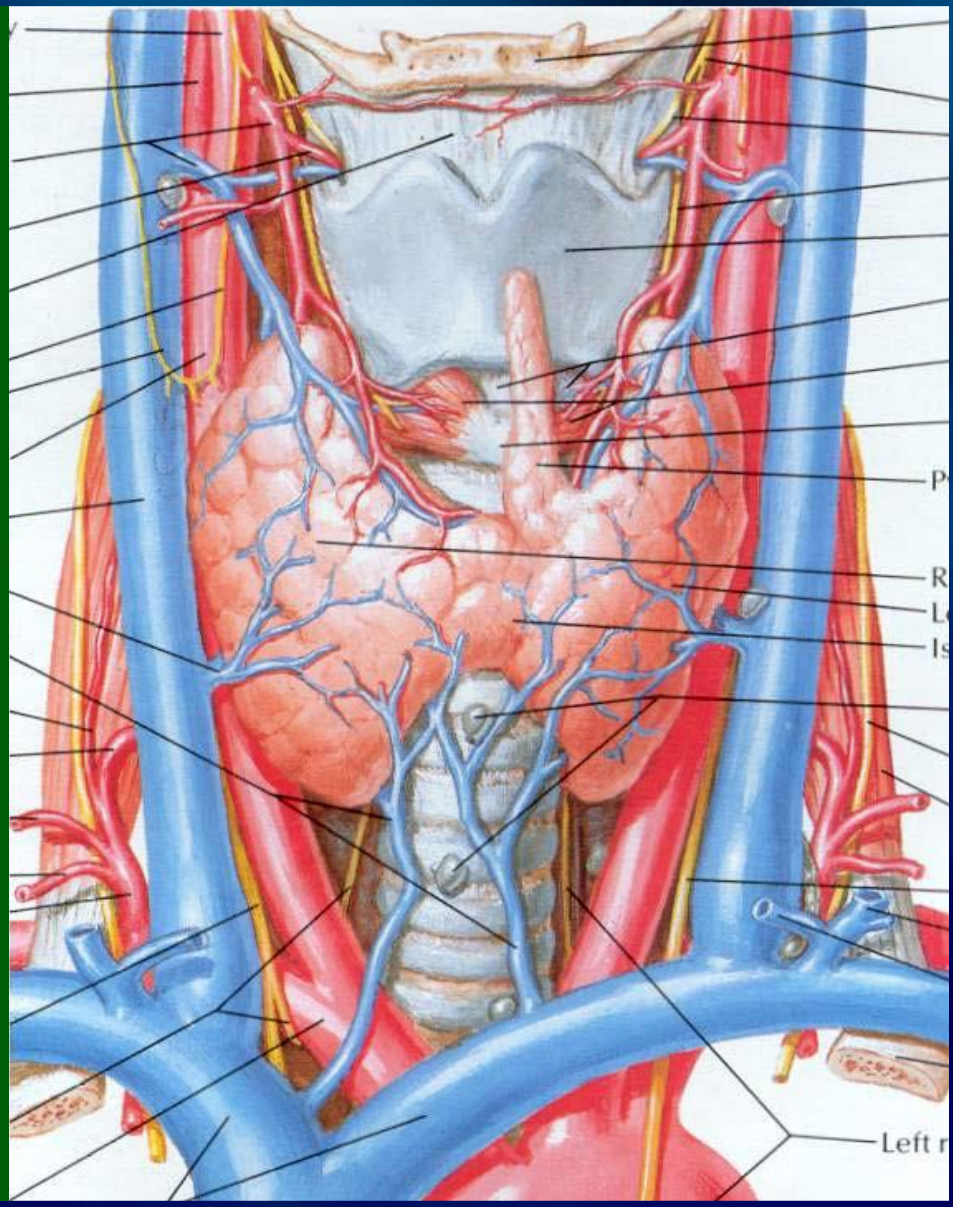
Thyroid Anatomy

- Internal jugular vein and common carotid artery lie postero-lateral to thyroid
- Recurrent laryngeal nerves an important structure lying between trachea and thyroid
- Highly vascular
- Main supply from superior (ECA) and inferior thyroid arteries (thyro-cervical trunk), absent in up to 6%
- Thyroidea ima directly from aorta, innominate artery or right common carotid artery, Present in up to 12%

Thyroid Anatomy

- Superior thyroid vein : IJV or common facial vein
- Inferior jugular vein : innominate vein or IJV
- Middle thyroid vein : IJV
- Lymphatic → paratracheal nodes → superior mediastinum & middle deep cervical node and lateral the neck





Anterior view

Embryology

- Median endodermal derivative that migrates from the tongue base to its normal position in the neck by 7th week
- The distal portion of this thyroglossal duct forms the thyroid gland

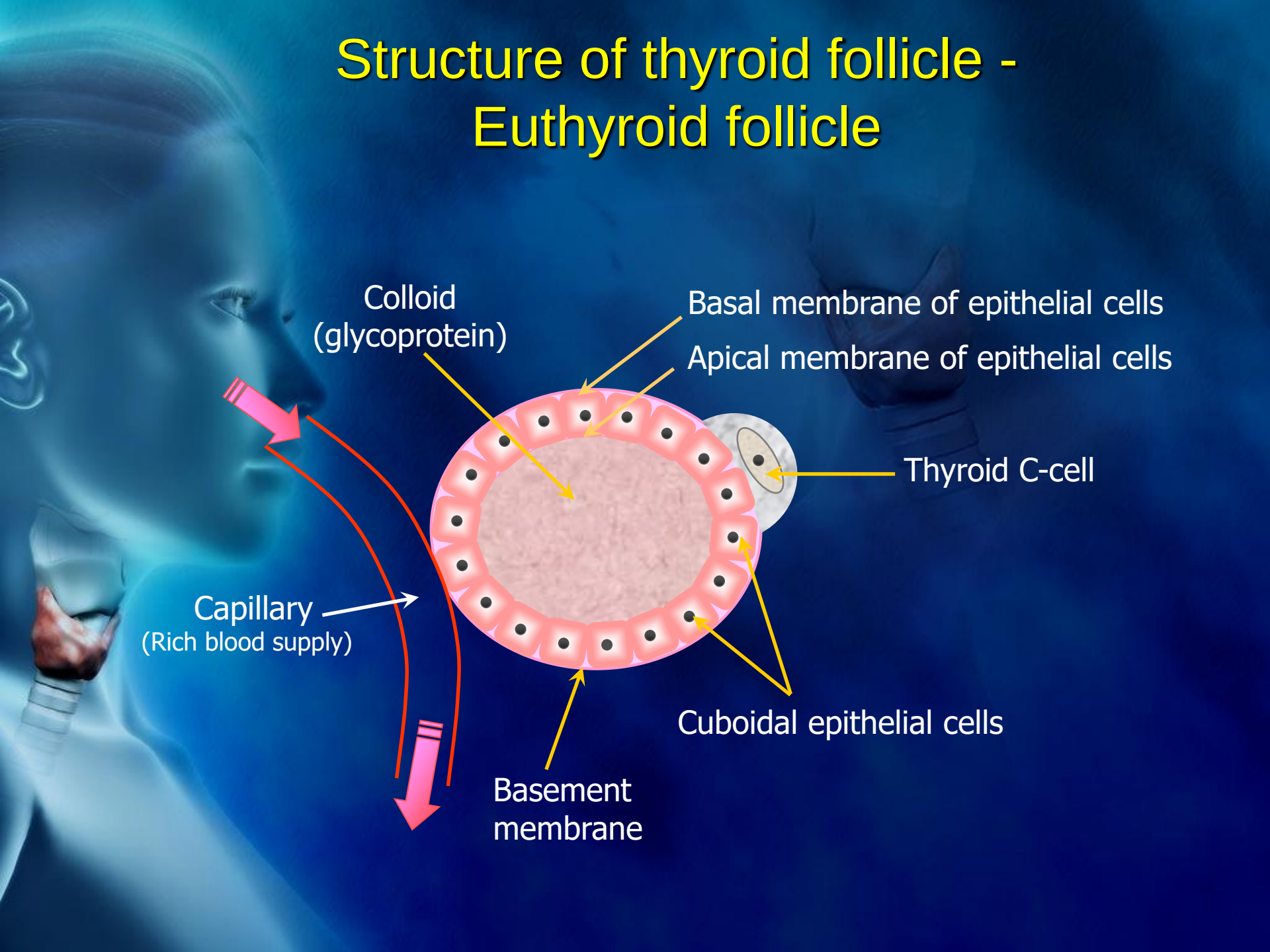
Thyroid Histology

- It is surrounded by a dense irregular collagenous connective tissue capsule
- Thyroid follicles are spherical structures filled with colloid, a viscous gel consisting mostly of iodinated thyroglobulin
- Thyroid follicles are enveloped by a layer of epithelial cells, called follicular cells, which in turn are surrounded by parafollicular cells.

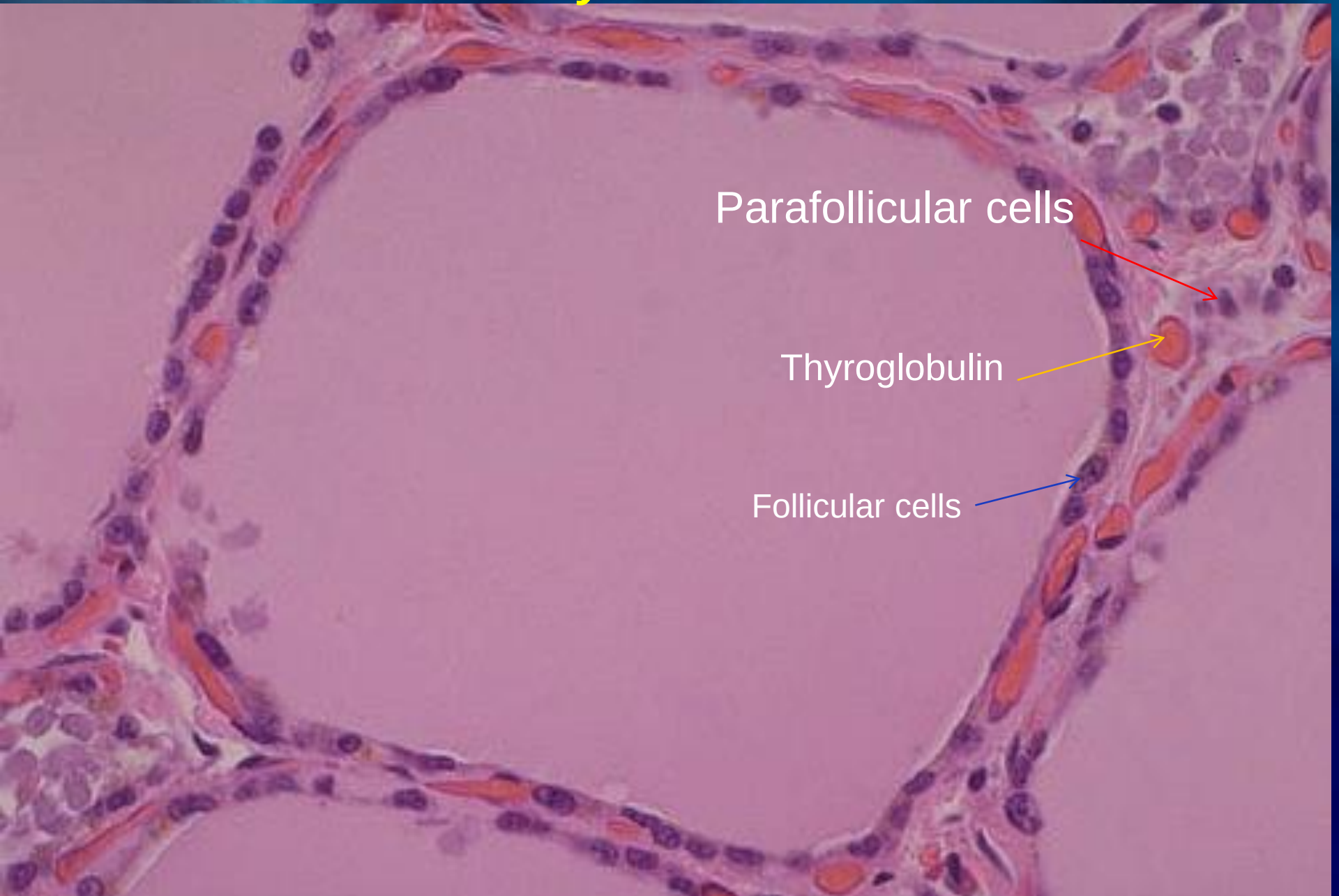
Thyroid Histology

- Follicular cells are normally cuboidal in shape but become columnar when stimulated & squamous when in active
- Follicular cells contain many small apical vesicles, involved in transport & release of thyroglobulin & into the colloid
- Function thyroid follicles synthesize and store thyroid hormones

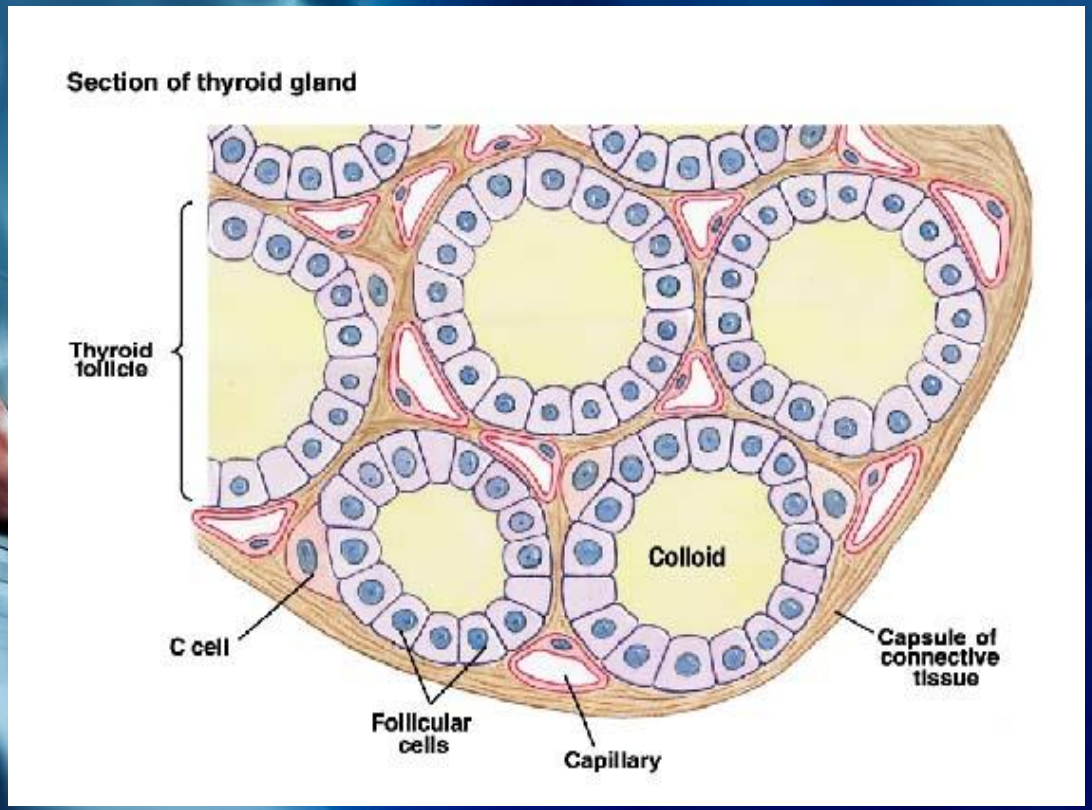
Structure of thyroid follicle - Euthyroid follicle



Thyroid Follicles



Follicles: the Functional Units of the Thyroid Gland



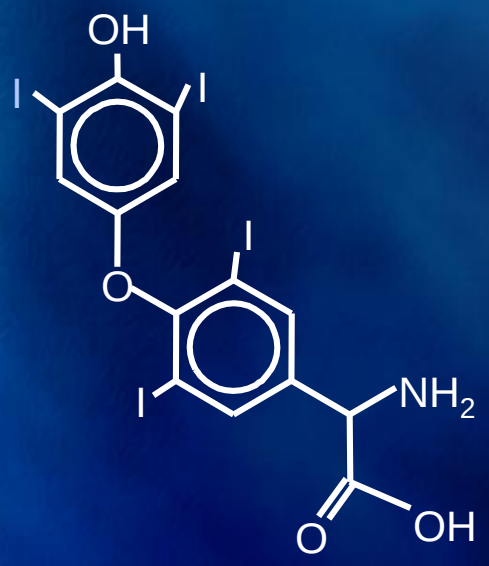
Follicles Are the Sites Where Key Thyroid Elements Function:

- Thyroglobulin (Tg)
- Tyrosine
- Iodine
- Thyroxine (T_4)
- Triiodotyrosine (T_3)

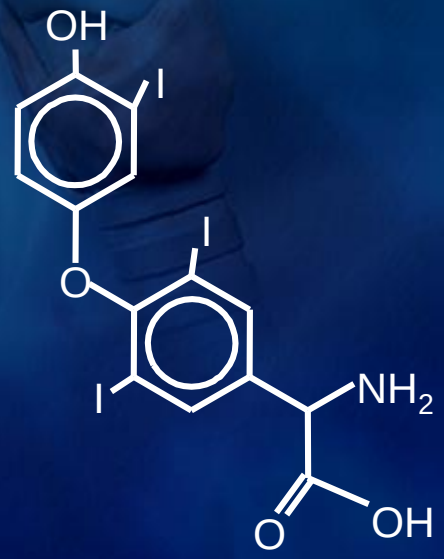
The Thyroid Produces and Secretes

- Two principal hormones
  - ✓Thyroxine (T4) and triiodothyronine (T3)
  - ✓Required for homeostasis of all cells
  - ✓Influence cell differentiation, growth, and metabolism
  - ✓Considered the major metabolic hormones because they target virtually every tissue

Thyroid Hormones



Thyroxine (T_4)



3,5,3’-Triiodothyronine (T_3)

The Thyroid Produces and Secretes

- The two principle raw materials for making thyroid hormones
  - ✓ Tyrosines are provided from a large glycoprotein called thyroglobulin, which is synthesized by thyroid epithelial cells and secreted into the lumen of the follicle
  - ✓ Iodine, or more accurately iodide (I-), is taken up from food

Iodine Sources

- Available through certain foods (eg, seafood, bread, dairy products), iodized salt, or dietary supplements, as a trace mineral
- The recommended minimum intake is 150 µg/day

Biosynthesis of T4 and T3

The process includes

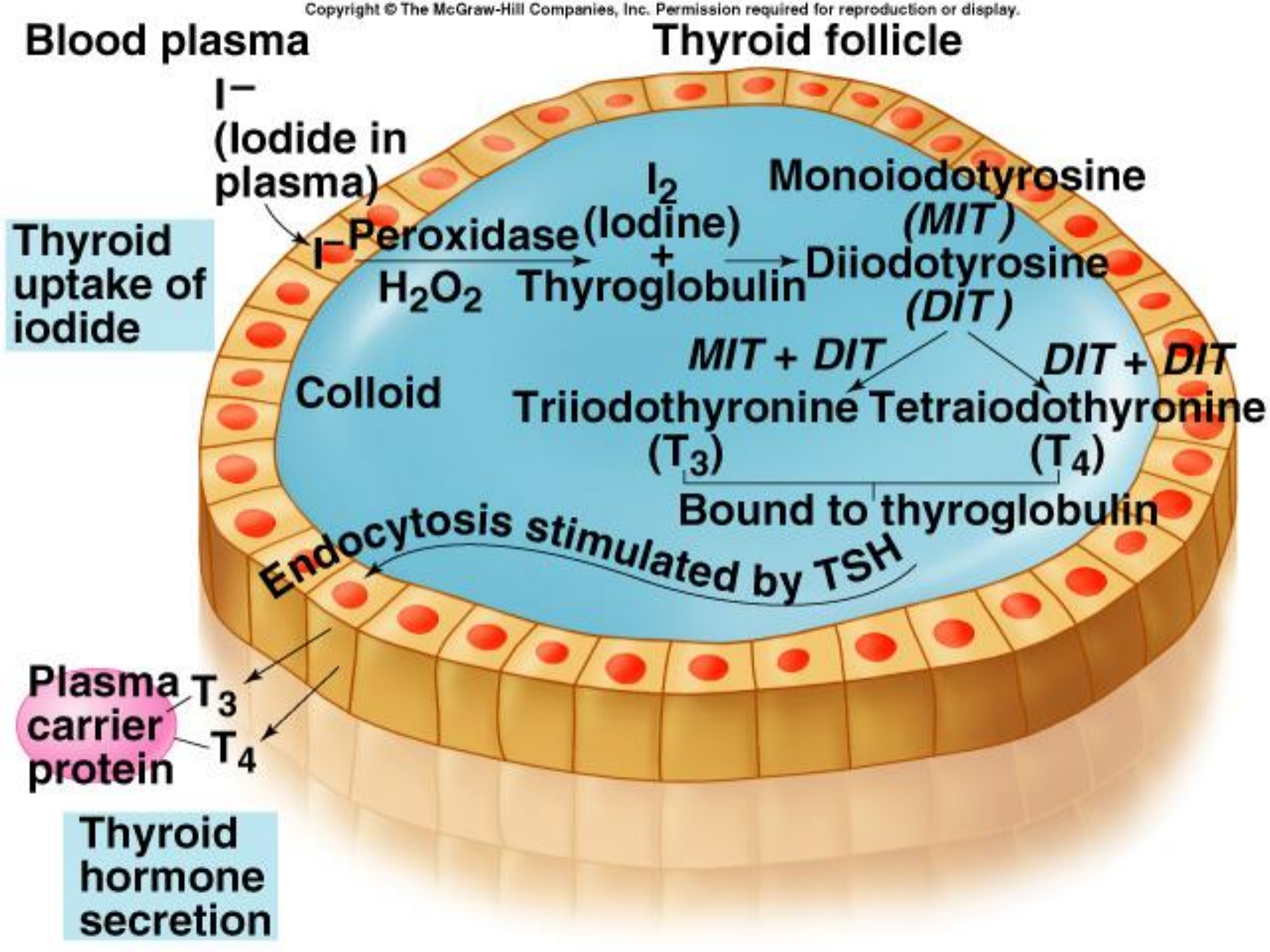
- Dietary iodine (I) ingestion
- Active transport and uptake of iodide (I-) by thyroid gland
- Oxidation of I- and iodination of thyroglobulin (Tg) tyrosine residues
- Coupling of iodotyrosine residues (MIT and DIT) to form T4 and T3
- Proteolysis of Tg with release of T4 and T3 into the circulation

Active Transport and I- Uptake by the Thyroid

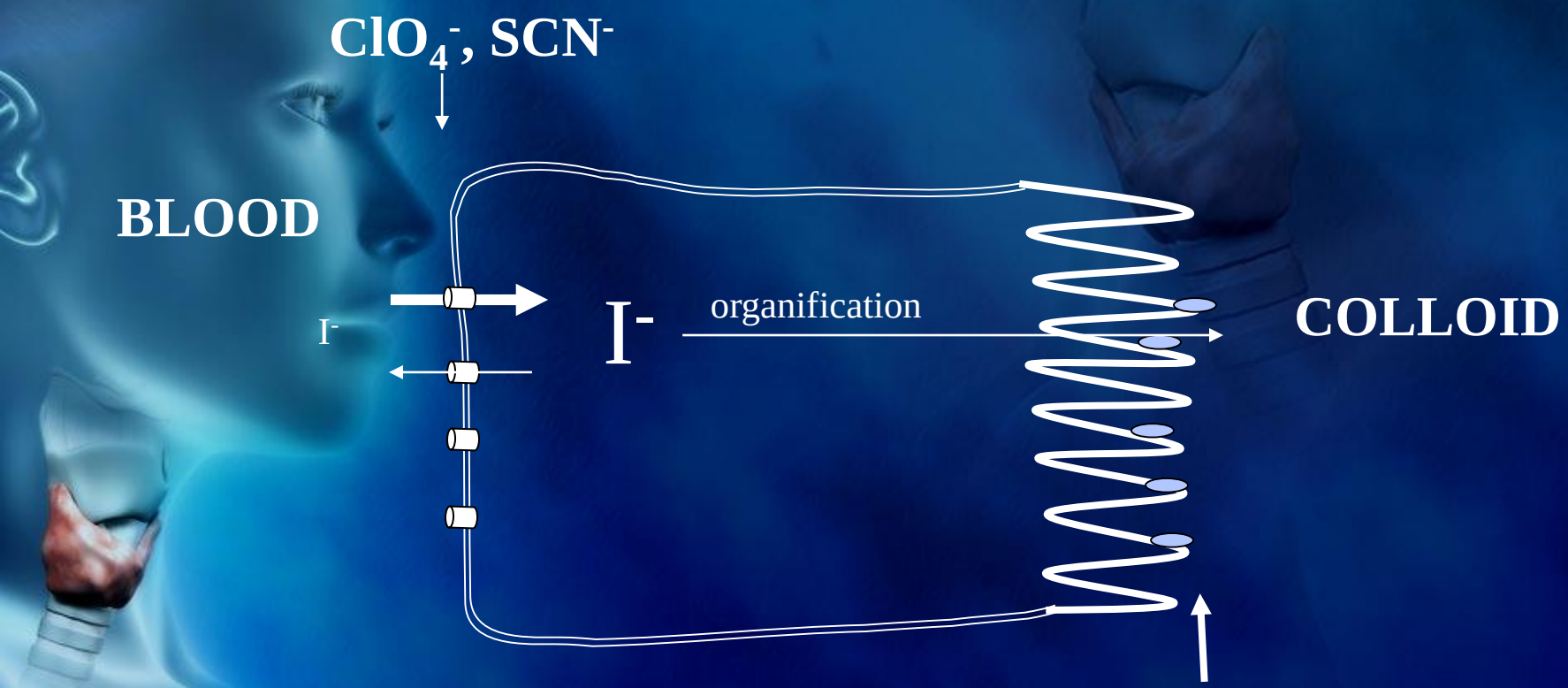
- Dietary iodine reaches the circulation as iodide anion (I-)
- The thyroid gland transports I- to the sites of hormone synthesis
- I- accumulation in the thyroid is an active transport process that is stimulated by TSH

Iodide Active Transport is Mediated by the Sodium-Iodide Symporter (NIS)

- NIS is a membrane protein that mediates active iodide uptake by the thyroid
- It functions as a I- concentrating mechanism that enables I- to enter the thyroid for hormone biosynthesis
- NIS confers basal cell membranes of thyroid follicular cells with the ability to effect “iodide trapping” by an active transport mechanism
- Specialized system assures that adequate dietary I- accumulates in the follicles and becomes available for T4 and T3 biosynthesis



Ion Transport By The Follicular cells

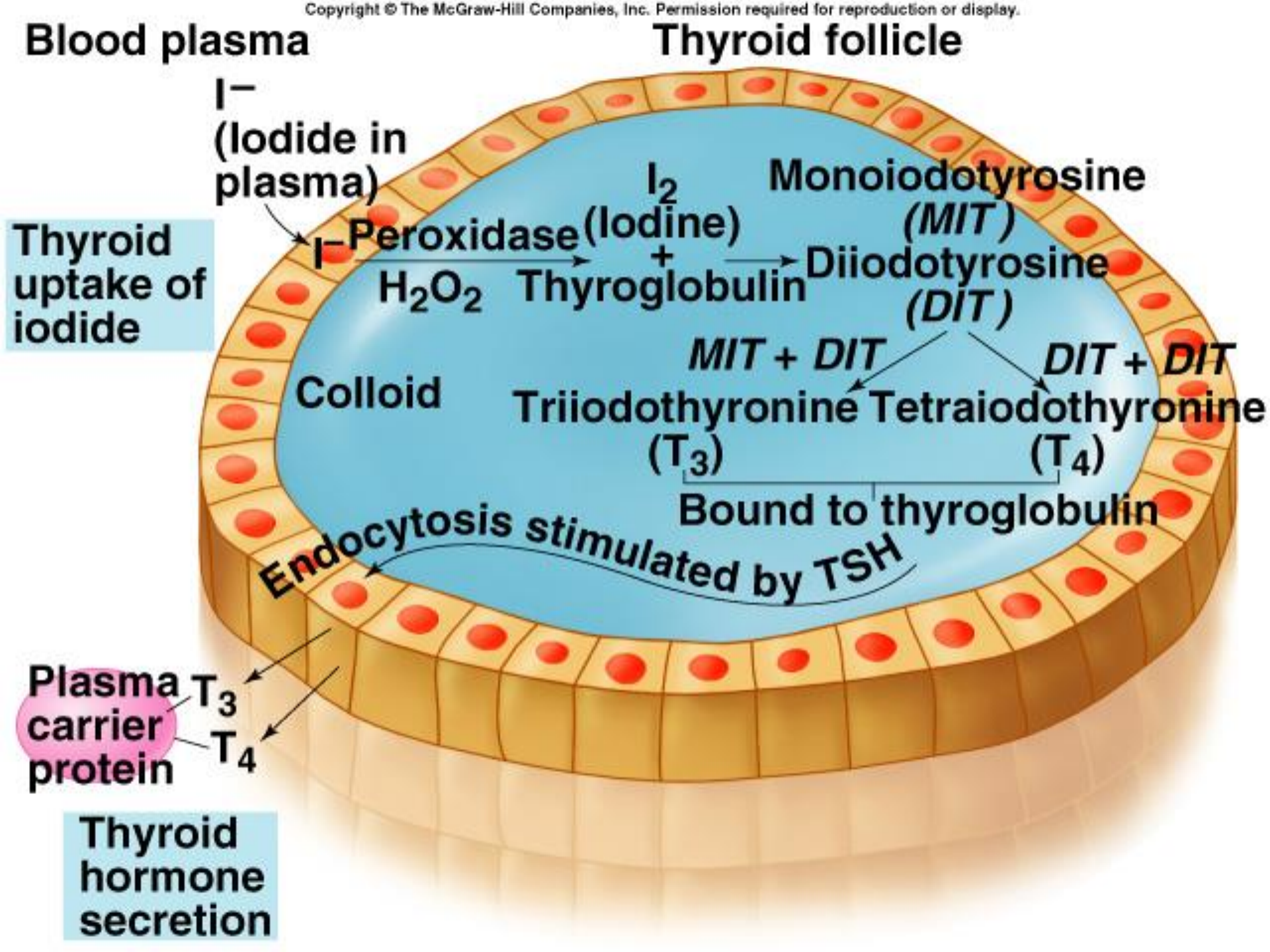


- **NaI symporter (NIS)**
- **Thyroid peroxidase (TPO)**

Propylthiouracil (**PTU**) blocks iodination of thyroglobulin

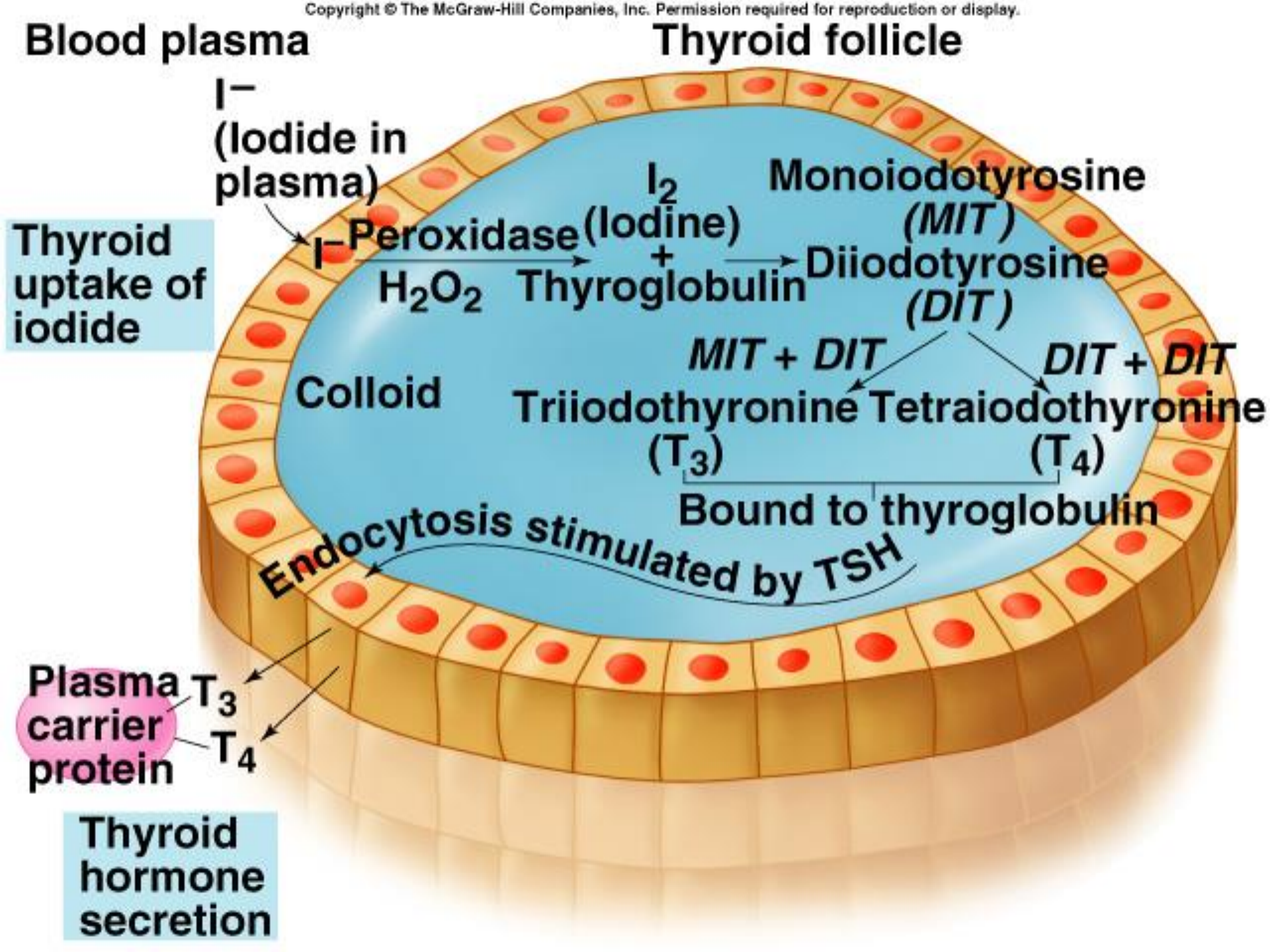
Oxidation of I- and Iodination of Thyroglobulin (Tg) Tyrosyl Residues

- I- must be oxidized to be able to iodinate tyrosyl residues of Tg
- Iodination of the tyrosyl residues then forms monoiodotyrosine (MIT) and diiodotyrosine (DIT), which are then coupled to form either T3 or T4
- Both reactions are catalyzed by TPO



Thyroperoxidase (TPO)

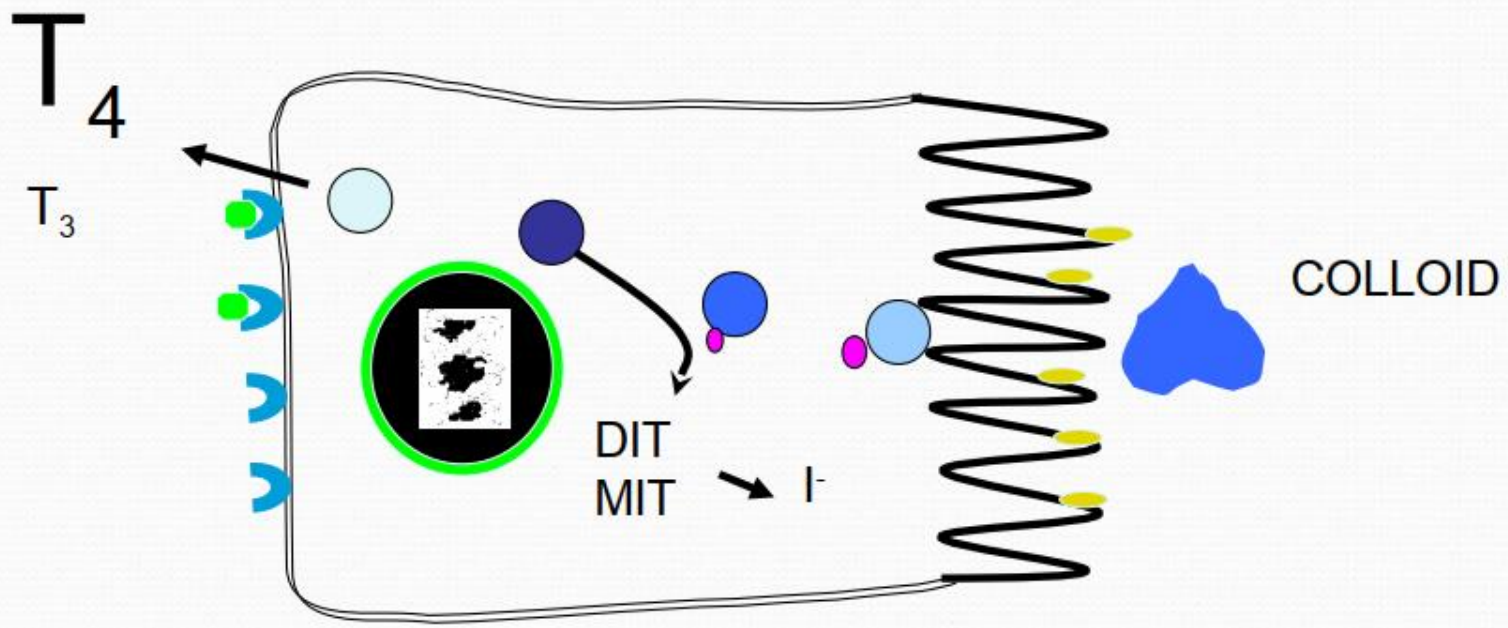
- TPO catalyzes the oxidation steps involved in I- activation, iodination of Tg tyrosyl residues, and coupling of iodotyrosyl residues
- TPO has binding sites for I- and tyrosine
- TPO uses H_2O_2 as the oxidant to activate I- to hypoiodate (OI-), the iodinating species



Thyroid Hormone Deiodinases

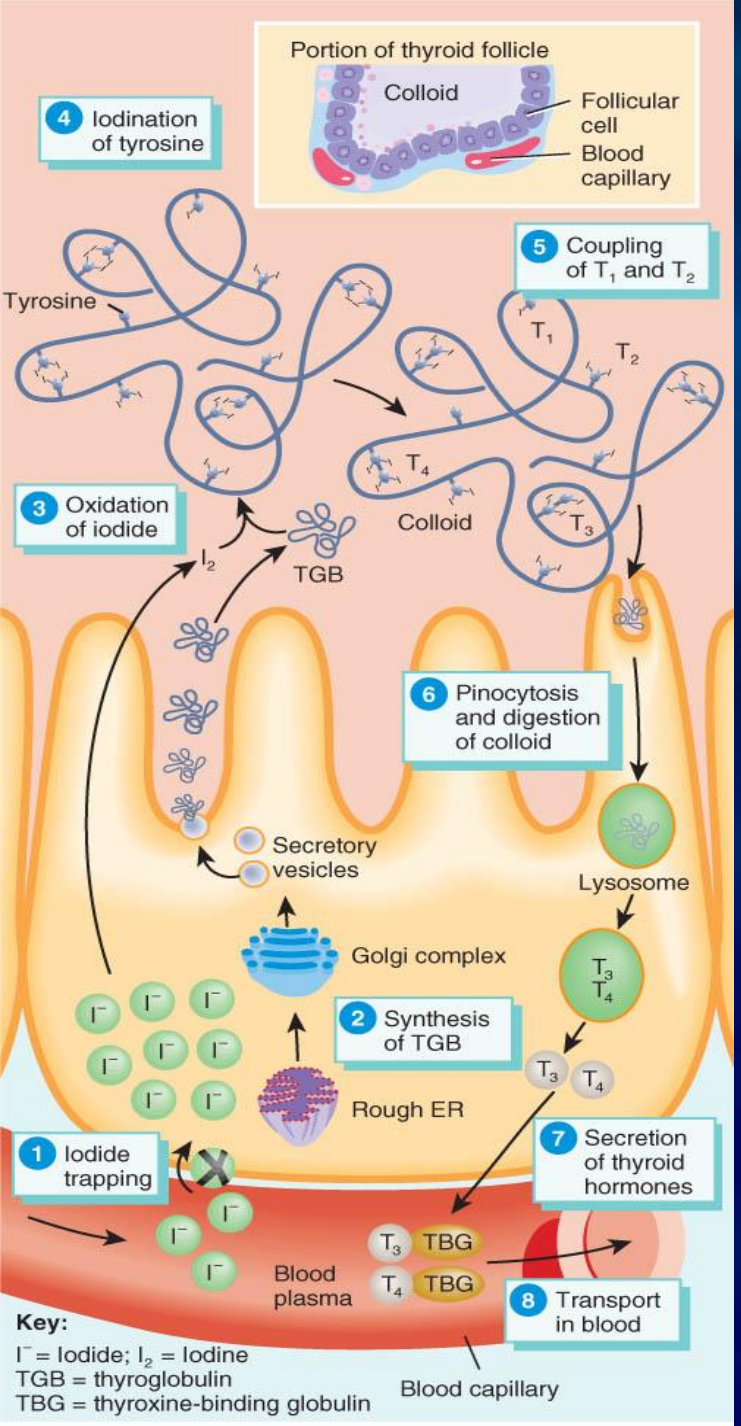
- T4 and T3 are synthesized and stored within the Tg molecule
- Proteolysis is an essential step for releasing the hormones
- To liberate T4 and T3, Tg is resorbed into the follicular cells in the form of colloid droplets, which fuse with lysosomes to form phagolysosomes
- Tg is then hydrolyzed to T4 and T3, which are then secreted into the circulation

THYROID HORMONE SECRETION BY THE THYROID FOLLICULAR CELL



TSH

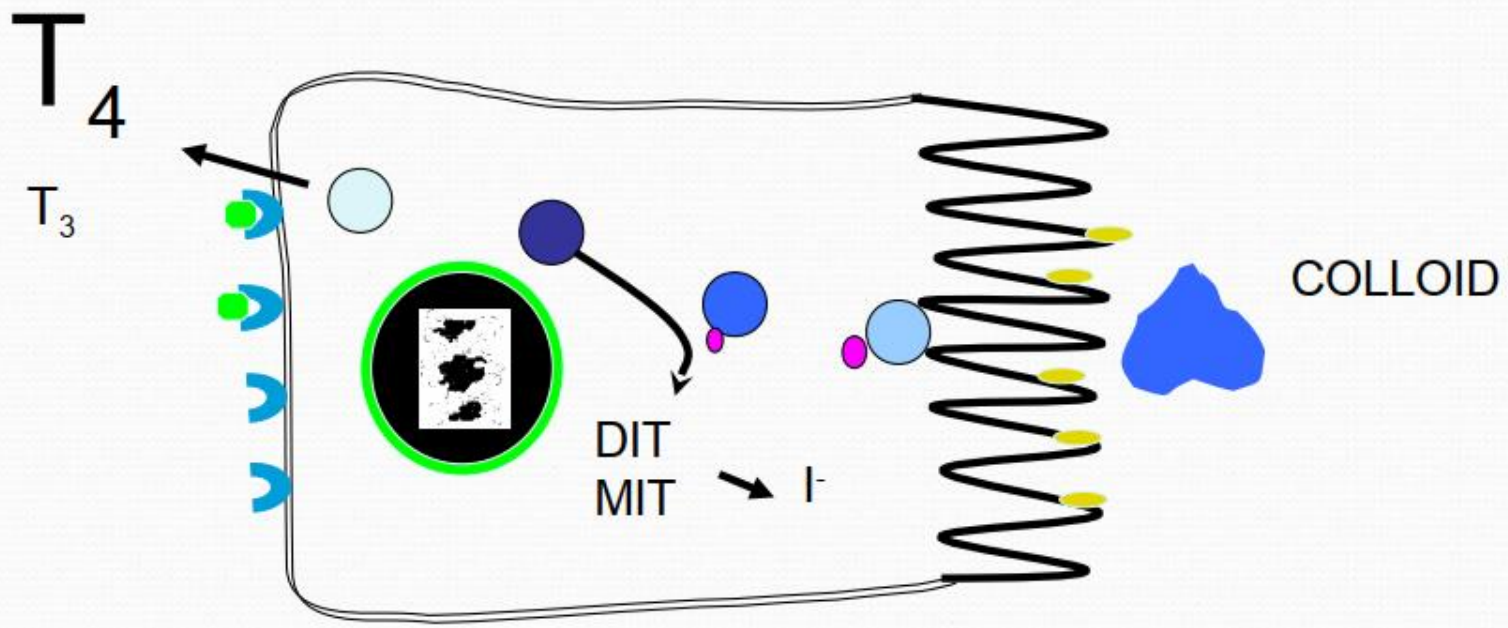
TSH receptor



Formation of Thyroid Hormone

- Iodide trapping by follicular cells
- Synthesis of thyroglobulin (TGB)
- Release of TGB into colloid
- Iodination of tyrosine in colloid
- Formation of T3 & T4 by combining T1 and T2 together
- Uptake & digestion of TGB by follicle cells
- Secretion of T3 & T4 into blood

THYROID HORMONE SECRETION BY THE THYROID FOLLICULAR CELL



TSH

TSH receptor

Thyroid Hormone Deiodinases

- Types 1 and 2 deiodinases convert T4 to T3
  - ✓D1 primarily in liver and kidney, supplies plasma T3
  - ✓D2 in pituitary, brain, placenta, brown fat, muscle and thyroid; produces T3 for “local” use as well as plasma T3
- Type 3 deiodinase (D3) removes an inner ring iodine
  - ✓Converts T4 to reverse T3, and T3 to T2
  - ✓D3 inactivates thyroid hormone

Thyrotropin-Releasing Hormone (TRH)

- Produced by Hypothalamus
- Tripeptide-amide (pyroglutamyl-histidyl-proline-amide
- Release is pulsatile, circadian
- Down regulated by T 3
- Travels through portal venous system to adenohypophysis
- Stimulates TSH formation

Thyroid-Stimulating Hormone (TSH)

- 28 kDa glycoprotein dimer composed of non-covalently linked alpha and beta chains.
- The alpha chain is shared by TSH, FSH, LH and HCG
- The biological specificity of each glycoprotein hormone is conferred by the beta chain
- TSH receptors are members of the large family of G-protein coupled receptors.
- The major second messenger is cAMP.

Thyroid-Stimulating Hormone (TSH)

- Up regulated by TRH
- Down regulated by T4, T3
- Travels through portal venous system to cavernous sinus, body.
- Stimulates several processes
  - ✓ Iodine uptake
  - ✓ Colloid endocytosis
  - ✓ Growth of thyroid gland
- Produced by AdenohypophysisThyrotrophs

TSH Regulation of thyroid function

- TSH binds to specific cell surface receptors that stimulate adenylate cyclase to produce cAMP.
- TSH increases metabolic activity that is required to synthesize Thyroglobulin (Tg) and generate peroxide.
- TSH stimulates both I^- uptake and iodination of tyrosine resides on Thyroglobulin.

Hypothalamic-Pituitary-Thyroid Axis Negative Feedback Mechanism

HYPOTHALAMUS - TRH

ANT. PITUITARY - TSH

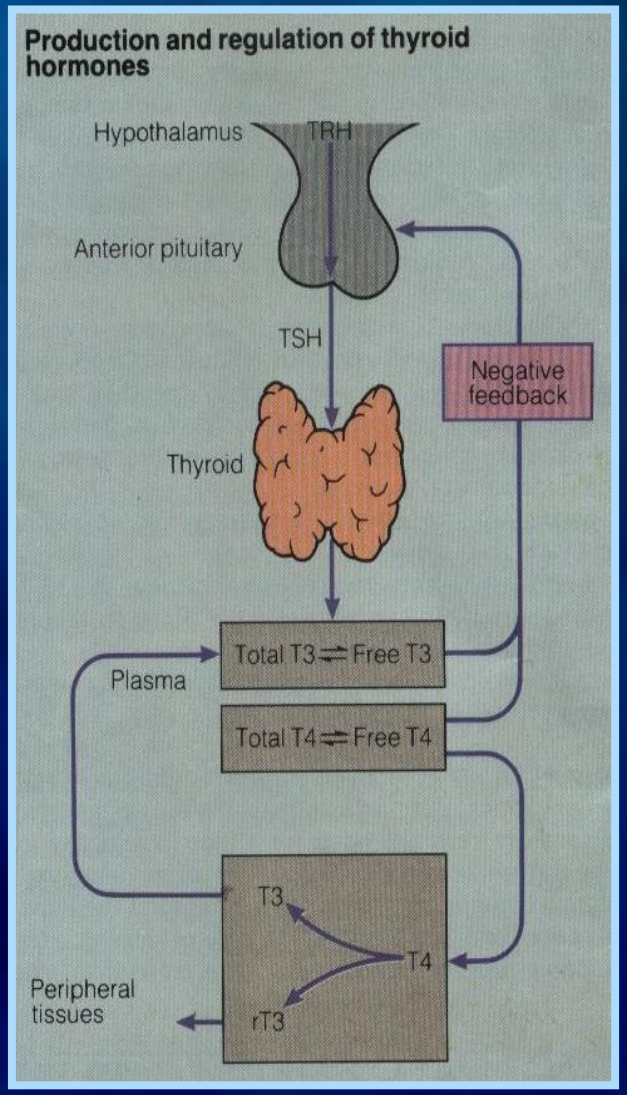
TSH -R

THYROID T4 and T3

PLASMA T4 + FT4

PLASMA T3 + FT3

TISSUES FT4 to FT3, rT3



Daily Rate of Secretion of Thyroxine and Triiodothyronine

- About 93 per cent of the thyroid hormone released from the thyroid gland is normally thyroxine and only 7 per cent is triiodothyronine

- During the ensuing few days, about one half of the thyroxine is slowly deiodinated to form additional triiodothyronine.

Production of T4 and T3

- T4 is the primary secretory product of the thyroid gland, which is the only source of T4
- The thyroid secretes approximately 70-90 μg of T4 per day
- T3 is derived from 2 processes
  - ✓The total daily production rate of T3 is about 15-30 μg
  - ✓About 80% of circulating T3 comes from deiodination of T4 in peripheral tissues
  - ✓About 20% comes from direct thyroid secretion

T4: A Prohormone for T3

- T4 is biologically inactive in target tissues until converted to T3
  - ✓Activation occurs with 5' iodination of the outer ring of T4
- T3 then becomes the biologically active hormone responsible for the majority of thyroid hormone effects

Sites of T4 Conversion

- The liver is the major extrathyroidal T4 conversion site for production of T3
- Some T4 to T3 conversion also occurs in the kidney and other tissues

T4 Disposition

- Normal disposition of T4
  - ✓ About 41% is converted to T3
  - ✓ 38% is converted to reverse T3 (rT3), which is metabolically inactive
  - ✓ 21% is metabolized via other pathways, such as conjugation in the liver and excretion in the bile
- Normal circulating concentrations
  - ✓ T4 4.5-11 □g/dL
  - ✓ T3 60-180 ng/dL (~100-fold less than T4)

Carriers for Circulating Thyroid Hormones

- More than 99% of circulating T4 and T3 is bound to plasma carrier proteins
  - ✓ Thyroxine-binding globulin (TBG), binds about 75%
  - ✓ Transthyretin (TTR), also called thyroxine-binding prealbumin (TBPA), binds about 10%-15%
  - ✓ Albumin binds about 7%
  - ✓ High-density lipoproteins (HDL), binds about 3%
- Carrier proteins can be affected by physiologic changes, drugs, and disease

Free Hormone

- Only unbound (free) hormone has metabolic activity and physiologic effects
  - ✓ Free hormone is a tiny percentage of total hormone in plasma (about 0.03% T4; 0.3% T3)
- Total hormone concentration
  - ✓ Normally is kept proportional to the concentration of carrier proteins
  - ✓ Is kept appropriate to maintain a constant free hormone level

Changes in TBG Concentration

- Increased TBG
  - Total serum T4 and T3 levels increase
  - Free T4 (FT4), and free T3 (FT3) concentrations remain unchanged
- Decreased TBG
  - Total serum T4 and T3 levels decrease
  - FT4 and FT3 levels remain unchanged

Drugs and Conditions That Increase Serum T_4 and T_3 Levels by Increasing TBG

- Drugs that increase TBG
  - ✓ Oral contraceptives and other sources of estrogen
  - ✓ Methadone
  - ✓ Clofibrate
  - ✓ 5-Fluorouracil
  - ✓ Heroin
  - ✓ Tamoxifen
- Conditions that increase TBG
  - ✓ Pregnancy
  - ✓ Infectious/chronic active hepatitis
  - ✓ HIV infection
  - ✓ Biliary cirrhosis
  - ✓ Acute intermittent porphyria
  - ✓ Genetic factors

Hormones of adrenal cortex and adrenal medulla

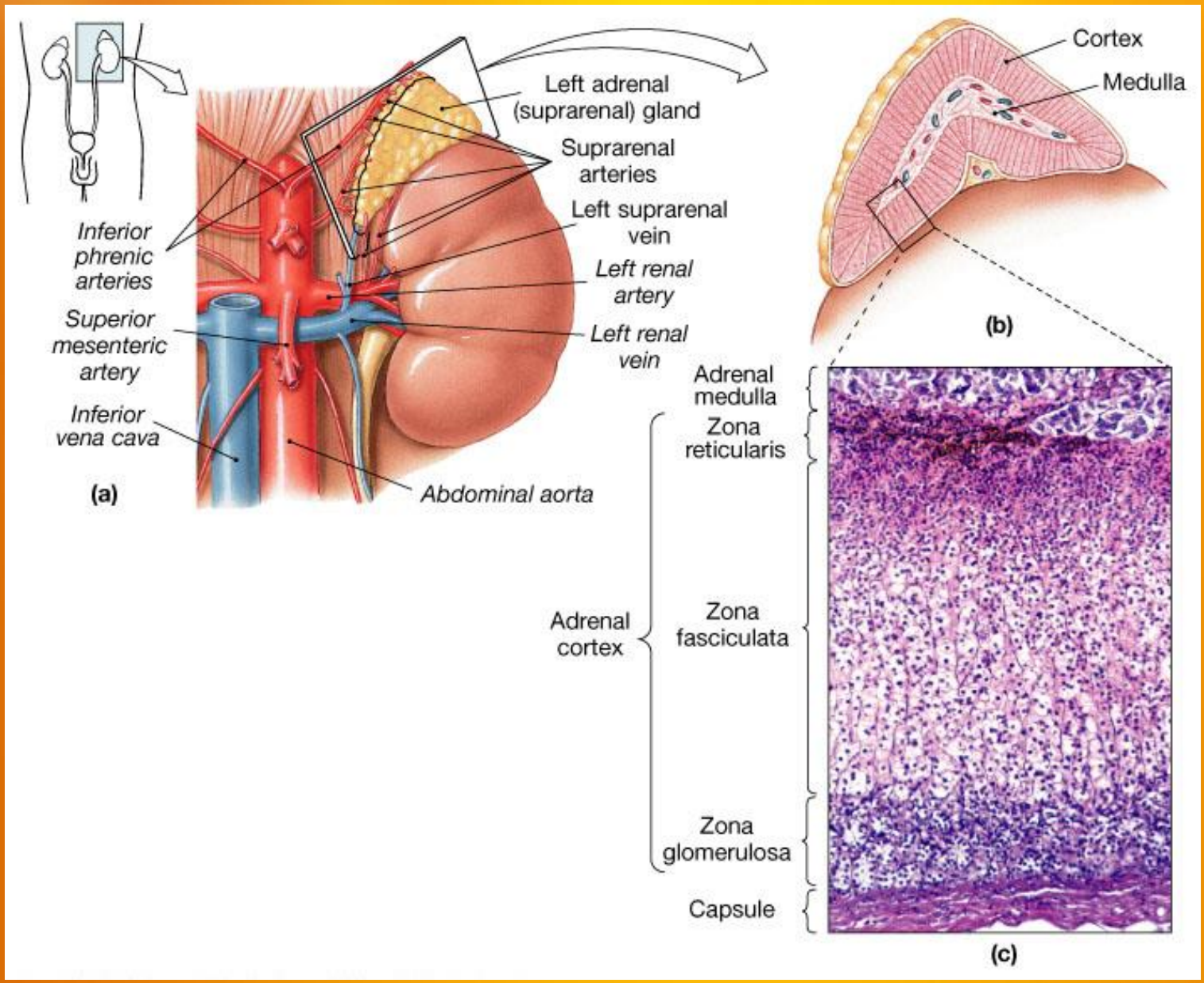
Adrenal glands

- The two adrenal glands
- Weighs about 4 grams
- lie at the superior poles of the two kidneys
- Two distinct parts, the adrenal medulla and the adrenal cortex

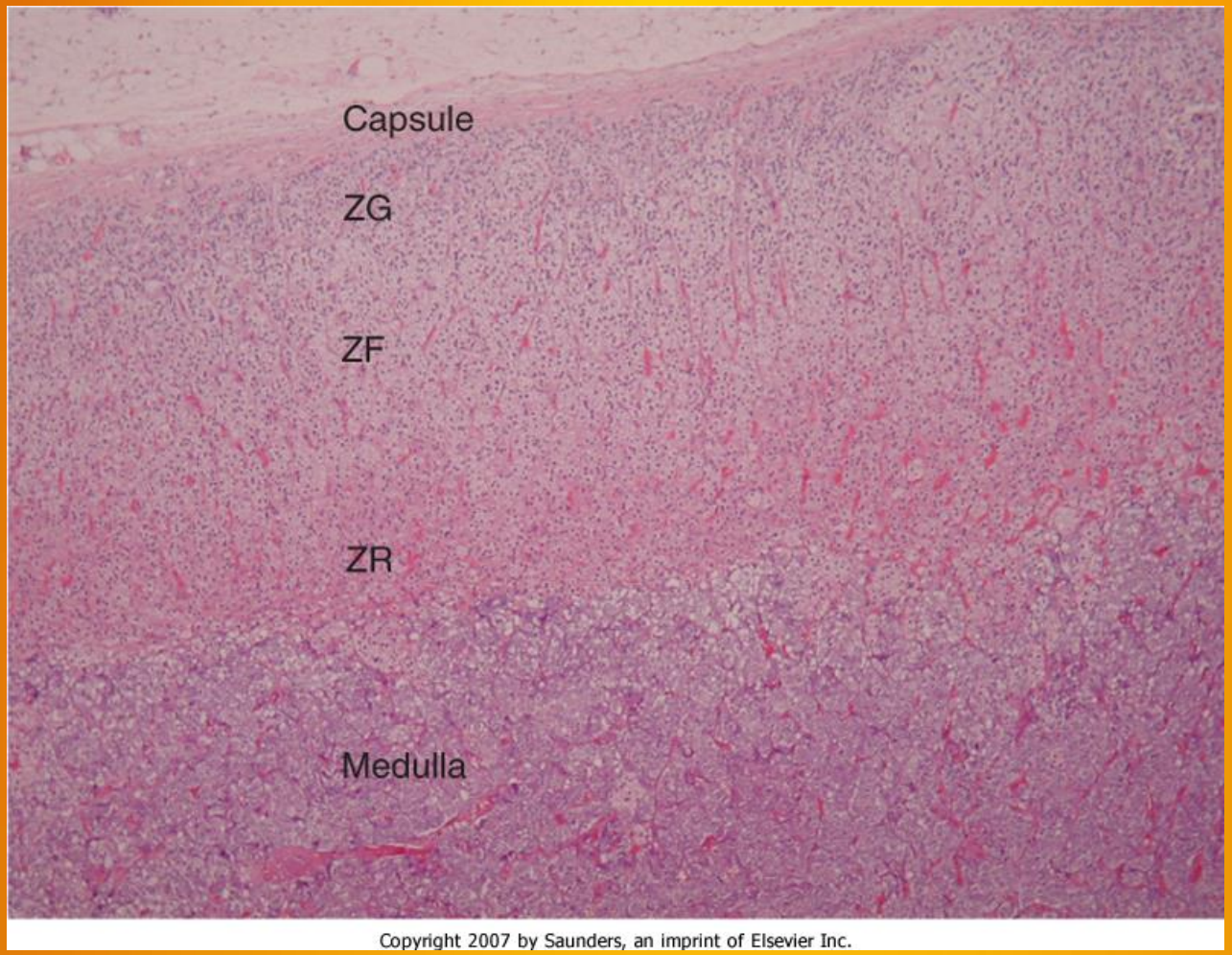
Adrenal glands

- Cortex - 80% : synthesis of steroid hormones
  - zona glomerulosa - mineralocorticoids
  - zona fasciculata – glukocorticoids
  - zona reticularis – adrenal androgens

- Medulla - 20% : synthesis of noradrenaline and adrenaline
  - Functionally: a part of sympathetic nervous system


Left adrenal (suprarenal) gland
Suprarenal arteries
Left suprarenal vein
Left renal artery
Left renal vein
Inferior phrenic arteries
Superior mesenteric artery
Inferior vena cava
Abdominal aorta
(a)
Cortex
Medulla
(b)
Adrenal medulla
Zona reticularis
Zona fasciculata
Zona glomerulosa
Capsule
Adrenal cortex
(c)

Histology of adrenal gland



The adrenal cortex

- The central 80 per cent of the gland
- Secretes an entirely different group of hormones, called corticosteroids
- These hormones are all synthesized from the steroid cholesterol

The adrenal medulla

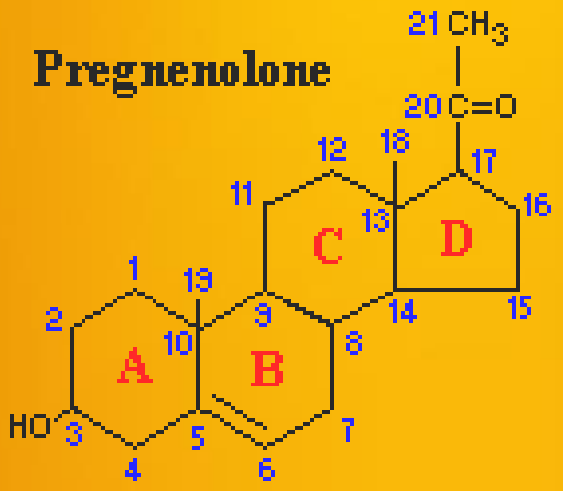
- The central 20 per cent of the gland, functionally related to the sympathetic nervous system,
- Secretes the hormones epinephrine and norepinephrine in response to sympathetic stimulation
- In turn, these hormones cause almost the same effects as direct stimulation of the sympathetic nerves in all parts of the body.
- These two hormones are called catecholamines and are involved in the “fight or flight” mechanism of the nervous system

Steroid Hormones

- Steroid hormones: produced in the adrenal cortex, testis, ovary, and some peripheral tissues (adipose tissue, the brain!)
- All steroid hormones share a typical (but not identical) ring structure.

Steroid hormones

- All steroid hormones are derived from cholesterol and differ only in the ring structure and side chains attached to it.
- All steroid hormones are lipid soluble



Types of steroid hormones

- Glucocorticoids; cortisol is the major representative in most mammals
- Mineralocorticoids; aldosterone being most prominent
- Androgens such as testosterone
- Estrogens, including estradiol and estrone
- Progestogens (also known a progestins) such as progesterone

Steroid hormones

- Are not packaged, but synthesized and immediately released
- Are all derived from the same parent compound: Cholesterol
- Enzymes which produce steroid hormones from cholesterol are located in mitochondria and smooth ER
- Steroids are lipid soluble and thus are freely permeable to membranes so are not stored in cells

Steroid hormones

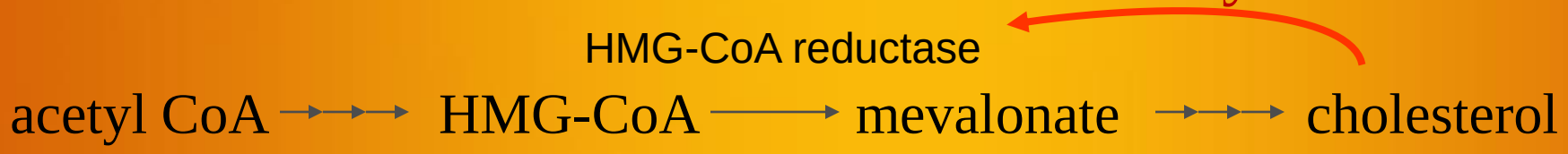
- All three layers secrete corticosteroids of which cholesterol is the common precursor. On the basis of their primary actions, the adrenal steroids can be divided into 3 categories
  - ✓ mineralocorticoids- aldosterone, which influences mineral or electrolyte balance; from z. glomerulosa
  - ✓ glucocorticoids- cortisol, which plays a role in glucose metabolism and proteins and lipids as well;from z. fasciculata
  - ✓ sex hormones- identical to those produced by the gonads (male – testes; female – ovaries); from z. reticularis

Steroid hormones

- Steroid hormones are not water soluble so have to be carried in the blood complexed to specific binding globulins
- Corticosteroid binding globulin carries cortisol
- Sex steroid binding globulin carries testosterone and estradiol
- In some cases a steroid is secreted by one cell and is converted to the active steroid by the target cell: an example is androgen which secreted by the gonad and converted into estrogen in the brain

Sources of cholesterol for steroid synthesis

- Cholesterol can be made within the cell from acetyl CoA (*de novo synthesis*)
- This is a multistep process, involving many enzymatic reactions
- A key rate-limiting enzyme is HMG-CoA reductase
- There is negative feedback regulation of HMG-CoA reductase activity by cholesterol, so that high intracellular cholesterol inhibits de novo synthesis.



Sources of Cholesterol for Steroid Synthesis

- Cholesterol is also taken up by the cell in the form of low density lipoprotein (LDL)

  - LDL is a complex composed of cholesterol, phospholipids, triglycerides, and proteins (proteins and phospholipids make LDL soluble in blood)

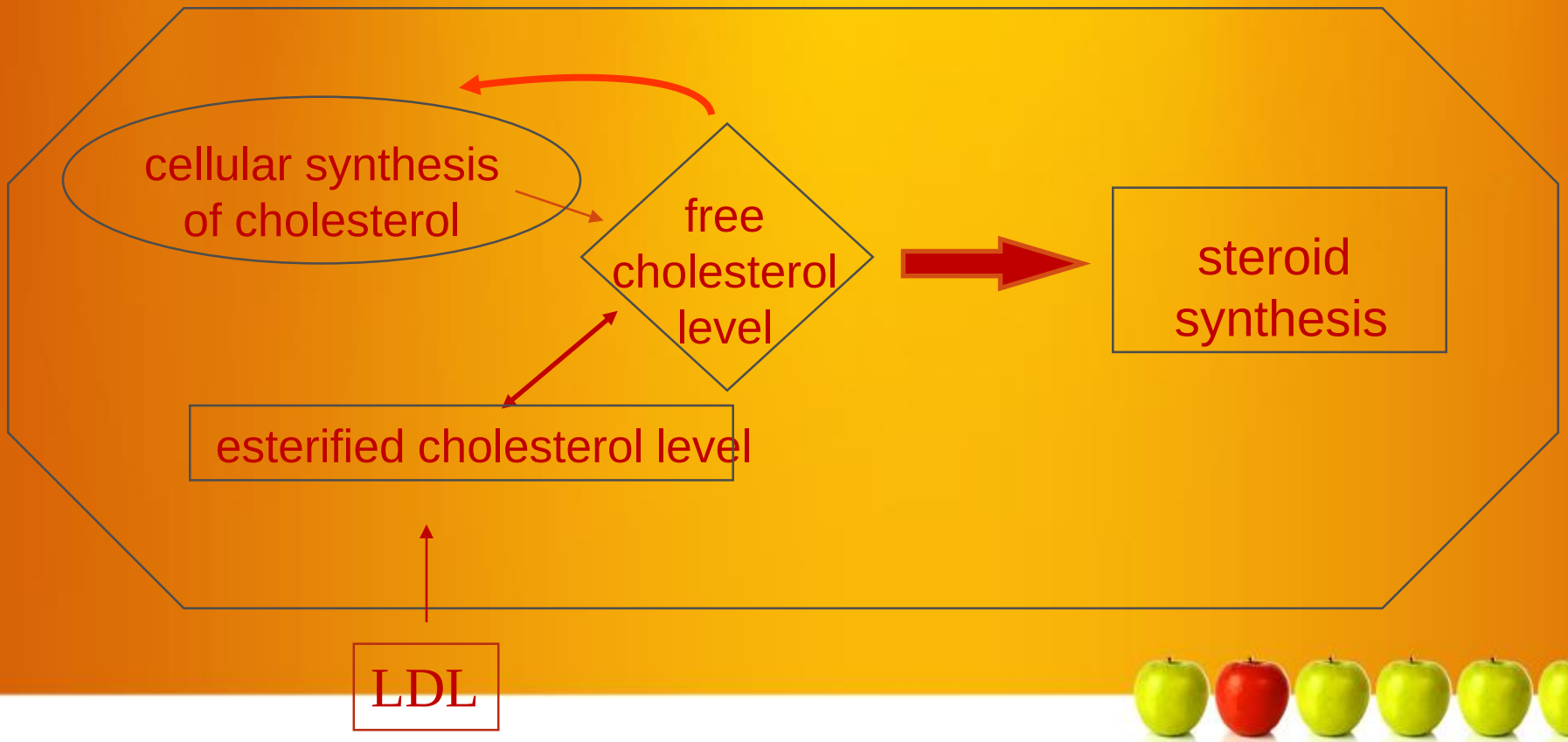
  - LDL is taken into cells via LDL receptors, and broken down into esterified cholesterol, and then free cholesterol:

The role of cholesterol in steroid synthesis

- The *first* ***enzymatic*** *step* in the production of steroid hormone begins with enzymatic modification of cholesterol

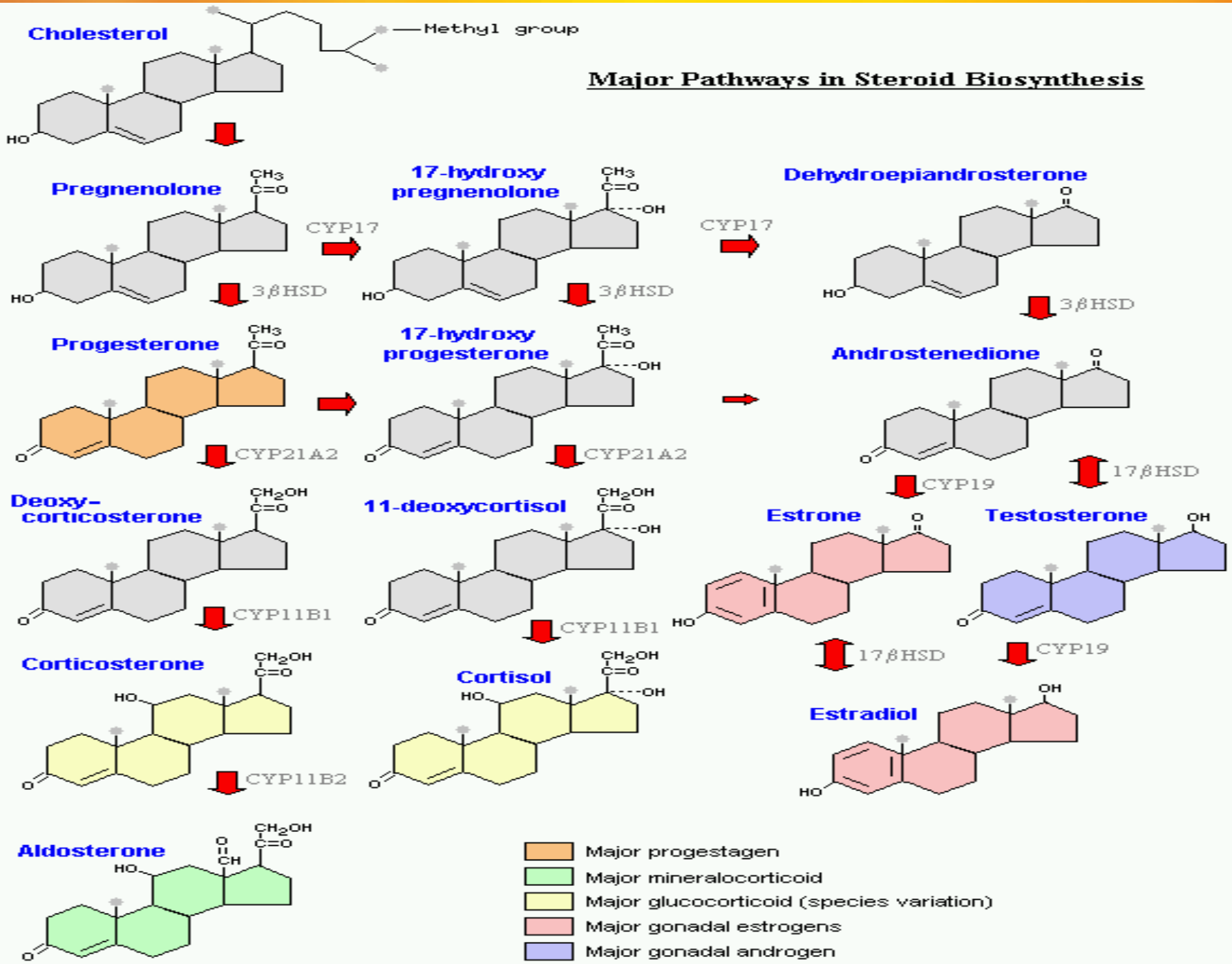
Source of Cholesterol for Steroid Synthesis

- The amount of free cholesterol in the cell is maintained relatively constant:



Steroidogenic enzymes

Common name	"Old" name	Current name
Side-chain cleavage enzyme; desmolase	$P450_{SCC}$	CYP11A1
3 beta-hydroxysteroid dehydrogenase	3 beta-HSD	3 beta-HSD
17 alpha-hydroxylase/17,20 lyase	$P450_{C17}$	CYP17
21-hydroxylase	$P450_{C21}$	CYP21A2
11 beta-hydroxylase	$P450_{C11}$	CYP11B1
Aldosterone synthase	$P450_{C11AS}$	CYP11B2
Aromatase	$P450_{aro}$	CYP19


Cholesterol
Methyl group
Major Pathways in Steroid Biosynthesis
Pregnenolone
CYP17
17-hydroxy pregnenolone
CYP17
Dehydroepiandrosterone
3βHSD
3βHSD
3βHSD
Progesterone
17-hydroxy progesterone
Androstenedione
CYP21A2
CYP21A2
CYP19
17βHSD
Deoxy-corticosterone
11-deoxycortisol
Estrone
Testosterone
CYP11B1
CYP11B1
17βHSD
CYP19
Corticosterone
Cortisol
Estradiol
CYP11B2
Aldosterone
Major progestagen
Major mineralocorticoid
Major glucocorticoid (species variation)
Major gonadal estrogens
Major gonadal androgen

Steroid hormone synthesis

All steroid hormones are derived from cholesterol. A series of enzymatic steps in the mitochondria and ER of steroidogenic tissues convert cholesterol into all of the other steroid hormones and intermediates.

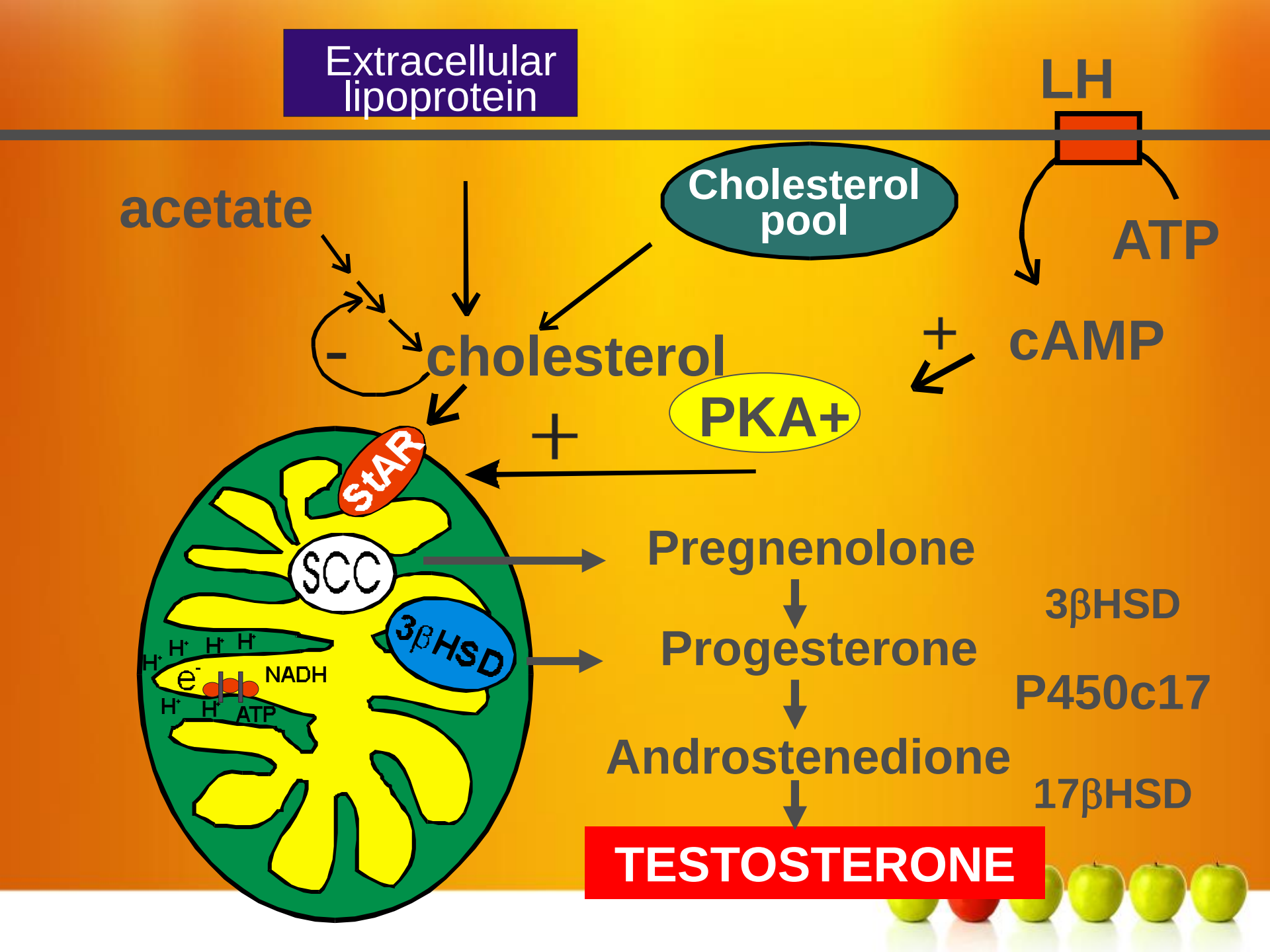
The rate-limiting step in this process is the transport of free cholesterol from the cytoplasm into mitochondria. This step is carried out by the Steroidogenic Acute Regulatory Protein (StAR)

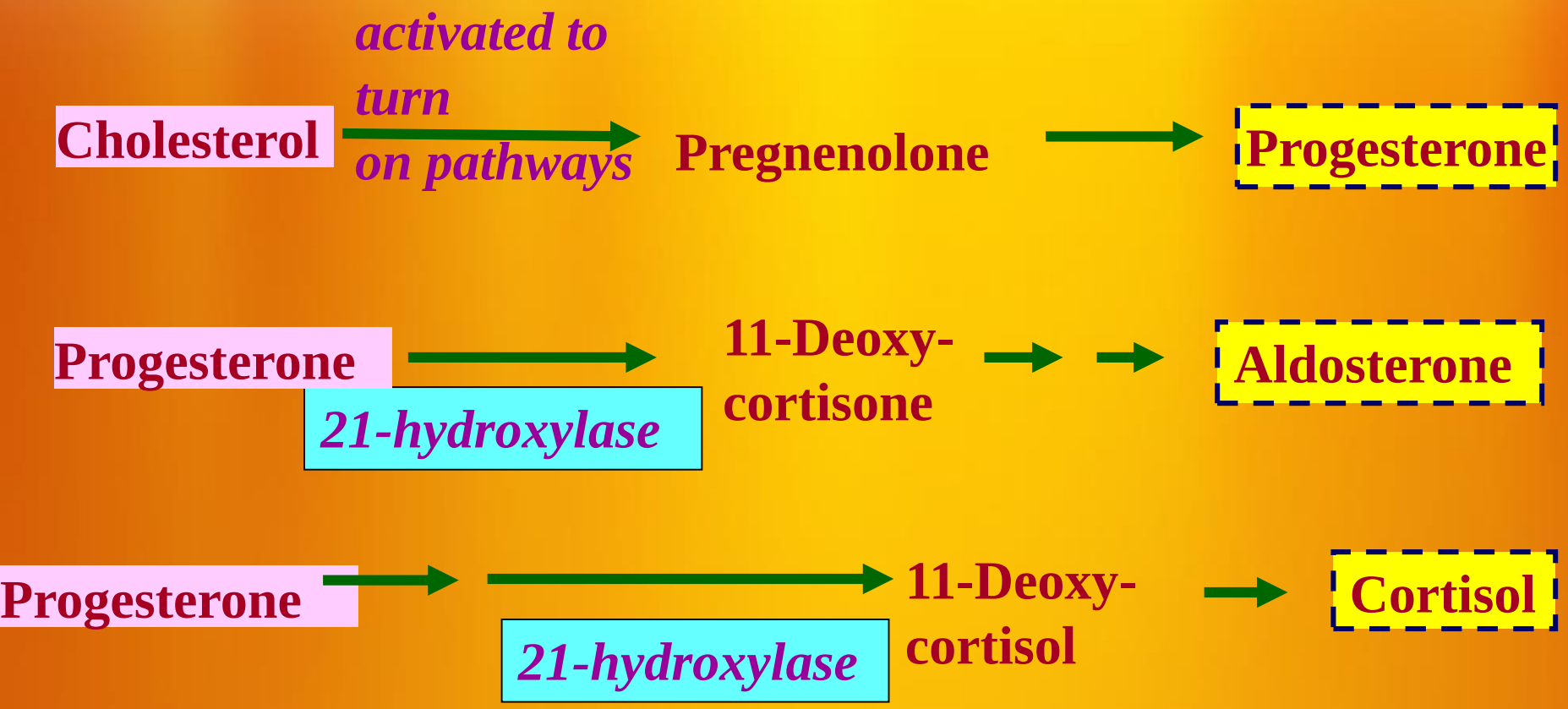
Steroid hormone synthesis

- The cholesterol precursor comes from cholesterol synthesized within the cell from acetate, from cholesterol ester stores in intracellular lipid droplets or from uptake of cholesterol-containing low density lipoproteins.
- Lipoproteins taken up from plasma are most important when steroidogenic cells are chronically stimulated

Cellular localization of cholesterol metabolism for steroid production

- The first *enzymatic* step in steroid synthesis is the conversion of cholesterol into pregnenolone.
- The enzyme that catalyzes this reaction is located in the inner mitochondrial membrane


Extracellular lipoprotein
LH
acetate
Cholesterol pool
ATP
-
cholesterol
+
cAMP
PKA+
+
StAR
SCC
3βHSD
H+ H+ H+ H+
e-
NADH
H+ H+ ATP
Pregnenolone
3βHSD
Progesterone
P450c17
Androstenedione
17βHSD
TESTOSTERONE



General pathways for the synthesis of aldosterone and cortisol in the adrenal cortex

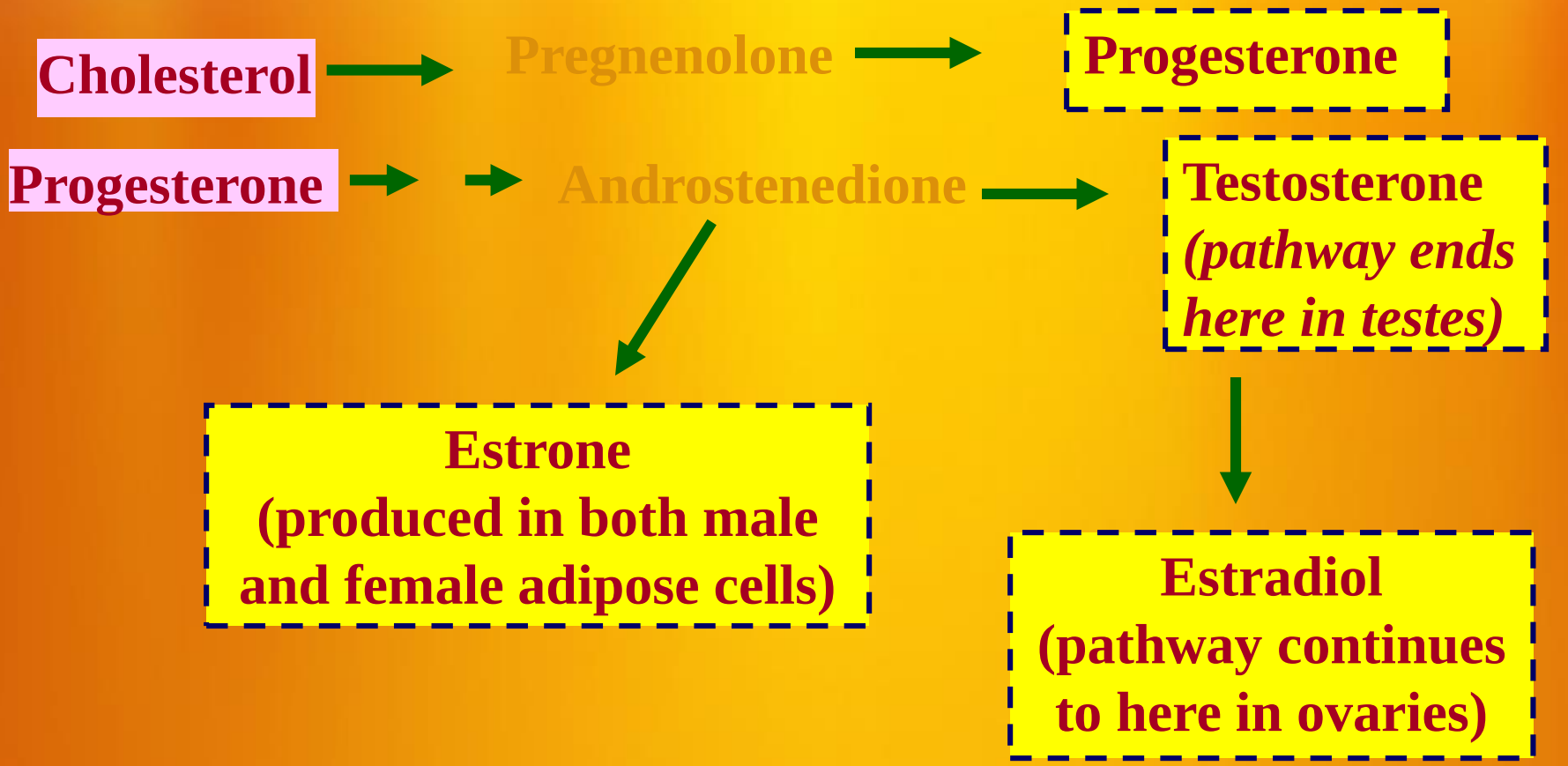
Pregnenolone → → DHEA → Androstenedione

"Andro"

Pathway for formation of androgens in the adrenal cortex.

Beware of the hype about taking DHEA

Cortisol made in same cells as androstenedione



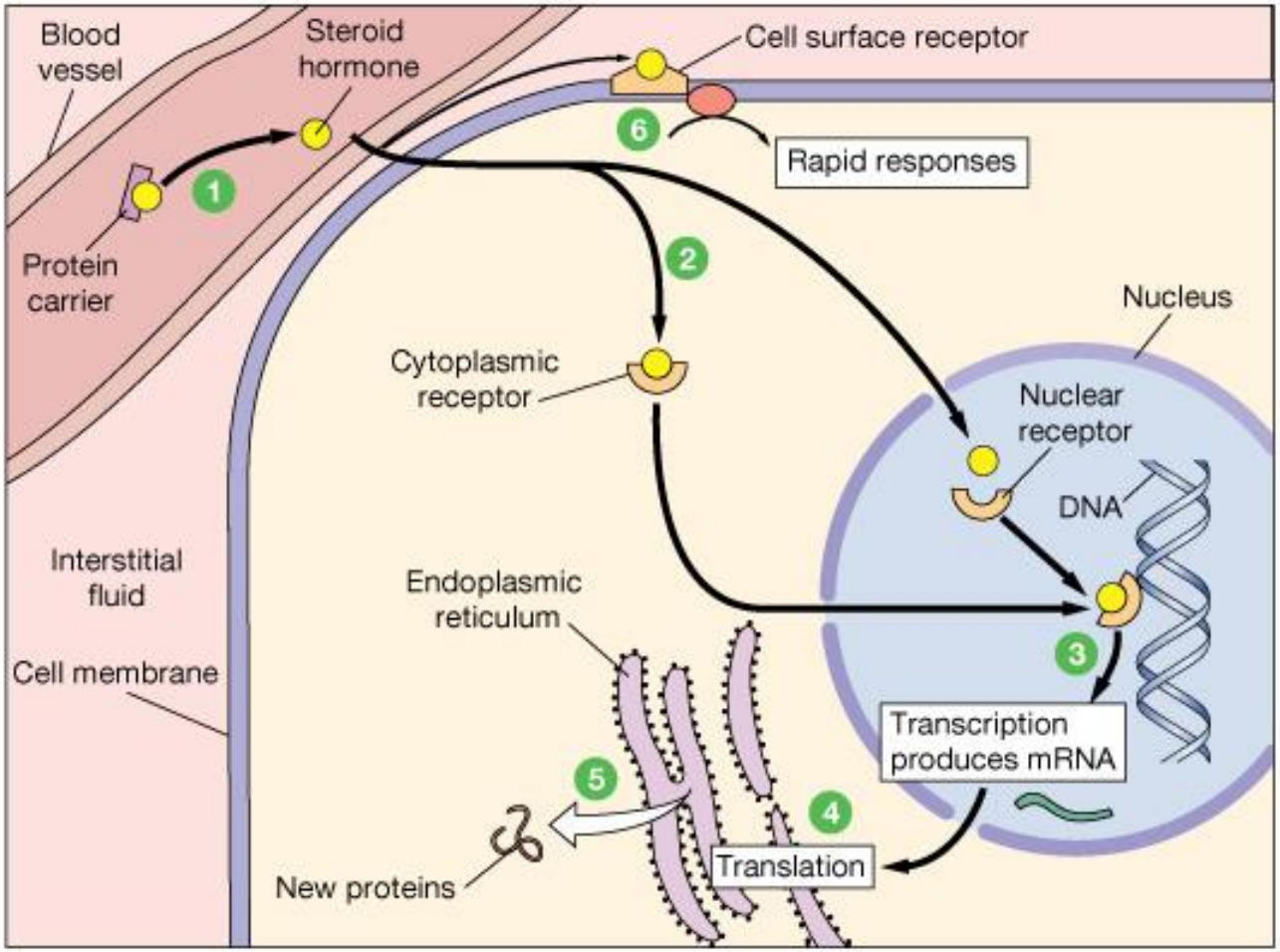
In obese men, overproduction of estrogen in fat cells can cause gynecomastia = excessive male breast development

Pathways for the synthesis of testosterone (testes) and the estrogens estradiol (ovaries) and estrone (adipose cells)

Adrenal Cortex: Steroid Hormone Production

- Aldosterone, sex hormones, cortisol
- Synthesized from cholesterol-steroid ring

Steroid Hormones: Action

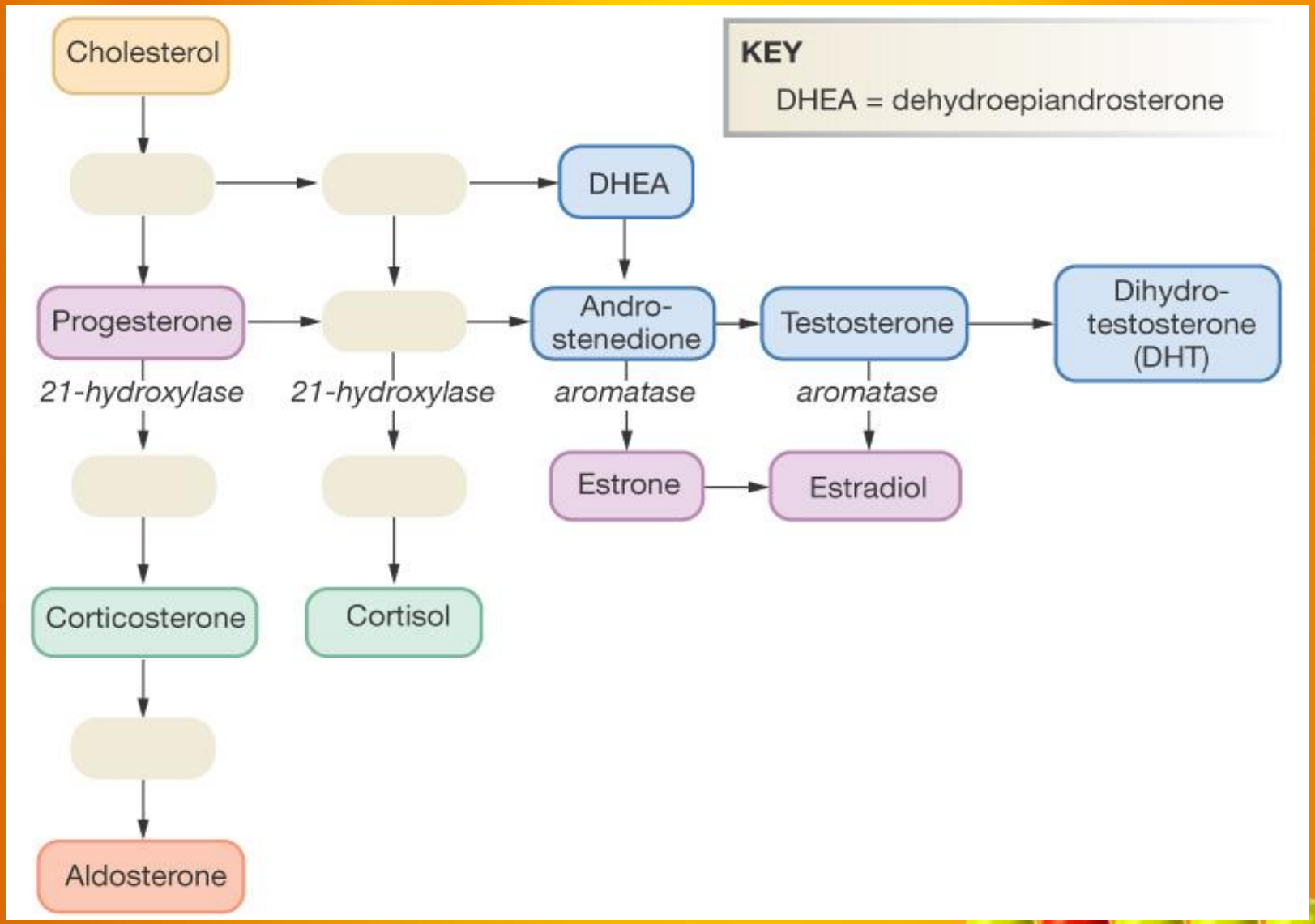


1. Most hydrophobic steroids are bound to plasma protein carriers. Only unbound hormones can diffuse into the target cell.
2. Steroid hormone receptors are in the cytoplasm or nucleus.
3. The receptor-hormone complex binds to DNA and activates or represses one or more genes.
4. Activated genes create new mRNA that moves back to the cytoplasm.
5. Translation produces new proteins for cell processes.
6. Some steroid hormones also bind to membrane receptors that use second messenger systems to create rapid cellular responses.

Corticosteroids

- Mineralocorticoids
- Glucocorticoids
- Androgens

Adrenal Cortex: steroid hormone production



Mineralocorticoids

- Aldosterone (very potent, accounts for about 90 per cent of all mineralocorticoid activity)
- Desoxycorticosterone (1/30 as potent as aldosterone, but very small quantities secreted)
- Corticosterone (slight mineralocorticoid activity)
- 9a-Fluorocortisol (synthetic, slightly more potent than aldosterone)
- Cortisol (very slight mineralocorticoid activity, but large quantity secreted)
- Cortisone (synthetic, slight mineralocorticoid activity)

Glucocorticoids

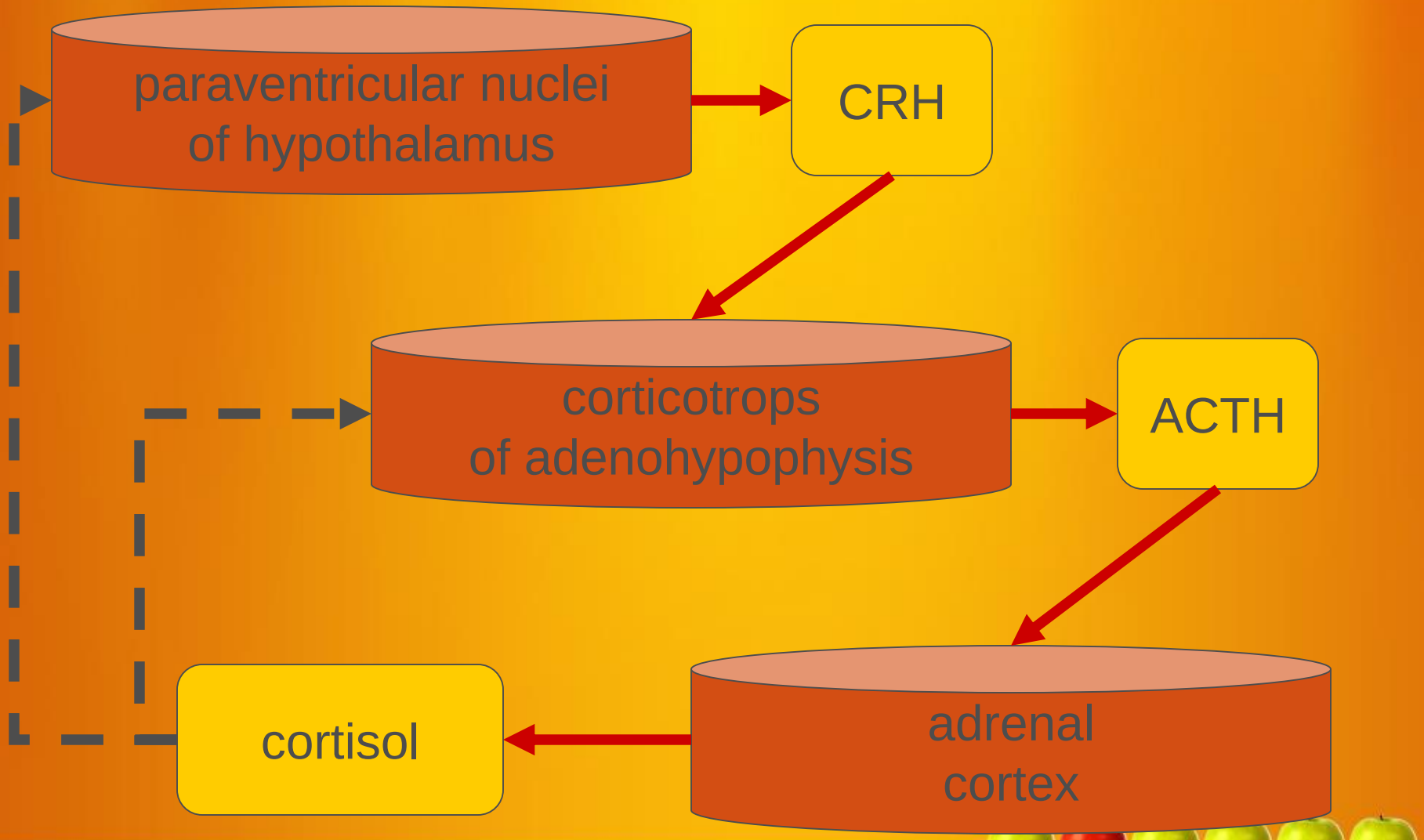
- Cortisol very potent, accounts for about 95 per cent of all glucocorticoid activity
- Corticosterone provides about 4 per cent of total glucocorticoid activity, but much less potent than cortisol
- Cortisone synthetic, almost as potent as cortisol
- Prednisone synthetic, four times as potent as cortisol
- Methylprednisone synthetic, five times as potent as cortisol
- Dexamethasone synthetic, 30 times as potent as cortisol)

Adrenal Steroid Hormones in Adults; Synthetic Steroids and Their Relative Glucocorticoid and Mineralocorticoid Activities

Steroids	Average Plasma Concentration (free and bound, μg/100 ml)	Average Amount Secreted (mg/24 hr)	Glucocorticoid Activity	Mineralocorticoid Activity
Adrenal Steroids				
Cortisol	12	15	1	1
Corticosterone	0.4	3	0.3	15.0
Aldosterone	0.006	0.15	0.3	3000
Deoxycorticosterone	0.006	0.2	0.2	100
Dehydroepiandrosterone	175	20	—	—
Synthetic Steroids				
Cortisone	—	—	1.0	1.0
Prednisolone	—	—	4	0.8
Methylprednisone	—	—	5	—
Dexamethasone	—	—	30	—
9a-fluorocortisol	—	—	10	125

Glucocorticoid and mineralocorticoid activities of the steroids are relative to cortisol, with cortisol being 1.0.

Regulation of cortisol secretion



ACTH stimulates cortisol secretion

- ACTH secreted by the anterior pituitary gland
- ACTH, also enhances the production of adrenal androgens
- It is a large polypeptide, having a chain length of 39 amino acids. A smaller polypeptide, a digested product of ACTH having a chain length of 24 amino acids, has all the effects of the total molecule
- ACTH secretion is controlled by corticotropin-releasing factor from the hypothalamus
- ACTH Activates Adrenocortical Cells to Produce Steroids by Increasing cAMP

ACTH stimulates cortisol secretion

- The most important of all the ACTH-stimulated steps for controlling adrenocortical secretion is activation of the enzyme protein kinase A
- Which causes initial conversion of cholesterol to pregnenolone
- This initial conversion is the “rate-limiting” step for all the adrenocortical hormones, which explains why ACTH
- Long-term stimulation of the adrenal cortex by ACTH causes hypertrophy and proliferation of the adrenocortical cells, especially in the zona fasciculata and zona reticularis, where cortisol and the androgens are secreted

Corticotropin-releasing factor from the hypothalamus

- Peptide composed of 41 amino acids
- Paraventricular nucleus of the hypothalamus
- This nucleus in turn receives many nervous connections from the limbic system and lower brain stem
- The anterior pituitary gland can secrete only minute quantities of ACTH in the absence of CRF

Proopiomelanocortin

- Synthesis and Secretion of ACTH in Association with
  - Melanocyte-Stimulating Hormone
  - Lipotropin
  - Endorphin
- causes the formation of a considerably larger protein, a preprohormone called proopiomelanocortin (POMC), which is the precursor of ACTH as well as several other peptides, including melanocyte-stimulating hormone (MSH), b-lipotropin, b-endorphin

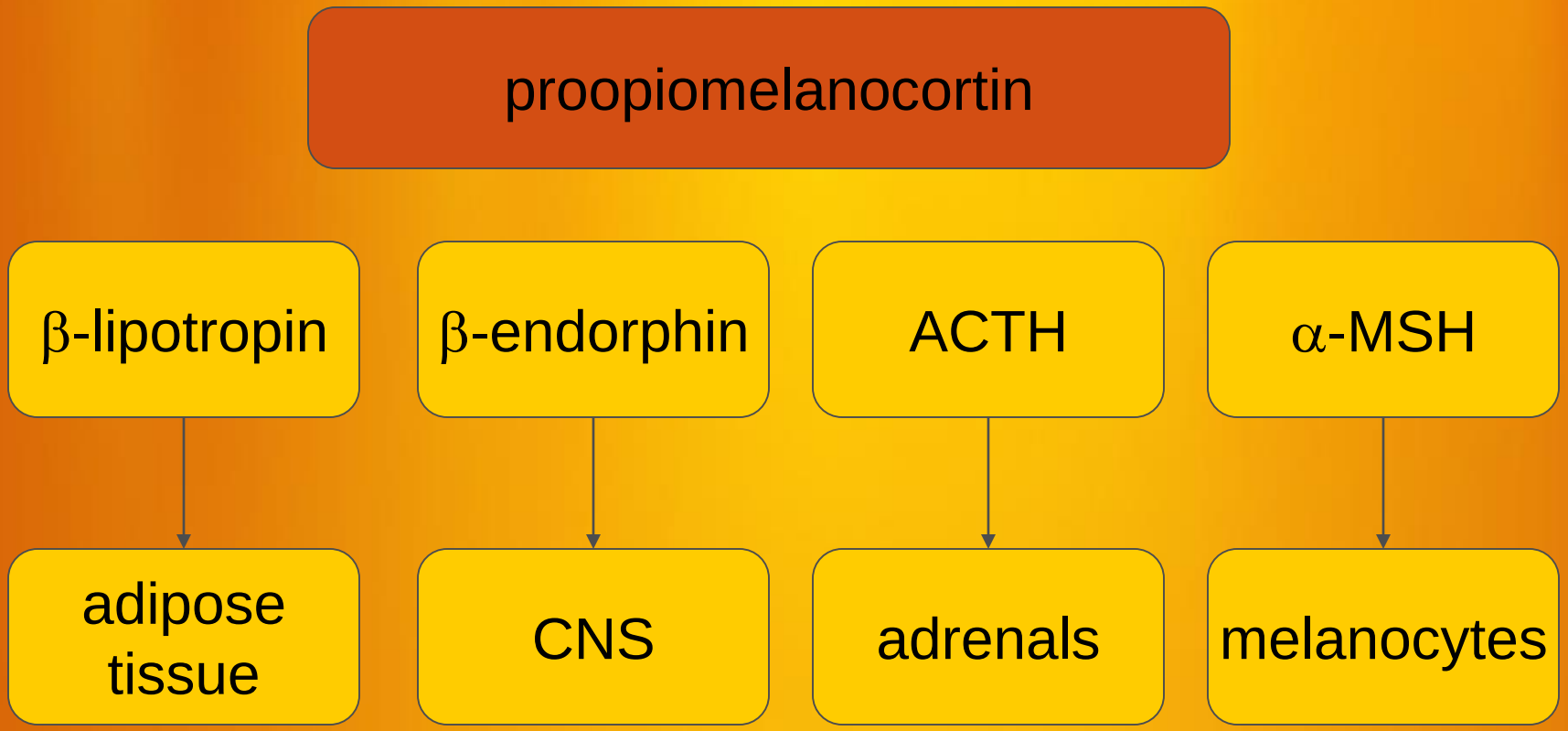
The POMC gene is actively transcribed in several tissues

- The POMC gene is actively transcribed in several tissues, including the
  - Corticotroph cells of the anterior pituitary
  - POMC neurons in the arcuate nucleus of the hypothalamus
  - Cells of the dermis
  - Lymphoid tissue

ACTH and a-MSH

- The a-MSH formed by neurons of the hypothalamus plays a major role in appetite regulation
- ACTH, because it contains an MSH sequence, has about 1/30 as much melanocyte-stimulating effect as MSH. Furthermore, because the quantities of pure MSH secreted in the human being are extremely small, whereas those of ACTH are large, it is likely that ACTH normally is more important than MSH in determining the amount of melanin in the skin

Secretion of ACTH



Control of Cortisol Secretion: Feedback Loops

- External stimuli
- Hypothalamic
- Anterior Pituitary
- Adrenal cortex
- Tissues

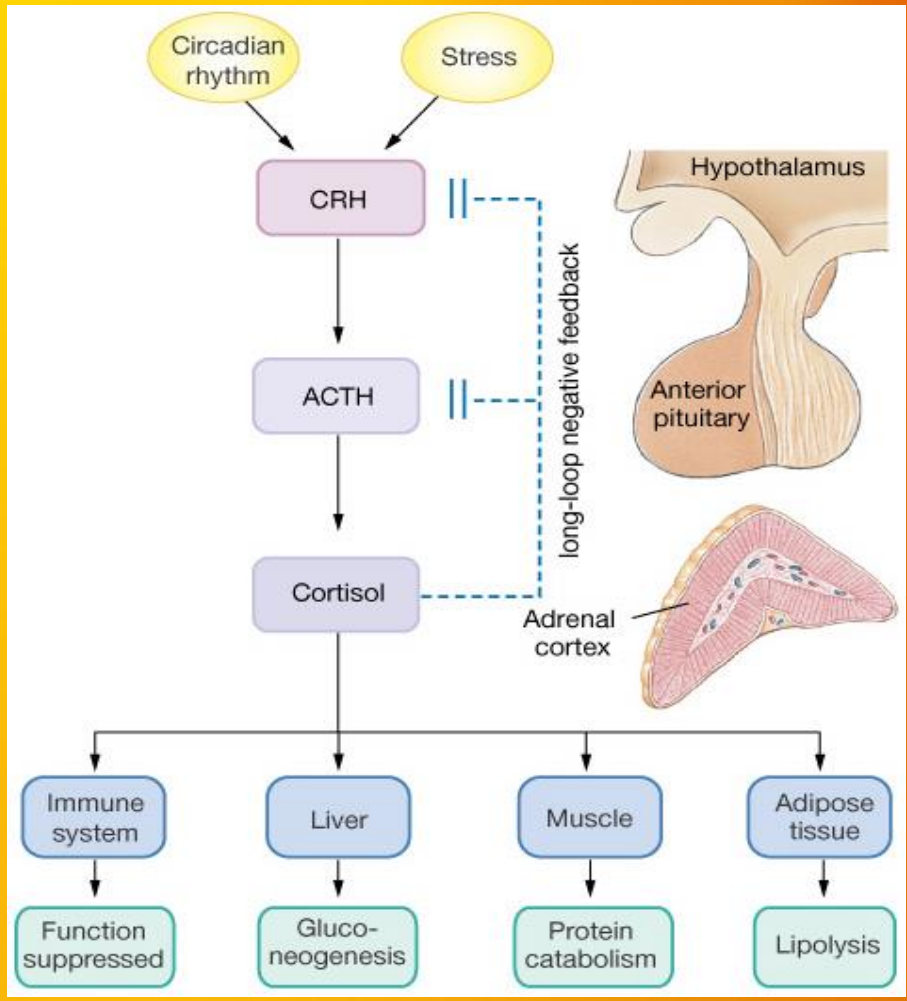
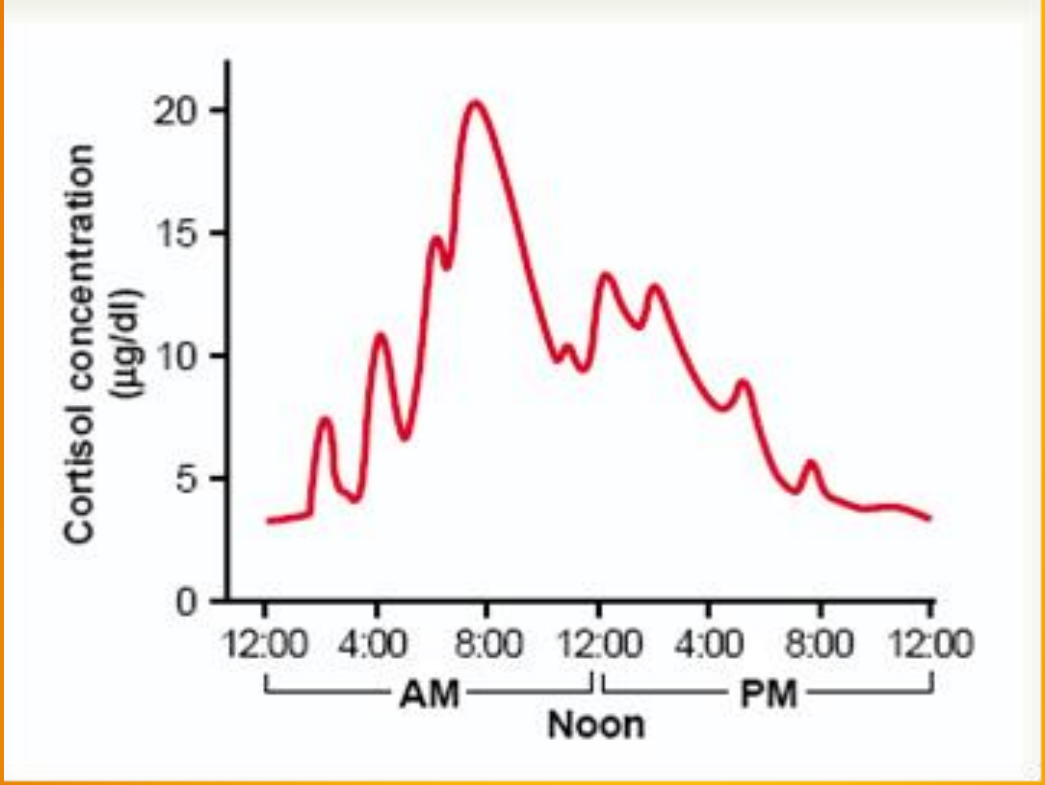


Figure 23-3: The control pathway for cortisol

Secretion of ACTH and cortisol

- Ultradian rhythm (period less than 24 h)
  - episodic pulses
- Circadian rhythm (period close to 24 h)
  - secretion maximum at 8-10 h
  - secretion minimum at 23 h
- The plasma cortisol level ranges between a high of about 20 mg/dl an hour before arising in the morning and a low of about 5 mg/dl around midnight.

Circadian Rhythm of Glucocorticoid Secretion



Adrenocortical hormones are bound to plasma proteins to perform functions

- Binding of adrenal steroids to the plasma proteins may serve as a reservoir to lessen rapid fluctuations in free hormone concentrations, as would occur, for example, with cortisol during brief periods of stress and episodic secretion of ACTH
- This reservoir function may also help to ensure a relatively uniform distribution of the adrenal hormones to the tissues

Adrenocortical hormones are metabolized in the liver

- Adrenal steroids are degraded mainly in the liver and conjugated especially to glucuronic acid and, to a lesser extent, sulfates
- The conjugated forms are inactive
- 25 % per cent of these conjugates are excreted in the bile and then in the feces
- 75% conjugates formed by the liver enter the circulation but are not bound to plasma proteins, are highly soluble in the plasma, and are therefore filtered readily by the kidneys and excreted in the urine

Transport of cortisol in the blood

- 90% - 95% bound to CBP (corticosteroid binding protein = cortisol binding globulin = transcortin)
- 4% bound to albumin
- 6% free

- the effect of cortisol after 1-2 hours
- circulating half-life 60-90 minutes

- The normal concentration of aldosterone in blood is about 6 nanograms (6 billionths of a gram) per 100 ml, and the average secretory rate is approximately 150 µg/day (0.15 mg/day).
- The concentration of cortisol in the blood averages 12 µg/100ml, and the secretory rate averages 15 to 20 mg/day.

Cortisol effects on carbohydrate metabolism

- Cortisol main effect is to increase concentration of blood glucose at the expense of fat and proteins.
  - ↑ **Gluconeogenesis** – **this is the conversion of non CHO** precursors(aa) into CHO within the liver, primarily. Between meals or during periods of fasting, when no new nutrients are being absorbed into the blood.
  - enzymes required to convert amino acids into glucose are increased (activation of DNA transcription)
  - Mobilization of amino acids from tissues (muscles)
  - Increase in glycogen storage in liver cells
- Decreased glucose utilization by the cells

Cortisol effects with respect to Protein metabolism

- mobilization of amino acids from non-hepatic tissues
- Cortisol stimulates protein degradation in all cells **except liver cells**
  - Decreased protein synthesis
  - Decreased amino acids transport into extrahepatic tissues (muscles, lymphatic tissues)
- Cortisol promotes formation of proteins (anabolism) by the liver
  - Enhanced liver proteins
  - Increased plasma proteins

Cortisol on Lipid Metabolism

- Increases lipolysis or increased fatty acids in the blood from adipose tissue
- Moderately enhance the oxidation of fatty acids (lower glucose utilization stimulates the cells to utilize energy from fatty acids)

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Mineralocorticoid

- Aldosterone Is the Major Mineralocorticoid Secreted by the Adrenals 90%
- Cortisol, the major glucocorticoid secreted by the adrenal cortex, also provides a significant amount of mineralocorticoid activity
- Aldosterone's mineralocorticoid activity is about 3000 times greater than that of cortisol, but the plasma concentration of cortisol is nearly 2000 times that of aldosterone

Regulation of aldosterone secretion

- Hypovolemia, (decrease of natremia)
- Decrease of renal perfusion pressure
- Renin secretion by juxtaglomerular apparatus
- Conversion of angiotenzinogen to angiotenzin I
- Conversion of angiotenzin I to angiotenzin II
- Stimulation of aldosterone production

Transport of aldosterone in the blood

- 60% bound to plasma proteins
- 40% free

- Effect of aldosterone after 30 min
- Circulating half-life 15-20 minut
- Most aldosterone is metabolically inactivated during a single passage through the liver

Effect of aldosterone: on tubular processes

Increases absorption of sodium and excretion of potassium

- ✓ Total lack of aldosterone causes loss of 20 g Na^+ / day

Increased secretion of aldosterone

- hypokalemia – decrease from 4.5 mmol/l (norm) to 1 - 2 mmol/l (muscle weakness)
- Alkalosis (increased excretion of H^+)

Decreased secretion of aldosterone

- Increase plasma K^+ 60 - 100% above normal level - hyperkalemia (cardiac toxicity)
- Acidosis (decreased excretion of H^+)

Nongenomic actions of aldosterone and other steroid hormones

- Many steroids, including aldosterone, elicit not only slowly developing genomic effects that have a latency of 60 to 90 minutes and require gene transcription and synthesis of new proteins, but also rapid nongenomic effects that take place in a few seconds or minutes
- These nongenomic actions are believed to be mediated by binding of steroids to cell membrane receptors that are coupled to second messenger systems, similar to those used for peptide hormone signal transduction

Nongenomic actions of aldosterone and other steroid hormones (example)

- Aldosterone has been shown to increase formation of cAMP in vascular smooth muscle cells and in epithelial cells of the renal collecting tubules in less than two minutes, a time period that is far too short for gene transcription and synthesis of new proteins
- In other cell types, aldosterone has been shown to rapidly stimulate the phosphatidyl-inositol second messenger system
- Nongenomic actions of steroids well understood

Actions of aldosterone

- Stimulates sodium reabsorption by distal tubule and collecting duct of the nephron and promotes potassium and hydrogen ion excretion
  - Increases transcription of Na/K pump
  - Increases the expression of apical Na channels and an Na/K/Cl cotransporter
- Expands ECF volume

Mineralocorticoids

- Aldosterone secretion is stimulated by:
  - Decreasing blood volume or pressure (renin-angeotensin system) is the major stimulant
  - Low blood Na^+
  - Rising blood levels of K^+
  - ACTH

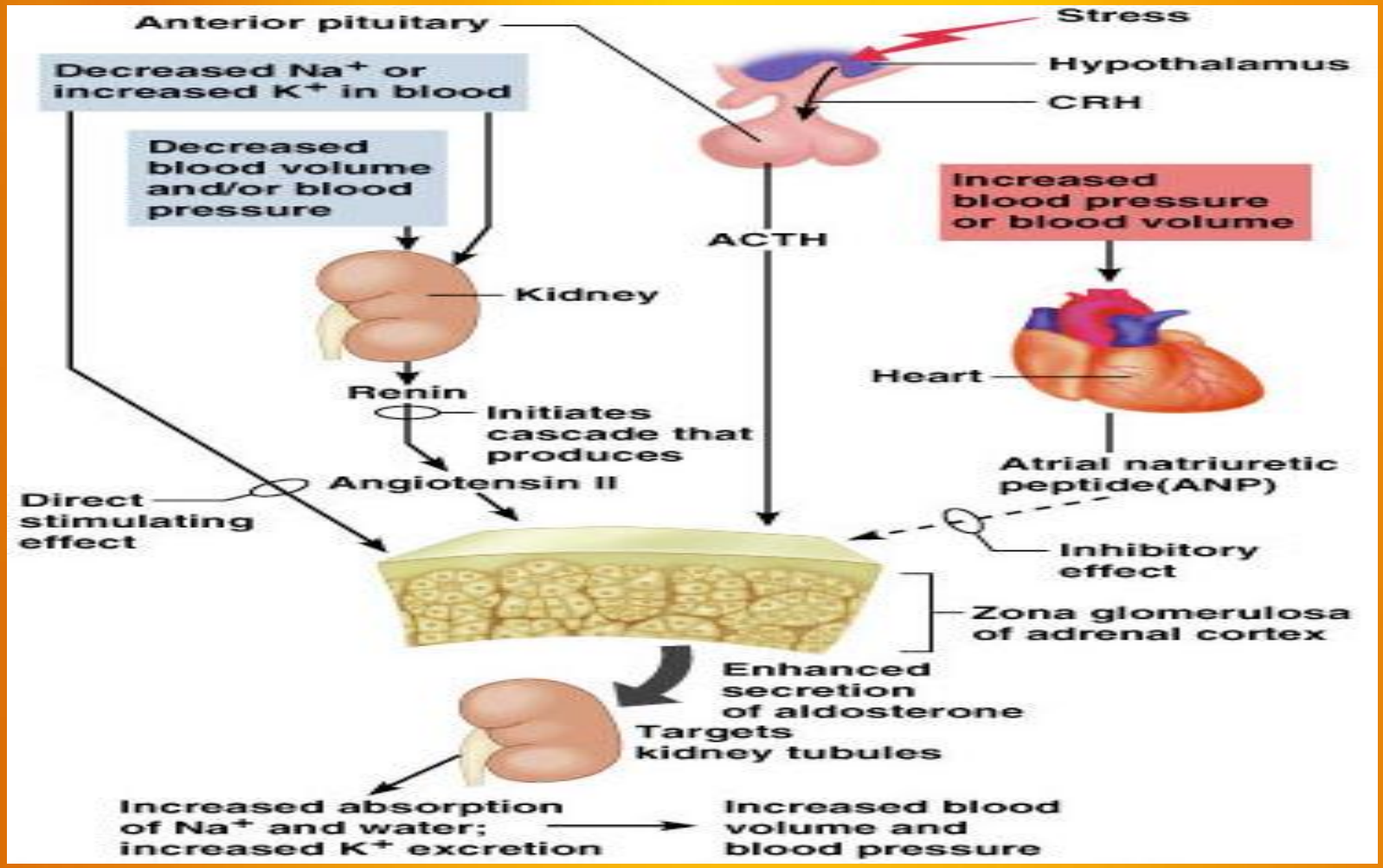
The Four Mechanisms of Aldosterone Secretion

- Renin-angiotensin mechanism – kidneys release renin, which is converted into **angiotensin II** that in turn stimulates aldosterone release
- Plasma concentration of sodium and potassium – directly influences the zona glomerulosa cells
- ACTH – causes small increases of aldosterone during stress
- Atrial natriuretic peptide (ANP) – inhibits activity of the zona glomerulosa

- potassium ion concentration and the renin-angiotensin system are by far the most potent in regulating aldosterone secretion

- The effects of sodium ion concentration per se and of ACTH in controlling aldosterone secretion are usually minor

The four mechanisms of aldosterone secretion



Actions of Aldosterone

Stimulates sodium reabsorption by distal tubule and collecting duct of the nephron and promotes potassium and hydrogen ion excretion

- Increases transcription of Na/K pump
- Increases the expression of apical Na channels and an Na/K/Cl cotransporter

- Expands ECF volume

Aldosterone: Role in diseases

- Complete failure to secrete aldosterone leads to death (dehydration, low blood volume).

- Hyperalsdosterone states: Contribute to hypertension associated with increased blood volume.

Overproduction of aldosterone

- Primary causes, ie. Conn's syndrome
  - Adenoma, nodular hyperplasia of zona glomerulosa
- Secondary
  - cirrhosis, ascites, nephrotic syndrome
- Symptoms, signs
  - headache, hypokalemia causing muscle weakness, hypernatremia, hypervolemia, nocturnal polyuria, hand cramping

Hyperaldosteronism

- Primary (Conn syndrome) or secondary
  - HTN, Low K+(<3.0), High Na+, Alkalosis
    - K+ normal in 20% of patients- usually bilateral adrenal hyperplasia
  - 1% of HTN patients
  - Symptoms: HA, muscle weakness, polyuria, cramps, visual disturbances, paralysis
    - Related to HTN and/or low K+ and/or excess fluid
    - Low K+ can cause baroreceptor paralysis and postural hypotension

Cortisol and Stress

- Stress is defined as the generalized nonspecific response to the body to any factor that overwhelms, or threatens to overwhelm the body's compensatory abilities to maintain homeostasis

- The *stressor is the agent* inducing the response while *stress is the state induced by the stressor*

Types of stimuli that can induce a stress response

- Physical - trauma, surgery, intense heat or cold, restraining the person
- Chemical - ↓O2 supply, acid-base imbalance
- Physiological – heavy exercise, pain, hemorrhagic shock
- Psychological or emotional – anxiety (exams), fear, sorrow
- Social – personal conflicts, changes in lifestyle

Cortisol and Stress

- Any of these stresses can cause an immediate and marked increase in ACTH from the anterior pituitary thereby causing an increase in cortisol from the adrenal cortex

- Why cortisol is released in stress is unknown but consider the example of a primitive human or animal faced with life threatening situation where eating is not a plausible event at that time

- Result is increase blood glucose for the brain, increase free fatty acids for energy and increase amino acids for liver proteins

Stages of inflammation

- Release from the damaged tissue cells of chemical substances that activate the inflammation process, such as histamine, bradykinin, proteolytic enzymes, prostaglandins, and leukotrienes
- An increase in blood flow in the inflamed area caused by some of the released products from the tissues, an effect called erythema or hyperaemia
- Leakage of large quantities of almost pure plasma out of the capillaries into the damaged areas because of increased capillary permeability, thus causing a pitting type of edema
- Infiltration of the area by leukocytes
- After days or weeks, ingrowth of fibrous tissue that often helps in the healing process

Anti-inflammatory Effect of cortisol

- Cortisol Prevents the Development of Inflammation

- Cortisol Causes Resolution of Inflammation

Cortisol Prevents the Development of Inflammation

- Cortisol stabilizes the lysosomal membranes. Therefore, most of the proteolytic enzymes that are released by damaged cells to cause inflammation, which are mainly stored in the lysosomes, are released in greatly decreased quantity

- Cortisol decreases the permeability of the capillaries, probably as a secondary effect of the reduced release of lysosomal proteolytic enzymes. This prevents loss of plasma into the tissues (oedema)

Cortisol Prevents the Development of Inflammation

- Cortisol decreases both migration of white blood cells into the inflamed area and phagocytosis of the damaged cells. These effects probably result from the fact that cortisol diminishes the formation of prostaglandins and leukotrienes that otherwise would increase vasodilation, capillary permeability, and mobility of white blood cells
- Cortisol suppresses the immune system, causing T-lymphocyte and antibodies reproduction to decrease markedly
- Cortisol attenuates fever mainly because it reduces the release of interleukin-1 from the white blood cells

Cortisol Causes Resolution of Inflammation

- Cortisol can often reduce inflammation within hours to a few days. The immediate effect is brought through:
- It blocks most of the factors that are promoting the inflammation.
- It enhances the rate of healing. This probably results from the same factors that allow the body to resist many other types of physical stress when large quantities of cortisol are secreted
  - Perhaps this results from the mobilization of amino acids and use of these to repair the damaged tissues
  - Perhaps it results from the increased gluconeogenesis that makes extra glucose available in critical metabolic systems
  - Perhaps it results from increased amounts of fatty acids available for cellular energy
  - Perhaps it depends on some effect of cortisol for inactivating or removing inflammatory products

Regardless of the precise mechanisms by which the anti-inflammatory effect occurs, this effect of cortisol plays a major role in combating certain types of diseases, such as rheumatoid arthritis, rheumatic fever, and acute glomerulonephritis. All these diseases are characterized by severe local inflammation, and the harmful effects on the body are caused mainly by the inflammatory process itself

Cortisol Blocks the Inflammatory Response to Allergic Reactions

- The basic allergic reaction between antigen and antibody is not affected by cortisol, and even some of the secondary effects of the allergic reaction still occur. However, because the inflammatory response is responsible for many of the serious and sometimes lethal effects of allergic reactions, administration of cortisol, can be lifesaving. For instance, cortisol effectively prevents shock or death in anaphylaxis, which otherwise kills many people

Effect on blood cells and on immunity in infectious diseases

- Cortisol decreases the number of eosinophils and lymphocytes in the blood
  - Lymphocytopenia or eosinopenia is an important diagnostic criterion for overproduction of cortisol by the adrenal gland
  - decreases the output of both T cells and antibodies from the lymphoid tissue
- Cortisol increases the production of red blood cells by mechanisms that are unclear
- Glucocorticoids to suppress immunity makes them useful drugs in preventing immunological rejection of transplanted hearts, kidneys, and other tissues

Adrenal Androgens

- Most important of which is dehydroepiandrosterone DHEA, are continually secreted by the adrenal cortex, especially during fetal life
- progesterone and estrogens, which are female sex hormones, are secreted in minute quantities. Normally, the adrenal androgens have only weak effects in humans.
- The adrenal androgens also exert mild effects in the female, not only before puberty but also throughout life. Much of the growth of the pubic and axillary hair in the female results from the action of these hormones

ADRENAL INSUFFICIENCY

Classification

- Primary: destruction or impairment of the adrenal cortex (classic Addison's disease)
  - Thomas Addison described this rare condition in his classical monograph published in 1855.

- Secondary (Central): reduced ACTH secretion by the pituitary gland or failure of the hypothalamus to produce CRH (corticotrophin-releasing hormone)

Etiologies – primary insufficiency

- Autoimmune
  - Autoimmune Polyglandular Syndrome
    - Type I: Addison's disease, chronic mucocutaneous candidiasis, hypoparathyroidism
    - Type II (Schmidt's syndrome): Addison's disease, primary hypothyroidism, primary hypogonadism, insulin-dependent diabetes
- Infection
  - Tuberculosis, HIV, Fungal
- Infiltrative
  - Amyloidosis, Sarcoidosis, Hemochromatosis, Adrenoleukodystrophy

Etiologies – Primary Insufficiency

- Neoplasm
  - Adrenal metastases (lung and breast), Lymphoma
- Hemorrhage or infarct
  - Meningococcemia (Waterhouse-Friderichsen), DIC, Lupus (antiphospholipid antibody), Anticoagulation
- Iatrogenic
  - Bilateral adrenalectomy, Drugs that inhibit P-450 enzymes (ketoconazole, etomidate)
- Congenital adrenal hypoplasia
- ACTH resistance syndromes

Etiologies – secondary insufficiency

- Inadequate ACTH production
  - Usually other pituitary hormones deficient, and patients present with partial or complete hypopituitarism
  - Isolated ACTH deficiency rare
    - Lymphocytic hypophysitis
    - Abnormal post-translational processing of POMC to ACTH
- Removal of ACTH-secreting pituitary adenoma
  - Function of ‘normal’ corticotrophs suppressed

Manifestations of Adrenal Insufficiency

- Primary and Secondary Insufficiency
  - Weakness, fatigue, mental depression
  - Anorexia, weight loss
  - Nausea, vomiting, diarrhea
  - Postural dizziness, hypotension
  - Hyponatremia, hypoglycemia, mild normocytic anemia, lymphocytosis, eosinophilia

Manifestations of sdrenal insufficiency

- Primary Insufficiency
  - Hyperpigmentation
  - Vitiligo
  - Hyperkalemia, acidosis, elevated creatinine
  - Salt craving
  - Autoimmune thyroid disease
  - CNS symptoms in adrenomyeloneuropathy

Definitions

- Cushing's Syndrome
  - Excess cortisol in the blood
- Cushing's Disease
  - Excess cortisol in the blood due to an ACTH secreting pituitary tumour

Cushing's Syndrome

- Excess Cortisol
  - Protein catabolic state
  - Liberation of amino acids by muscle
  - AA are transformed into glucose and glycogen and then transformed into fat
  - Loss of calcium in urine
  - Weakened muscles and elastic tissues

Cushing's Syndrome

- Central obesity
- Moon face
- Buffalo hump
- Thin skin, easy bruising
- Osteoporosis
- Diabetes
- Excess hair growth
- Irregular periods
- Problems conceiving
- Impotence
- High blood pressure
- Fluid retention

- changes in protein and fat metabolism
- changes in sex hormones
- salt and water retention

Cushing's syndrome

- Excess ACTH secretion is the most common cause of Cushing's syndrome and is characterized by high plasma levels of ACTH as well as cortisol
- Primary overproduction of cortisol by the adrenal glands accounts for about 20 to 25 per cent of clinical cases of Cushing's syndrome and is usually associated with reduced ACTH levels due to cortisol feedback inhibition of ACTH secretion by the anterior pituitary gland
- Administration of large doses of dexamethasone, a synthetic glucocorticoid, can be used to distinguish between ACTH-dependent and ACTH-independent Cushing's syndrome

- A special characteristic of Cushing's syndrome is mobilization of fat from the lower part of the body, with concomitant extra deposition of fat in the thoracic and upper abdominal regions, giving rise to a buffalo torso

- About 80 per cent of patients have hypertension, pre-sumably because of the slight mineralocorticoid effects of cortisol

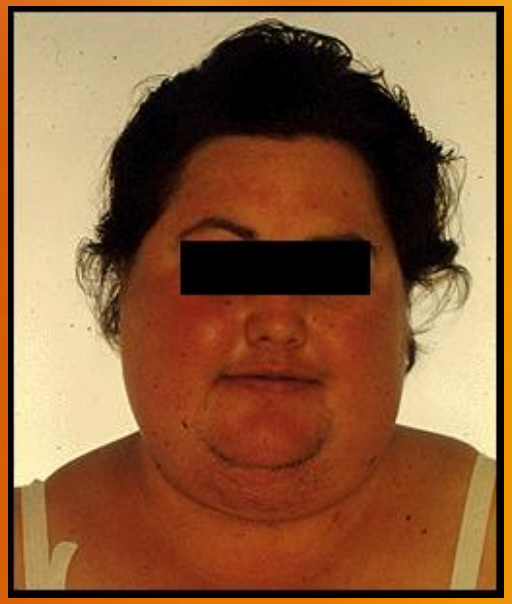
Effects on carbohydrate metabolism

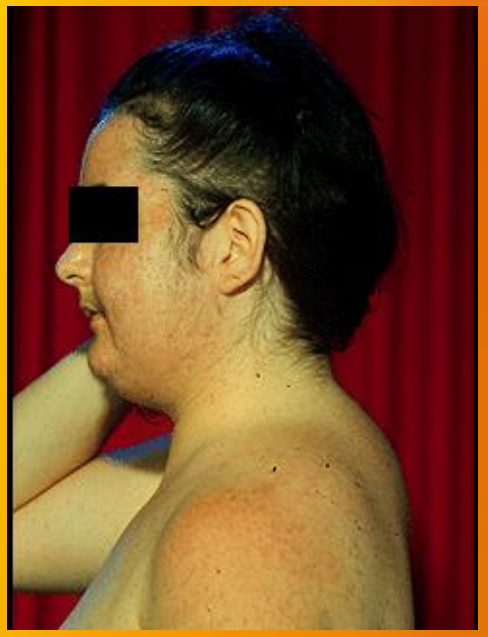
- increased blood glucose concentration, sometimes to values as high as 200 mg/dl after meals -as much as twice normal. This results mainly from enhanced gluconeogenesis and decreased glucose utilization by the tissues.

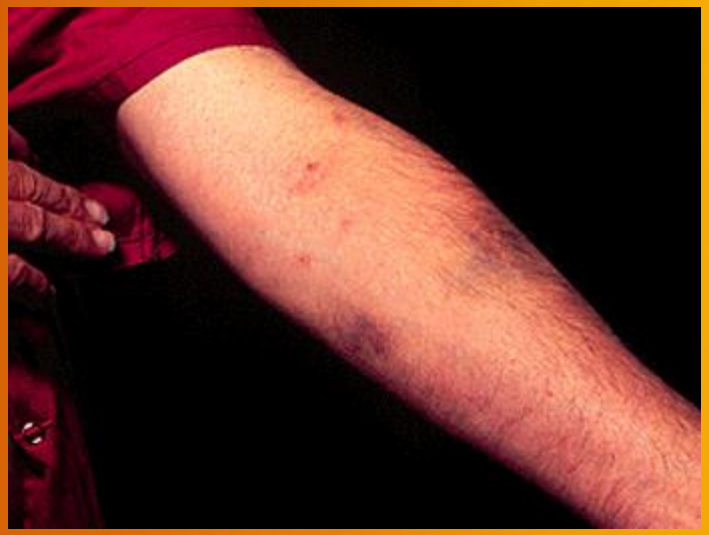
Effects on Protein Metabolism

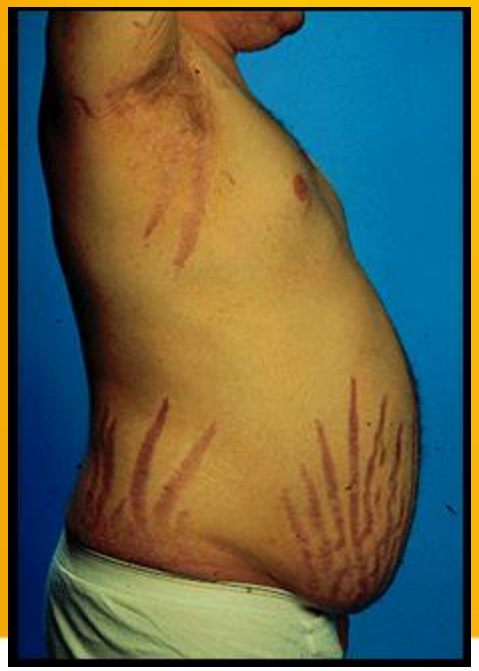
- Decreased tissue proteins almost everywhere in the body with the exception of the liver
- The loss of protein from the muscles in particular causes severe weakness
- The loss of protein synthesis in the lymphoid tissues leads to a suppressed immune system, so that many of these patients die of infections
- Even the protein collagen fibers in the subcutaneous tissue are diminished so that the subcutaneous tissues tear easily, resulting in development of large purplish striae where they have torn apart
- In addition, severely diminished protein deposition in the bones often causes severe osteoporosis with consequent weakness of the bones

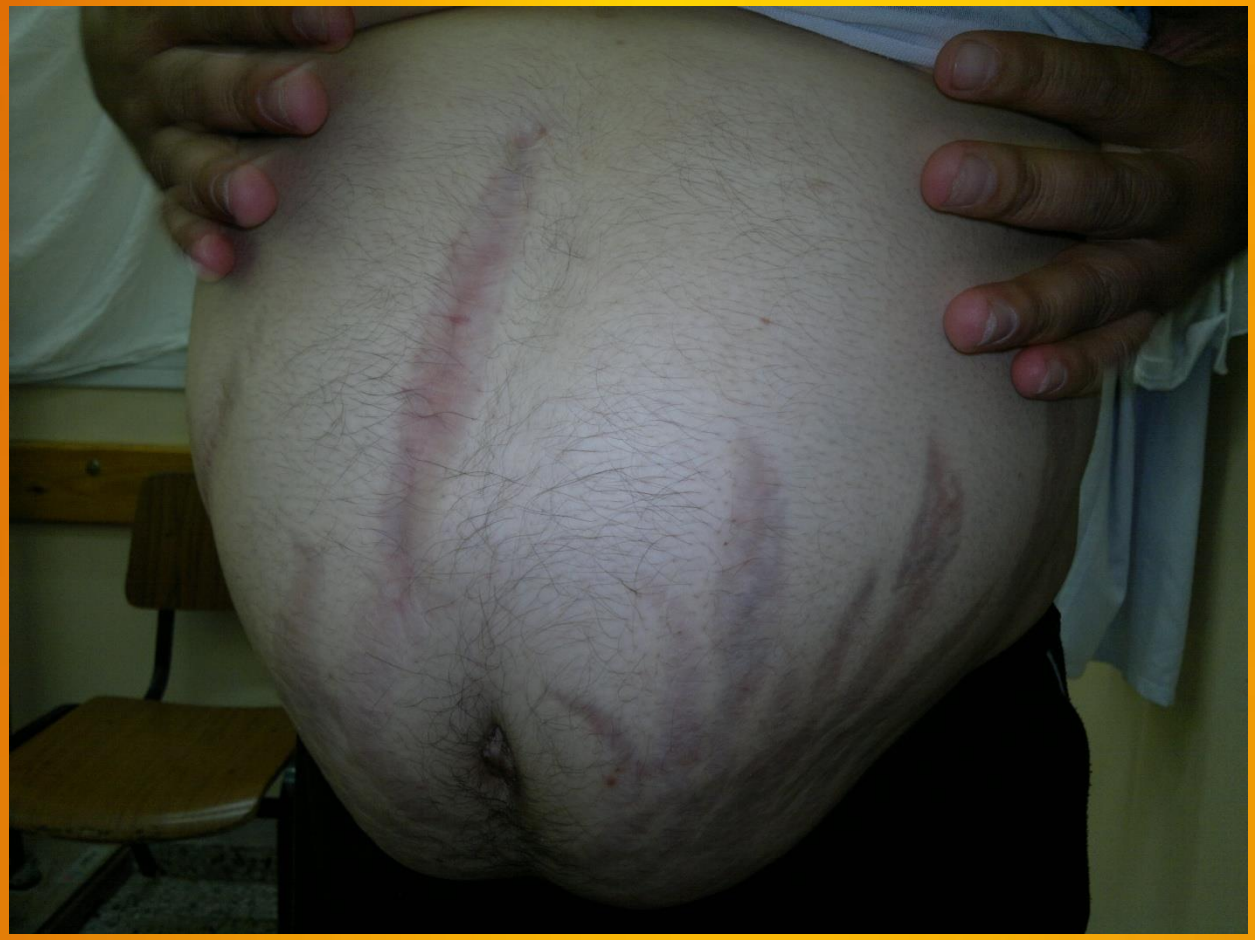
Cushing's Syndrome

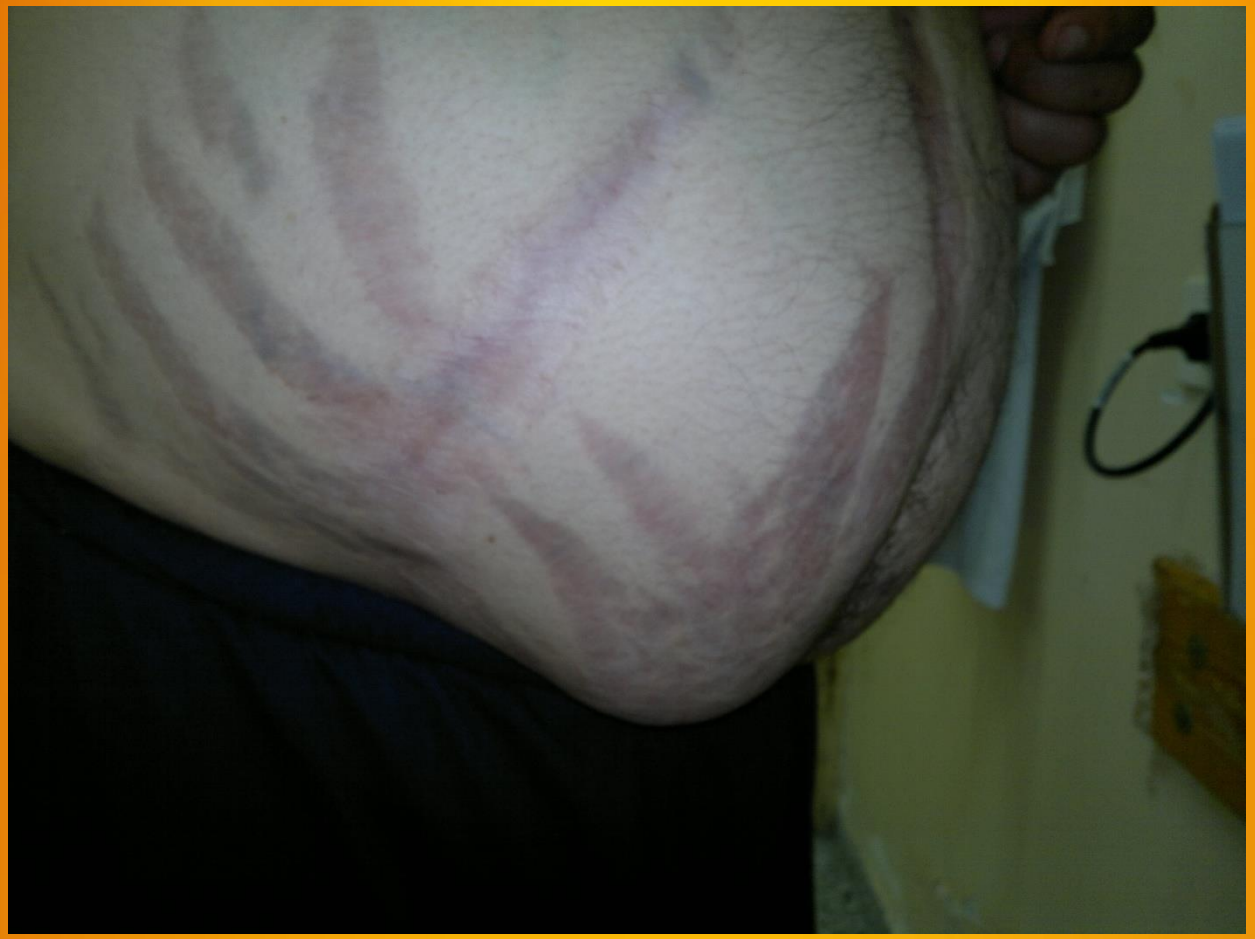










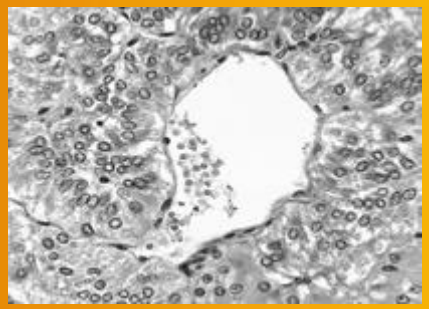


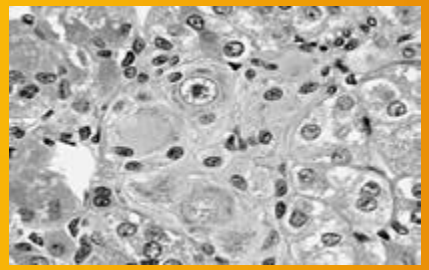
The Adrenal Medulla

- Contains two types of secretory cells
- One produces **epinephrine (adrenaline)**
  - 75% to 80% of medullary secretions
- The other produces **norepinephrine (noradrenaline)**
  - 20% to 25% of medullary secretions

Histology of adrenal gland

- Adrenal medulla is the purple stained cells at the bottom called pheochromocytes
- Pheochromocytes are the secretory cells containing dark granules of
- hormone in vesicles
  - Also called chromaffin cells because they stain dark with chromium
- Ganglion cells innervate the gland to signal the release of hormones

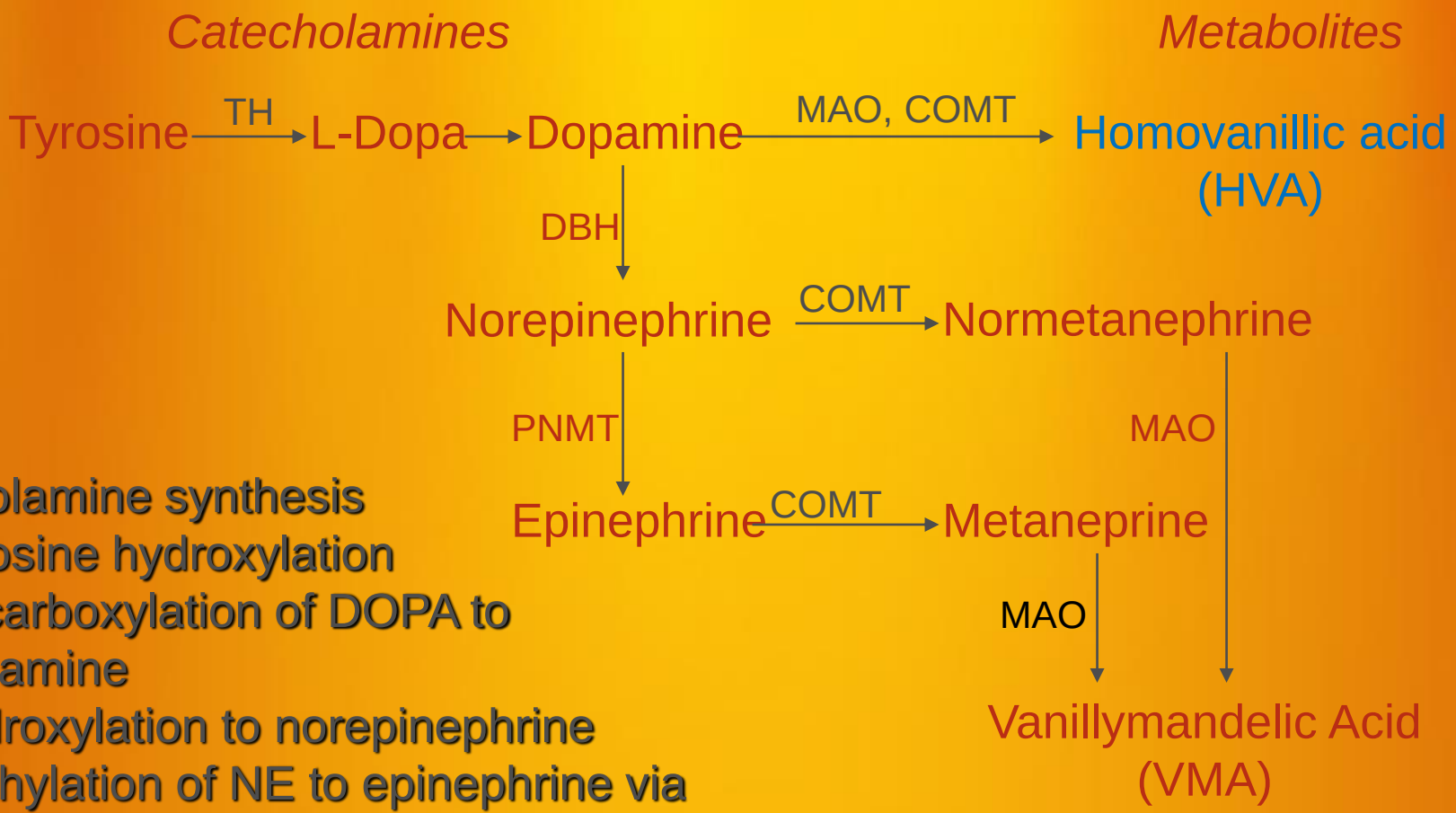




Hormones

- Pheochromocytes are modified, axonless neurons with a purely secretory function
- A cell produces either epinephrine or norepinephrine, but not both
- • Other hormones produced by the medulla are: dopamine, met-enkephalin (opioids), ADH, NPY, and adrenomedullin

catecholamine synthesis

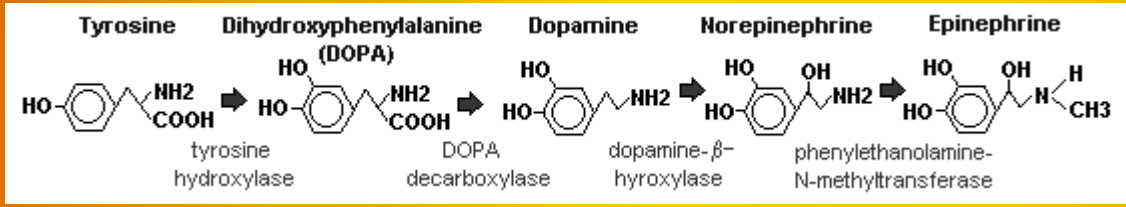


Catecholamine synthesis

- Tyrosine hydroxylation
- Decarboxylation of DOPA to dopamine
- Hydroxylation to norepinephrine
- Methylation of NE to epinephrine via PMNT

Monoamine oxidase (MAO)
Catechol-O-methyltransferase (COMT)

Synthesis of Catecholamines



- Rate of synthesis determined by tyrosine hydroxylase.
  - TH is released when catecholamines are exocytosed
  - TH is synthesized after chronic stimulation
  - Catecholamines inhibit activity
- • PNMT also feedback regulated
  - - Glucocorticoids stimulate synthesis and activity
  - - Catecholamines inhibit

Synthesis

- In adults, epinephrine is the major product of the adrenal medulla (80%)
- Norepinephrine is more prevalent in infants
- Catecholamines are also synthesized in the central nervous system and sympathetic postganglionic

neurons

  – Can act as neurotransmitters instead of as systemic hormones

Storage

- Catecholamies are actively transported into vesicles
- In the vesicles, the enzyme Dopamine β-hydroxylase completes conversion to norepinephrine
- Protein chromogranin A is also in the vesicles
- There may be thousands of vesicles in a single cell

Steps of secretion

- Sympathetic preganglionic stimulation from splanchnic nerve (acetylcholine is released)
- Calcium channels open and calcium enters cell
- Hormones are secreted through exocytosis
  - This process dumps large amounts of catecholamines into the blood for immediate transport and rapid physiological responses
  - Can be compared to a long neural pulse all through the body

Metabolism

- Catecholamines have a very short half life in the blood ~ 2 minutes
- Some are taken up by receptors of effector cells
- Reuptake by the catechol-secreting cells
- Metabolized by the liver and excreted by thekidney as vanilmandelic acid (VMA) or metanephrines
  - Enzymes important in metabolism are catecholamine-O-transferase (COMT) and monoamine oxidase (MAO)

Adrenergic receptors

Receptor	Hormone	Effect
α1	E and NE	↑ IP3, DAG
α2	E and NE	↓ cAMP
β1	E and NE	↑ cAMP
β2	E	↑ cAMP
β3	NE	↑ cAMP

Adrenergic receptors

- Alpha-Adrenergic Receptors
  - ✓ α_1: vasoconstriction, intestinal relaxation, uterine
  - ✓ contraction, pupillary dilation
  - ✓ α_2: ↓ presynaptic NE (clonidine), platelet aggregation,
  - ✓ vasoconstriction, ↓ insulin secretion
- Beta-Adrenergic Receptors
  - ✓ β_1: ↑ HR/contractility, ↑ lipolysis, ↑ renin secretion
  - ✓ β_2: vasodilation, bronchodilation, ↑ glycogenolysis
  - ✓ β_3: ↑ lipolysis, ↑ brown fat thermogenesis

Adrenergic receptors

- Present on many different tissues throughout the body
- Different types of receptors on a cell can cause different effects (e.g.. vasodilatation vs. vasoconstriction)

Metabolic effects

- Basal metabolic rate and body temp ⇑
- Protein degradation ⇓
  - This conserves energy
- Fat lipolysis ⇑
  - This frees fatty acids for energy
- • Blood glucose ⇑ allows for rapid energy availability
  - Glycogenolysis ⇑
  - Gluconeogenesis ⇑
  - Insulin ⇓ and glucagon ⇑

Cardiovascular effects

- Heart rate and pumping strength ⇑ (β1)
- Blood is directed to muscle and important response areas and away from non-vital organs
  - Vasodilatation (β2) and vasoconstriction (α)
- Blood clotting time is decreased (α)
- Respiratory bronchodilatation (β2) allows for increased oxygen availability

- Low levels have no discernable pathologic effect
- Adrenal catecholamines non-essential for life
- High levels lead to hypertension
  - Usually caused by a tumor called a pheochromocytoma
  - Can be detected by measuring plasma hormone levels

    or by testing the urine for the metabolites VMA and metanephrines
  - Clonadine supression test
  - Chromogranin A test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Insulin, Glucagon, and Diabetes Mellitus IV

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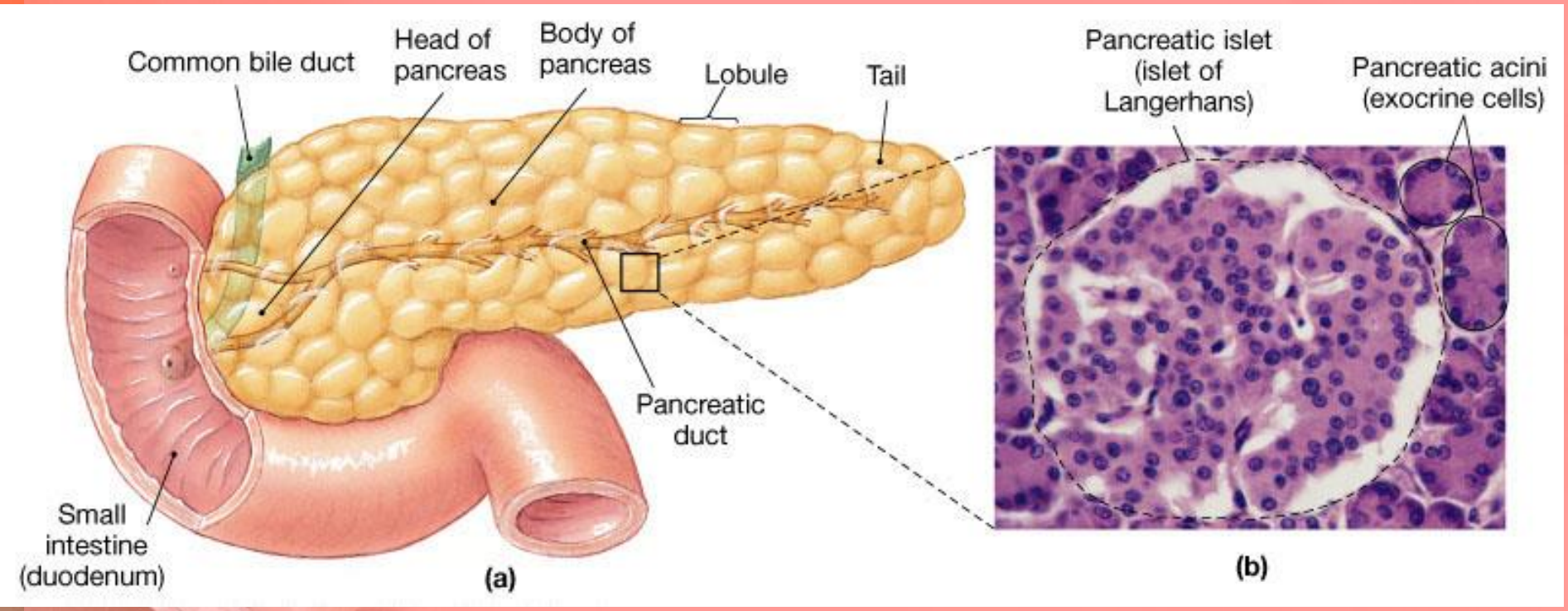
Glucose and Lipid Metabolism: Definitions of Key Terms

Glucose	the primary circulating sugar in the blood and the major energy source of the body – used to produce ATP
Gluconeogenesis	the formation of new glucose from protein or fat (to store energy)
Glycolysis	the breakdown of glucose (to produce energy)
Glycogen	the main form of carbohydrate storage primarily in the liver and muscle tissue; readily converted to glucose to satisfy its energy needs
Glycogenesis	formation of glycogen from glucose (to store energy)
Glycogenolysis	breakdown of glycogen to glucose (to produce energy)
Lipid	fat; found almost exclusively in foods of animal origin and continuously synthesized in the body
Lipogenesis	the formation of lipids (to store energy)
Lipolysis	the breakdown of lipids (to produce energy)

History

- Pancreas – derived from the Greek pan, “all”, and kreas, “flesh”, probably referring to the organ’s homogenous appearance
- Herophilus, Greek anatomist and Surgeon, first identified the pancreas in 335 – 280 BC
- Ruphos, another Greek anatomist, gave pancreas its name after few hundred years

The Endocrine Pancreas



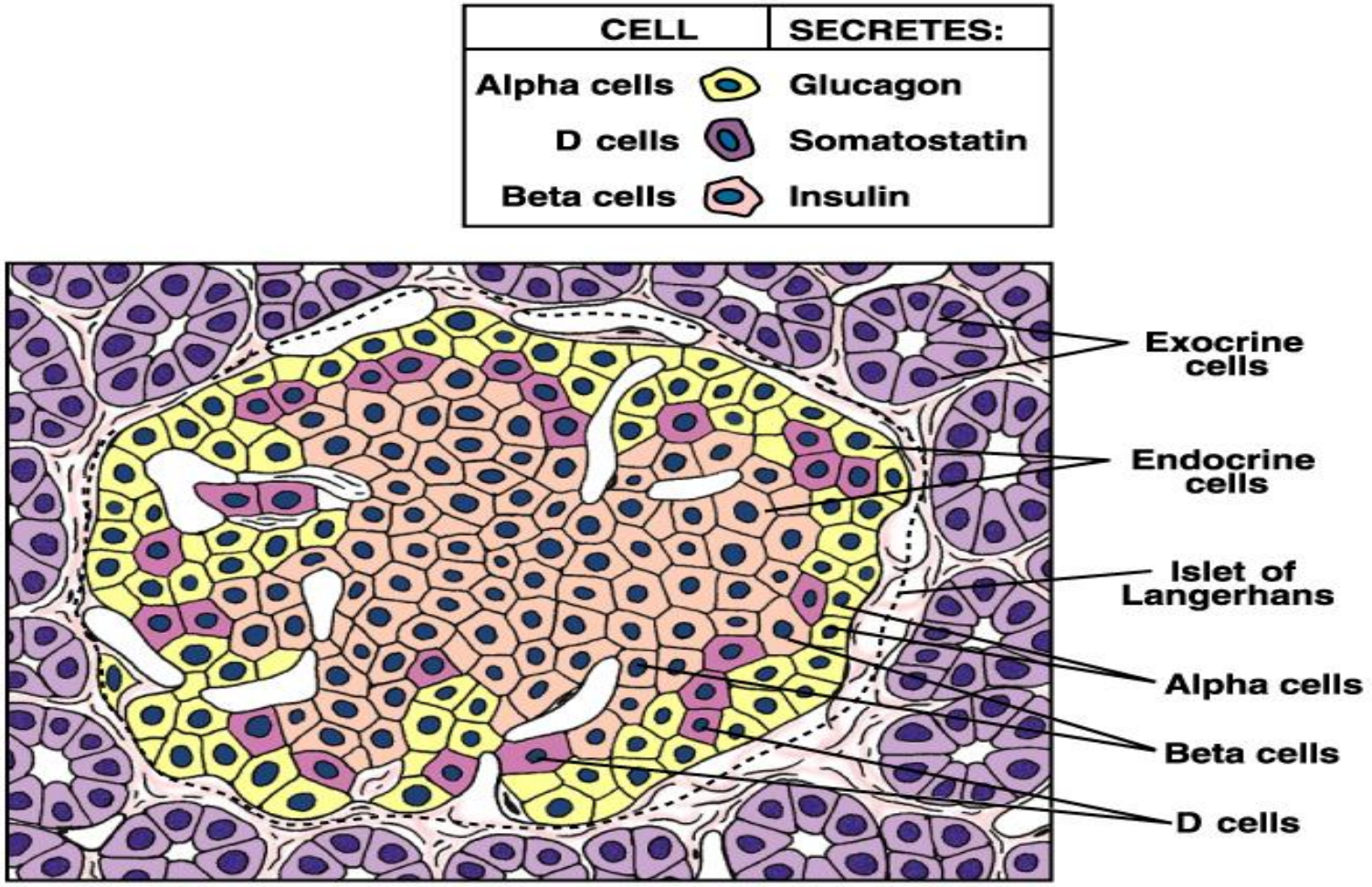
Pancreas

- A triangular gland, which has both exocrine and endocrine cells, located behind the stomach
- Acinar cells produce an enzyme-rich juice used for digestion (exocrine product)
- Pancreatic islets (**islets of Langerhans**) produce hormones involved in regulating fuel storage and use.

Pancreas

- Exocrine pancreas 85% of the volume of the gland
- Extracellular matrix – 10%
- Blood vessels and ducts - 4%
- Endocrine pancreas 1-2%

Histology of pancreas



Islets of Langerhans

- 1-2 million islets
- 1-2% of the pancreatic mass
- Beta (β) cells produce insulin and amylin, 60 %
- Alpha (α) cells produce glucagon 25%
- Delta (δ) cells produce somatostatin 10%
- PP(F) cells produce pancreatic polypeptide

Insulin

Insulin

JL on 12/15/22 and 2 mos later

Before insulin was discovered in 1921, everyone with type 1 diabetes died within weeks to years of its onset

Insulin Structure

1- Large polypeptide 51 AA (MW 6000)

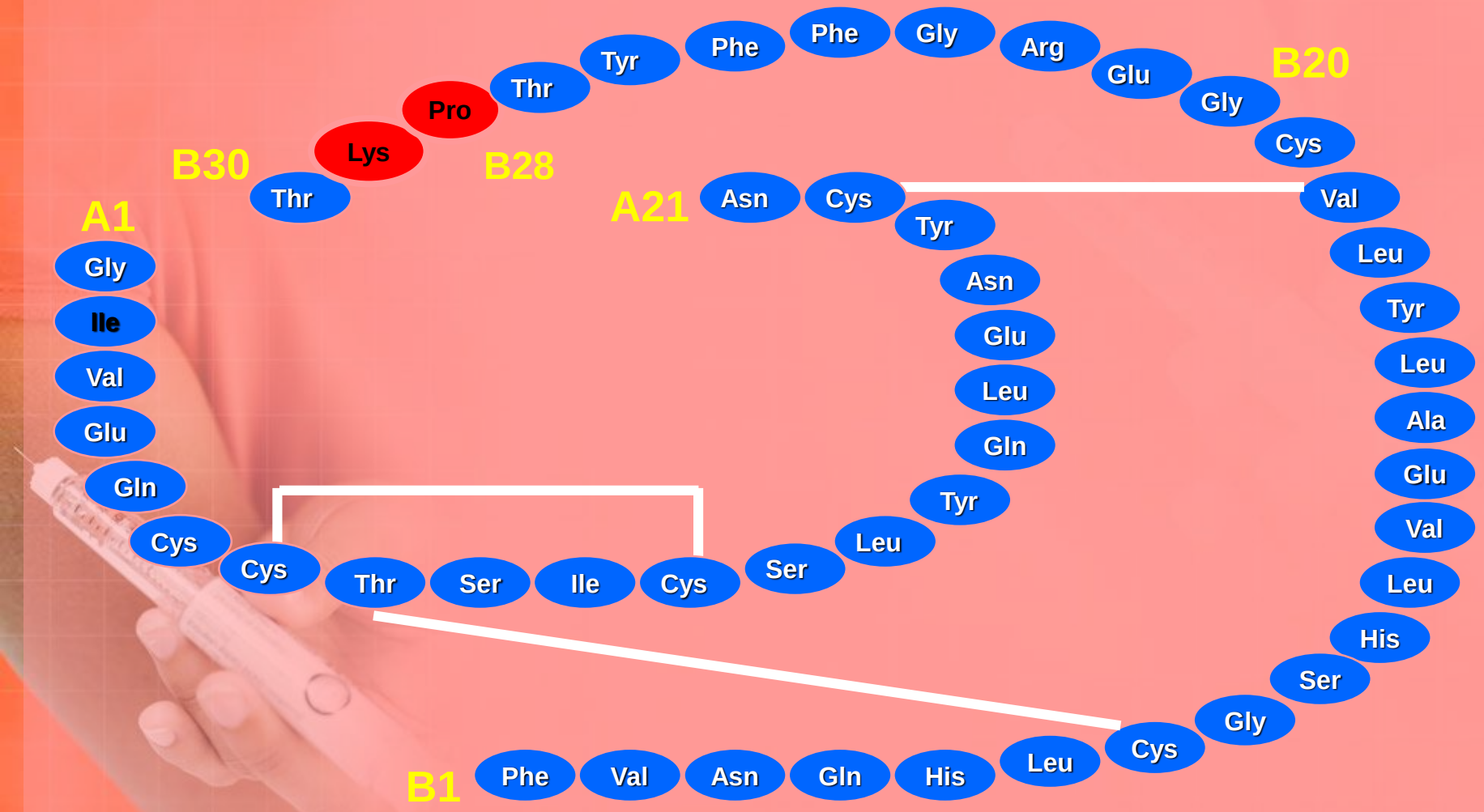
2- Tow chains linked by disulfide bonds.

A chain (21 AA)

B chain (30 AA)

3 disulfide bonds.

Human Insulin



Insulin Synthesis

- insulin gene encodes a large precursor of insulin (preproinsulin)
- During translation, the signal peptide is cleaved (proinsulin)
- During packaging in granules by Golgi, proinsulin is cleaved into insulin and C peptide

Insulin Synthesis

DNA (chromosome 11) in β cells

↓

mRNA

↓

Preproinsulin (signal peptide, A chain, B chain, and peptide C)

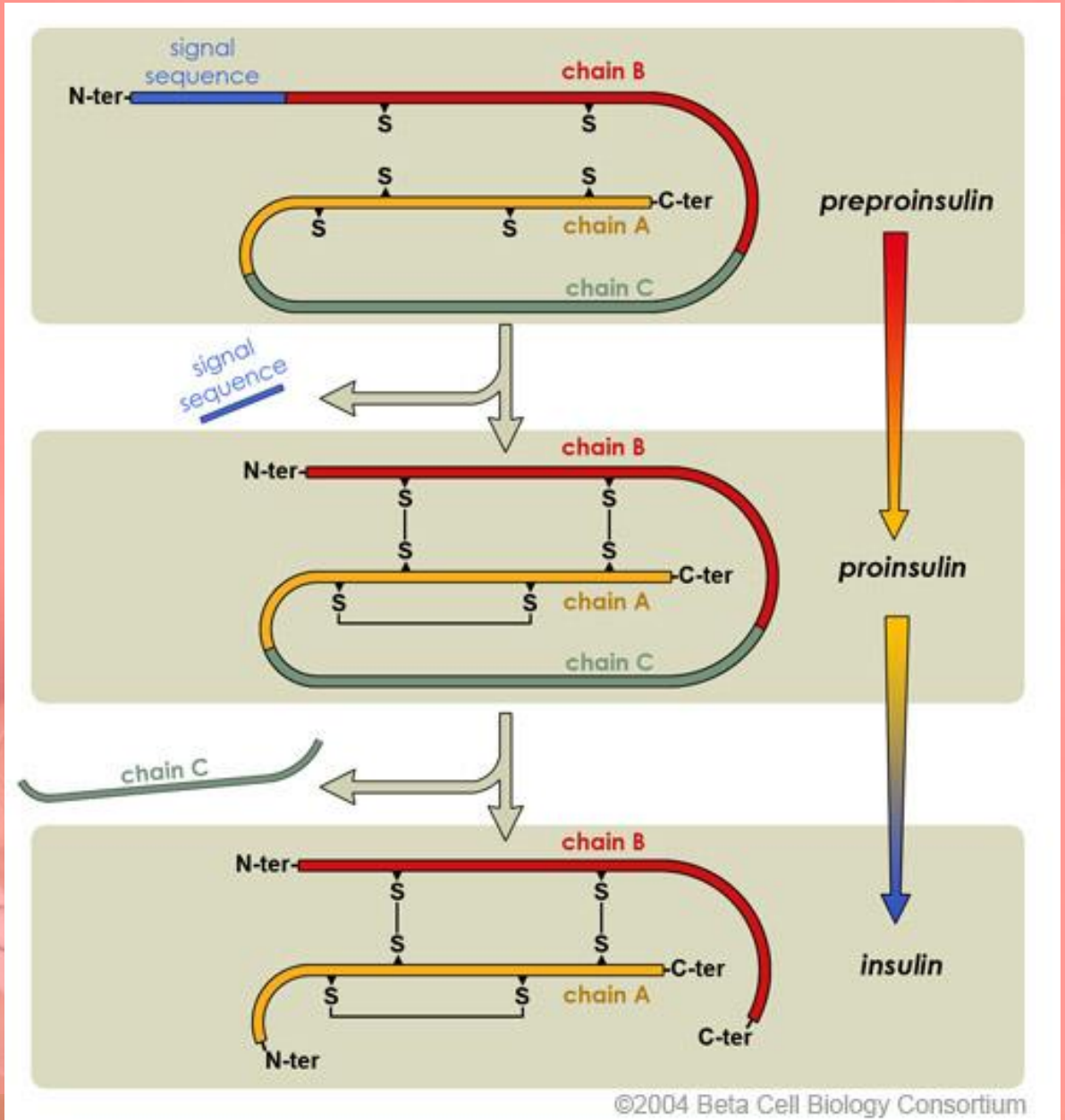
↓

proinsulin

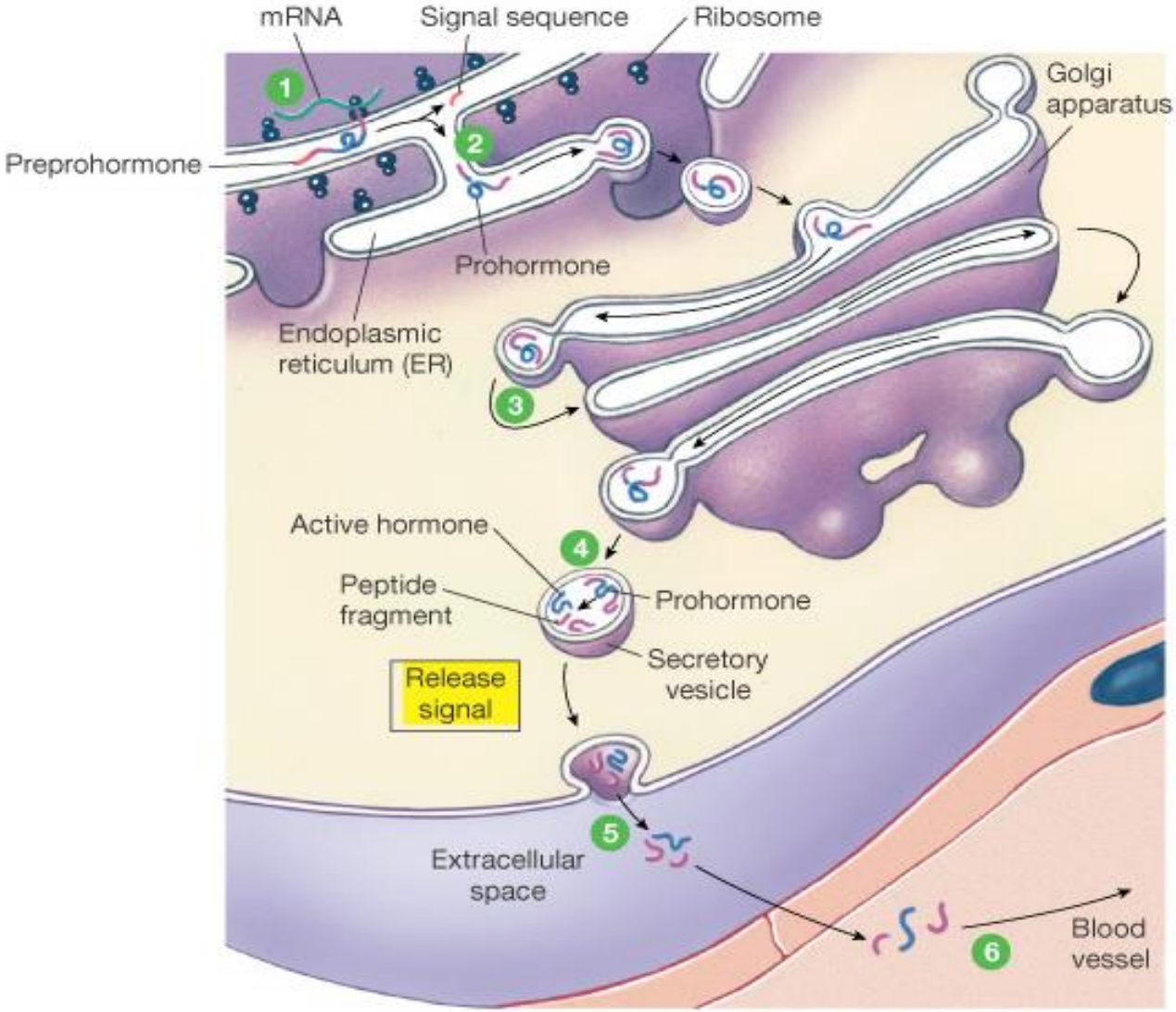
↓

insulin

Insulin Synthesis



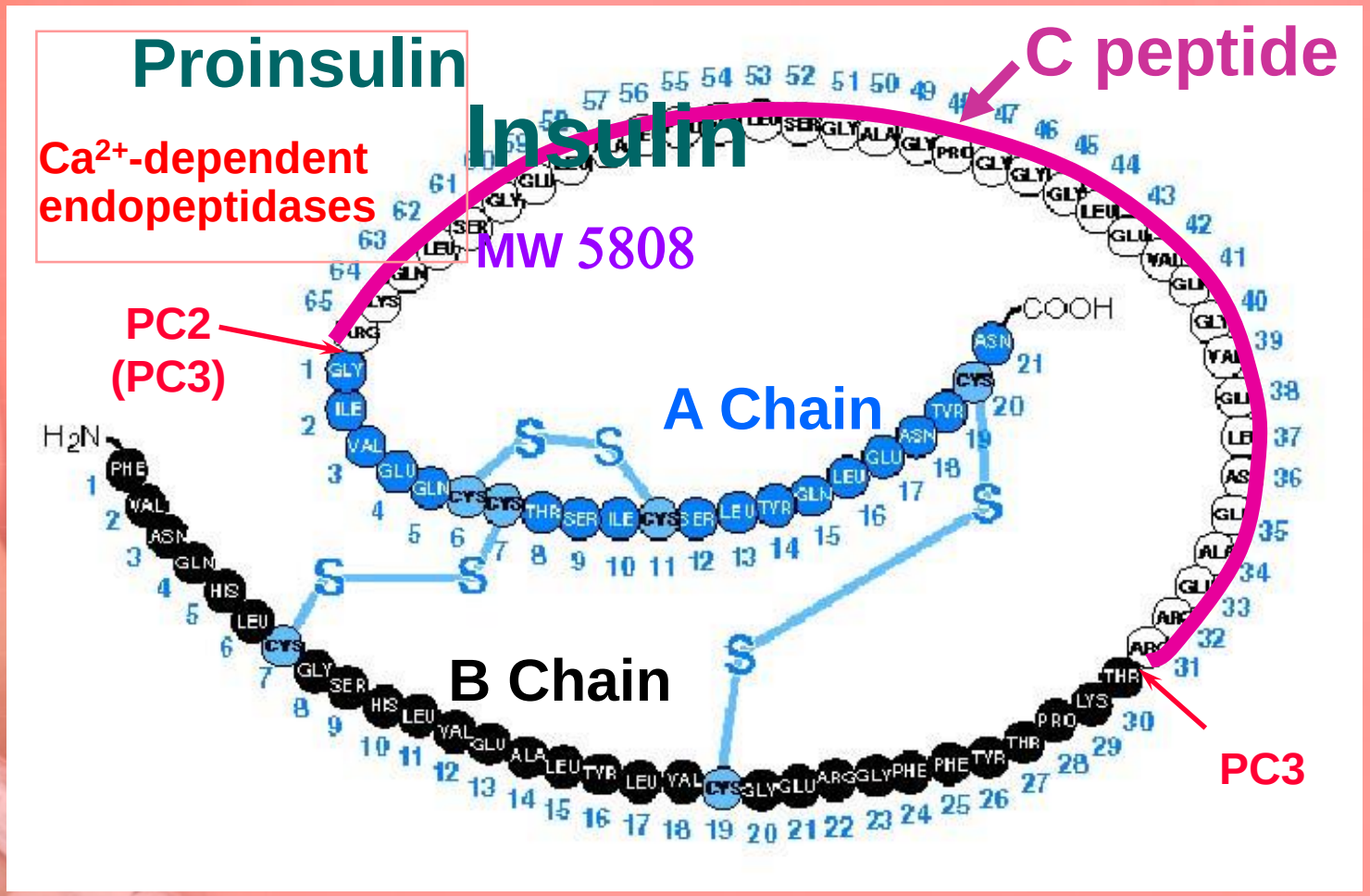
Protein and Polypeptide Synthesis and Release



1. Messenger RNA on the ribosomes of the ER binds amino acids into a peptide chain called a **preprohormone**. The chain is directed into the ER lumen by a **signal sequence** of amino acids.
2. Enzymes in the ER chop off the signal sequence, creating an inactive **prohormone**.
3. The prohormone passes from the ER through the Golgi apparatus.
4. Secretory vesicles containing enzymes and prohormone bud off the Golgi. The enzymes chop the prohormone into one or more active peptides plus additional peptide fragments.
5. The secretory vesicle releases its contents by exocytosis into the extracellular space.
6. The hormone moves into the circulation for transport to its target.

Insulin

- A protein hormone consisting of two amino acid chains linked by disulfide bonds
- Synthesized as part of proinsulin (86 AA) and then excised by enzymes, releasing functional insulin (51 AA) and C peptide (29 AA)
- Plasma half-life about 4- 6 minutes
- Cleared from the circulation within 10 to 15 minutes
- Degraded by the enzyme *insulinase* mainly in the liver, to a lesser extent in the kidneys and muscles


Proinsulin
Ca2+-dependent endopeptidases
Insulin
MW 5808
C peptide
PC2 (PC3)
A Chain
B Chain
PC3
H2N
COOH

Insulin, Proinsulin, and **C** peptide

- **C** peptide has no known biological activity
  - ✓ Secreted in 1:1 ratio with insulin (**A, B)**
  - ✓ Insulin is removed by liver (60%), **C** peptide is not
  - ✓ Therefore, **C** peptide is a good measure of insulin (**A, B)** secretion.
- Proinsulin (**B**, **C**, **A**) has modest insulin-like activity
  - ✓ 1/20th as potent as insulin (**A, B)**
  - ✓ β cell secretes about 5% as much proinsulin as insulin (**A, B)**.

Factors and Conditions That Increase or Decrease Insulin Secretion

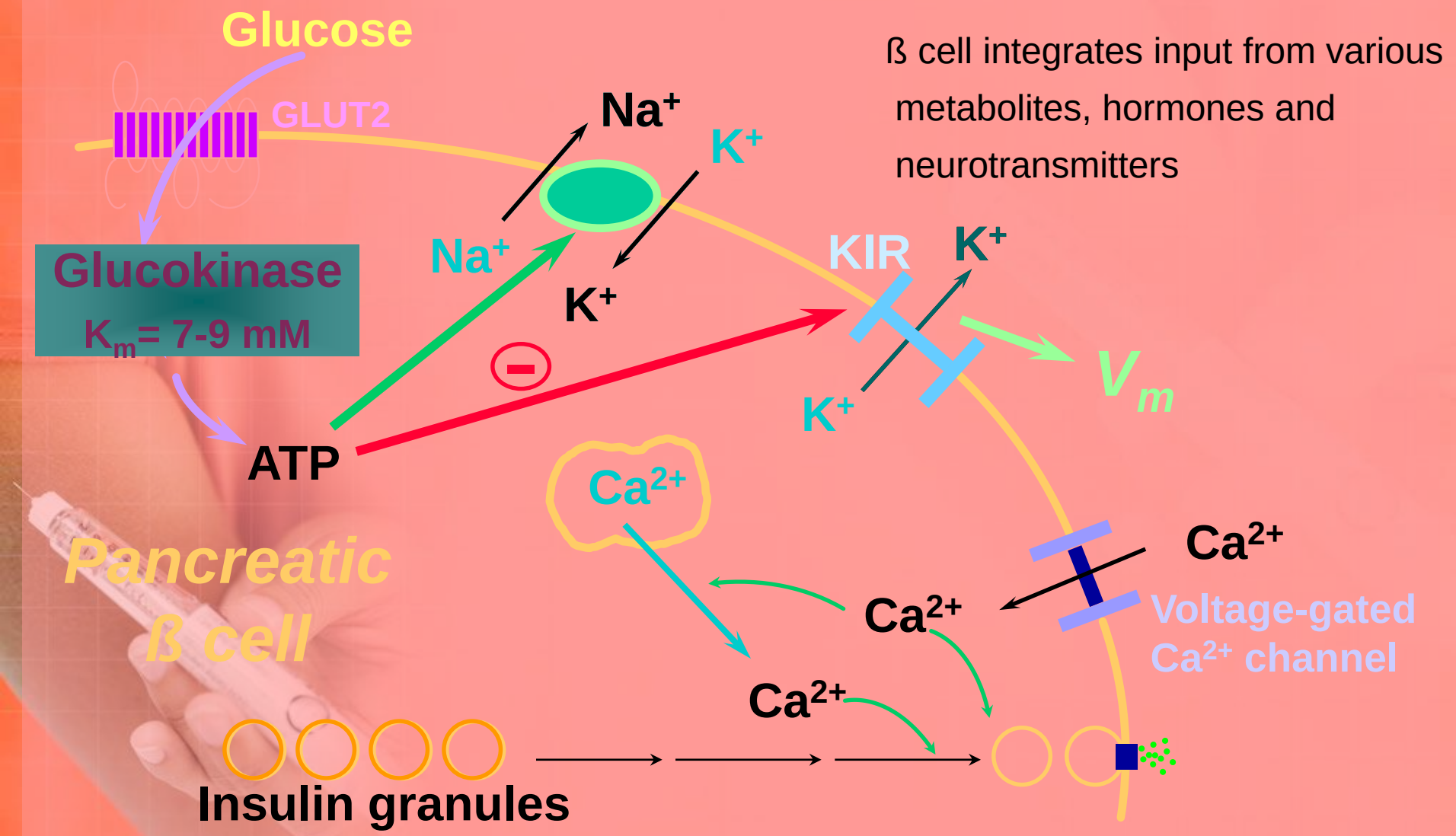
Stimulators of insulin secretion	Inhibitors of insulin secretion
↑ Serum glucose	↓ Glucose
↑ Serum amino acids	↓ Amino acids
↑ Serum free fatty acids	↓ Free fatty acids
↑ Serum ketone bodies	
Hormones	Hormones
Gastroinhibitory peptide (GIP)	Somatostatin
Glucagon	Epinephrine (α-receptor)
Gastrin	Leptin
Cholecystokinin (CCK)	
Secretin	
Vasoactive intestinal peptide (VIP)	
Epinephrine (β-receptor)	
Parasympathetic nervous system	Sympathetic nervous system stimulation

Sulfonylurea drugs (glyburide, tolbutamide

Regulation of Insulin Secretion

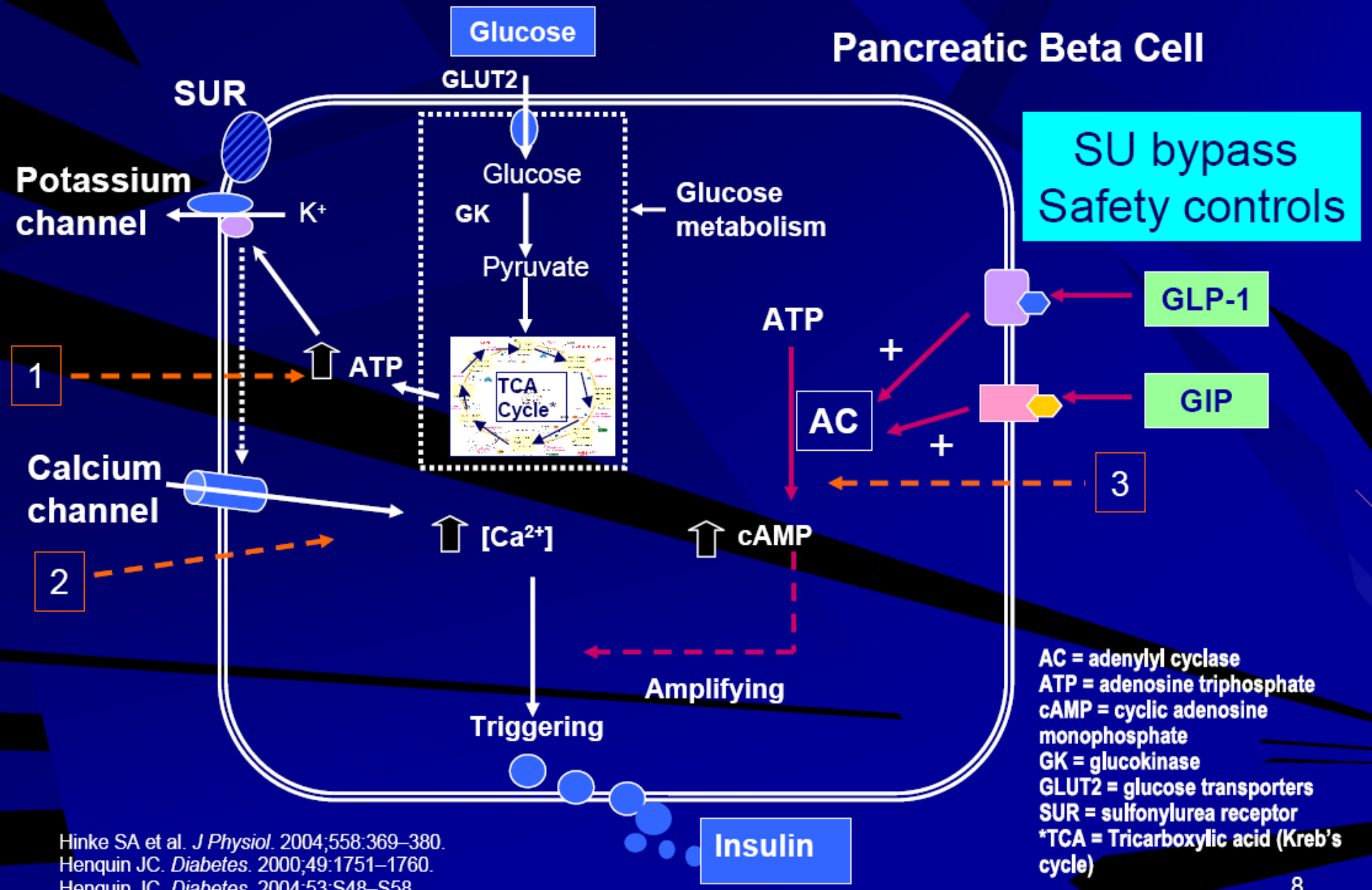
- No insulin is produced when plasma glucose below 50 mg/dl
- Half-maximal insulin response occurs at 150 mg/dl
- A maximum insulin response occurs at 300 mg/dl
- Insulin secretion is biphasic:
  - ✓ Upon glucose stimulation– an initial burst of secretion (5-15 min.)
  - ✓ Then a second phase of gradual increment that lasts as long as blood glucose is high

Glucose-stimulated insulin secretion



ß cell integrates input from various metabolites, hormones and neurotransmitters

Glucose-Stimulated Secretion of Insulin



AC = adenylyl cyclase
ATP = adenosine triphosphate
cAMP = cyclic adenosine monophosphate
GK = glucokinase
GLUT2 = glucose transporters
SUR = sulfonylurea receptor
*TCA = Tricarboxylic acid (Kreb's cycle)

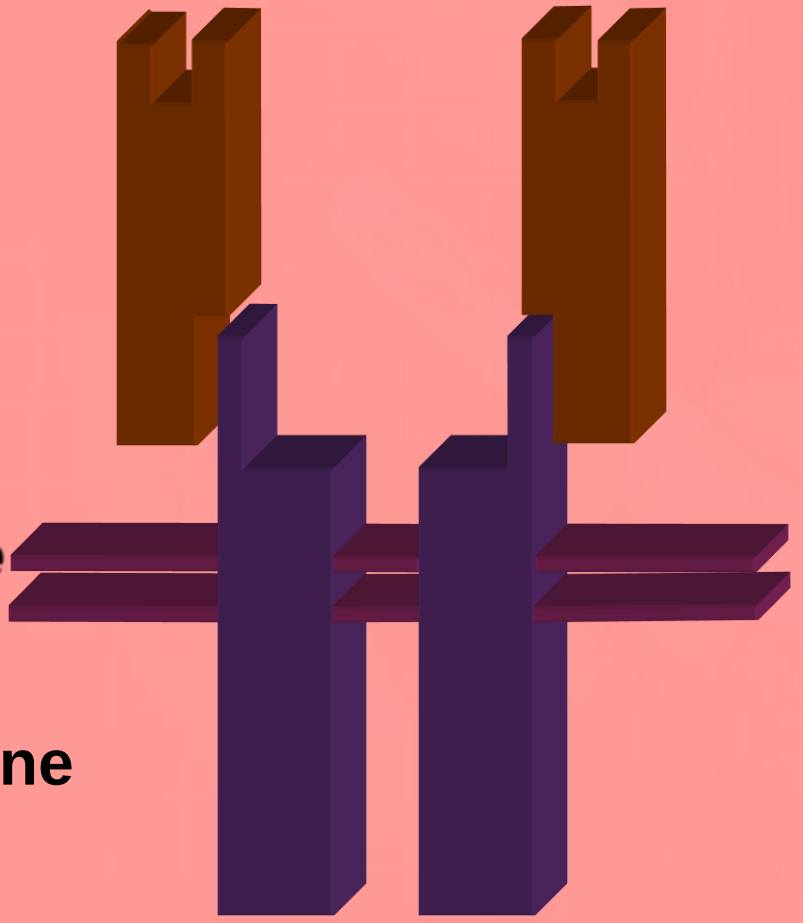
Hinke SA et al. *J Physiol*. 2004;558:369–380.
Henquin JC. *Diabetes*. 2000;49:1751–1760.
Henquin JC. *Diabetes*. 2004;53:S48–S58.

Insulin RECEPTOR

α subunits contain insulin binding sites

plasma membrane

β subunits have tyrosine kinase activity



Insulin Receptor Signaling

Insulin binding to α subunit regulates β subunit activity

↓

autophosphorylation of β subunit

↓

⇑ tyr kinase activity

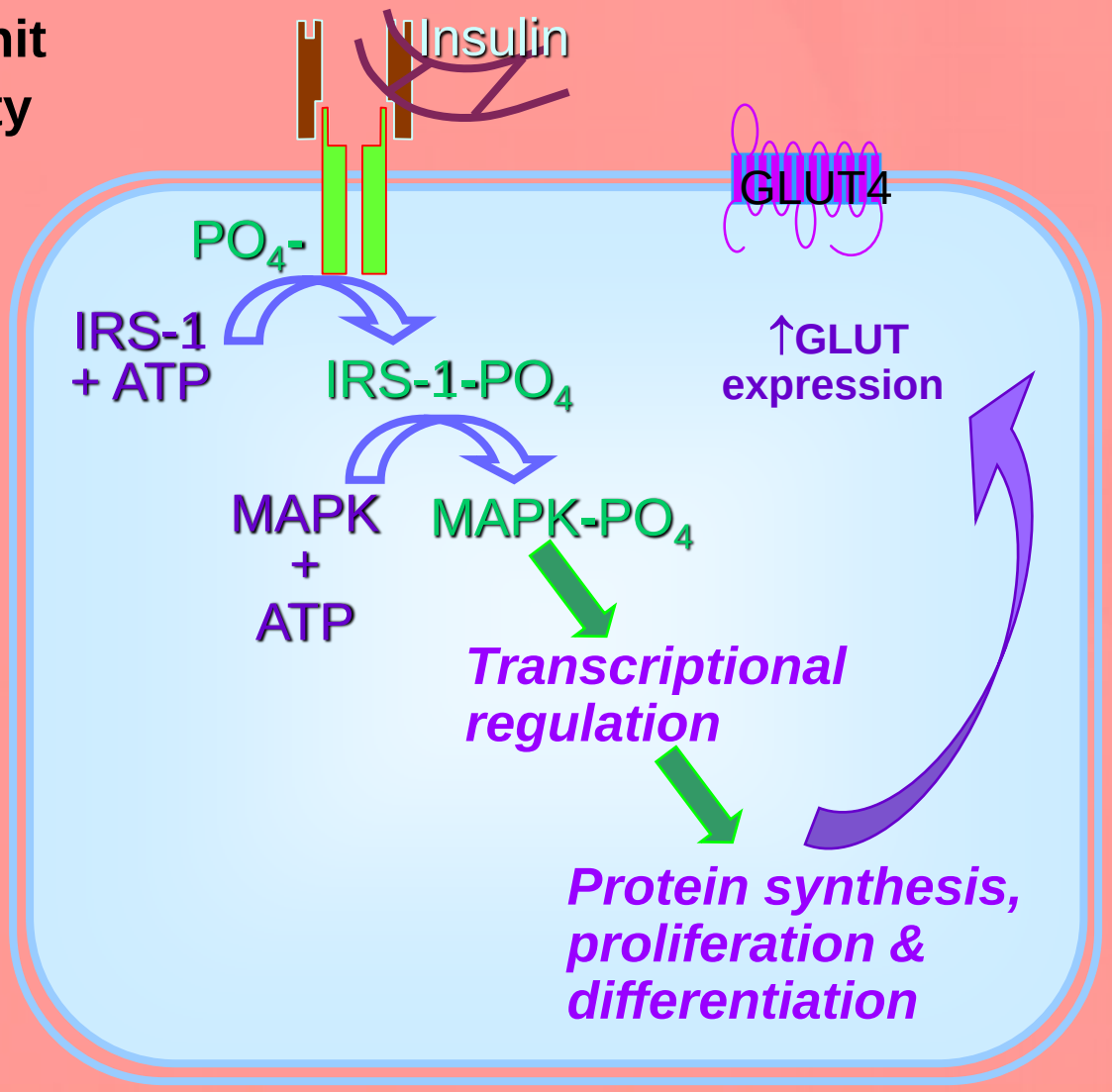
↓

phosphorylation of other substrates

↓

phosphorylation of MAP kinase

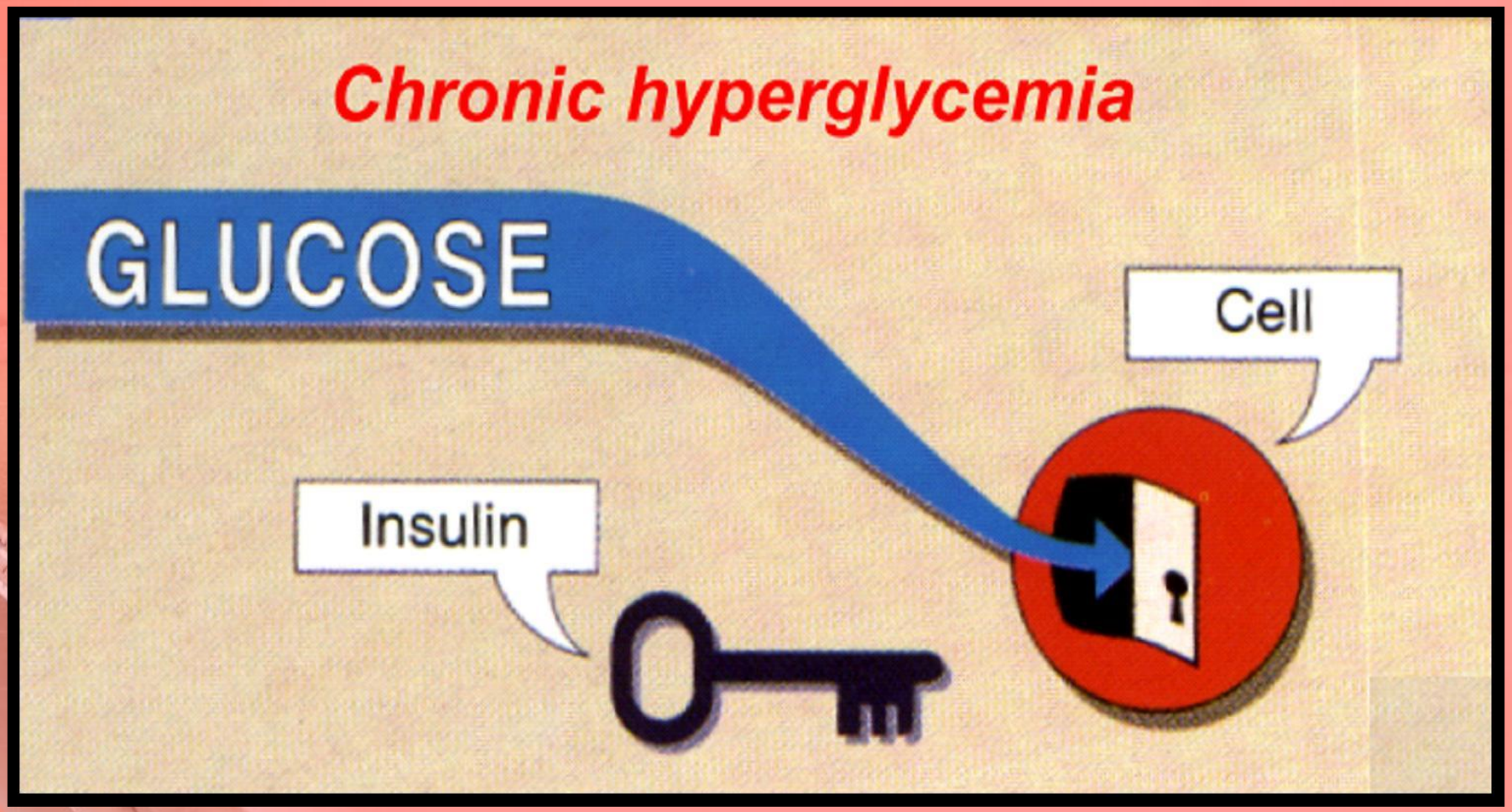
mitogen-activated protein kinases



How does Insulin Regulate Glucose Concentration?

- Activates glucose transporters
- Activates enzymes involved in lipid metabolism (energy storage)
- Activates transcription of genes that promote glycogen synthesis (energy storage)

Insulin the key of the cell door



Major development of insulin

Insulin preparations (1922-1980)

- 1922 Isolation of insulin
- 1928 Insulin a protein
- 1955 primary structure of insulin
- 1970 human synthesis of insulin

rDNA technology

- 1979 expressing human insulin in E. Coli
- 1989 Production of human insulin in E. Coli and yeast cells
- 1996 Insulin analogues – “ designer insulins “

Response to a meal

Islet hormone secretion varies with circulating glucose levels

Meal increases:

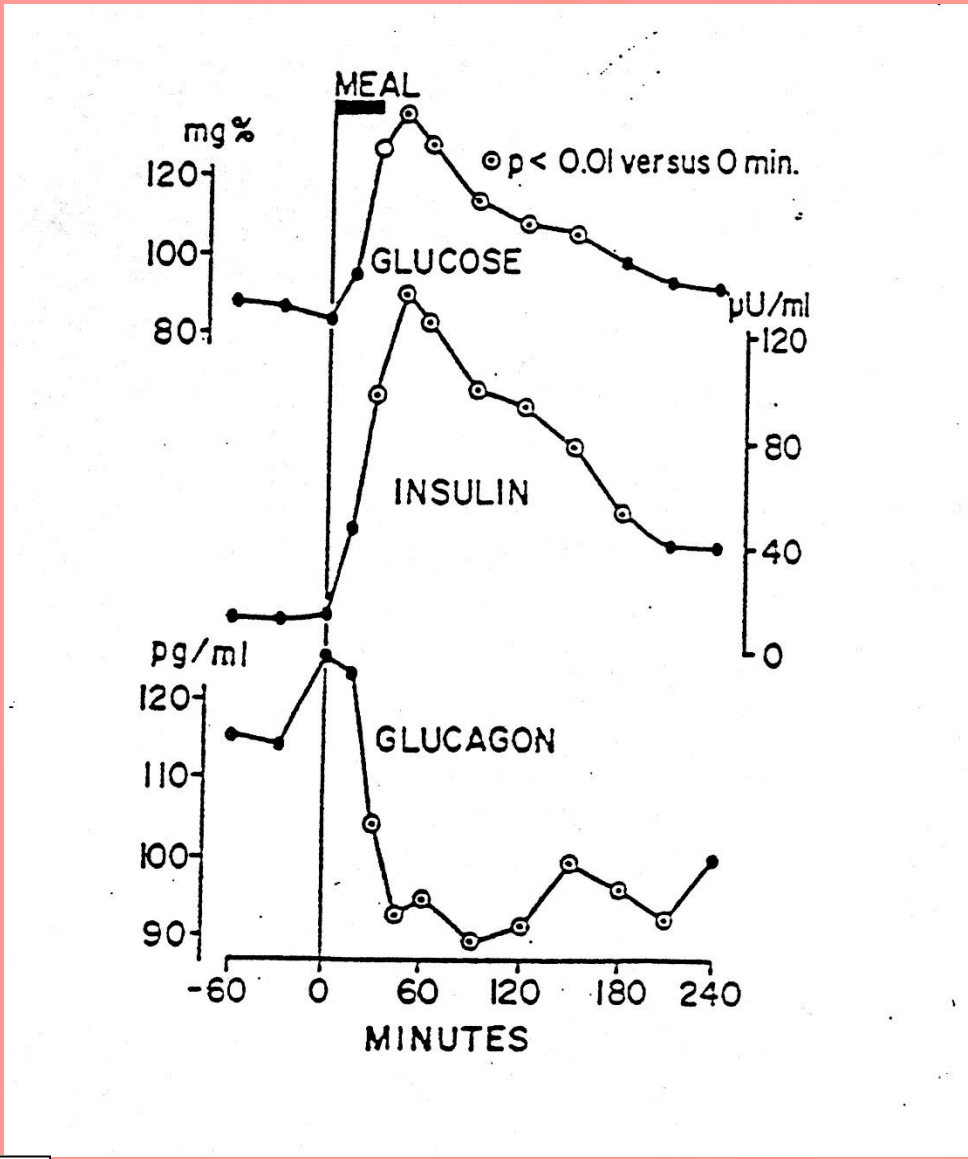
Glucose

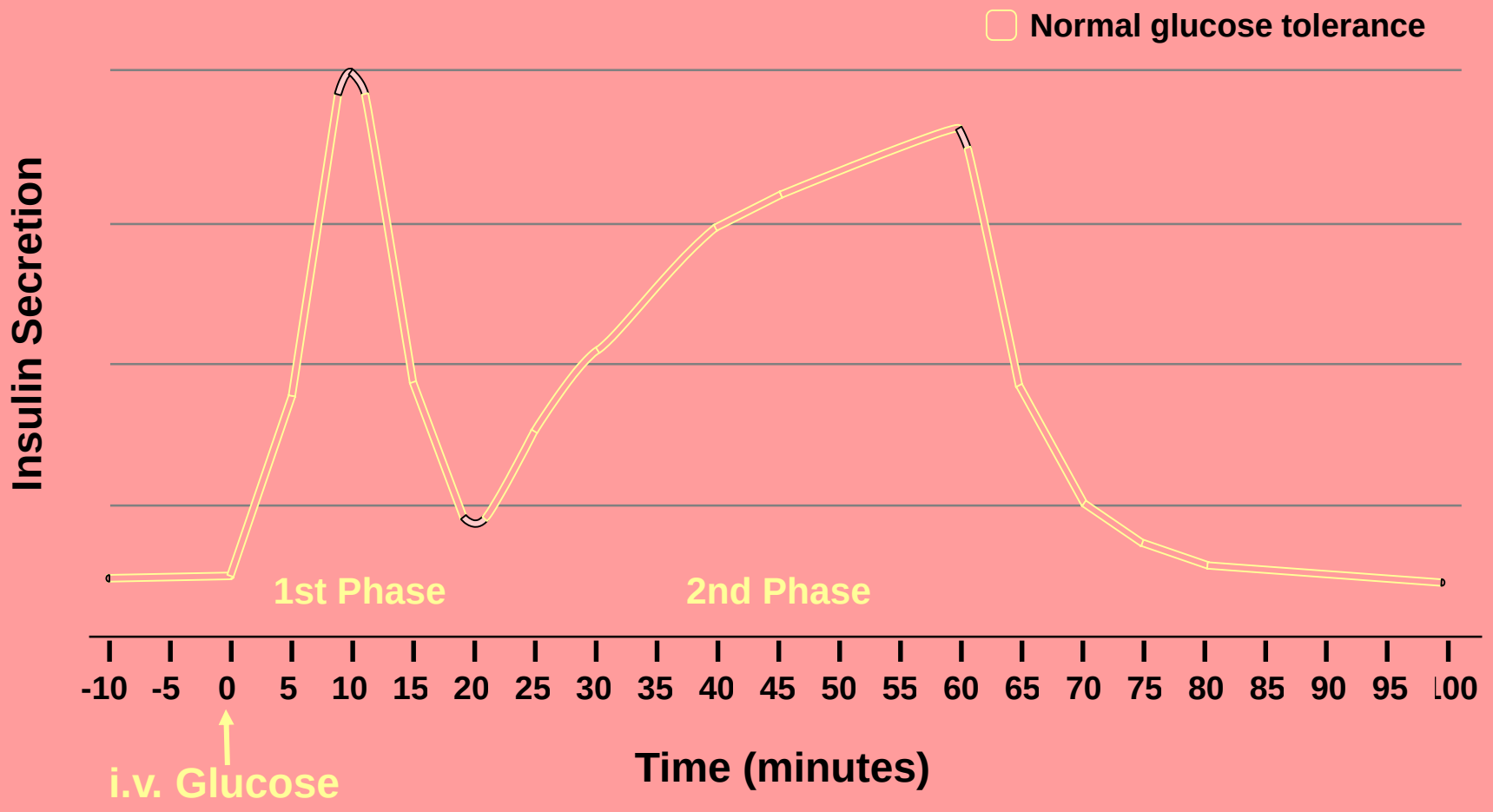
→ increased **insulin**

→ decreased **glucagon**

Amino acids, FA

→ increased **insulin**

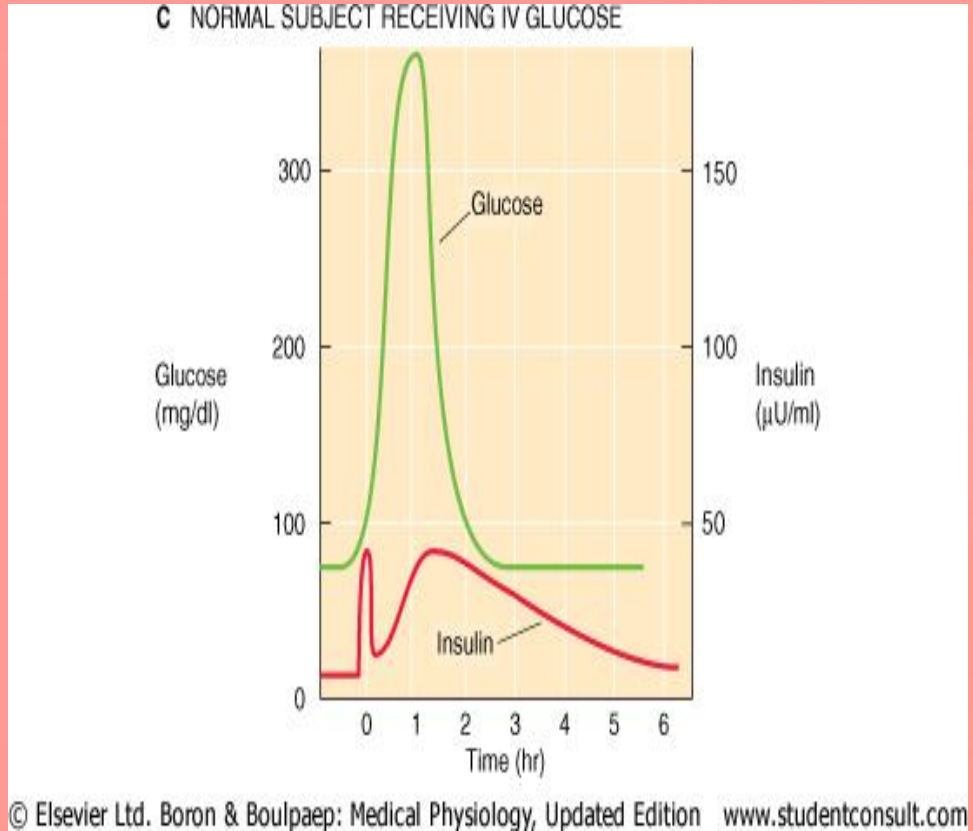



Normal glucose tolerance
Insulin Secretion
1st Phase
2nd Phase
-10 -5 0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100
i.v. Glucose
Time (minutes)

Intravenous Glucose

- Intravenous glucose administration increases plasma [glucose] very rapidly
- Causes 2 phases of insulin secretion
  - First phase
    - lasts 2-5 minutes
    - Secretion of preformed insulin
  - Second phase
    - Lasts as long as glucose levels are elevated
    - Secretion of preformed and newly synthesized insulin

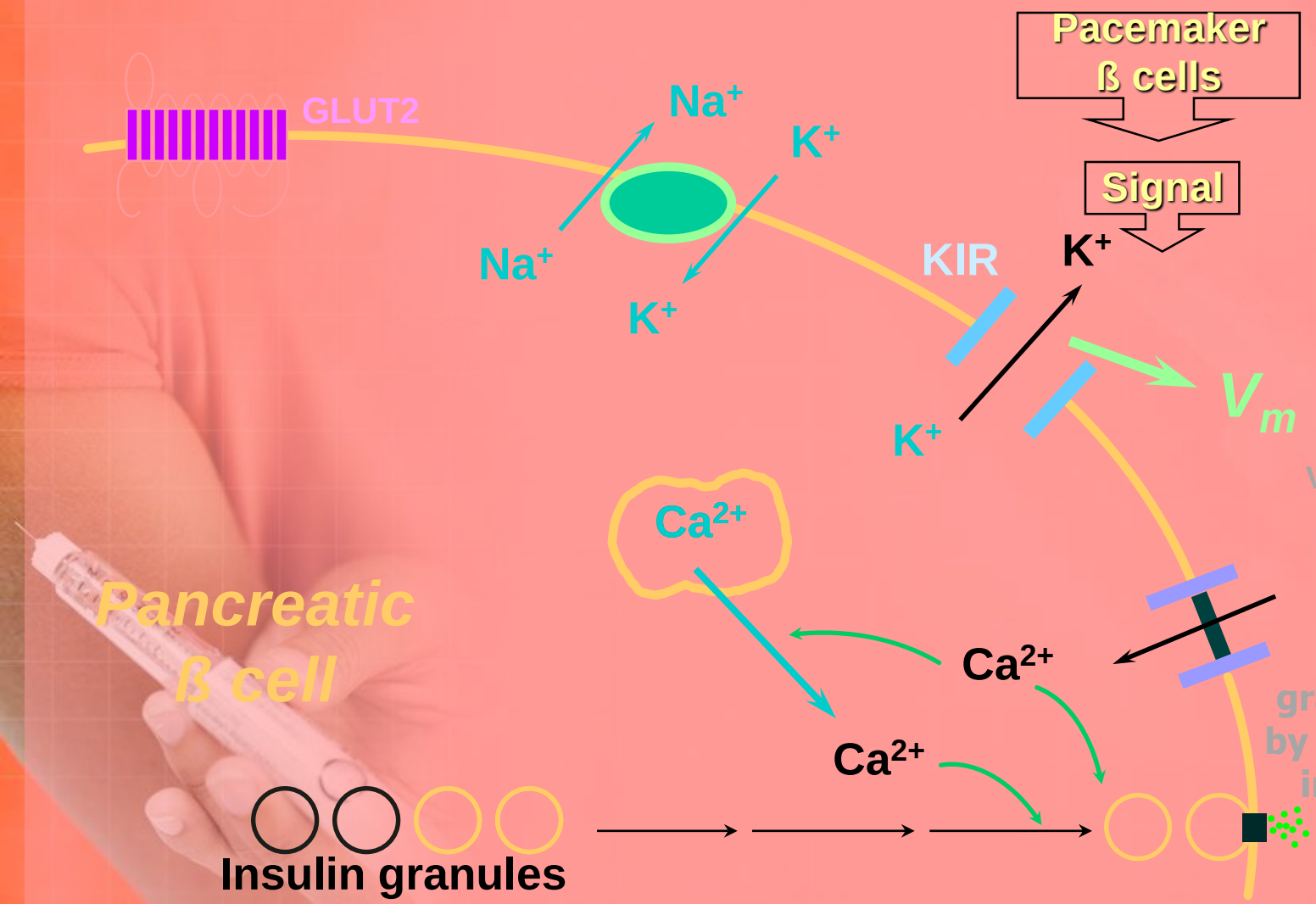
- Earliest detectable metabolic defects in diabetes is loss of first phase, detected by **glucose tolerance test**.



Glucose Transport

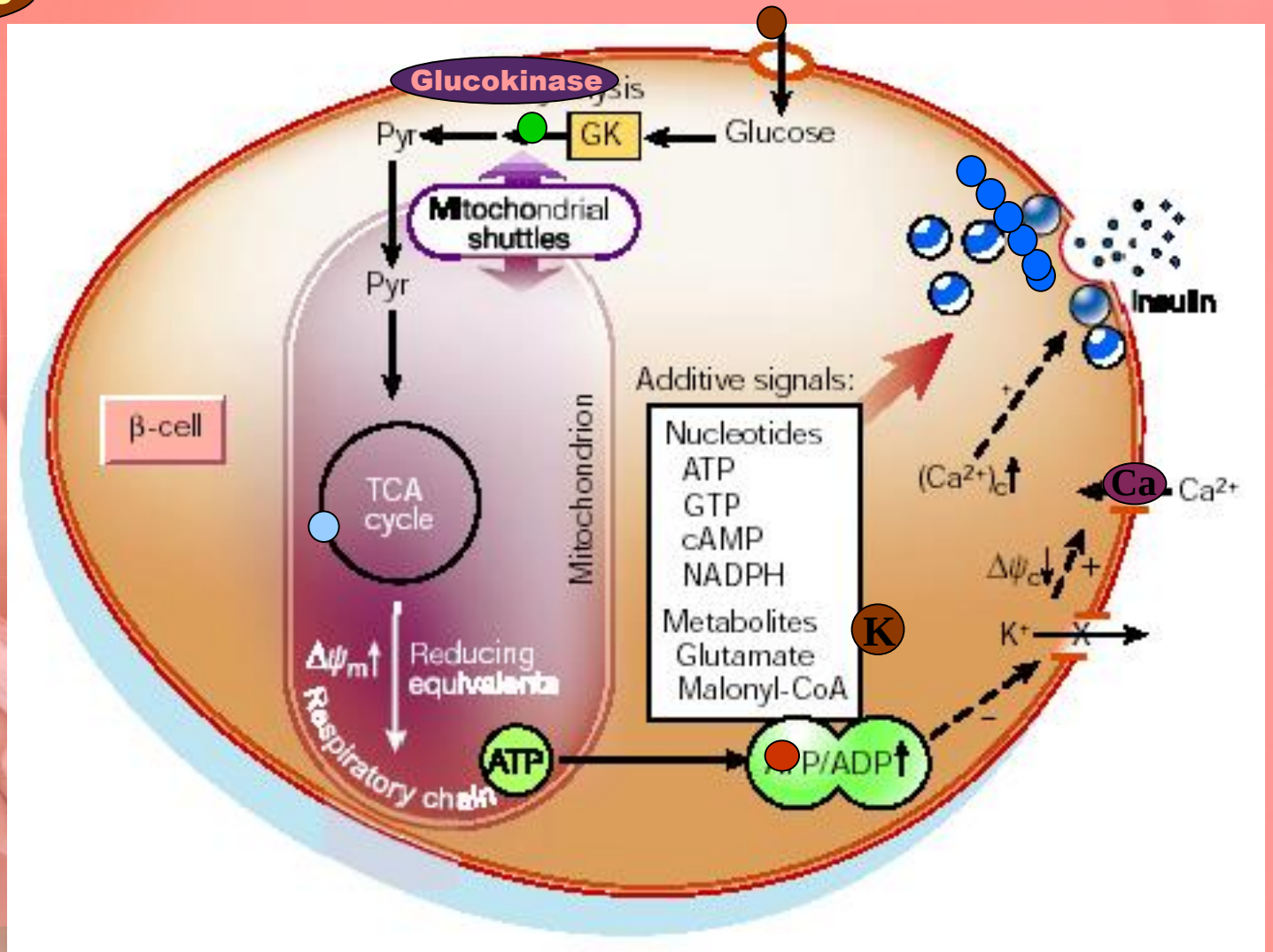
- GLUT2 (liver, pancreas)
- **GLUT4**, insulin sensitive transporter (muscle, adipose tissue)
- GLUT3 (brain)

Regulation of Basal insulin secretion

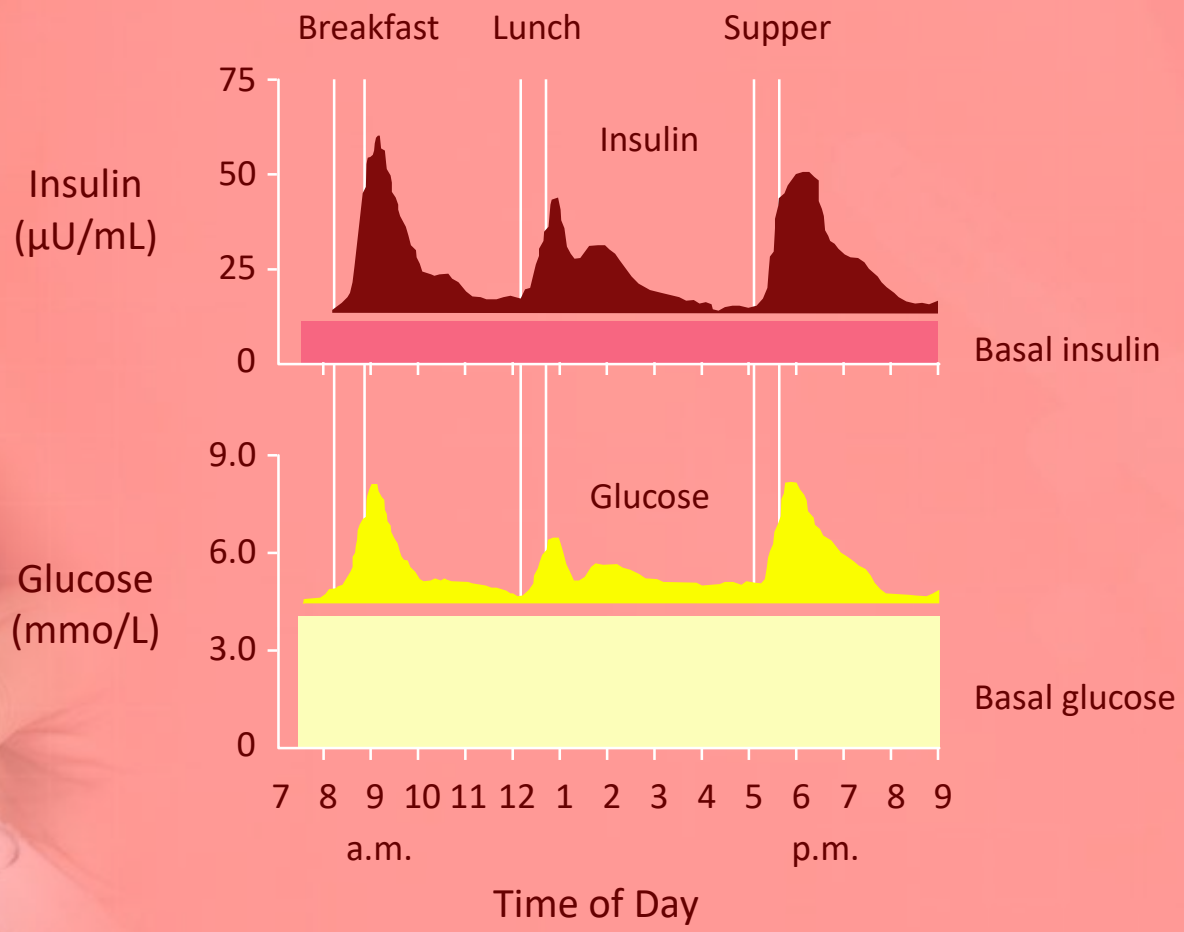


Post prandial insulin secretion

Glucose

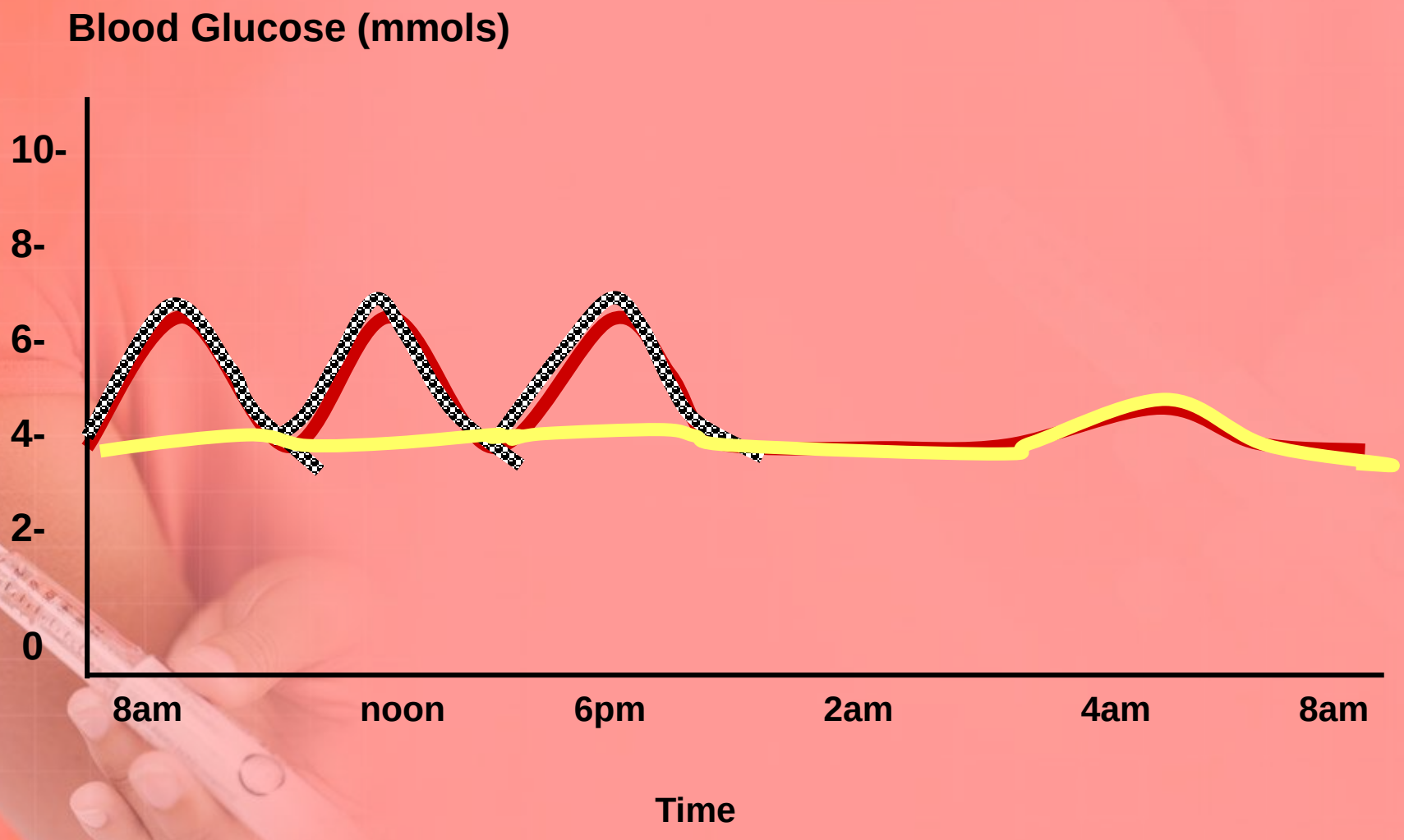


Insulin and Glucose Profiles



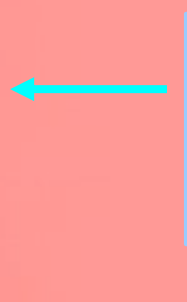
Normal Blood Glucose Levels

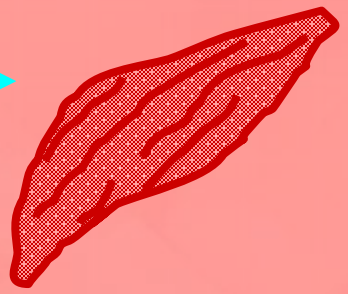
Normal Blood Glucose Levels

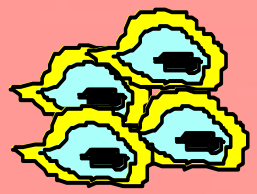


Insulin Action

The major targets for insulin are







- Increases glycogen synthesis
- Increases glycolysis
- Inhibits gluconeogenesis

FAT

- Increases glucose transport
- Increases lipogenesis
- Inhibits lipolysis

SKELETAL MUSCLE

- Increases glucose transport
- Increases glycogen synthesis
- Inhibits gluconeogenesis

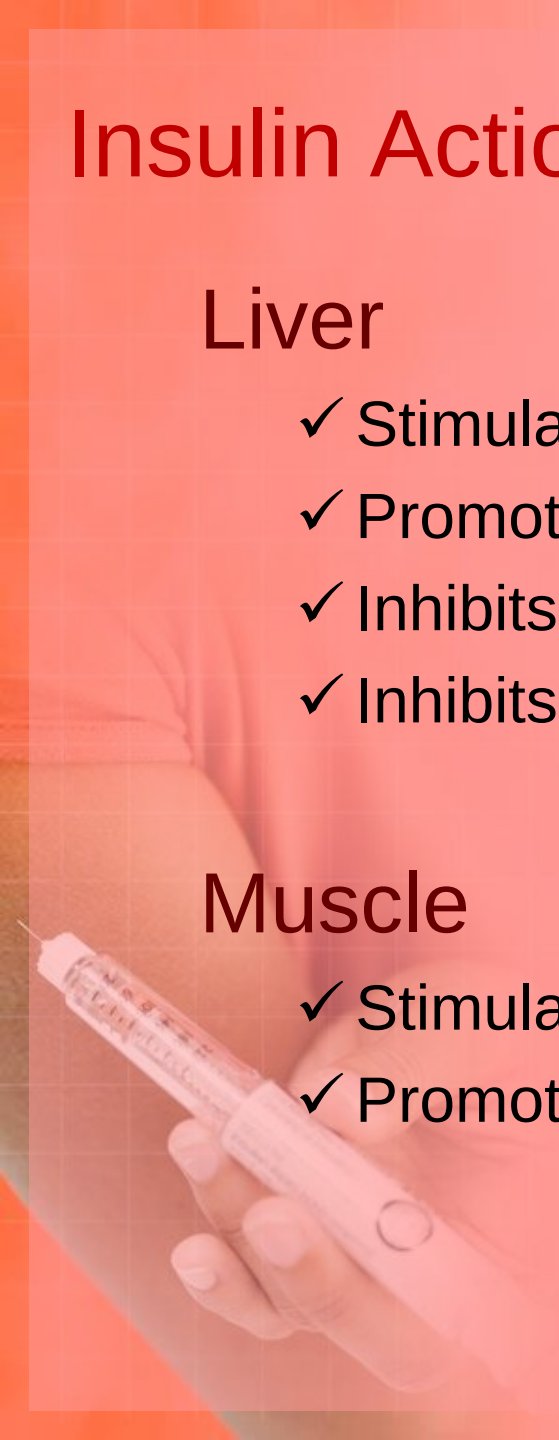
Insulin Action on Carbohydrate Metabolism

Liver

- ✓ Stimulates glucose oxidation
- ✓ Promotes glucose storage as glycogen
- ✓ Inhibits glycogenolysis
- ✓ Inhibits gluconeogenesis

Muscle

- ✓ Stimulates glucose uptake (GLUT4)
- ✓ Promotes glucose storage as glycogen



Insulin Action on Carbohydrate Metabolism

Adipose Tissue

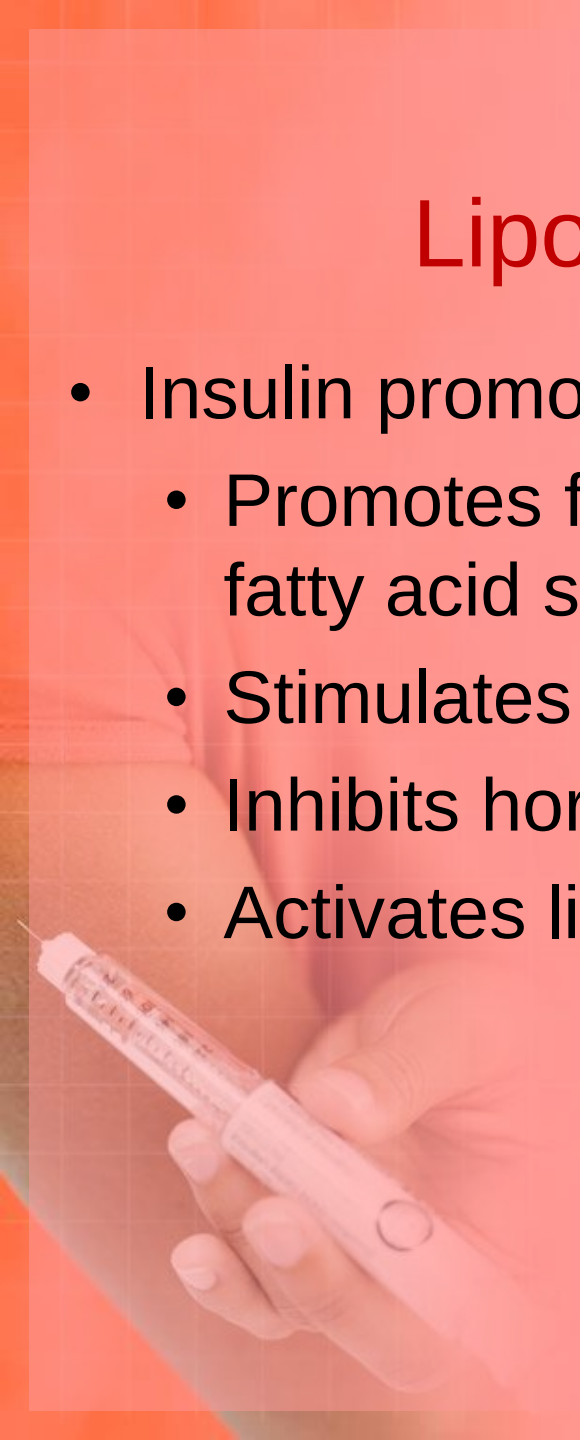
- Stimulates glucose transport into adipocytes
- Promotes the conversion of glucose into triglycerides and fatty acids

Glycogen Synthesis

- Short term storage of glucose
- Activates glycogen synthase
- Inhibit glycogen phosphorylase
- Glycolysis is also stimulated by insulin

Lipogenic and antilipolytic

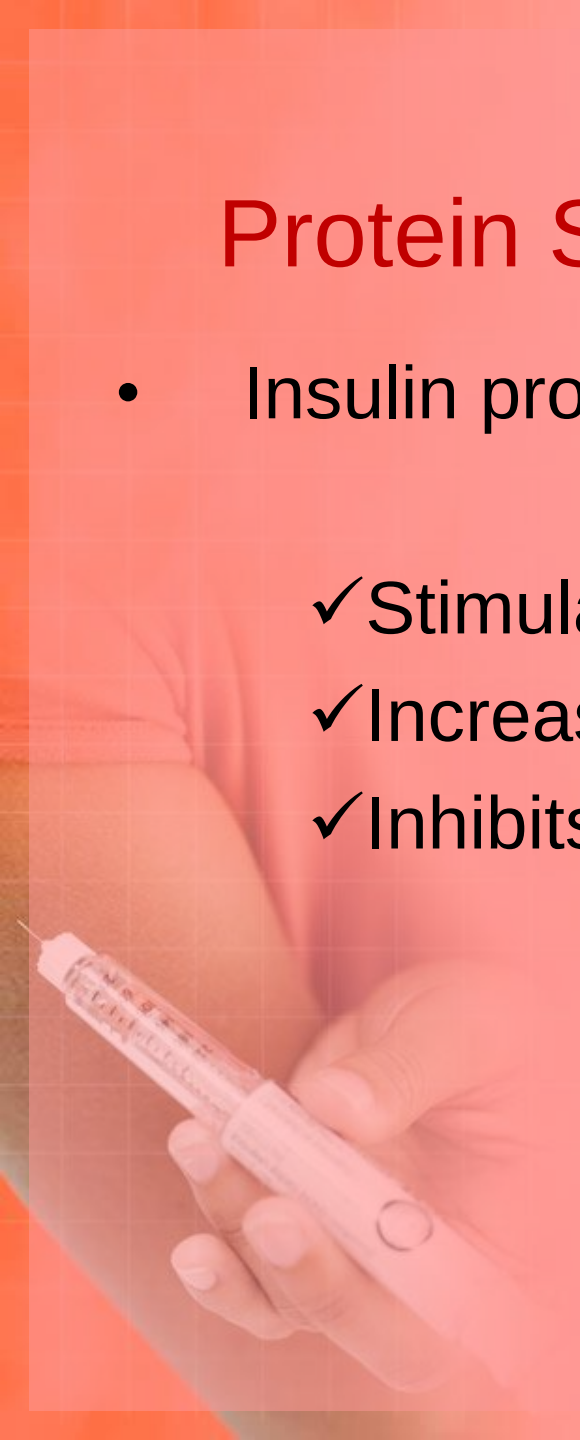
- Insulin promotes lipogenesis and inhibits lipolysis
  - Promotes formation of α-glycerol phosphate and fatty acid synthesis
  - Stimulates fatty acid synthase (FAS)
  - Inhibits hormone sensitive lipase (HSL)
  - Activates lipoprotein lipase (LPL)



Protein Synthesis and Degradation

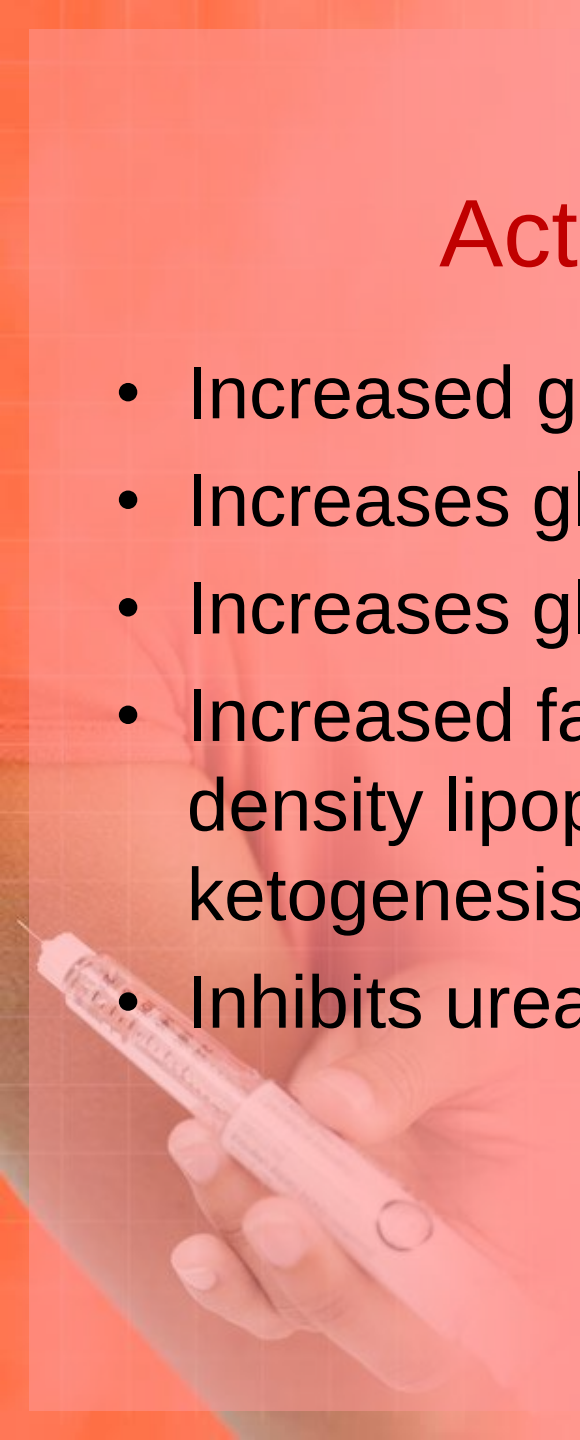
- Insulin promotes protein accumulation

  - ✓Stimulates amino acid uptake
  - ✓Increases the activity of protein synthesis
  - ✓Inhibits protein degradation



Action of insulin on Liver

- Increased glucose uptake
- Increases glycolysis, Inhibits gluconeogenesis
- Increases glycogenesis, Inhibits glycogenolysis
- Increased fatty acid synthesis and very-low-density lipoprotein formation, Inhibits ketogenesis
- Inhibits urea cycle activity

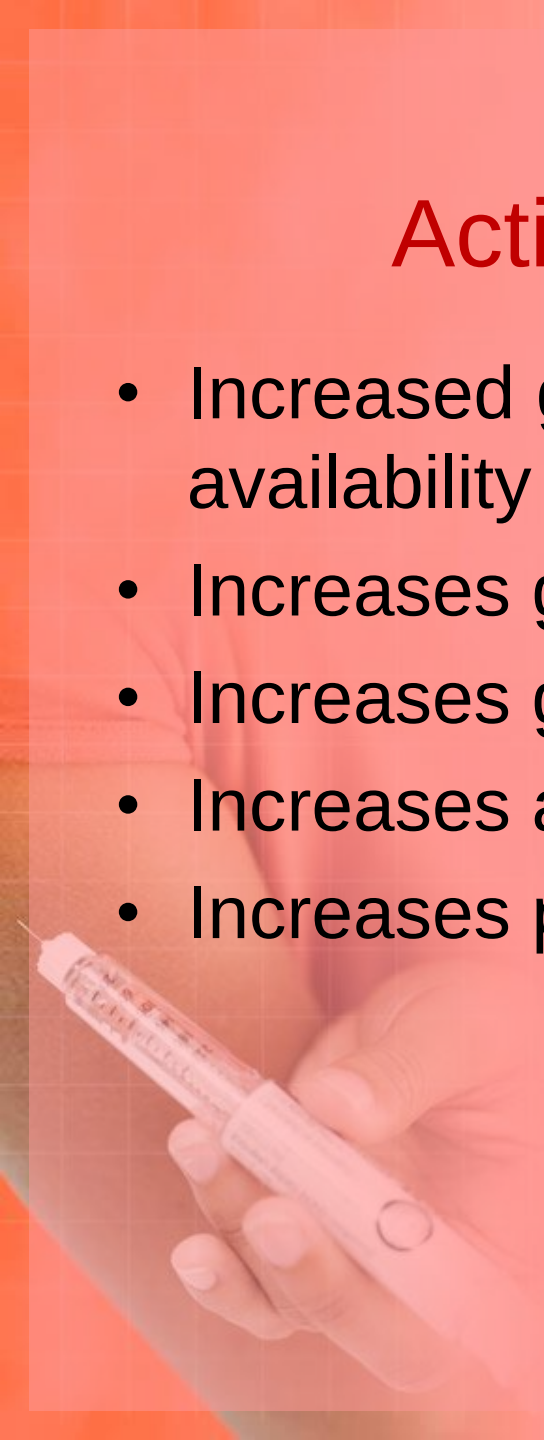


Action of insulin on Fat

- Increased glucose uptake by increasing GLUT4 availability
- Increases glycolysis
- Increases production of α- glycerol phosphate
- Increases esterification of fats
- inhibits lipolysis

Action of insulin on Muscle

- Increased glucose uptake by increasing GLUT4 availability
- Increases glycolysis
- Increases glycogenesis, Inhibits glycogenolysis
- Increases amino acid uptake
- Increases protein synthesis, Inhibits proteolysis



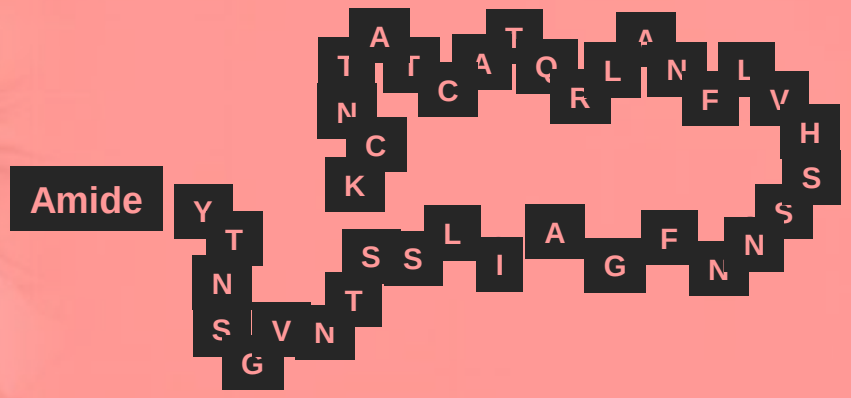
Insulin action (summary)

Dominates in Fed State Metabolism

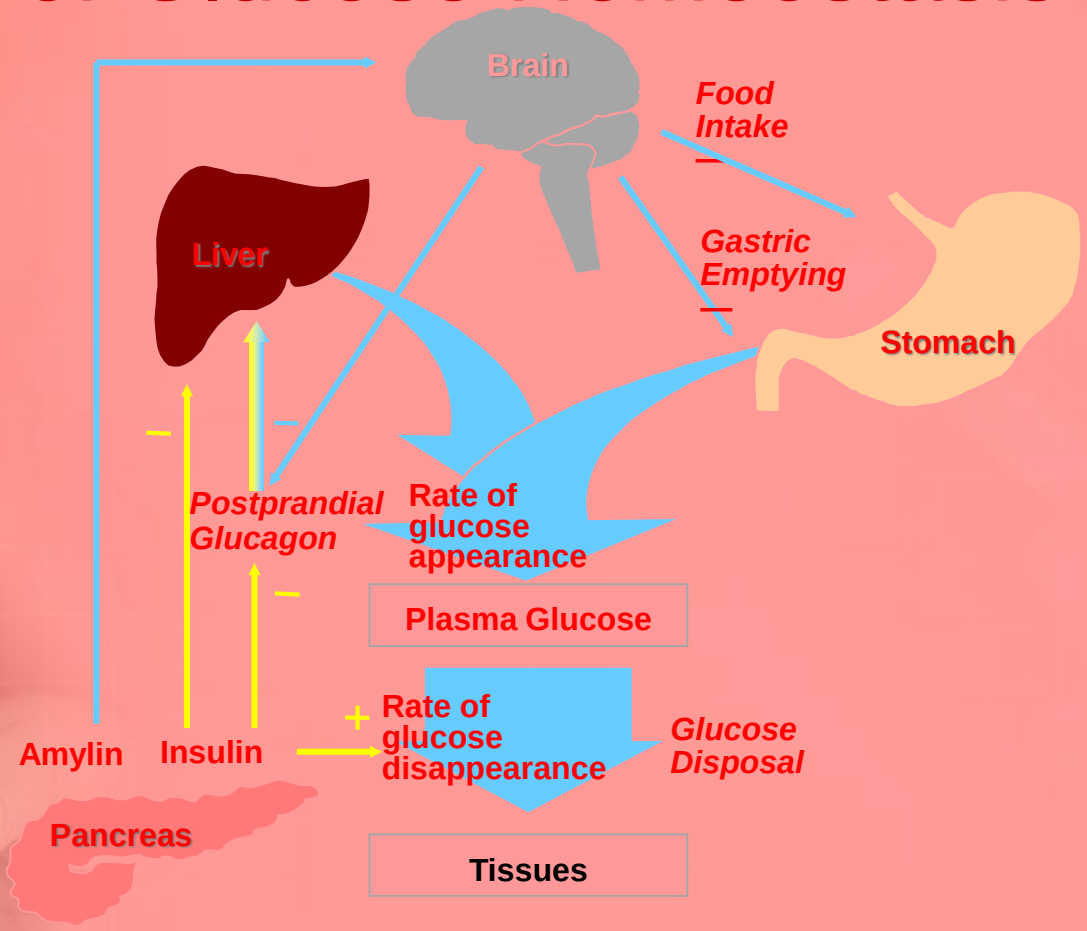
- ↑ glucose uptake in most cells
- ↑ glucose use & storage
- ↑ protein synthesis
- ↑ fat synthesis

Amylin the Hormone

- Reported in 1987
- 37-amino acid peptide
- Co-located and co-secreted with insulin from pancreatic β-cells
- Deficient in diabetes

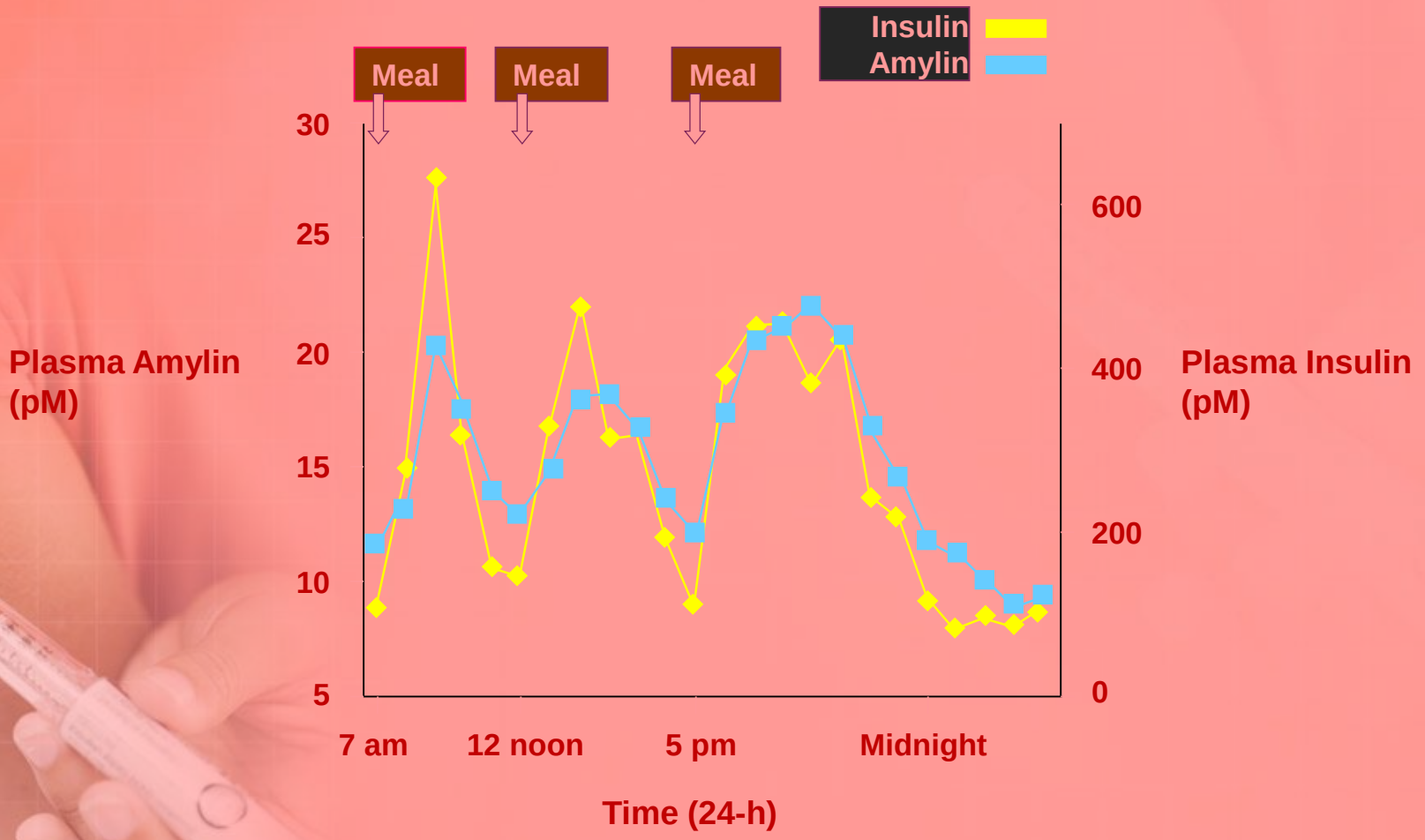


Model of Multihormonal Regulation of Glucose Homeostasis



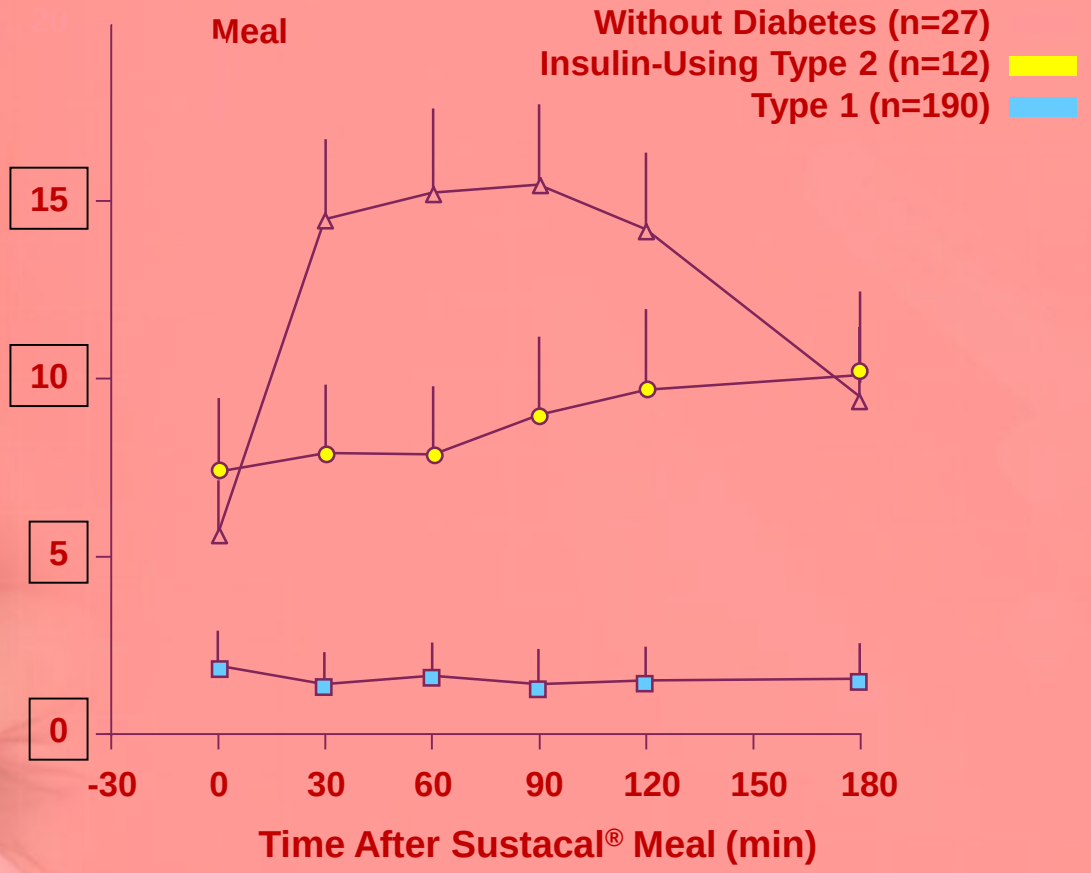
Model derived from animal studies

Amylin the Hormone: Co-Secreted With Insulin



Data from Kruger D, et al. *Diabetes Educ*

Amylin the Hormone: Deficient in Diabetes



Data from Kruger D, et al. *Diabetes Ed*

Glucagon

- A 29-amino-acid polypeptide hormone that is a potent hyperglycemic agent
- Produced by α cells in the pancreas
- Its major target is the liver, where it promotes:
  - ✓ Glycogenolysis – the breakdown of glycogen to glucose
  - ✓ Gluconeogenesis – synthesis of glucose from lactic acid and noncarbohydrates
  - ✓ Release of glucose to the blood from liver cells

Synthesis glucagon

DNA in α cells

↓

mRNA

↓

Preproglucagon

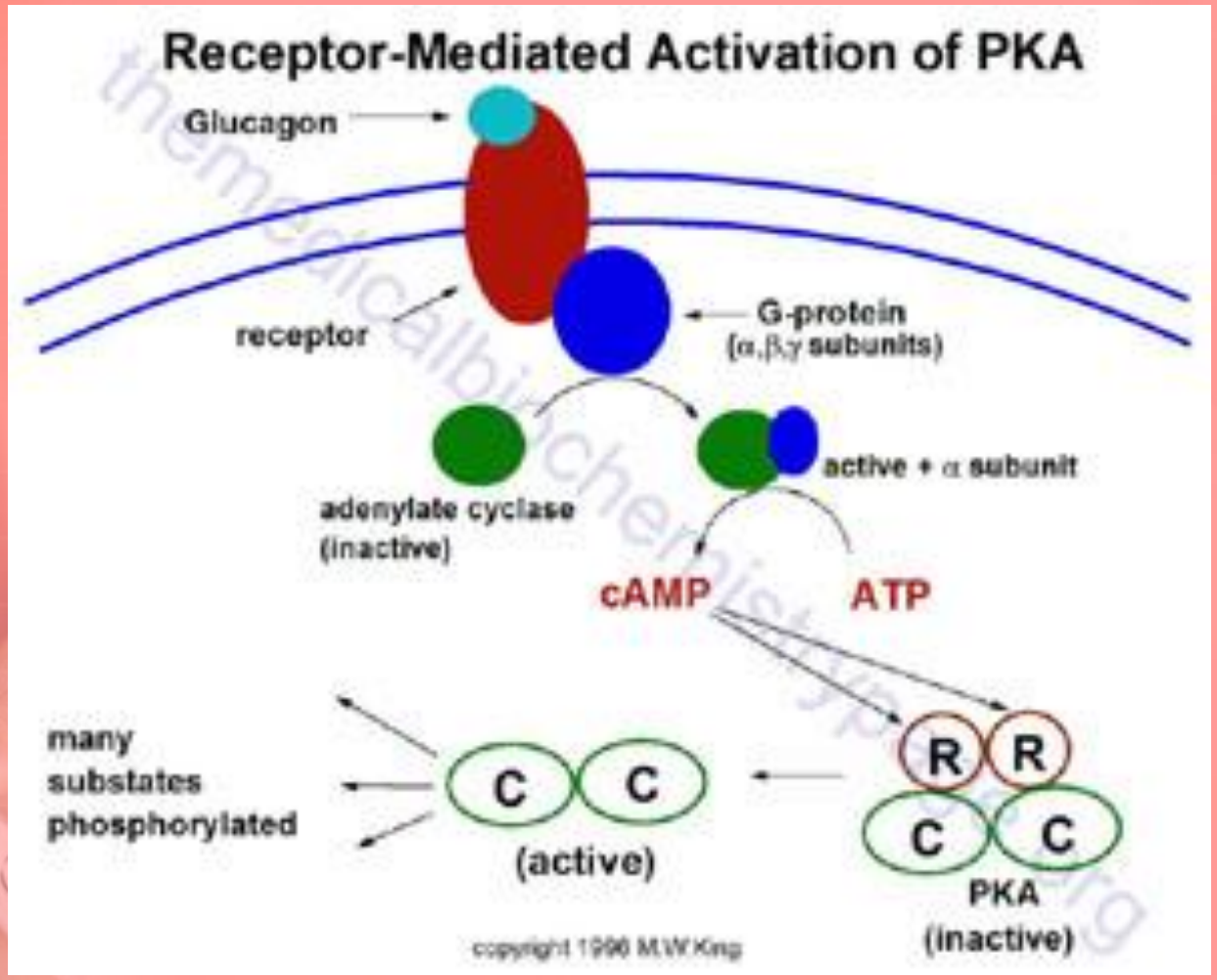
↓

proglucagon

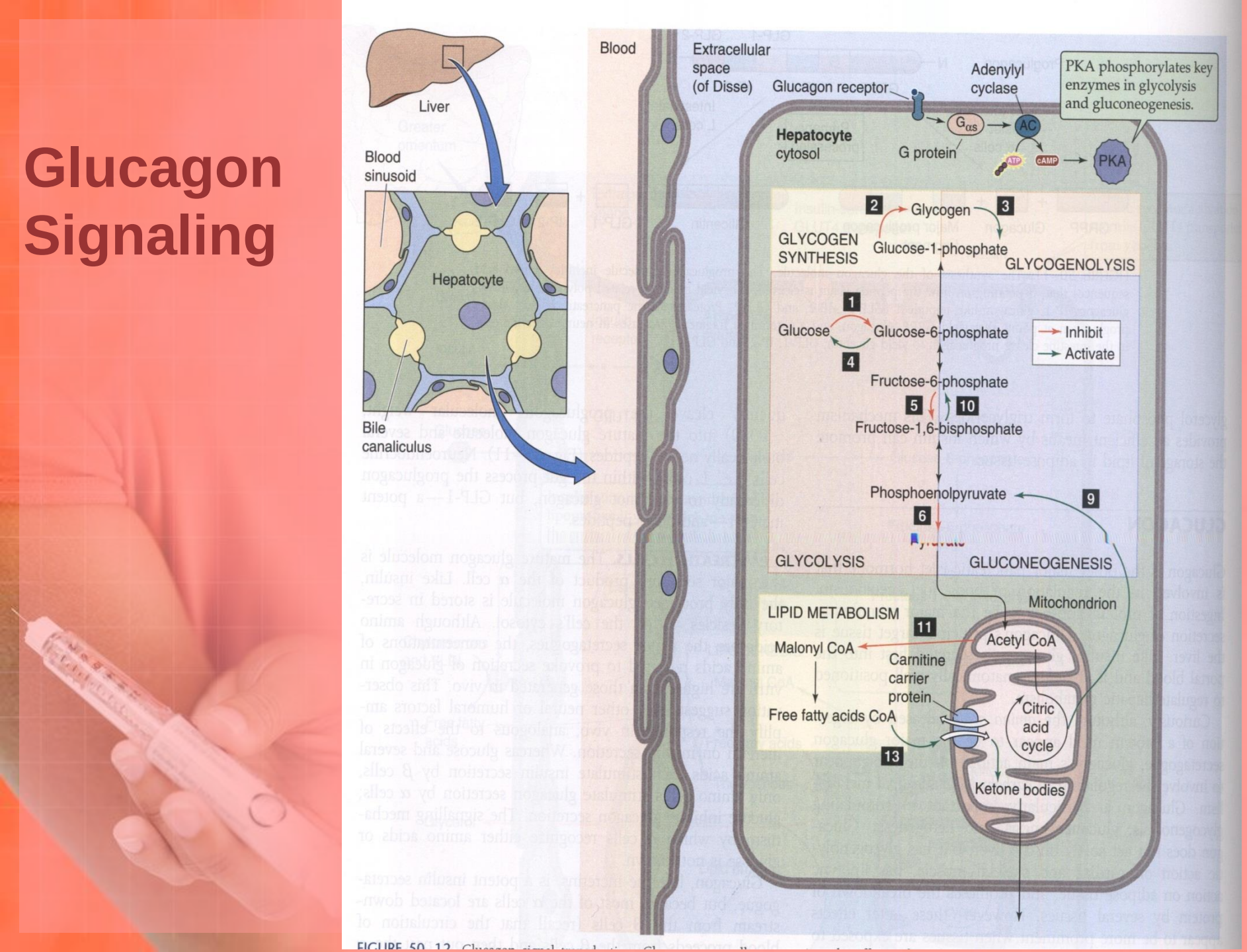
↓

glucagon

Glucagon – Mechanism of Action



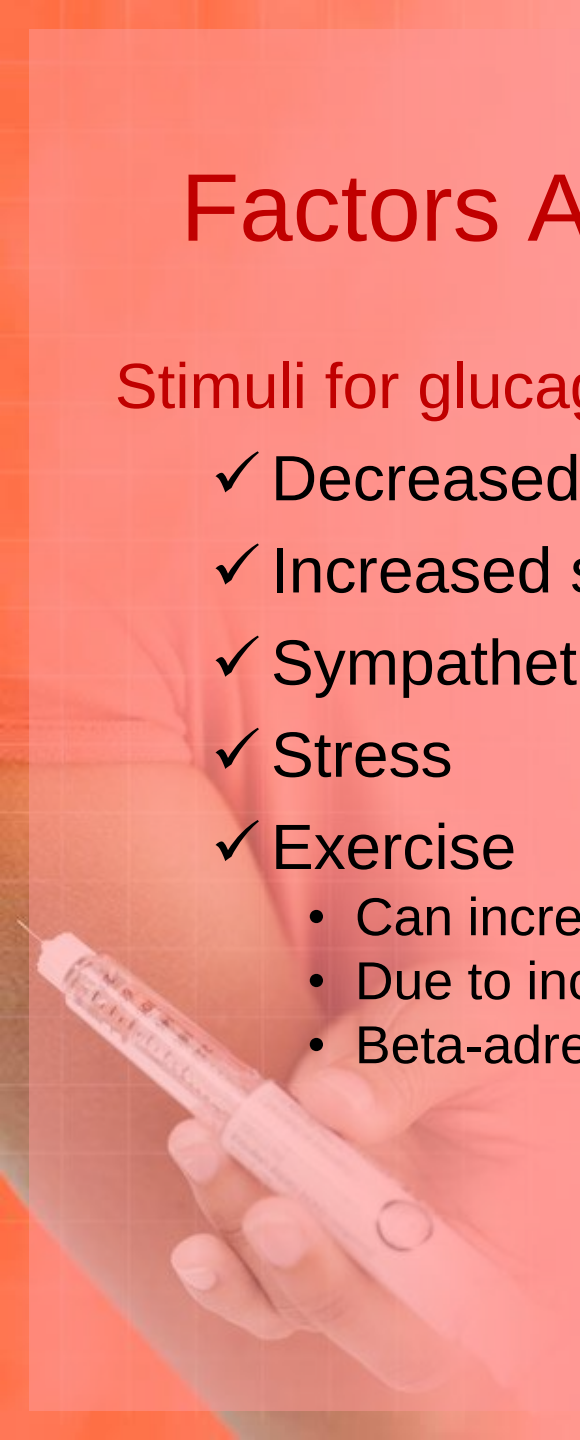
Glucagon Signaling



Factors Affecting Glucagon Secretion

Stimuli for glucagon secretion

- ✓ Decreased blood glucose
- ✓ Increased serum amino acids(arginine, alanine)
- ✓ Sympathetic nervous system stimulation
- ✓ Stress
- ✓ Exercise
  - Can increase glucagon 4-5 fold
  - Due to increased amino acids?
  - Beta-adrenergic stimulation of the islets of Langerhans?



Factors Affecting Glucagon Secretion

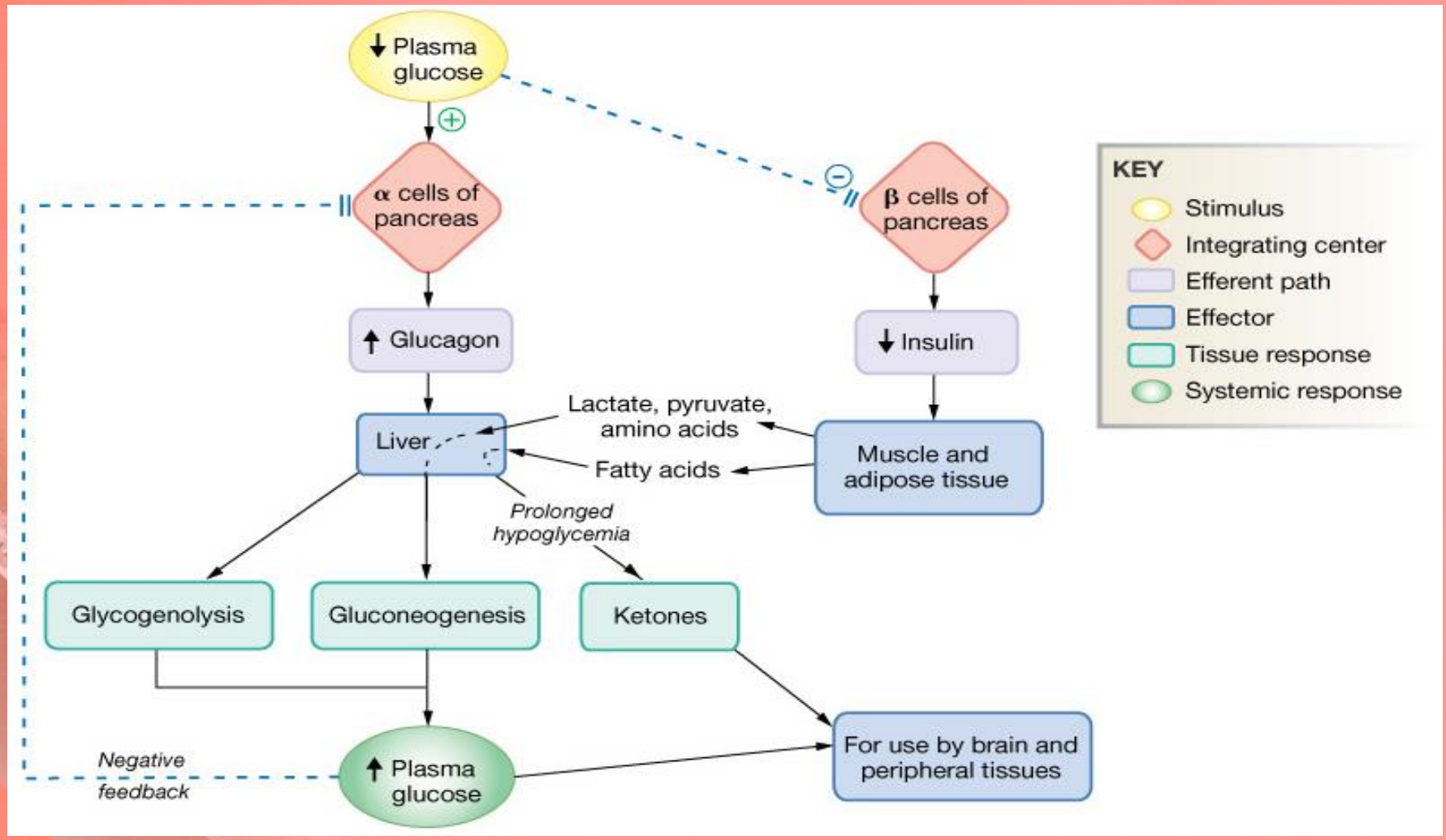
Inhibitors for glucagon secretion

- ✓ Somatostatin
- ✓ Insulin
- ✓ Increased blood glucose

Glucagon

- Supra-physiological levels
  - Activation of adipose cell lipase
  - Inhibits storage of triglycerides in the liver
  - Increased blood levels of fatty acids
  - Enhances heart strength
  - Increases blood flow to kidneys
  - Enhances bile secretion
  - Inhibits gastric acid secretion

Glucagon Action on Cells: Dominates in Fasting State Metabolism



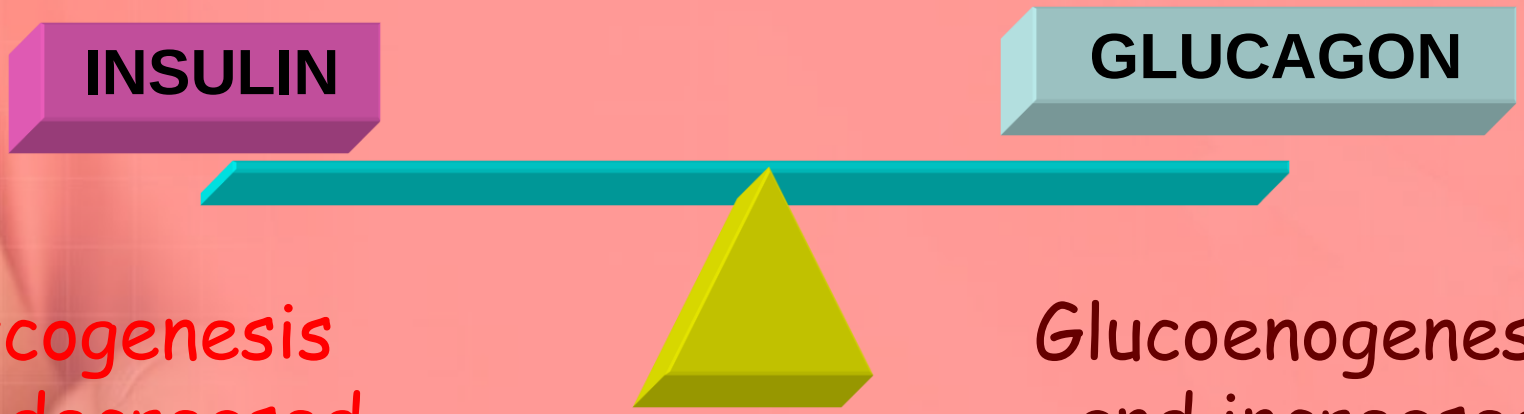
Glucagon

Cell of origin	Alpha cells of pancreas
Chemical nature	29-amino acid peptide
Biosynthesis	Typical peptide
Transport in the circulation	Dissolved in plasma
Half-life	4–6 minutes
Factors affecting release	Stimulated by plasma [glucose] < 200 mg/dL, with maximum secretion below 50 mg/dL; ↑ blood amino acids.
Target cells or tissues	Liver primarily
Target receptor/second messenger	G protein-coupled receptor linked to cAMP
Whole body or tissue action	↑ Plasma [glucose] by glycogenolysis and gluconeogenesis; ↑ lipolysis leads to ketogenesis in liver
Action at molecular level	Alters existing enzymes and stimulates synthesis of new enzymes
Feedback regulation	↑ Plasma [glucose] shuts off glucagon secretion
Other information	Member of secretin family along with VIP, GIP, and GLP-1

Insulin-Glucagon relationships

STORAGE

MOBILIZATION



Glycogenesis and decreased blood glucose

Glucoenogenesis and increased blood glucose

Somatostatin (GHIH)

- Short polypeptide (14 amino acids)
- Short half-life (3 min)

- Regulation:
  - Increased blood glucose
  - Increased amino acids
  - Increased fatty acids
  - Increased GI hormones

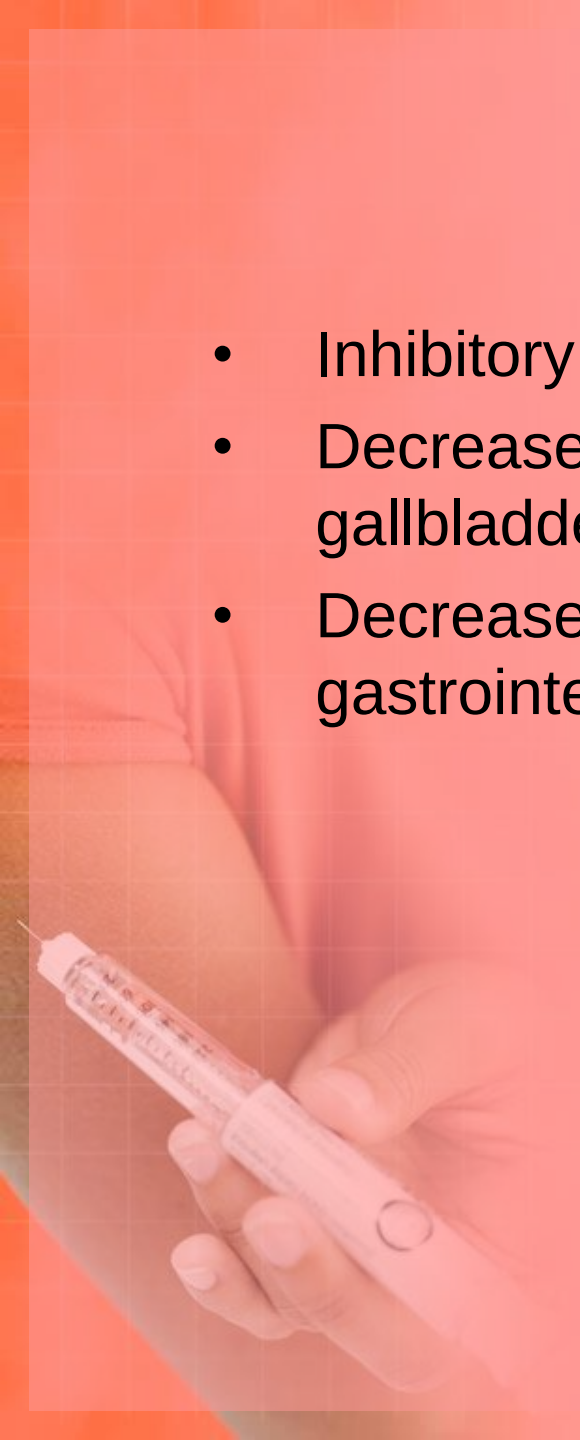
Somatostatin (GHIH)

- Short polypeptide (14 amino acids)
- Short half-life (3 min)

- Regulation:
  - Increased blood glucose
  - Increased amino acids
  - Increased fatty acids
  - Increased GI hormones

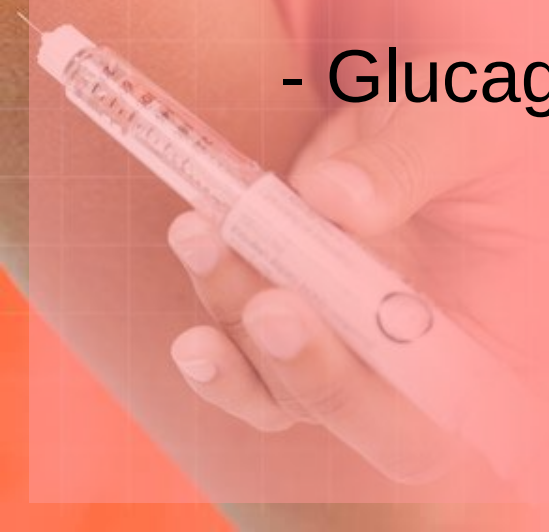
Somatostatin

- Inhibitory effect on both insulin and glucagon
- Decreases motility of stomach, duodenum and gallbladder
- Decreases secretion and absorption in the gastrointestinal tract



What are incretins?

- Hormones produced by the gastrointestinal tract in response to incoming nutrients, and have important actions that contribute to glucose homeostasis.
- Two hormones:
  - Gastric inhibitory polypeptide (GIP
  - Glucagon-like peptide-1 (GLP-1)



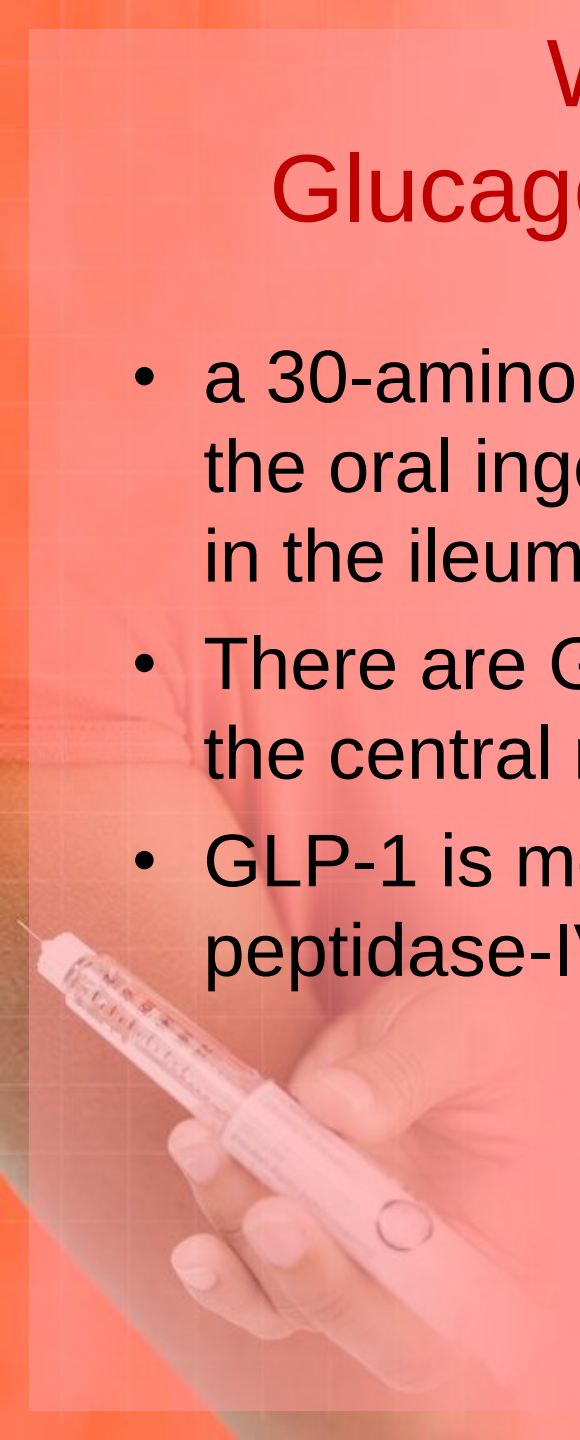
What are incretins?
Gastric Inhibitory Polypeptide (GIP)

- Secreted by the K cells of the proximal gut. However, type 2 diabetes patients are resistant to its action (high blood level), making it a less attractive therapeutic target

Gila Monster

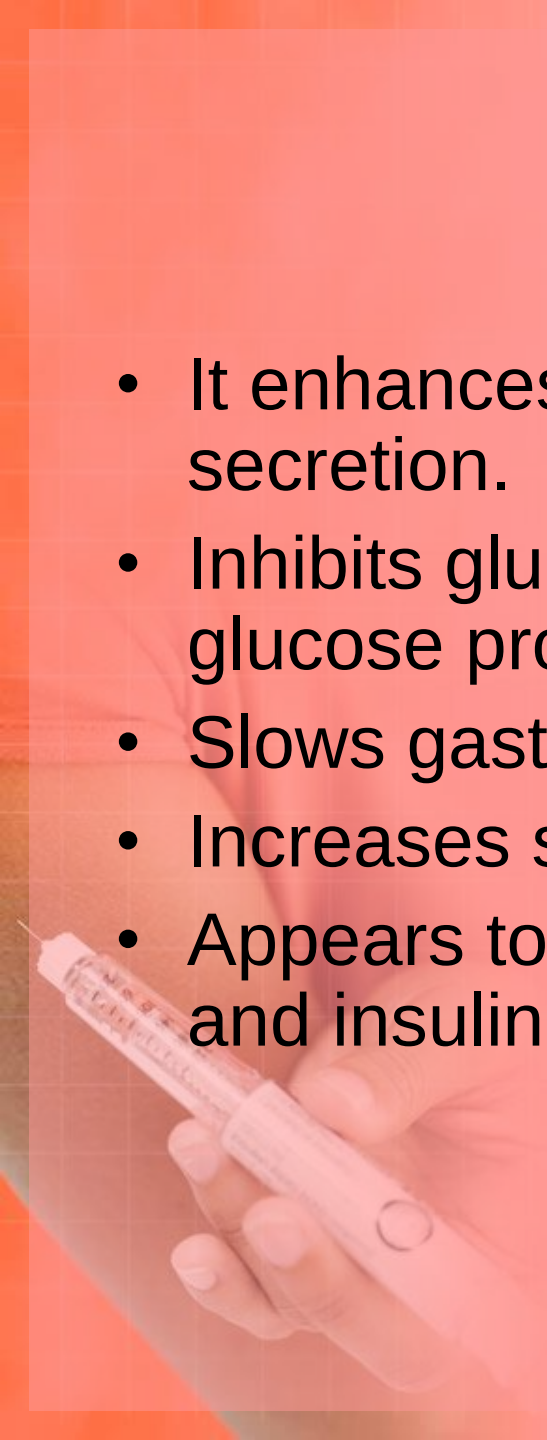
What are incretins?
Glucagon-like peptide-1 (GLP-1)

- a 30-amino acid peptide secreted in response to the oral ingestion of nutrients by L cells, primarily in the ileum and colon.
- There are GLP-1 receptors in islet cells and in the central nervous system, among other places.
- GLP-1 is metabolized by the enzyme dipeptidyl peptidase-IV (DPP-IV) .

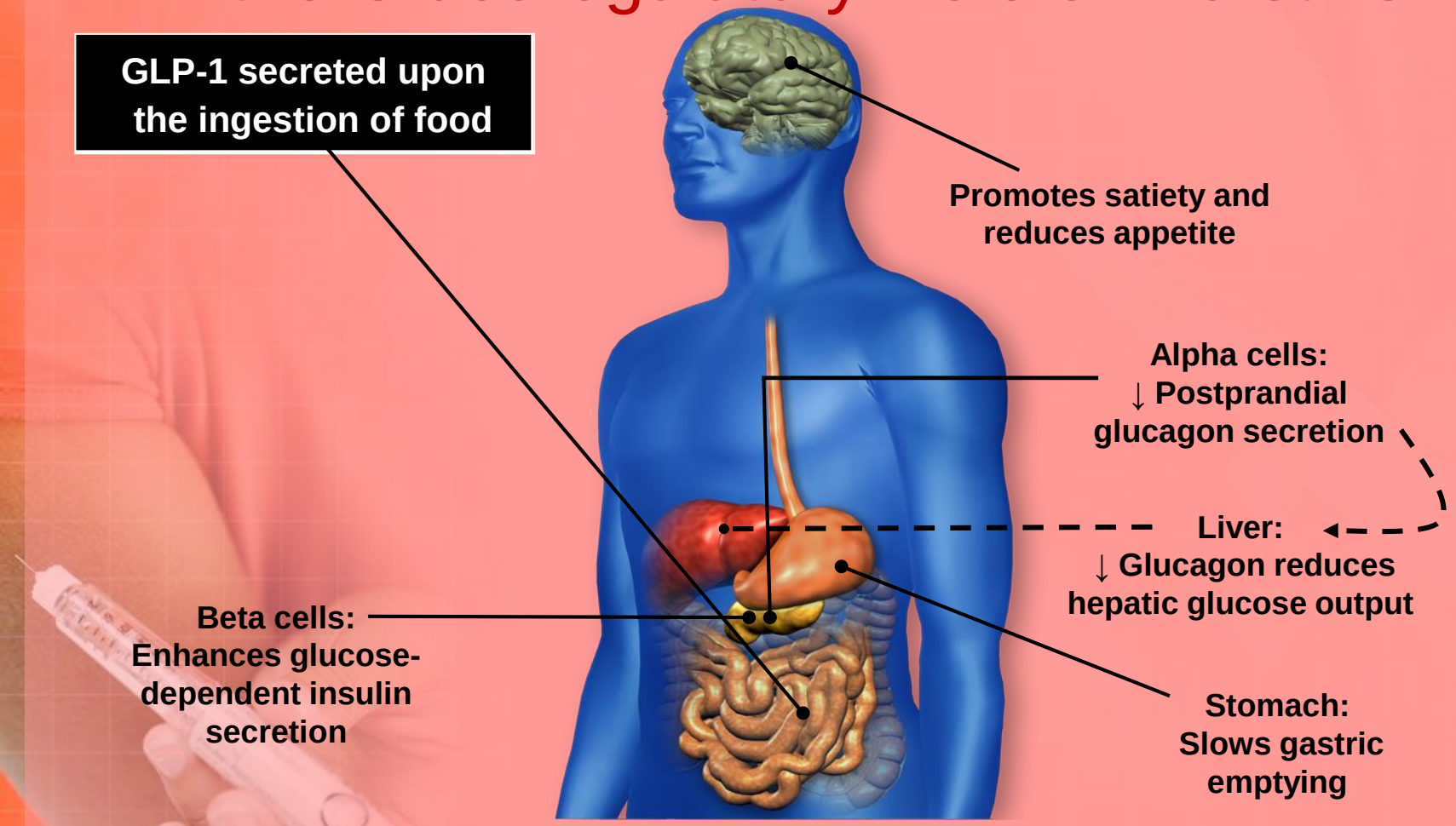


Actions of GLP-1

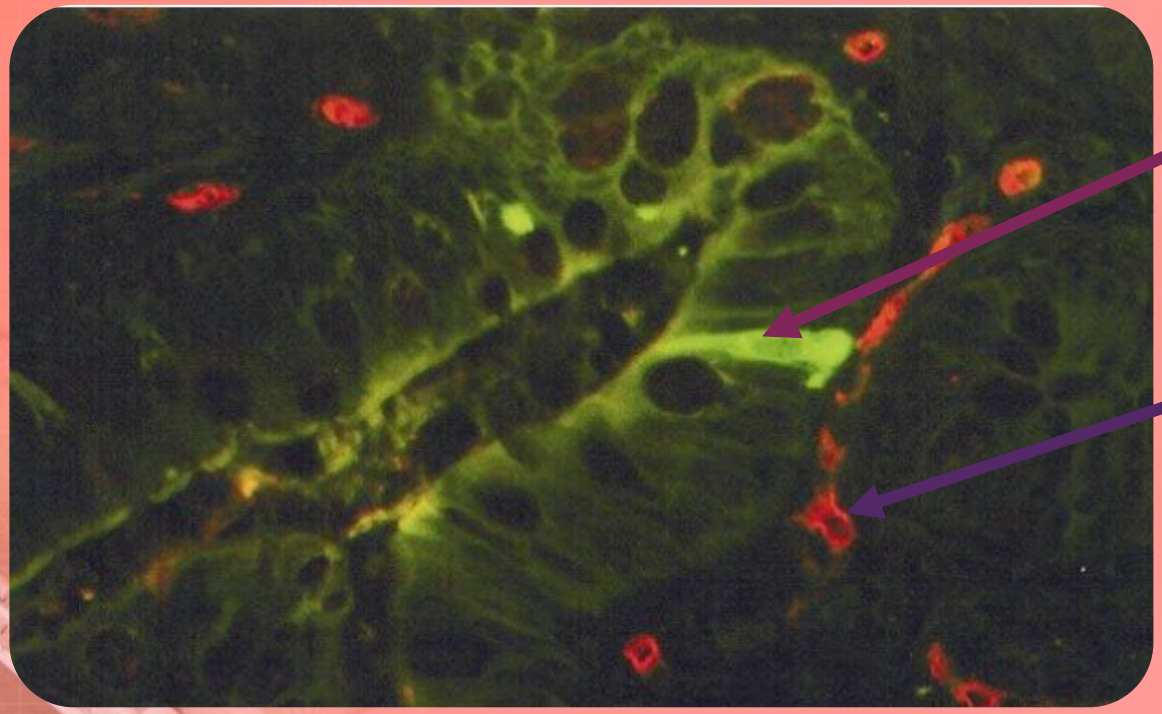
- It enhances glucose-dependent insulin secretion.
- Inhibits glucagon secretion and therefore hepatic glucose production.
- Slows gastric emptying.
- Increases satiety resulting in less food intake.
- Appears to stimulate insulin gene transcription and insulin synthesis.



GLP-1 Effects in Humans: Understanding the Glucoregulatory Role of Incretins



Native GLP-1 is rapidly degraded by DPP-IV

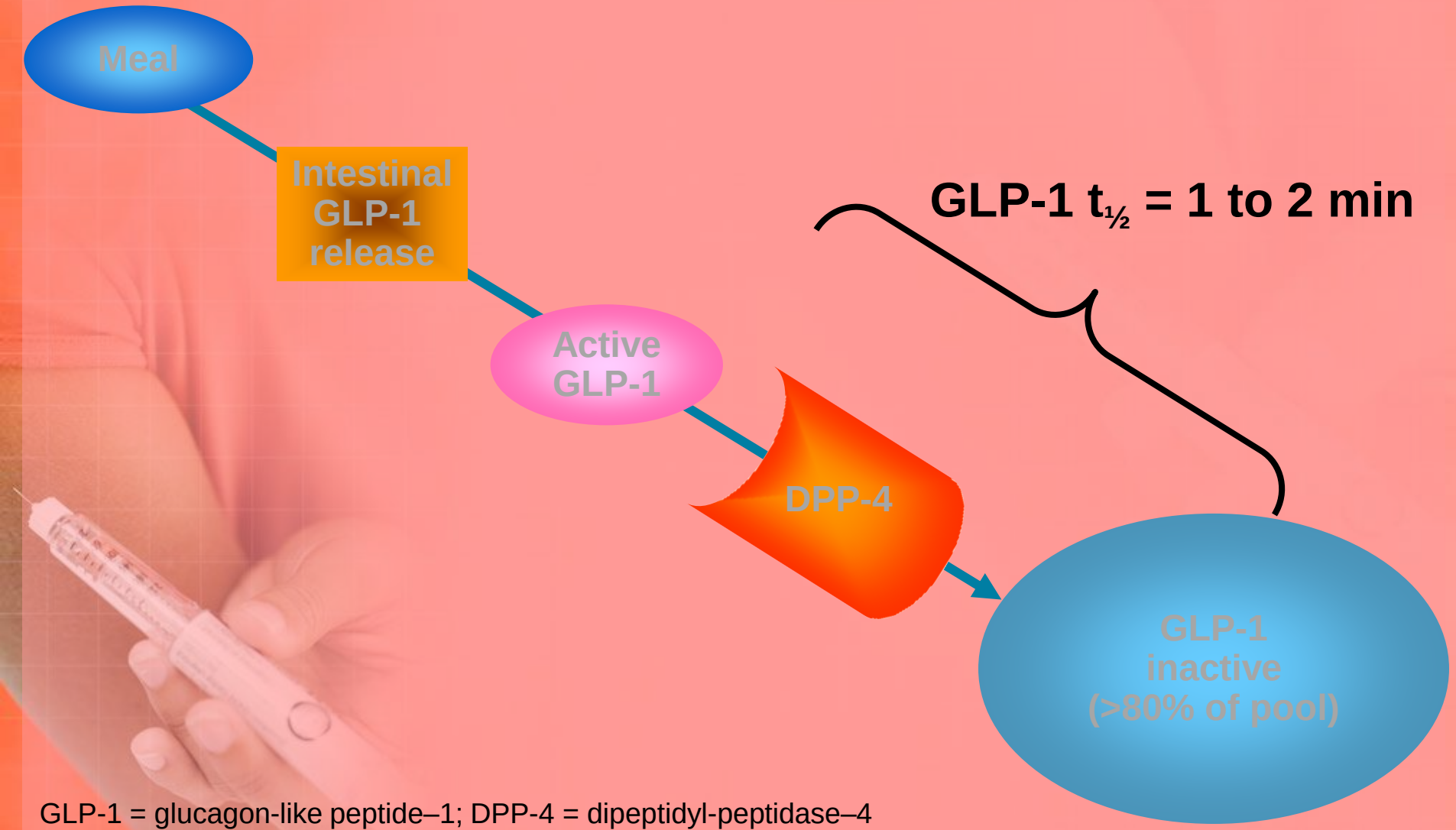


Human ileum, GLP-1 producing L-cells

Capillaries, Di-Peptidyl Peptidase-IV (DPP-IV)

Double immunohistochemical staining for DPP-IV (red) and GLP-1 (green) in the human ileum

GLP-1 Secretion and Inactivation by DPP-4



GLP-1 = glucagon-like peptide–1; DPP-4 = dipeptidyl-peptidase–4

Actions of GLP-1

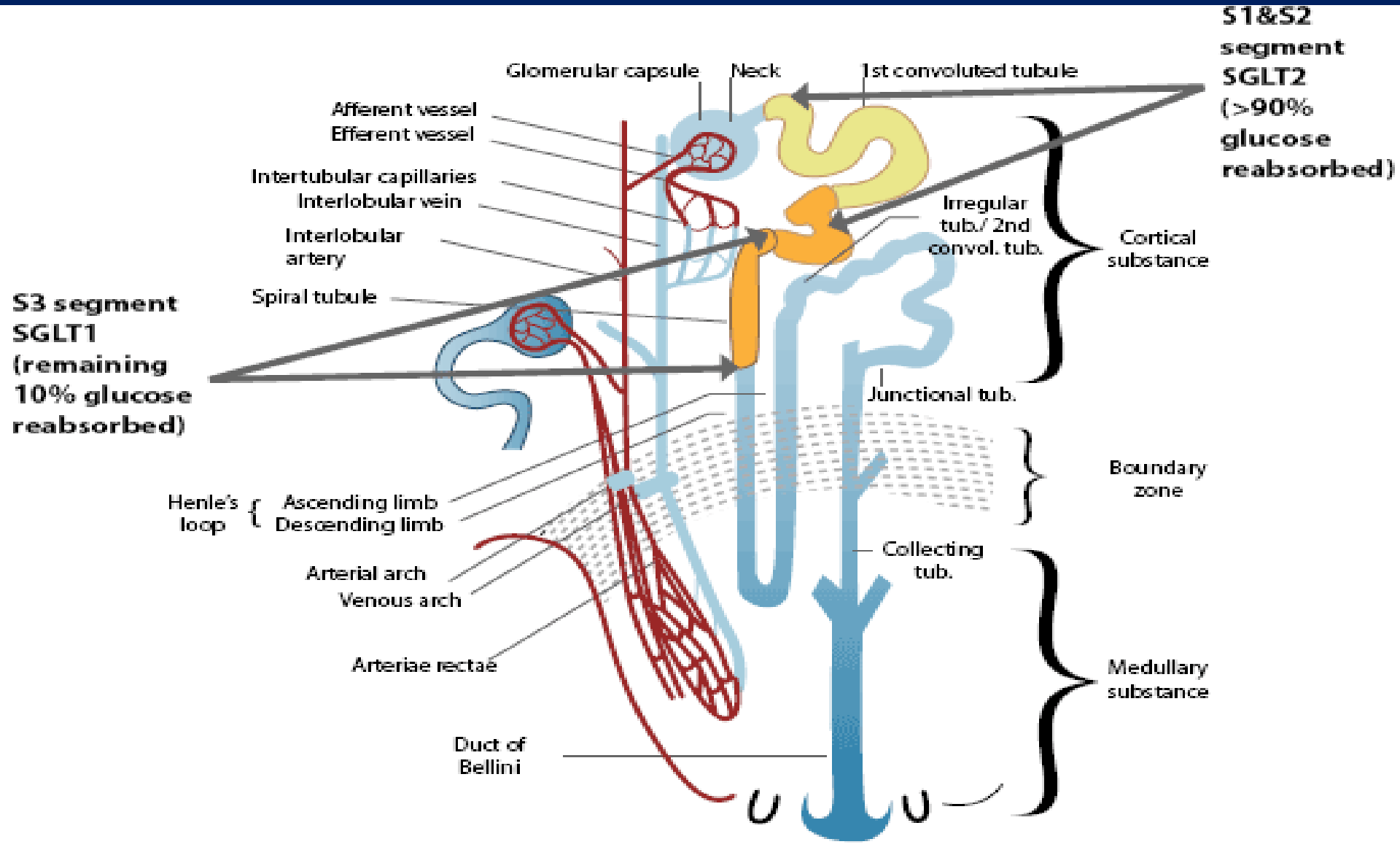
- In animal studies it increases beta-cell mass by:
  - Decreasing beta cell apoptosis.
  - Stimulating the growth of new beta cells

???... Long term benefit in reversing the progressive insulin deficiency.

kidney plays a vital role in the normal control of blood glucose

- Glucose in the blood is freely filtered by the glomerulus and has to be reabsorbed
- The kidney also contributes to gluconeogenesis
- In healthy individuals, the kidneys filter about 100 mg/minute of glucose; this amounts to 144 g/24 hours
- Nearly 100% of this glucose is reabsorbed, mostly in the proximal renal tubules
- Threshold of about 8-10 mmol/L (180 mg/dL)

Sodium-glucose transporter-2 (SGLT2)



Diabetes mellitus

It’s a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both.

Epidemiology of diabetes

There are 500 million people worldwide living with diabetes

Diabetes

2040 this will rise to 642 million

IDF. 2017

Classification of Diabetes

- Type 1 diabetes
  - ✓ β-cell destruction
- Type 2 diabetes
  - ✓ Progressive insulin secretory defect
- Other specific types of diabetes
  - ✓ Genetic defects in β-cell function, insulin action
  - ✓ Diseases of the exocrine pancreas
  - ✓ Drug- or chemical-induced
- Gestational diabetes mellitus

ADA. I. Classification and Diagnosis. *Diabetes Care* 2012;35(suppl 1):S11

Diagnostic Criteria

	Normo-glycemia	Pre-Diabetes	Diabetes
Fasting Plasma Glucose (FPG)	<100 mg/dl (Previously <110 mg/dl)	100-125 mg/dl (Impaired Fasting Glucose)	FPG ≥ 126 mg/dl
2-hour Plasma Glucose	<140 mg/dl	140-200 mg/dl (Impaired Glucose Tolerance)	≥ 200 mg/dl
Casual plasma glucose			≥ 200 mg/dl with symptoms
HbA1C	5.7	5.7–6.4%	6.5%.

Aetiology of Diabetes

- **Type 1 Diabetes** (10-15%)
  - results when the body's immune system destroys its own beta cells in the pancreas. No insulin production is then possible.

- **Type 2 Diabetes** (85-90%)
  results from either
  - Insulin resistance (overweight people)
  - Inadequate insulin production (lean people)
  - A combination of both

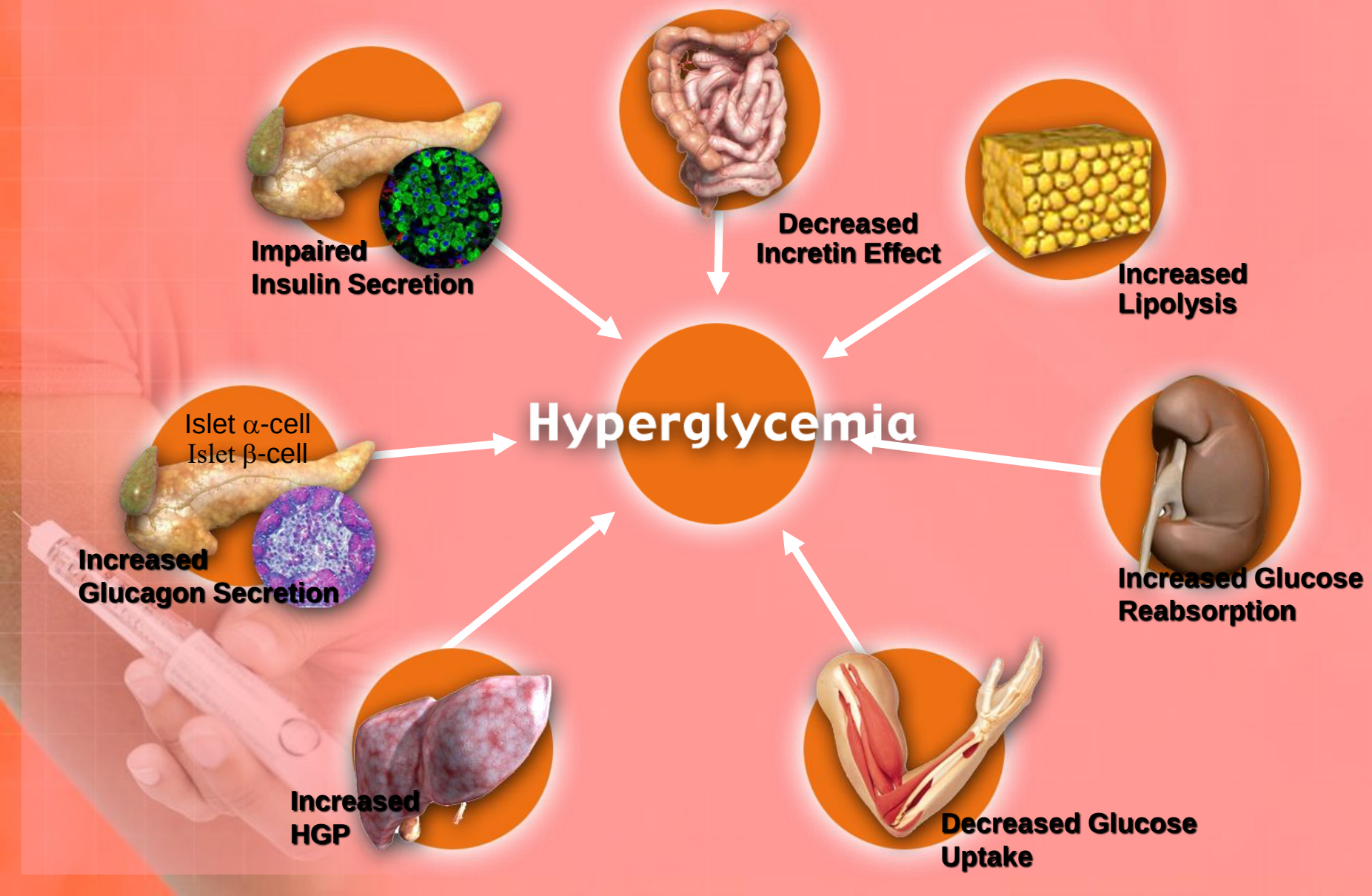
Type 1 Diabetes

- Usually under 30 yrs of age
- Autoimmune disorder
- Sudden onset of severe symptoms
- Rapid weight loss
- Total lack of insulin in the body
- Insulin injections essential for life
- Ketones produced
- Genetic predisposition, though 80% have no relatives with the disease

Type 2 Diabetes

- Usually over 40 yrs of age though the age of diagnosis is getting younger
- Gradual onset with mild symptoms
- Most produce a normal amount of insulin but it is unable to work properly due to insulin resistance
- Many have complications at diagnosis

Pathogenesis of Type 2 Diabetes



Type 2 Diabetes Risk Factors

- Increasing age
- Obesity – especially abdominal
  - Women with BMI > 35 compared to 22 have a 93 fold increased risk
  - Men with BMI > 35 have 40 fold increased risk
- Physical inactivity
- Family history
- Ethnic background
- High blood pressure
- High Cholesterol
- Previous gestational diabetes

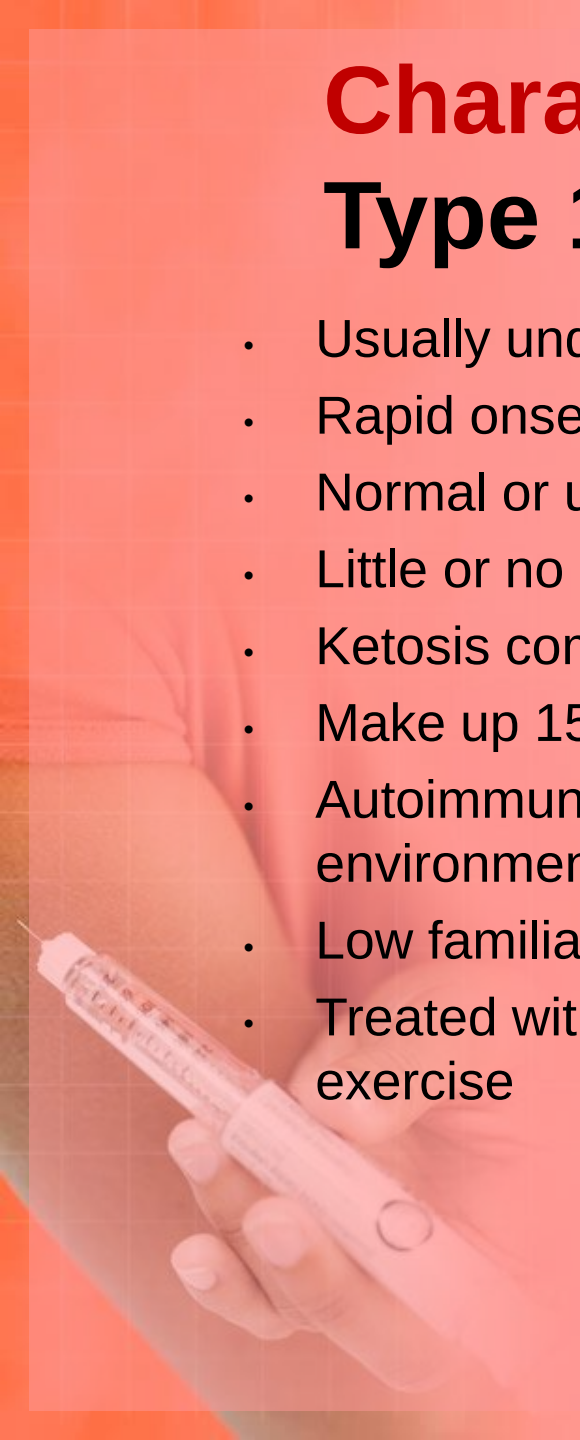
Characteristics of Diabetes

Type 1

- Usually under 30
- Rapid onset
- Normal or underweight
- Little or no insulin
- Ketosis common
- Make up 15% of cases
- Autoimmune plus environmental factors
- Low familial factor
- Treated with insulin, diet and exercise

Type 2

- Usually over 40
- Gradual onset
- 80% are overweight
- Most have insulin resistance
- Ketosis rare
- 85% of diagnosed cases
- Part of metabolic insulin resistance syndrome
- Strongly hereditary
- Diet & exercise, progressing to tablets, then insulin



Diabetes Mellitus Type 1

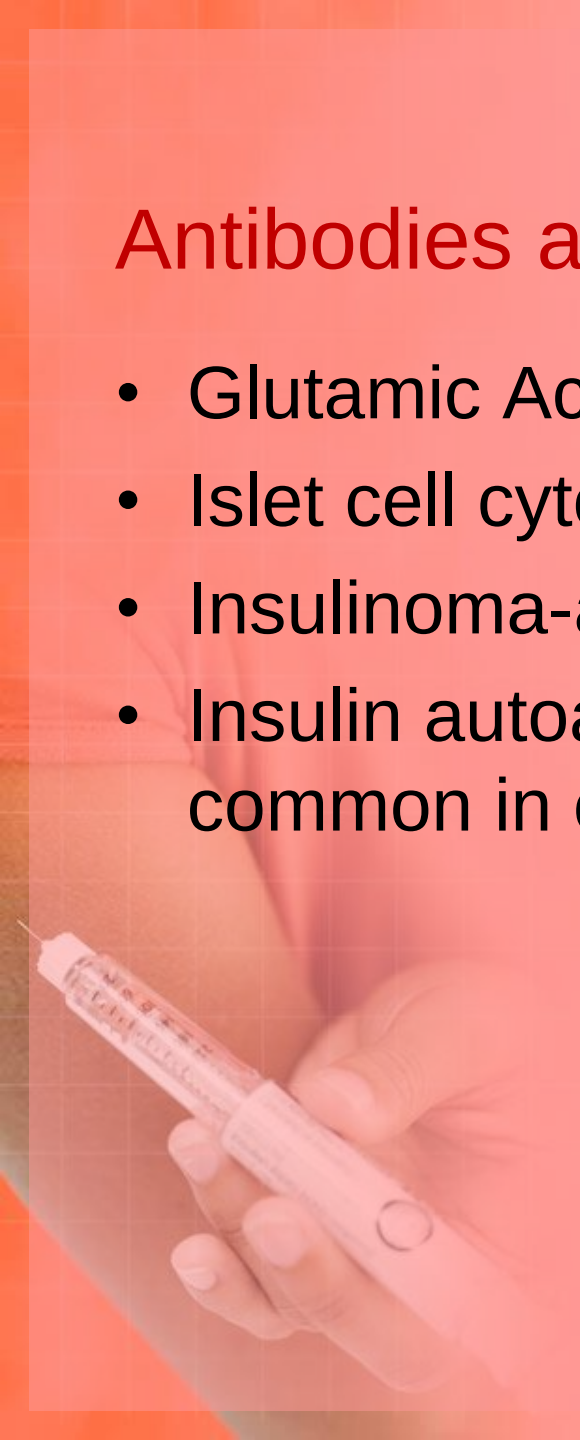
- Clinical Manifestations:
  - Polyuria –increased urine
  - Polydipsia –increased thirst
  - Polyphagia –increased hunger
  - Weight loss
  - Fatigue
  - Nausea, vomiting
- Ketoacidosis may be a presenting sign

Diabetes Mellitus Type 1

- Usually develop symptoms over a short period of time, and the condition is often diagnosed in an emergency setting
- In addition to high glucose levels, acutely ill type 1 diabetics have high levels of ketones.
  - As cells cannot get glucose, they burn fats as an alternate energy source
  - Ketones are produced by the breakdown of fat and muscle, and are toxic at high levels
  - Ketones in the blood cause a condition called "acidosis ”or (“ketoacidosis") (low blood pH)
  - Urine testing detects ketones in the urine
  - Blood glucose levels are also high.

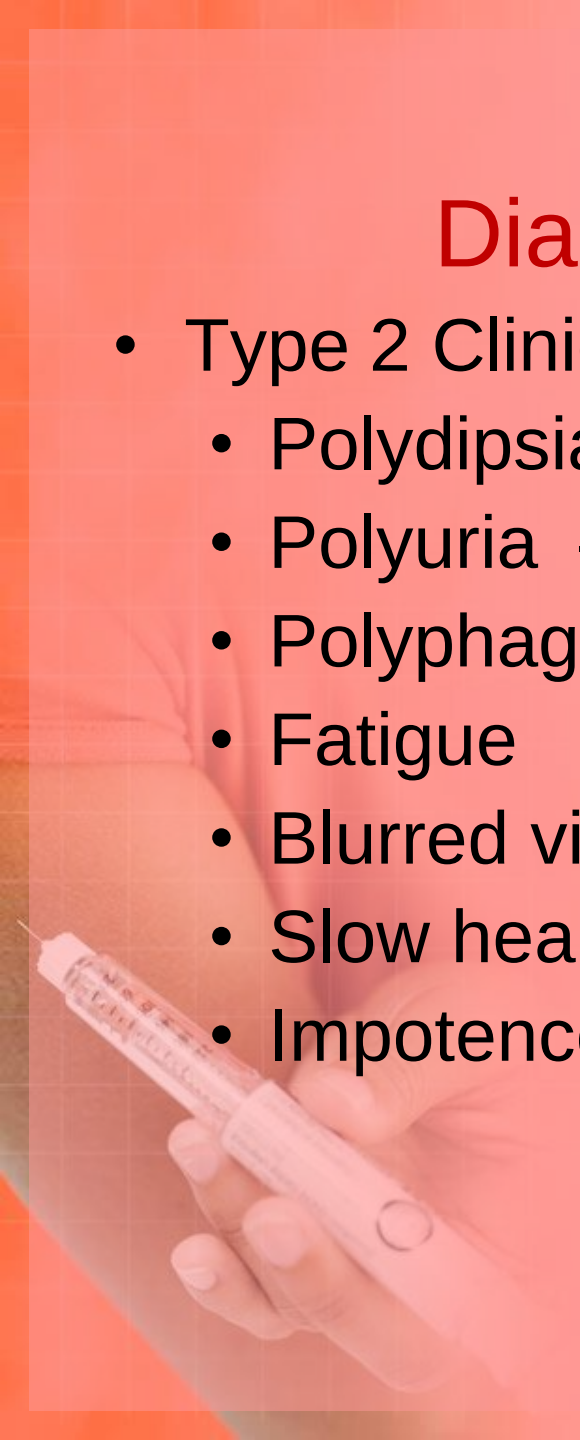
Antibodies associated with type 1 diabetes

- Glutamic Acid Decarboxylase anti-GAD65
- Islet cell cytoplasmic autoantibodies (ICAs)
- Insulinoma-associated-2 autoantibodies (IA-2As)
- Insulin autoantibodies (IAAs), which are more common in children than adults

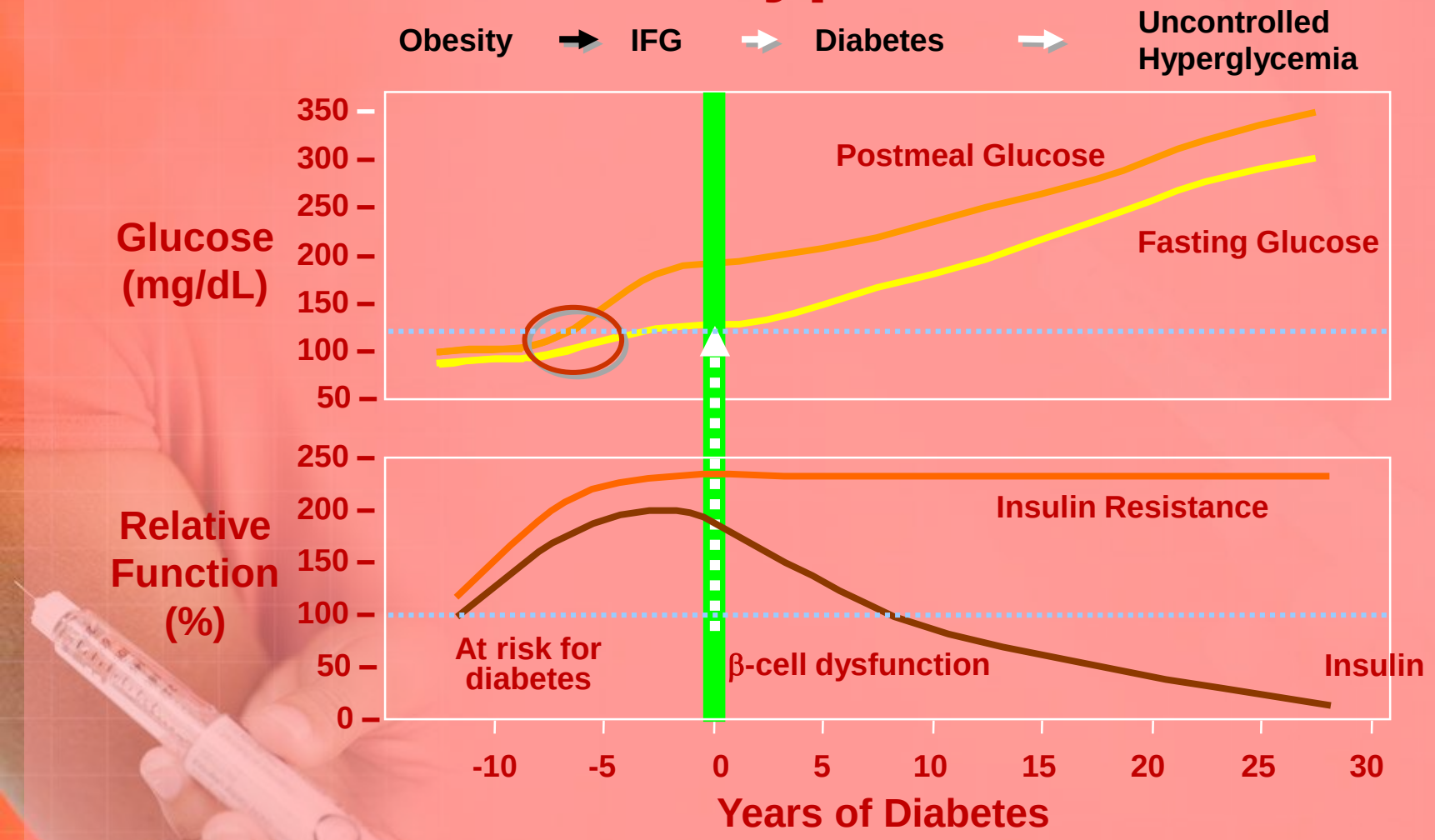


Diabetes Mellitus Type 2

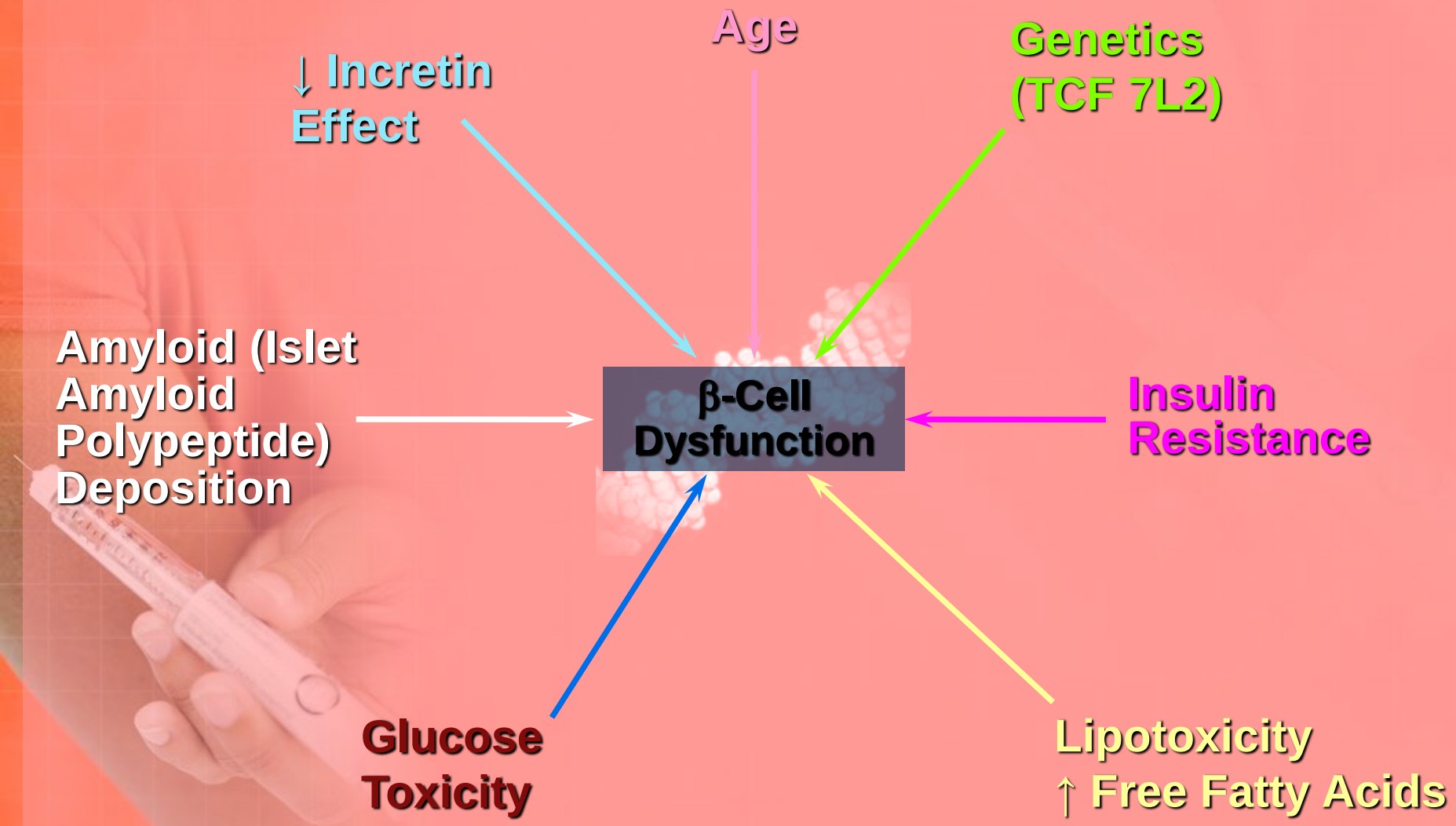
- Type 2 Clinical Manifestations:
  - Polydipsia –increased thirst
  - Polyuria –increased urine
  - Polyphagia –increased hunger
  - Fatigue
  - Blurred vision
  - Slow healing infections
  - Impotence in men



Course of Type 2 Diabetes

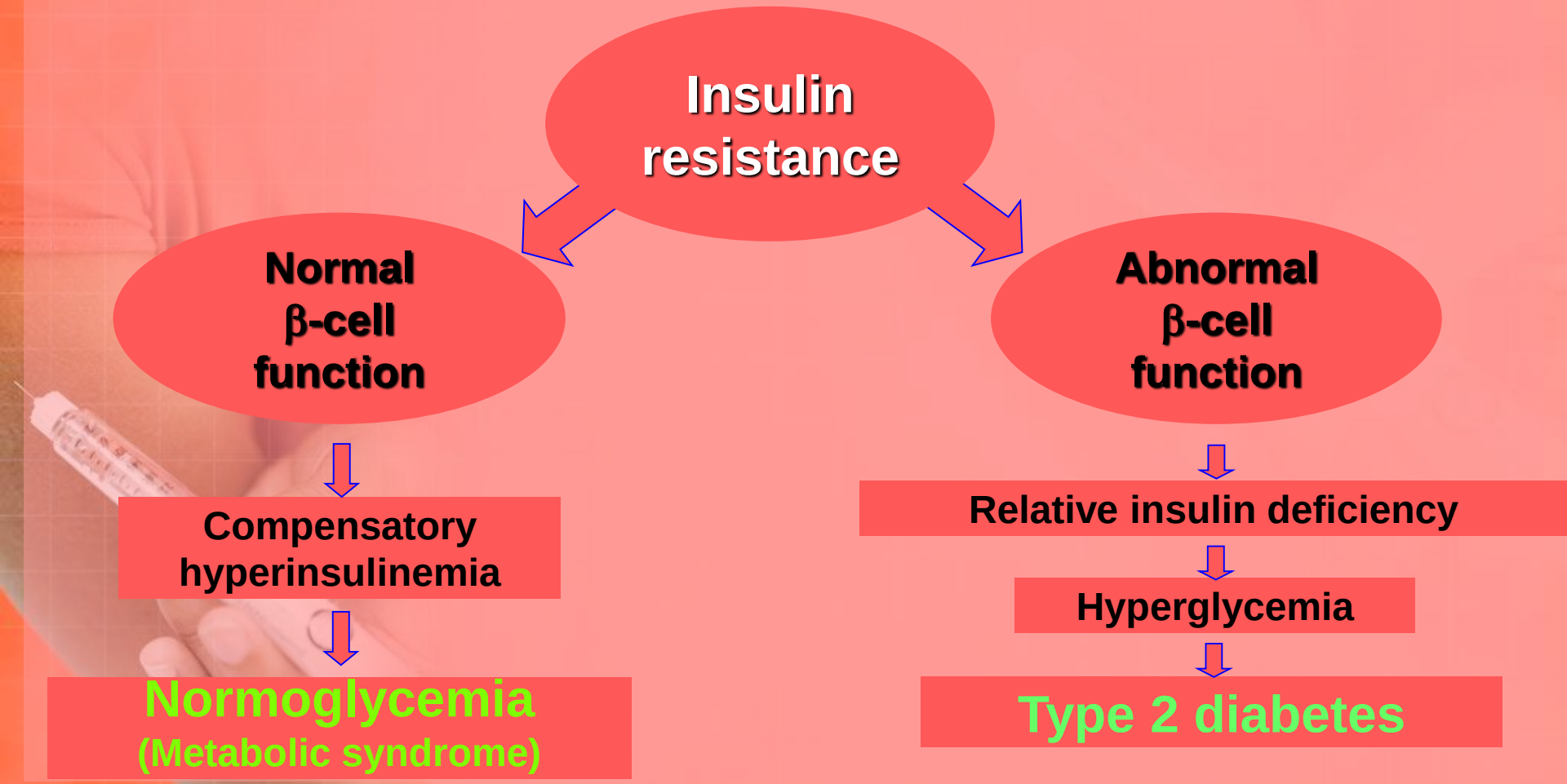


Etiology of β-Cell Dysfunction in Type 2 Diabetes



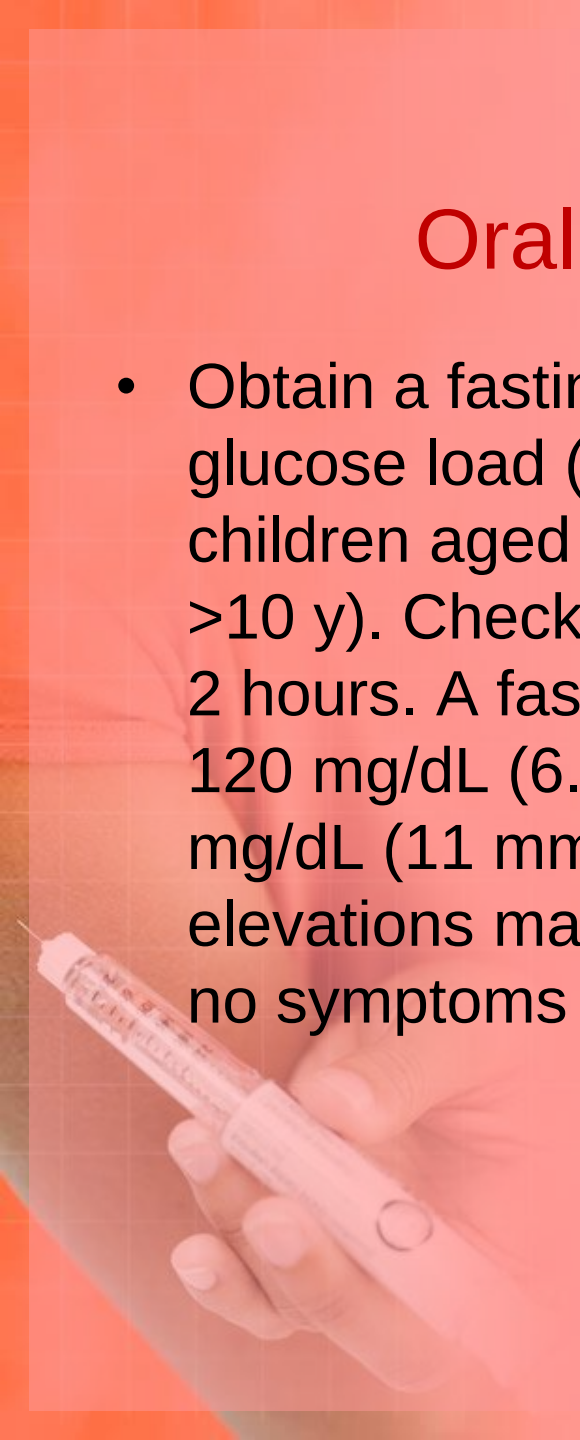
Type 2 Diabetes: Insulin Resistance Plus Impaired β-Cell Function

Both insulin resistance and β-cell dysfunction are present at the time of diagnosis of type 2 diabetes



Oral Glucose Tolerance Test

- Obtain a fasting blood sugar level, then administer an oral glucose load (2 g/kg for children aged < 3 y, 1.75 g/kg for children aged 3-10 y [max 50 g], or 75 g for children aged >10 y). Check the blood glucose concentration again after 2 hours. A fasting whole-blood glucose level higher than 120 mg/dL (6.7 mmol/L) or a 2-hour value higher than 200 mg/dL (11 mmol/L) indicates diabetes. However, mild elevations may not indicate diabetes when the patient has no symptoms and no diabetes-related antibodies.



What is Insulin Resistance?

- condition in which the body does not utilise insulin efficiently
- Insulin resistance is the decreased response of the liver and peripheral tissues (muscle, fat) to insulin
  - Insulin resistance is a primary defect in the majority of patients with Type 2 diabetes

Causes of Insulin Resistance

- Obesity/overweight (especially excess visceral adiposity)
- Excess glucocorticoids (Cushing's syndrome or steroid therapy)
- Excess growth hormone (acromegaly)
- Pregnancy, gestational diabetes
- Polycystic ovary disease
- Lipodystrophy (acquired or genetic; associated with lipid accumulation in liver)
- Autoantibodies to the insulin receptor
- Mutations of insulin receptor
- Mutations of the peroxisome proliferators' activator receptor γ (PPARγ)
- Mutations that cause genetic obesity (e.g., melanocortin receptor mutations)
- Hemochromatosis (a hereditary disease that causes tissue iron accumulation)

Metabolic Syndrome

- Obesity, especially accumulation of abdominal fat
- Insulin resistance
- Fasting hyperglycemia
- Lipid abnormalities, such as increased blood Triglycerides and decreased blood high-density lipoprotein-cholesterol
- Hypertension

Prediabetes

FPG 100–125 mg/dL (5.6–6.9 mmol/L): IFG OR
2-h plasma glucose 140–199 mg/dL (7.8–11.0 mmol/L): IGT OR
A1C 5.7–6.4%

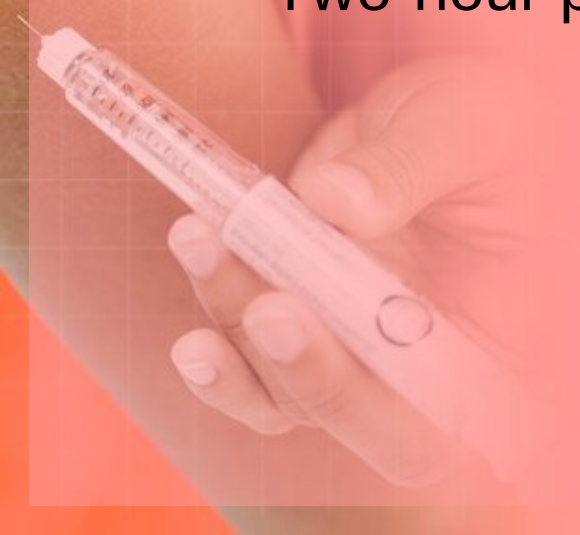
For all three tests, risk is continuous, extending below the lower limit of a range and becoming disproportionately greater at higher ends of the range.

American Diabetes Association Standards of Medical Care in Diabetes. Classification and diagnosis of diabetes. *Diabetes Care* 2016; 39 (Suppl. 1): S13-S22

Glycemic Targets in Pregnancy

For women with gestational diabetes or preexisting type 1 or type 2 diabetes in pregnancy, the following targets are recommended:

- Fasting ≤95 mg/dL (5.3 mmol/L)
  and either
- One-hour postprandial ≤140 mg/dL (7.8 mmol/L) or
- Two-hour postprandial ≤120 mg/dL (6.7 mmol/L)



Glycemic recommendations for nonpregnant adults with diabetes

- A1C <7.0% (53 mmol/mol)
- Preprandial capillary plasma glucose 80–130 mg/dl (4.4–7.2 mmol/L)
- Peak postprandial capillary plasma glucose <180 mg/dL (10.0 mmol/L)

National Glycohemoglobin Standardization Program (NGSP) and standardized

Type 1 Diabetes: Glycemic Control

Blood glucose goal range		A1C	Rationale
Before meals	Bedtime/ overnight		
90–130 mg/dL (5.0–7.2 mmol/L)	90–150 mg/dL (5.0–8.3 mmol/L)	<7.5%	A lower goal (<7.0%) is reasonable if it can be achieved without excessive hypos

- Goals should be individualized; lower goals may be reasonable.
- Modify BG goals in youth w/ frequent hypos or hypoglycemia unawareness.
- Measure postprandial BG if discrepancy between preprandial BG and A1C & to assess glycemia in basal–bolus regimens.

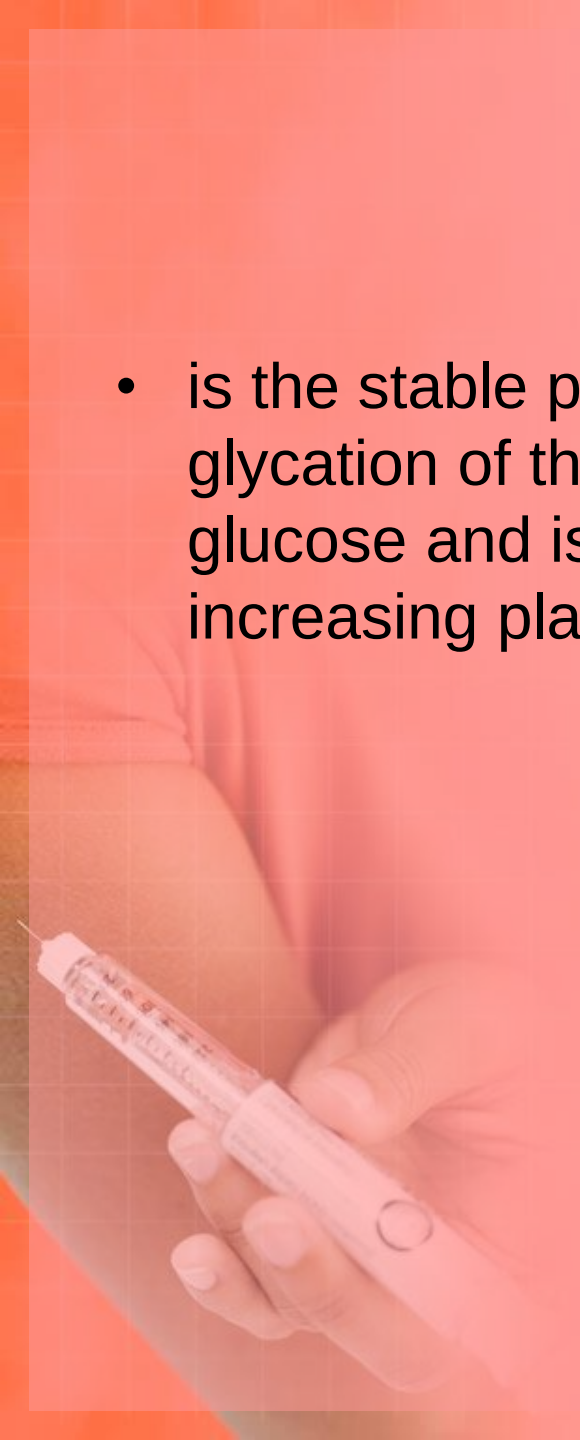
Criteria for the Diagnosis of Diabetes

A1C ≥6.5%

The test should be performed in a laboratory using an NGSP-certified method standardized to the DCCT assay*

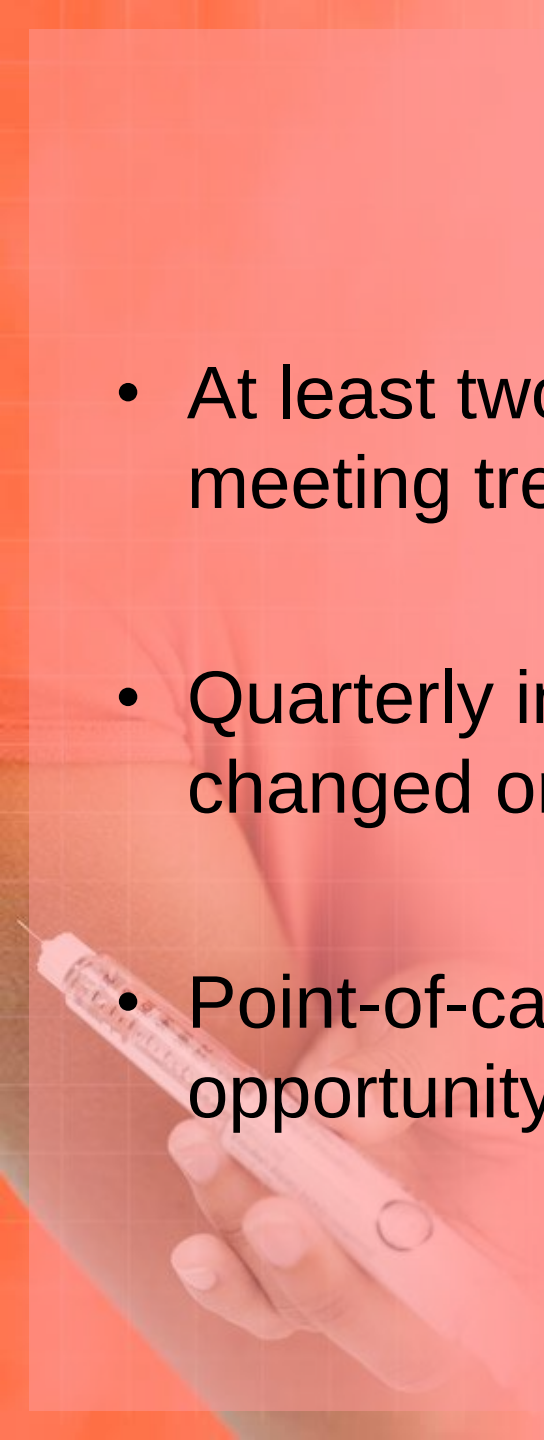
Hemoglobin A

- is the stable product of nonenzymatic irreversible glycation of the beta chain of hemoglobin by plasma glucose and is formed at rates that increase with increasing plasma glucose levels.



A1C Testing

- At least two times a year in patients who are meeting treatment goals
- Quarterly in patients whose therapy has changed or who are not meeting glycemic goals
- Point-of-care testing for A1C provides the opportunity for more timely treatment changes



A1C Testing

- A1C should be considered an additional optional diagnostic criterion, not the primary criterion for diagnosis of diabetes
- When feasible, suggest using traditional glucose criteria for diagnosis of diabetes
- A1C is not recommended for diagnosing type 1 diabetes
- A1C is not recommended for diagnosing gestational diabetes

A1C Reporting: NGSP vs. IFCC Units

NGSP (%)	IFCC (mmol/mol)
4.0	20
5.0	31
6.0	42
6.5	48
7.0	53
8.0	64
9.0	75
10.0	86
11.0	97
12.0	108

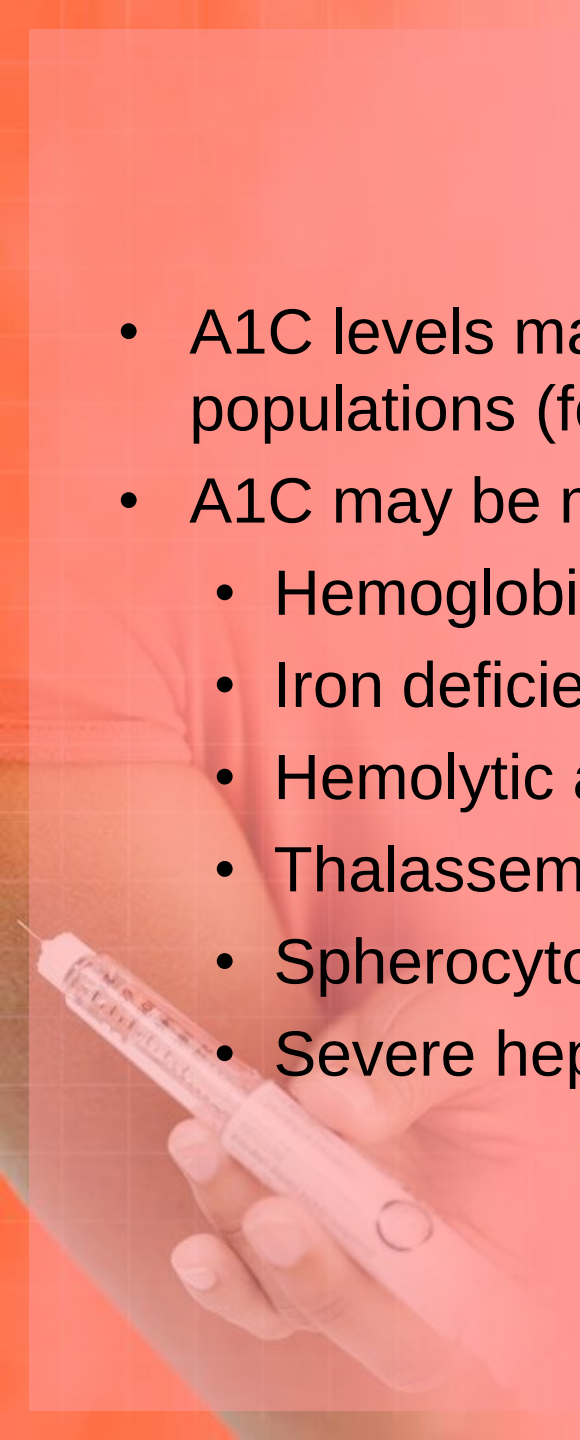
- Some countries report A1C in IFCC SI units (mmol/mol) instead of the NGSP units
- The equation below can be used to convert A1C from NGSP (%) to IFCC (mmol/mol)

IFCC (mmol/mol) = 10.93(NGSP%) – 23.50

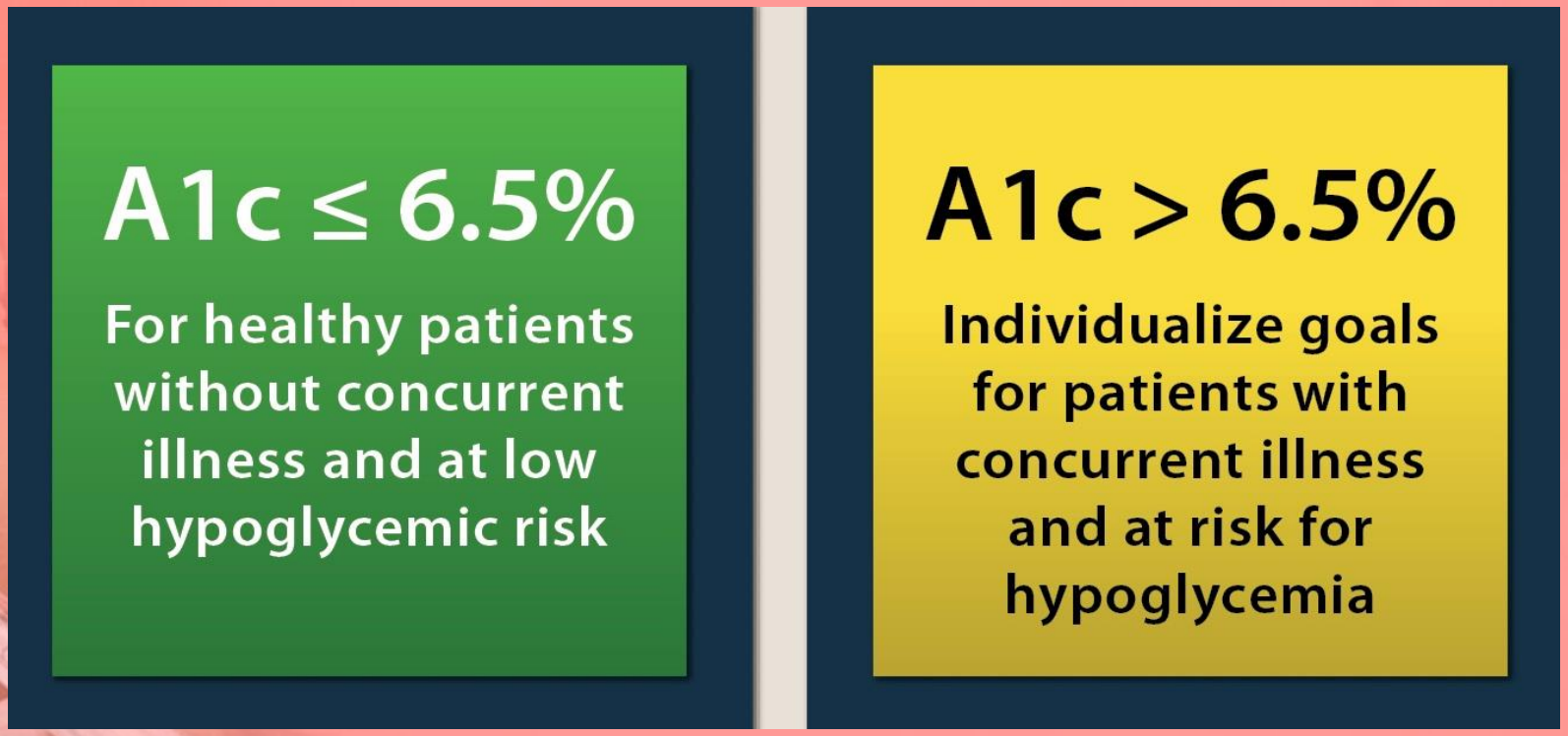
NGSP = National Glycohemoglobin Standardization Program; IFCC = International Federation of Clinical Chemistry and Laboratory Medicine

A1C Testing

- A1C levels may be misleading in several ethnic populations (for example, African Americans)
- A1C may be misleading in some clinical settings
  - Hemoglobinopathies
  - Iron deficiency
  - Hemolytic anemias
  - Thalassemias
  - Spherocytosis
  - Severe hepatic or renal disease



AACE :2018 Goals for glycemic control



Fructosamine

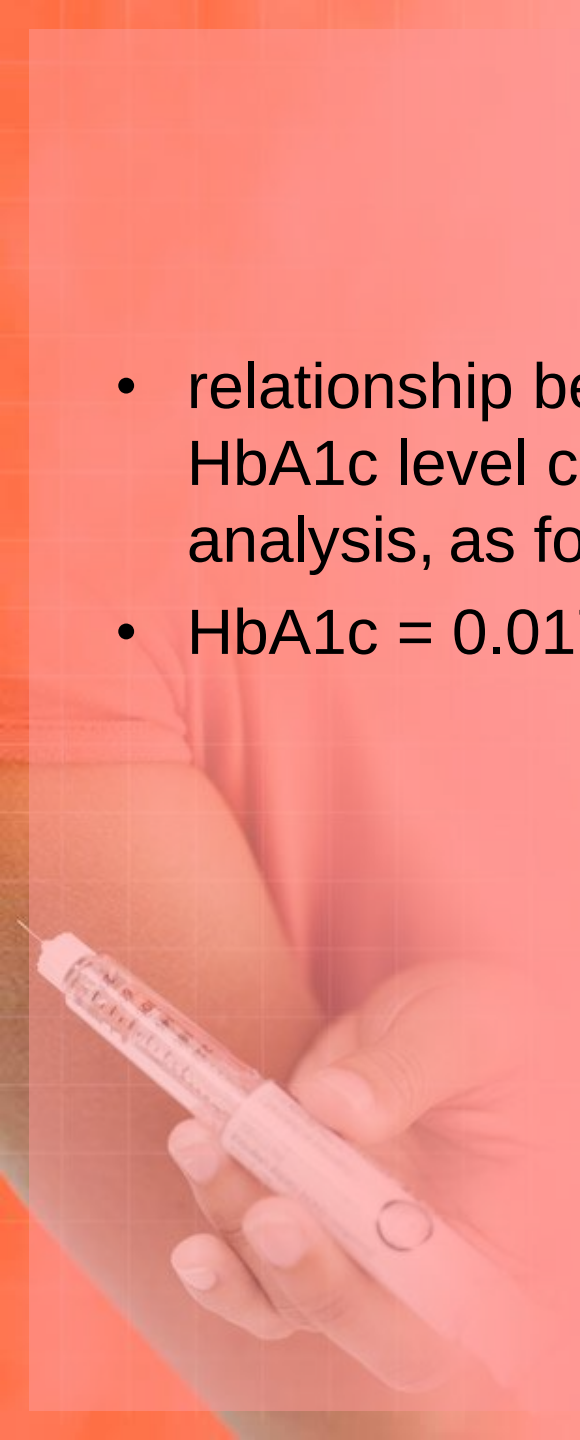
- is formed by nonenzymatic glycosylation of serum proteins, predominantly albumin.
- The degree of protein glycation is proportional to the concentration of plasma glucose over the lifetime of the protein
- Albumin, the most common serum protein, typically accounts for 80% of all fructosamine
- Reduction in serum albumin lowers the serum fructosamine value.
- Fructosamine levels indicate the average level of blood glucose control over the past 2-3 weeks

Fructosamine Collection and Panels

- Specimen type: Serum
- Collection method: Venipuncture
- Minimum specimen volume: 0.5 mL
- Specimen container: Serum separator tube; also acceptable is pink (K_2 EDTA) or green (lithium heparin)
- Unacceptable conditions: Hemolyzed specimens (may cause falsely elevated results)
- Methodology: Colorimetry or quantitative spectrophotometry
- Transport temperature: Room temperature
- Specimen stability: room temperature, 7 days; refrigerated, 14 days; frozen, 30 days

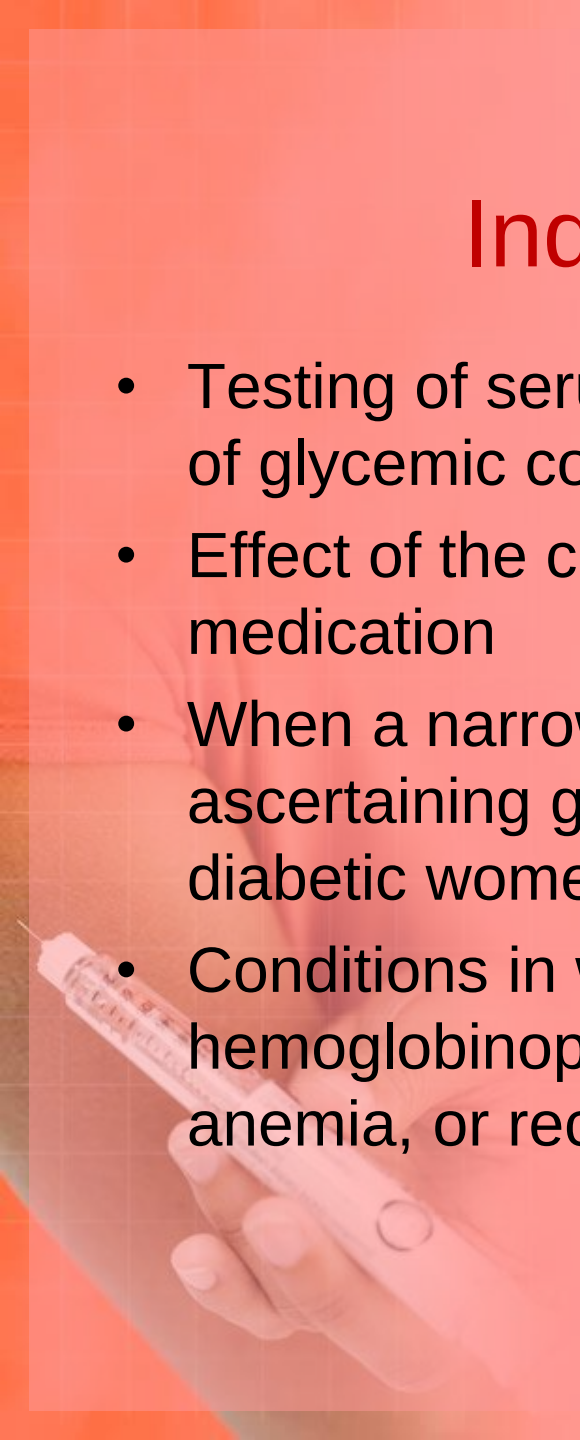
Fructosamine

- relationship between the fructosamine level and the HbA1c level can be present as a linear regression analysis, as follows:
- HbA1c = 0.017 X fructosamine level (µmol/L) + 1.61



Indications/applications

- Testing of serum fructosamine is indicated for monitoring of glycemic control in the following circumstances:
- Effect of the change (< 6 wk) in diet, exercise, or medication
- When a narrow time frame is required, such as for ascertaining glycemic control at the time of conception in diabetic women who recently became pregnant
- Conditions in which HbA1c may be unreliable, such as hemoglobinopathy (eg, sickle cell disease), hemolytic anemia, or recent blood loss



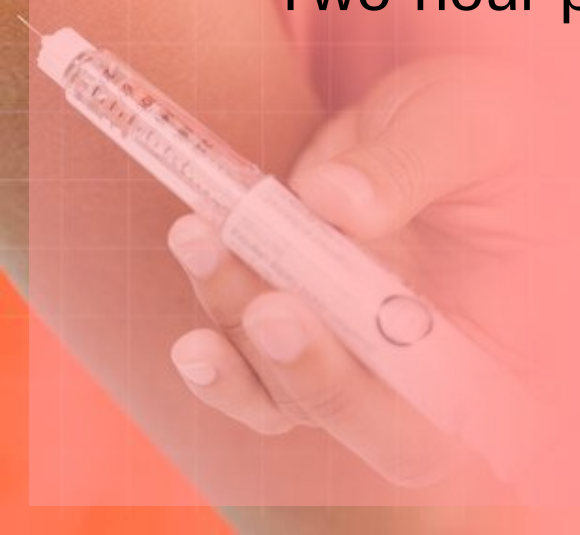
Considerations

- All conditions that affect serum albumin production (eg increased or decreased turnover) may affect the reliability of fructosamine assay, such as the following:
- Hepatic diseases (eg. cirrhosis)
- Nephritic syndrome
- Thyroid disease
- Paraproteinemia
- High levels of ascorbic acid interfere with the fructosamine assay. Patients should abstain from ascorbic acid supplements for a minimum of 24 hours prior to sample collection.

Glycemic Targets in Pregnancy

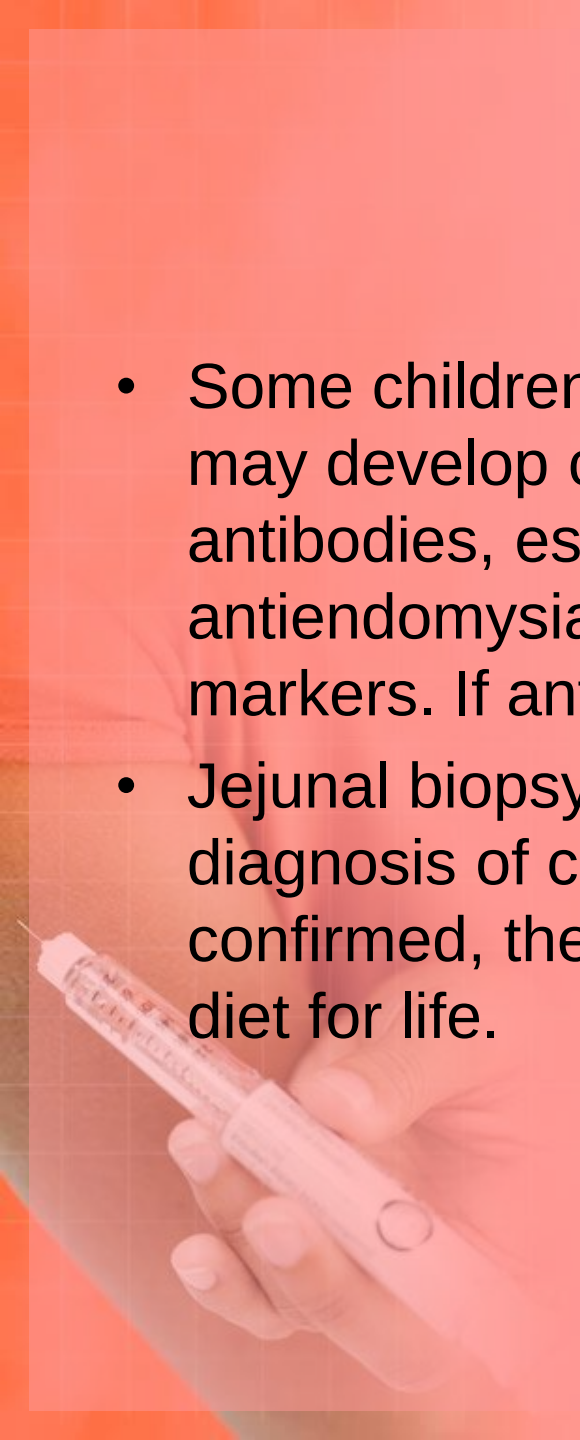
For women with gestational diabetes or preexisting type 1 or type 2 diabetes in pregnancy, the following targets are recommended:

- Fasting ≤95 mg/dL (5.3 mmol/L)
  and either
- One-hour postprandial ≤140 mg/dL (7.8 mmol/L) or
- Two-hour postprandial ≤120 mg/dL (6.7 mmol/L)



Celiac disease

- Some children with type 1 diabetes mellitus may have or may develop celiac disease. Positive antigliadin antibodies, especially specific antibodies (eg, antiendomysial, antitransglutaminase) are important risk markers. If antibody tests are positive,
- Jejunal biopsy is required to confirm or refute a diagnosis of celiac disease. Once celiac disease is confirmed, the individual should remain on a gluten-free diet for life.



- Thyroid function tests and antithyroid antibodies
- Lipid profile
  - ✓ are usually abnormal at diagnosis because of increased circulating triglycerides caused by gluconeogenesis. Apart from hypertriglyceridemia, primary lipid disorders rarely result in diabetes. Hyperlipidemia with poor metabolic control is common but returns to normal as metabolic control improves.
- Urinary albumin

Complications associated with DM

Acute:

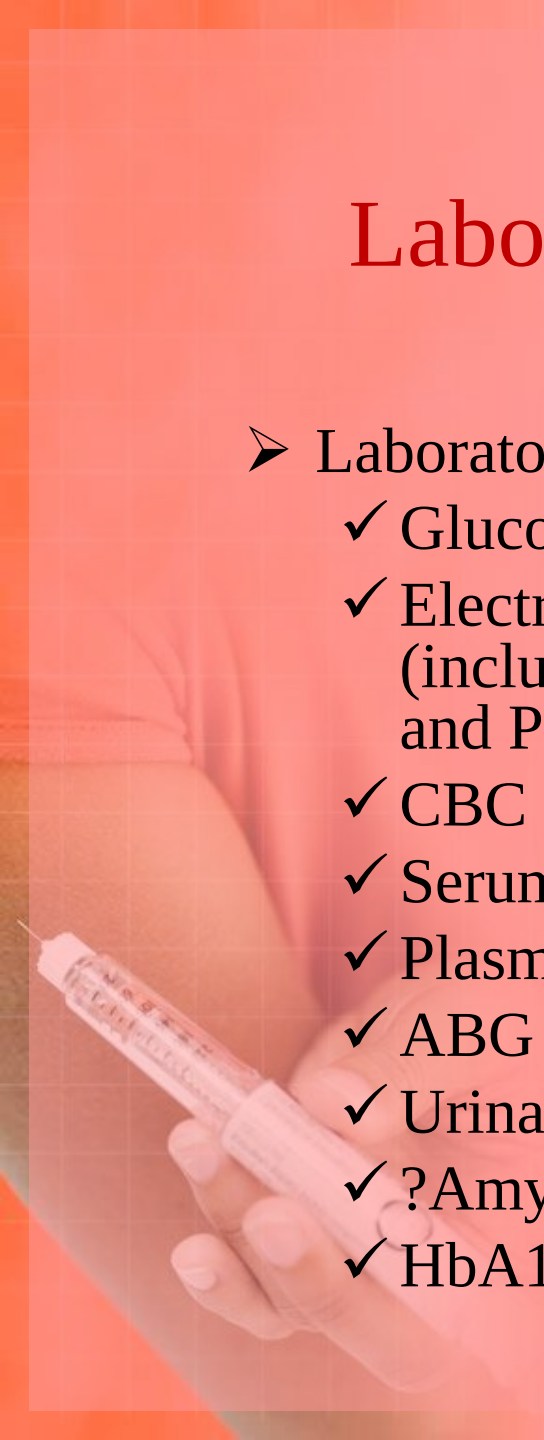
- Diabetic Ketoacidosis (DKA)
- Hyperglycemic Hyperosmolar State (HHS)
- Hypoglycemia

ADA Diagnostic Criteria

	DKA			
	Mild	Moderate	Severe	HHS
Glc (mg/dL)	> 250	> 250	> 250	> 600
pH	7.25-7.30	7.00-7.24	< 7.00	> 7.30
HCO^{3-} (mM)	15-18	10-14	< 10	> 18
Urine ketones	+	+	+	Small
Serum ketones	+	+	+	Small
Osmolality	Varies	Varies	Varies	> 320
Anion gap	> 10	> 12	> 12	< 12
Sensorium	Alert	Drowsy	Stupor/Coma	Stupor/Coma

Laboratory Investigations DKA

- Laboratory
  - ✓ Glucose
  - ✓ Electrolytes (including Mg, K, Ca and Phosphate)
  - ✓ CBC
  - ✓ Serum Ketones
  - ✓ Plasma Osmolality
  - ✓ ABG (?venous pH)
  - ✓ Urinalysis
  - ✓ ?Amylase/Lipase
  - ✓ HbA1c
- Other
  - ✓ Blood Culture
  - ✓ Urine Culture
  - ✓ Sputum Culture



Formulas you may need

- sOsm = 2 (Na) + Glu/18 + BUN/2.8

  normal OSM = 285 – 295 mOSM/L

- anion gap (AG) = Na - (Cl + HCO3)

  normal value: 8-12 mEq/L.

- Calculated serum Na = Na measured + 1.6 mEq/L. x (Glu - 100)/100

Ketones

- The three principles ketone bodies are β –hydroxybutyric acid, acetoacetate, and acetone
- And can go as high as 30 mM/L (normal values are up to 0.15 mM/L)
- β –hydroxybutyric acid and acetoacetate accumulate in the serum at a ratio of 3 :1 (mild DKA) to as high as 15 : 1 (severe DKA)
- Standard nitroprusside reagents (Acetesat, Ketostix) react with acetoacetate and not β –hydroxybutyric acid.

Using venous blood gases to assess the acid-base

- Arterial pH = 0.039 + (0.961 X venous pH)
- Arterial pCO2 = 7.735 + (0.572 X venous Pco2)
- Arterial HCO3- = 0.538 + (0.845 X venous HCO3-)

- Serum Electrolyte Panel
- effects of extremes in potassium levels.
- The serum sodium level usually is low in affected patients. The osmotic effect of hyperglycemia moves extravascular water to the intravascular space. For each 100 mg/dL of glucose over 100 mg/dL, the serum sodium level is lowered by approximately 1.6 mEq/L. When glucose levels fall, the serum sodium level rises by a corresponding amount.
- Additionally, serum chloride levels and phosphorus levels always are low in these patients.

Blood Gases

Arterial blood gas

Capillary blood gas

Venous blood gas

Amylase

- Hyperamylasemia may be seen in patients with diabetic ketoacidosis, even in the absence of pancreatitis
- Bicarbonate
- Use bicarbonate levels in conjunction with the anion gap to assess the degree of acidosis that is present.

Hypoglycemia

- Hypoglycemia is defined according to the following serum glucose levels:
- < 50 mg/dL in men
- < 45 mg/dL in women
- < 40 mg/dL in infants and children

Causes Hypoglycemia

Drugs

- Insulin- most common cause,
- Timing, dose, type
- clearance of insulin (eg, renal failure);
- altered counter regulation
- Sulfonylureas
- Metformin does not cause hypoglycemia
- High dose salicylates, b –blockers, quinine,quinolones

Causes Hypoglycemia

Renal failure

- Second gluconeogenic organ
- decreased clearance of renally excreted drugs or their metabolites (eg, insulin, chlorpropamide, metabolite of glyburide)

Hepatic Failure

- Decreased glycogenolysis
- Decresed gluconeogenesis
- Large functional reserve,(20% func required to prevent hypoglycemia)
- Genetic defects in glycometabolic pathways
- Finally, compromised drug metabolism (tolbutamide, glyburide, glipizide)

Causes Hypoglycemia

Endocrinopathies

- ✓ Adrenal (glucocorticoid) insufficiency
- ✓ Growth hormone deficiency
- ✓ Glucagon deficiency
- ✓ Pituitary disease (decreased combined corticotropin and GH deficiecy)

Poisoning

(ethanol, propanolol, salicylates)

- ✓ Ethanol inhibits gluconeogenesis
- ✓ Ethanol-induced **hypoglycemia** occurs 12-72 hrs after ingestion

Causes Hypoglycemia

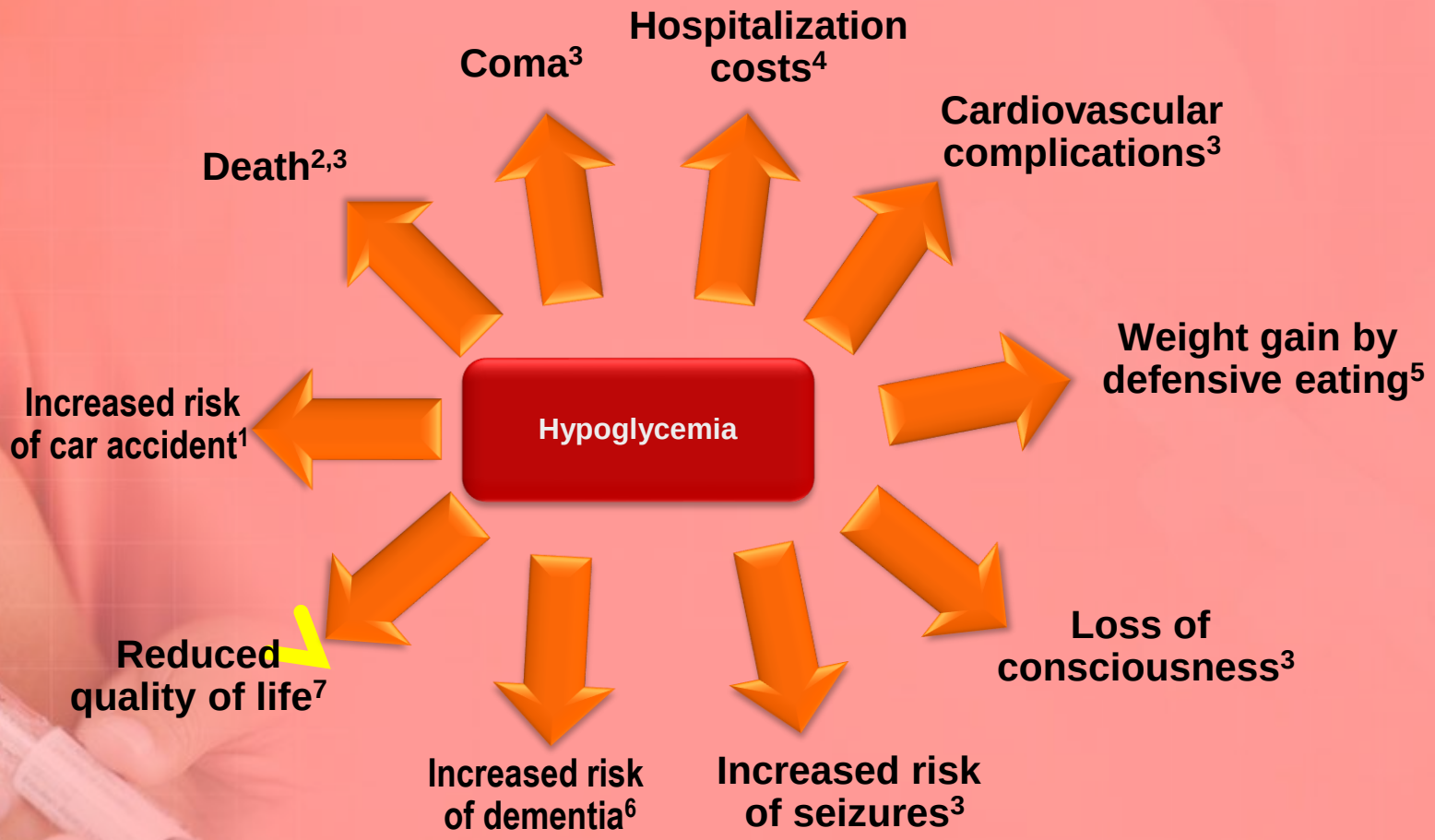
Neoplasm

- Non–islet-cell tumors
- Mesenchymal tumors,
- hepatocellular carcinoma,
- adrenocortical tumors,
- carcinoid tumors,
- leukemia, and lymphomas
- Most of these tumors secrete IGF –II molecule
- Some also secrete Glucagon- like peptide(GLP-1) and Somatostatin

What Are Symptoms of Hypoglycaemia?

Early symptoms	When the brain remains deprived of glucose, a later set of symptoms follows	Hypoglycaemia can also happen during sleep
Hunger Tremor Sweating Irritability Dizziness Headache Heart palpitations	Difficulty in thinking/speaking Confusion Seizures Coma	Crying out or having nightmares Pyjamas and sheets damp from perspiration Feeling tired, irritable, or confused after waking up

The consequences of hypoglycaemia



Hypoglycemia

Phase 1 Adrenergic fight	Phase 2 Neuroglucopenia	Consequences
Shaking	Drowsiness	Hospitalization
Tachycardia	Impaired judgement	Car accident
Nervousness	Disorientation	Loss of consciousness
Anxiety	Irritability	Seizures
Hunger	Headache	Coma
Sweating	Urr‘s	Death

72-Hour fast

Protocol

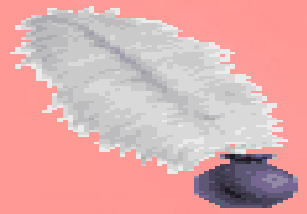
- Date the onset of the fast as the time of the last intake of calories
- Discontinue all non essential medications
- Allow the patient to drink calorie-free and caffeine-free beverages
- Collect blood specimens for measurement of plasma glucose, insulin, C-peptide, and proinsulin every six hours until the plasma glucose concentration is below 60 mg/dL (3.3 mmol/L) at this point, the frequency of sampling should be increased to every one to two hours.

Test end points and duration

- the plasma glucose concentration is ≤45 mg/dL (2.5 mmol/L)
- the patient has symptoms or signs of hypoglycemia,
- 72 hours have elapsed,
- or when the plasma glucose concentration is less than 55 mg/dL (3 mmol/L) if Whipple's triad is present
- Plasma beta-hydroxybutyrate and sulfonylurea levels are measured
- 1 mg of glucagon is given intravenously and the plasma glucose measured 10, 20, and 30 minutes later.

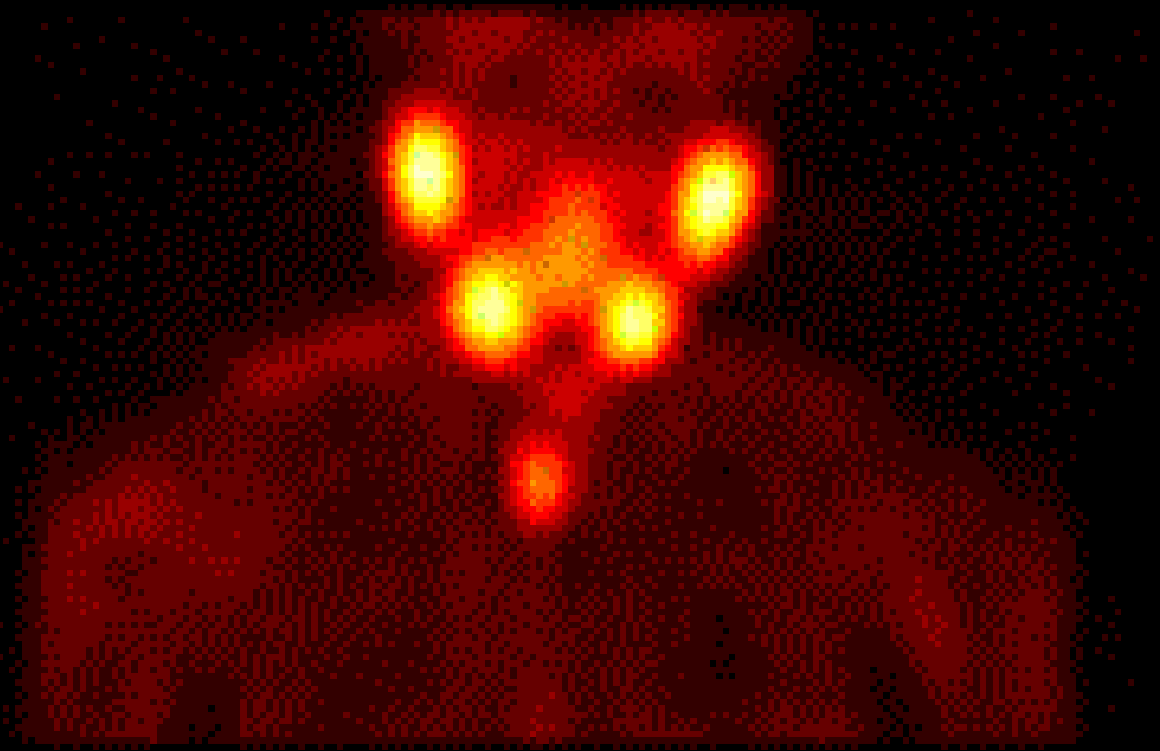
Interpretation of values after 72 hour test

Insulin	C Peptide	Proinsulin	Sulfonylurea	Insulin Antibody	Diagnosis
↑	↓	↓	–	–	Exogenous insulin
↑	↑	↑	–	–	Insulinoma, CHI
↑	↑	↑	+	–	Sulfonylurea
↑	↑	↑	–	+	Insulin autoimmune
± ↑	↓	↓	–	–	Insulin receptor autoimmune



Parathyroid Hormone, Calcitonin, Vitamin D3 and Calcium Homeostasis

Dr. Mohammed R. Zughbur
Endocrinologist, PhD, MD
Al-Azhar University



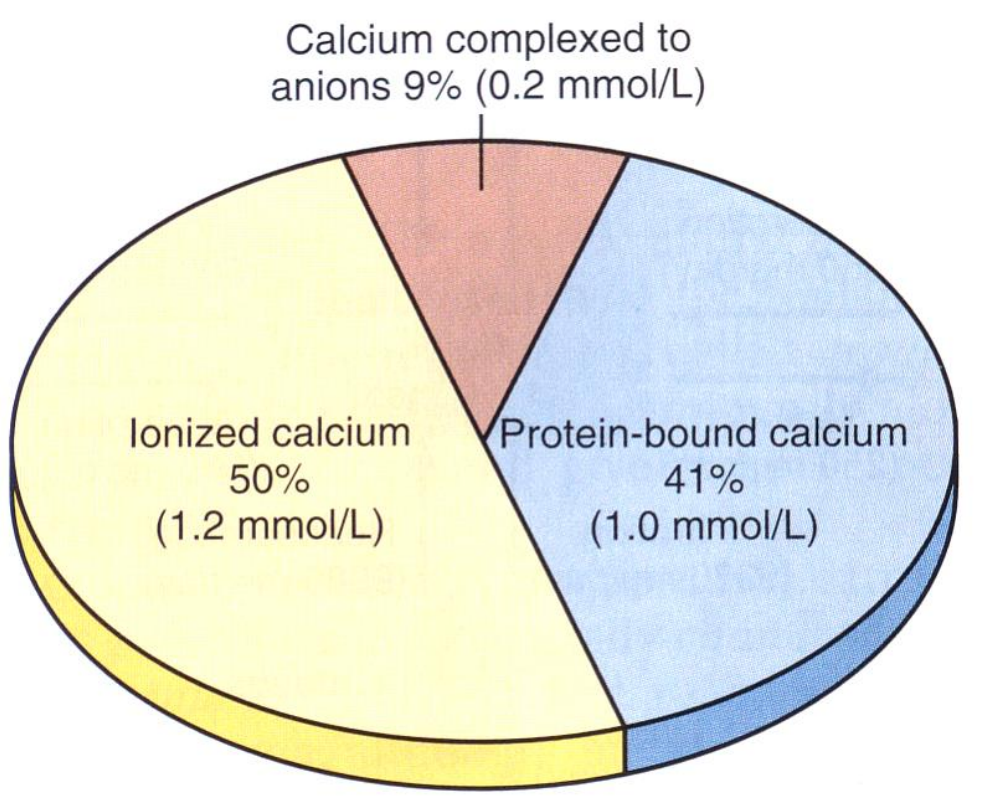
Calcium

- 2% of body weight
- 99% in bones
- 1% in body fluids

- Plasma **(Extracellular fluid)**
  - 2.25 – 2.75 mmol/l
- Cell **(Intracellular fluid)**
  - 10^{-8} – 10^{-7} mol/l = 10^{-5} – 10^{-4} mmol/l

Plasma Calcium Regulation

- Plasma calcium totals 2.4 mM (9.4 mg/dl)
  - Free calcium is 1.2 mM



Plasma Calcium

diffusible (through the capillary membrane)

- 48% (50%) Ca^{2+} ionized
- 6% (10%) combined with anions (citrate, phosphate) – non-dissociated

Nondiffusible (through the capillary membrane)

- 46% (40%) combined with plasma proteins
- combination with proteins depends on pH 0.2 mmol/l Ca^{2+} on each pH unit

Ionic composition of ICF and ECF

Ion	ECF mmol/l	ICF mmol/l
Na^+	136-146	20
K^+	3.8-5.4	150
Ca^{2+}	2.05-2.65	c. 10^{-4}
Cl^-	97-109	3
HCO_3^-	22-26	10

Intake of Calcium

- About 1000 mg of Ca^{2+} is ingested per day.
- About 350 mg of this is absorbed into the body.
- Absorption occurs in the small intestine, and requires vitamin D (stay tuned....)

Storage of Calcium

- The primary site of storage is our bones (about 1000 grams).
- Some calcium is stored within cells (endoplasmic reticulum and mitochondria).
- Bone is produced by osteoblast cells which produce collagen, which is then mineralized by calcium and phosphate (hydroxyapatite).
- Bone is remineralized (broken down) by osteoclasts, which secrete acid, causing the release of calcium and phosphate into the bloodstream.
- There is constant exchange of calcium between bone and blood.

Excretion of Calcium

- The major site of Ca^{2+} excretion in the body is the kidneys.
- The rate of Ca^{2+} loss and reabsorption at the kidney can be regulated.
- Regulation of absorption, storage, and excretion of Ca^{2+} results in maintenance of calcium homeostasis

Regulation of (Calcium)

- The important role that calcium plays in so many processes dictates that its concentration, both extracellularly and intracellularly, be maintained within a very narrow range.
- This is achieved by an elaborate system of controls

Extracellular Calcium

- When extracellular calcium falls below normal, the nervous system becomes progressively more excitable because of increase permeability of neuronal membranes to sodium

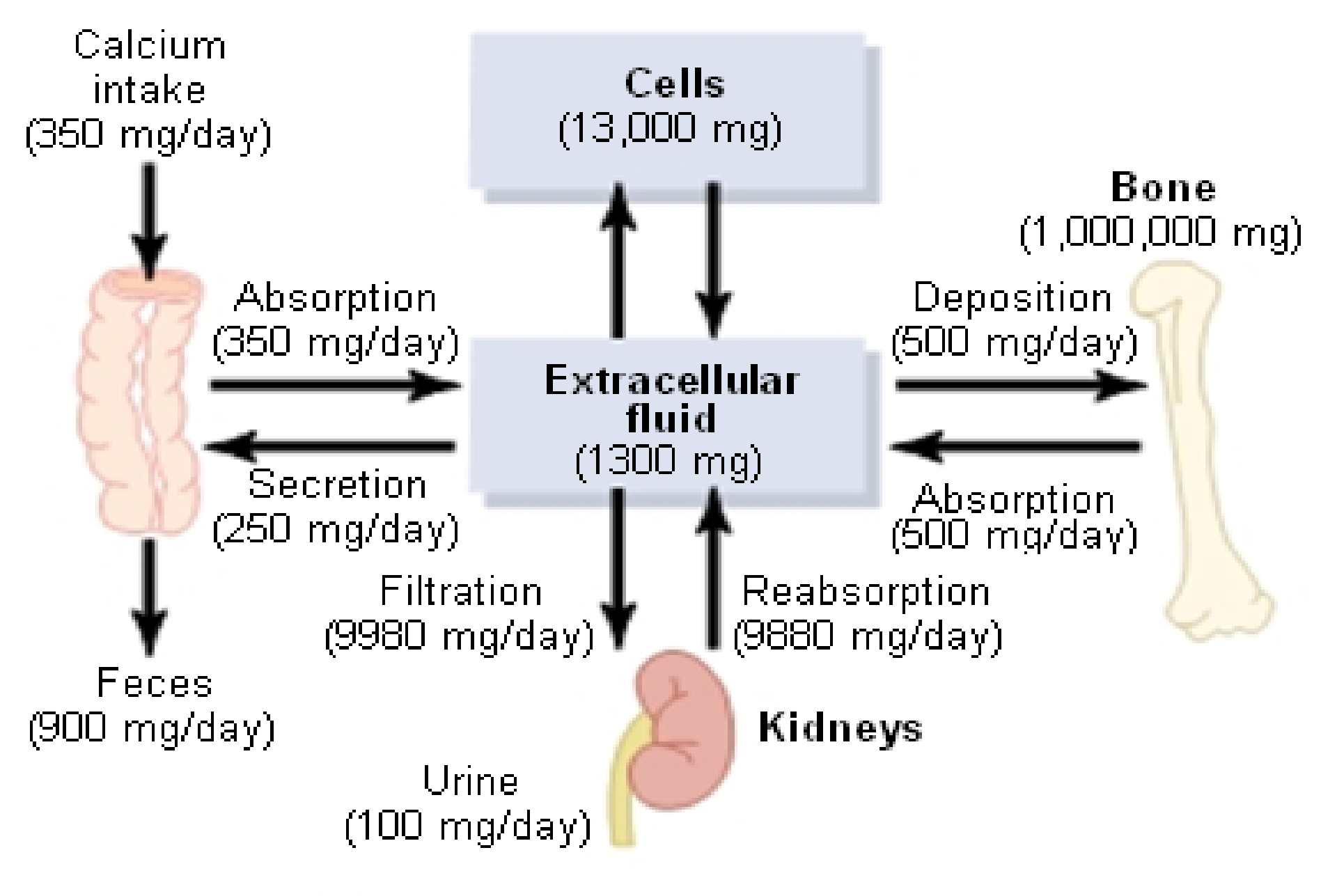
- Hyperexcitability causes tetanic contractions
  - Hypocalcemic tetany $[Ca^{2+}]_{cyt}$

Extracellular Calcium

- Three definable fractions of calcium in serum:
  - Ionized calcium 50%
  - Protein-bound calcium 40%
    - 90% bound to albumin
    - Remainder bound to globulins
  - Calcium complexed to serum constituents 10%
    - Citrate and phosphate

Extracellular Calcium

- Binding of calcium to albumin is pH dependent
- Acute alkalosis increases calcium binding to protein and decreases ionized calcium
- Patients who develop acute respiratory alkalosis have increased neural excitability and are prone to seizures due to low ionized calcium in the extracellular fluid which results in increased permeability to sodium ions



Calcium Turnover

Role Of Calcium

- excitability of cell membranes
- neuromuscular transmission and muscle contraction
- releasing of transmitters from synapses
- “second messenger”
- stimulates secretory activity of exocrine glands and releasing of hormones
- contractility of myocardium
- blood coagulation

Calcium in Blood and Bone

- Ca^{2+} normally ranges from 8.5-10 mg/dL in the plasma.
- The active free ionized Ca^{2+} is only about 48% 46% is bound to protein in a non-diffusible state while 6% is complexed to salt.
- Only free, ionized Ca^{2+} is biologically active.

Phosphates

- 80% bones and teeth
- 10% blood and muscles
- 10% different chemical complexes

- Plasma (ECF) 0.65 – 1.62 mmol/l
- Cell (ICF) 65 mmol/l (including organic P)

Phosphates

- calcium phosphate, hydroxyapatite (bone)
- inorganic anions: HPO_3^{2-}, H_2PO^{3-}
- organic:DNA, phospholipids
- ATP, cAMP, creatinphosphate molecules with metabolic significance

- **Ca, P rates of intake 1g/day**

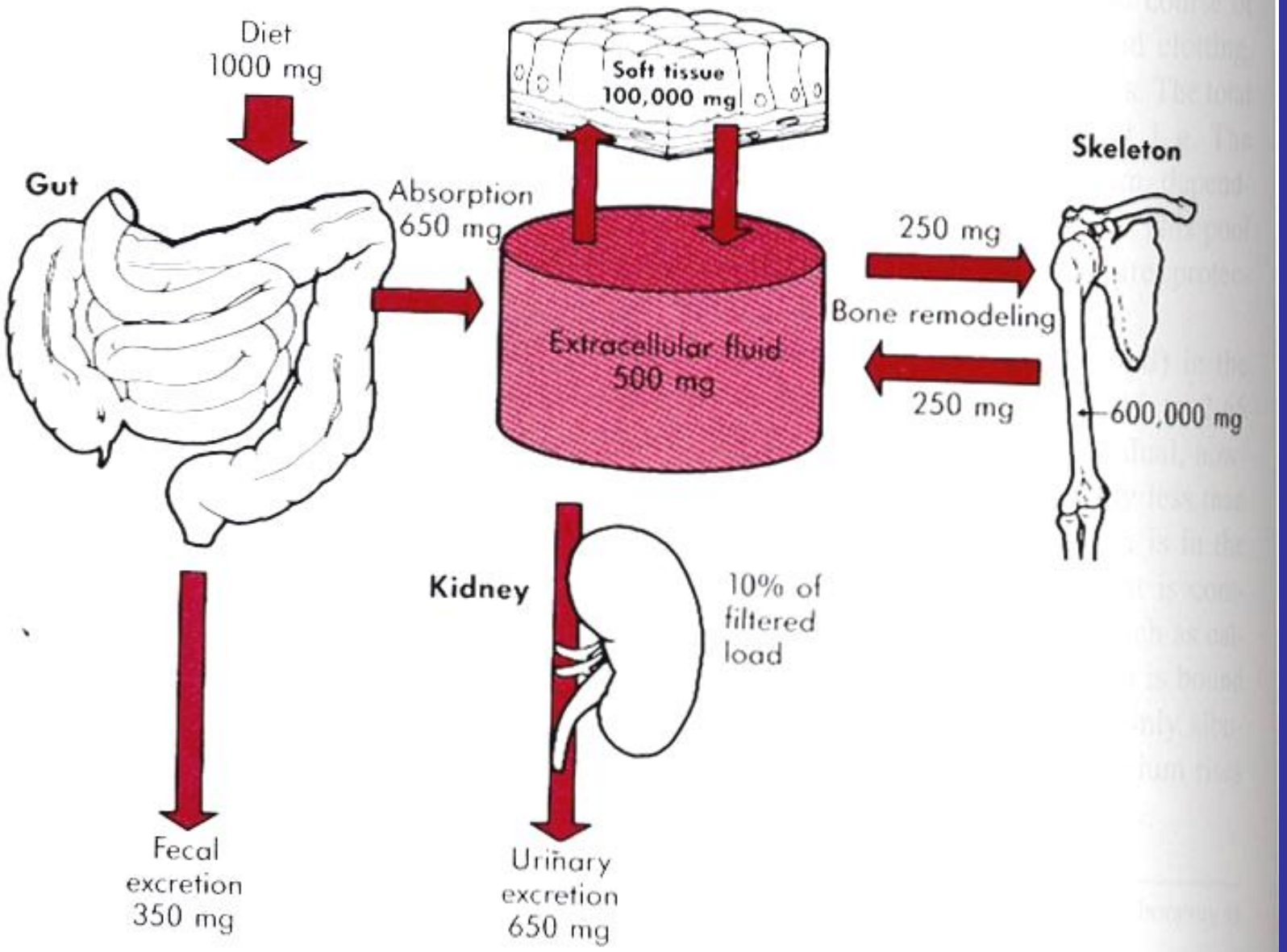
Phosphate Metabolism

- 85% present in skeleton
- Serum inorganic phosphate 0.84-1.45 mmol/L
- 10% protein bound, 35% complexed, rest free
- Integrity of bone
- Oxygen delivery
- Muscle contraction
- Role in ATP (energy), nucleotides, NADP, cell membranes, gene transcription, cell growth
- Balance maintained primarily by kidneys

Calcium and Phosphorous

- Ca is tightly regulated with P in the body
- P is an essential mineral necessary for ATP, cAMP 2nd messenger systems, and other roles

Phosphate Turnover



Phosphorous in Blood and Bone

- PO_4 normal plasma concentration is 3.0-4.5 mg/dL. 87% is diffusible, with 35% complexed to different ions and 52% ionized.
- 13% is in a non-diffusible protein bound state. 85-90% is found in bone.
- The rest is in ATP, cAMP, and proteins

Calcium and Bone

- 99% of Ca is found in the bone. Most is found in hydroxyapatite crystals. Very little Ca^{2+} can be released from the bone– though it is the major reservoir of Ca^{2+} in the body.

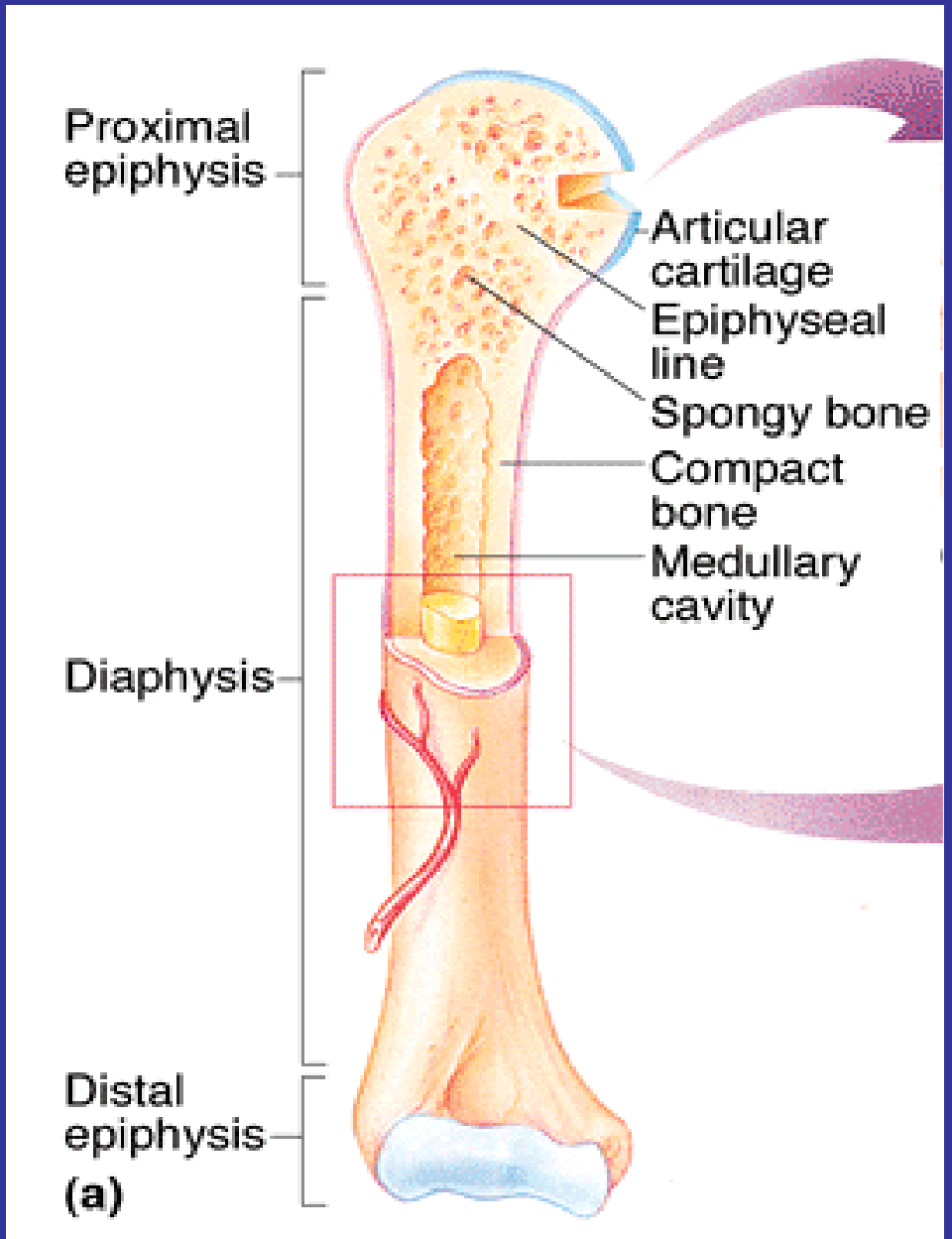
Features of a Long Bone

Epiphysis: Ends of the bone.

Diaphysis: The shaft of the bone which surrounds the medullary cavity.

Articular Cartilage: Cushions the ends of the bones and allows for smooth movement.

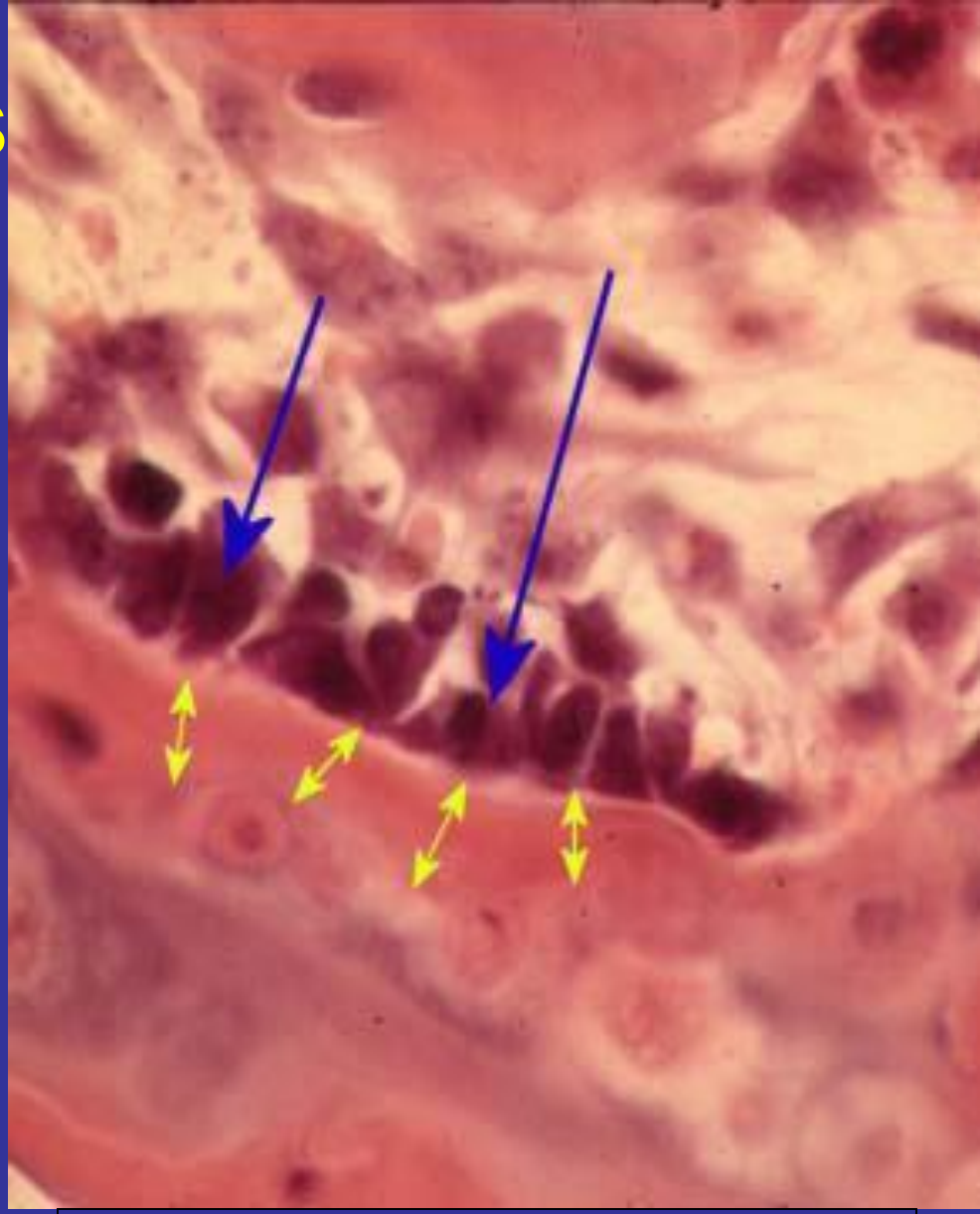
Epiphyseal Plate: Areas made of cartilage allowing for the growth of the bone.



Types of bone cells

1. Osteoblasts

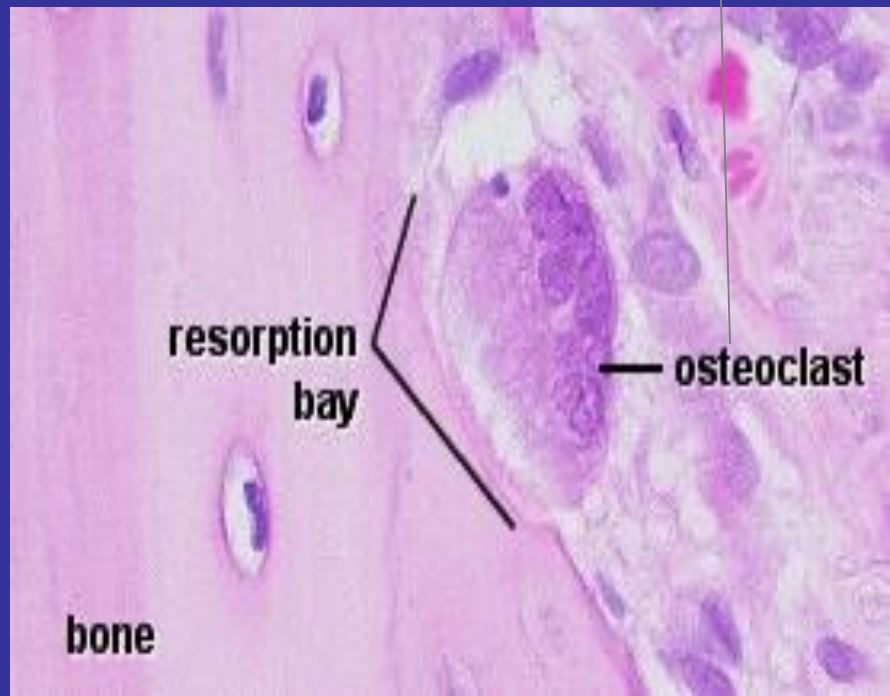
- Bone-forming cells found in all bone surfaces Bone-building cells.
- Synthesize and secrete collagen fibers and other organic components of bone matrix.
- serve as a framework for the deposition of calcium and phosphate calcification



The blue arrows indicate the osteoblasts. The yellow arrows indicate the bone matrix they've just secreted.

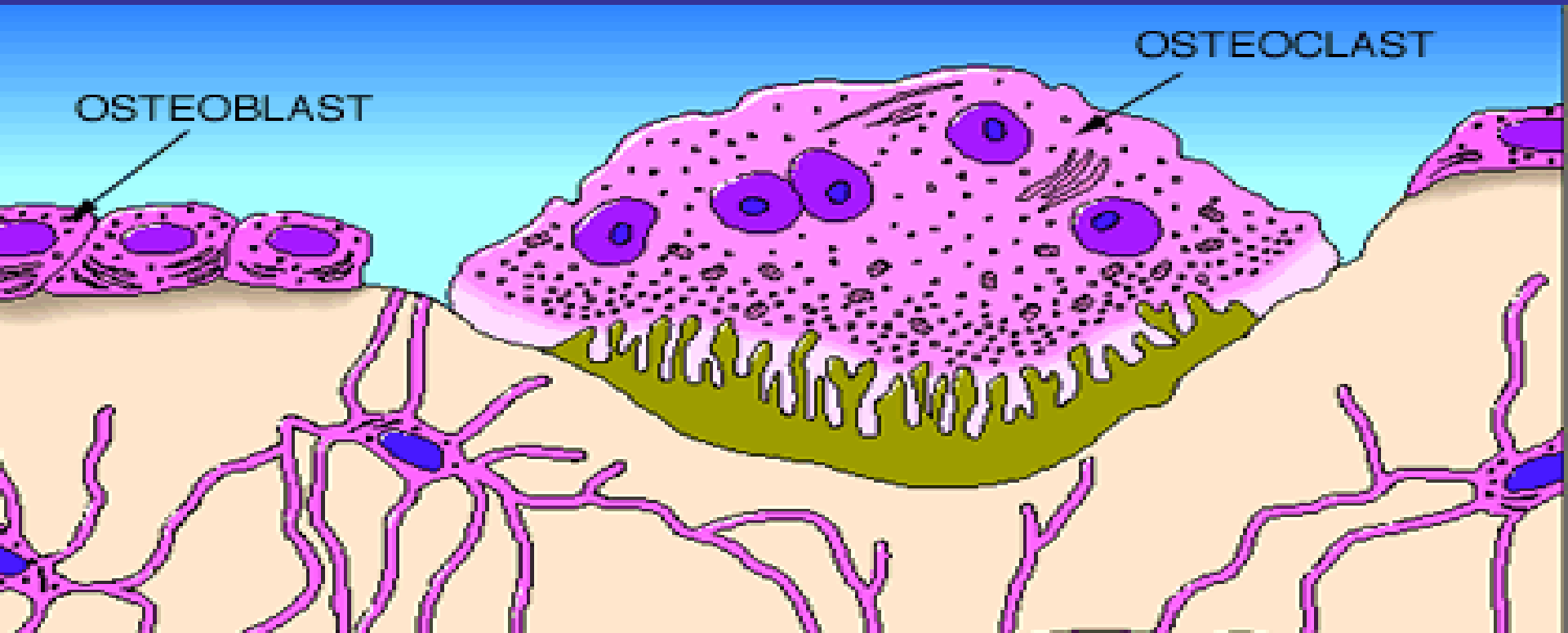
Types of bone cells

2. Osteoclasts
   - Giant multinucleate cells
   - Responsible for the active erosion of bone minerals
   - Contain large numbers of mitochondria and lysosomes

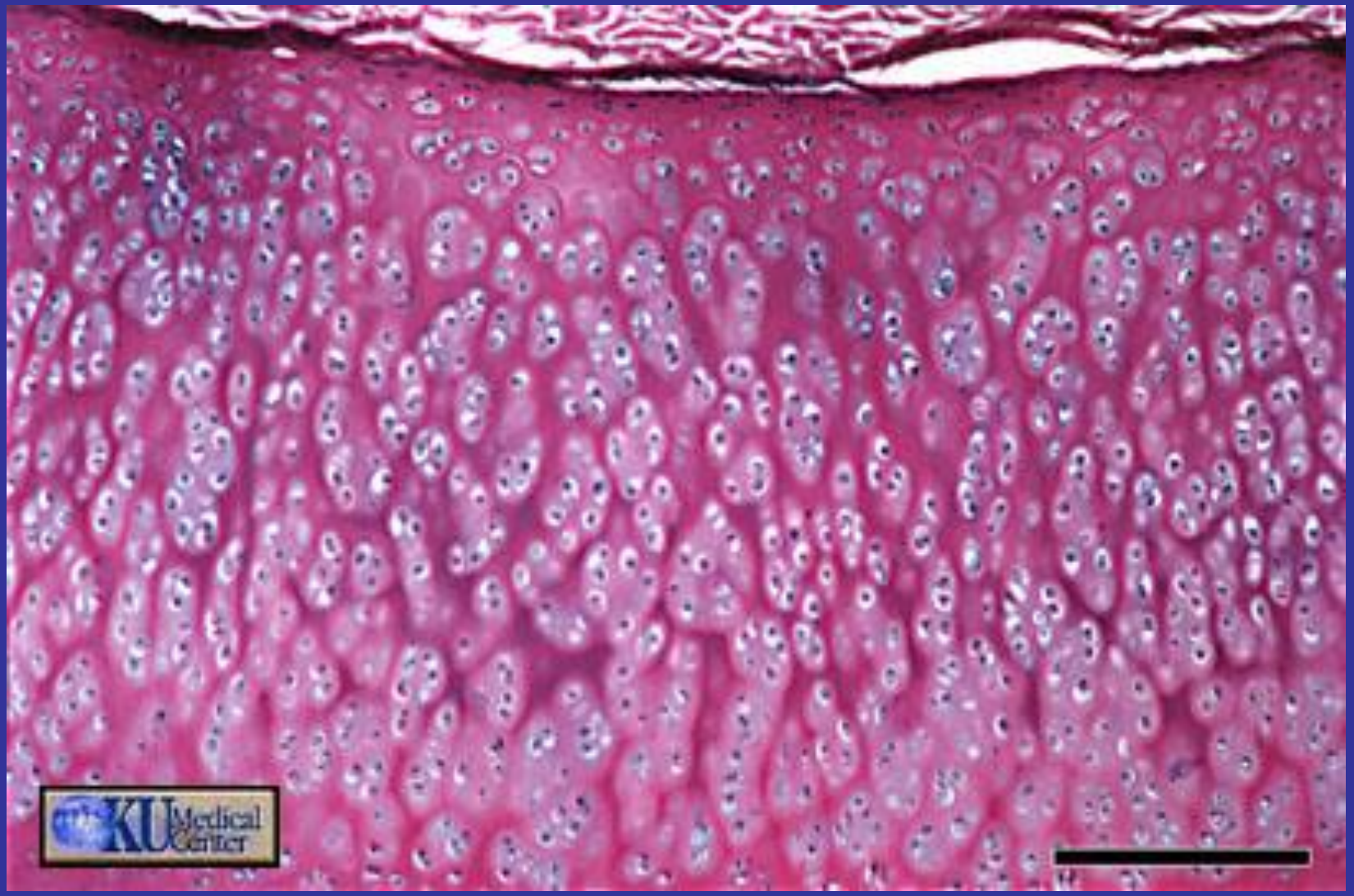


Types of bone cells

- 3. Osteocytes—mature, nondividing osteoblast surrounded by matrix, lying within lacunae



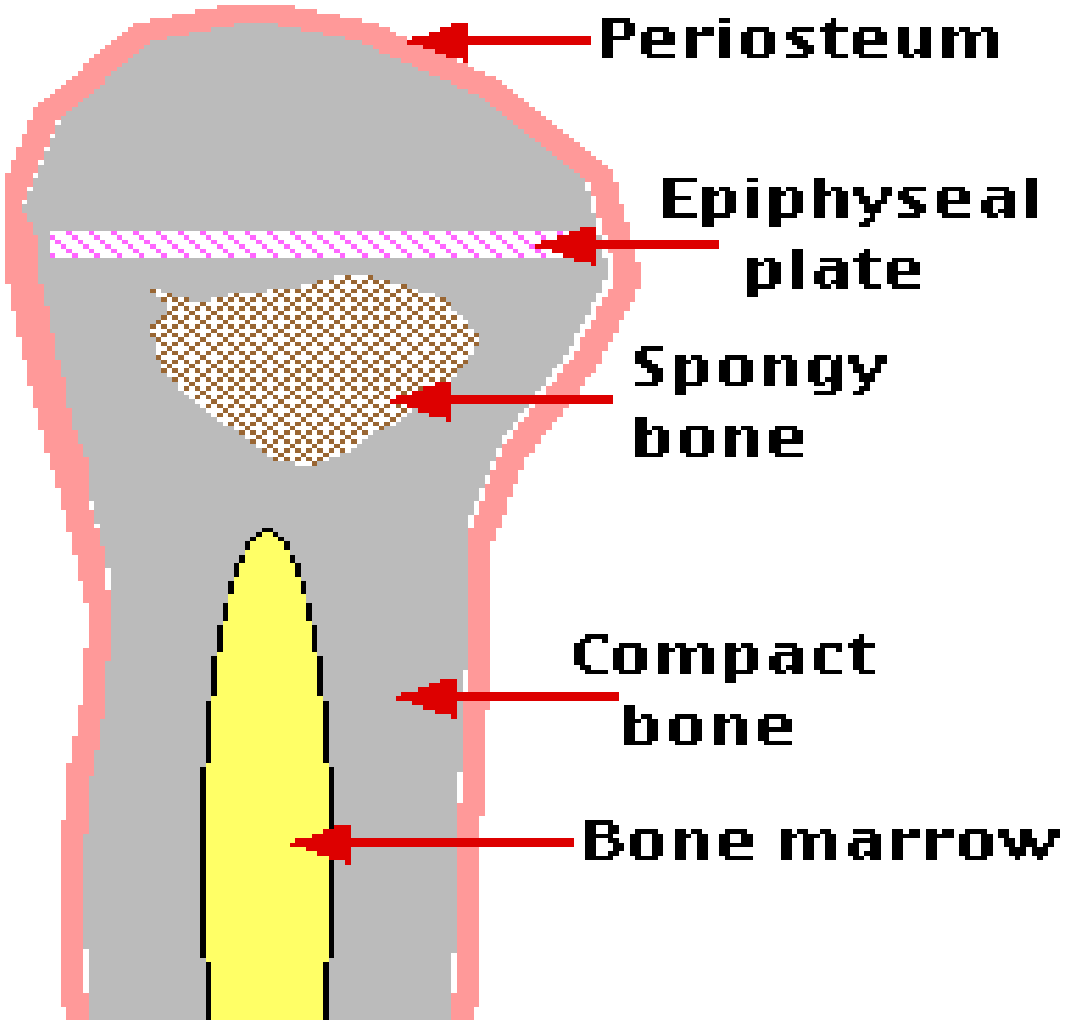
Cartilage



Bone Structure

- Periosteum – hard outer covering
  - Cells for growth and repair
- Compact bone – hard strong layer
  - Bone cells, blood vessels, protein with Ca and P
- Spongy bone – at ends of long bones
  - Has small open spaces to lighten weight
- Marrow cavity – hollow in middle of long bones

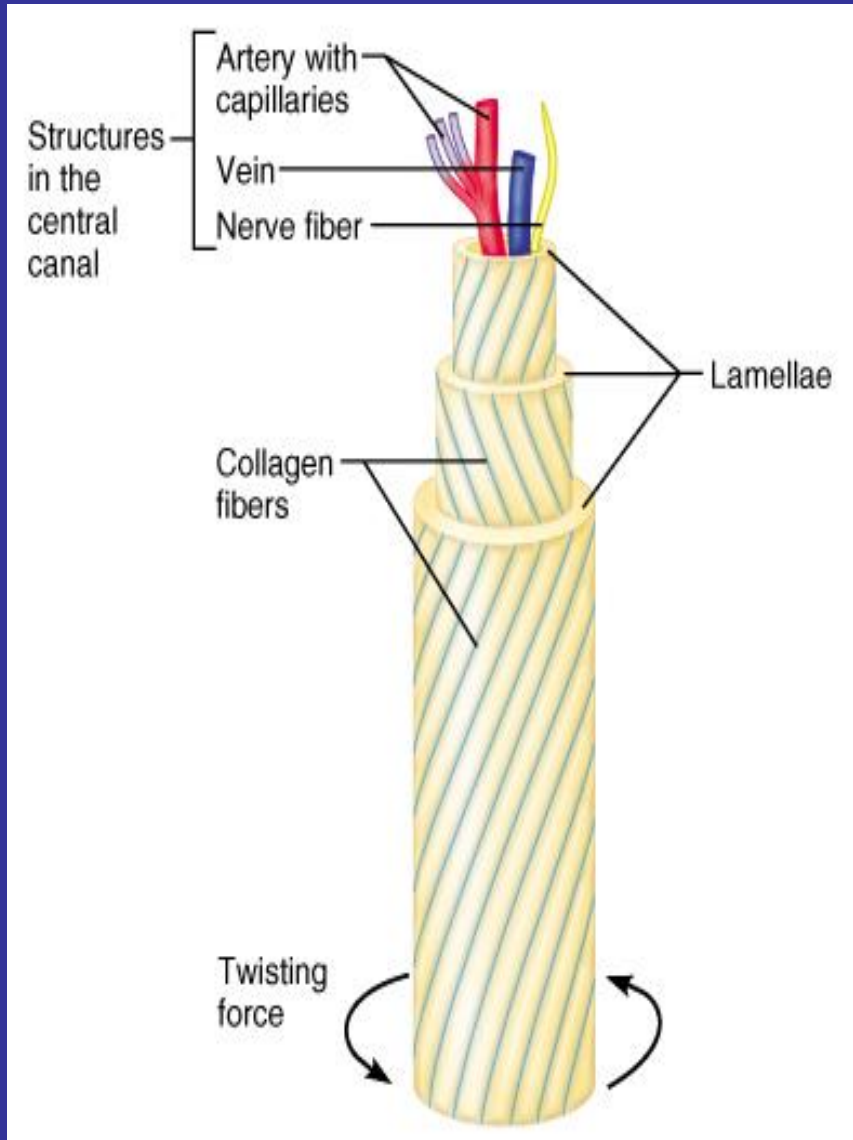
Bone Structure



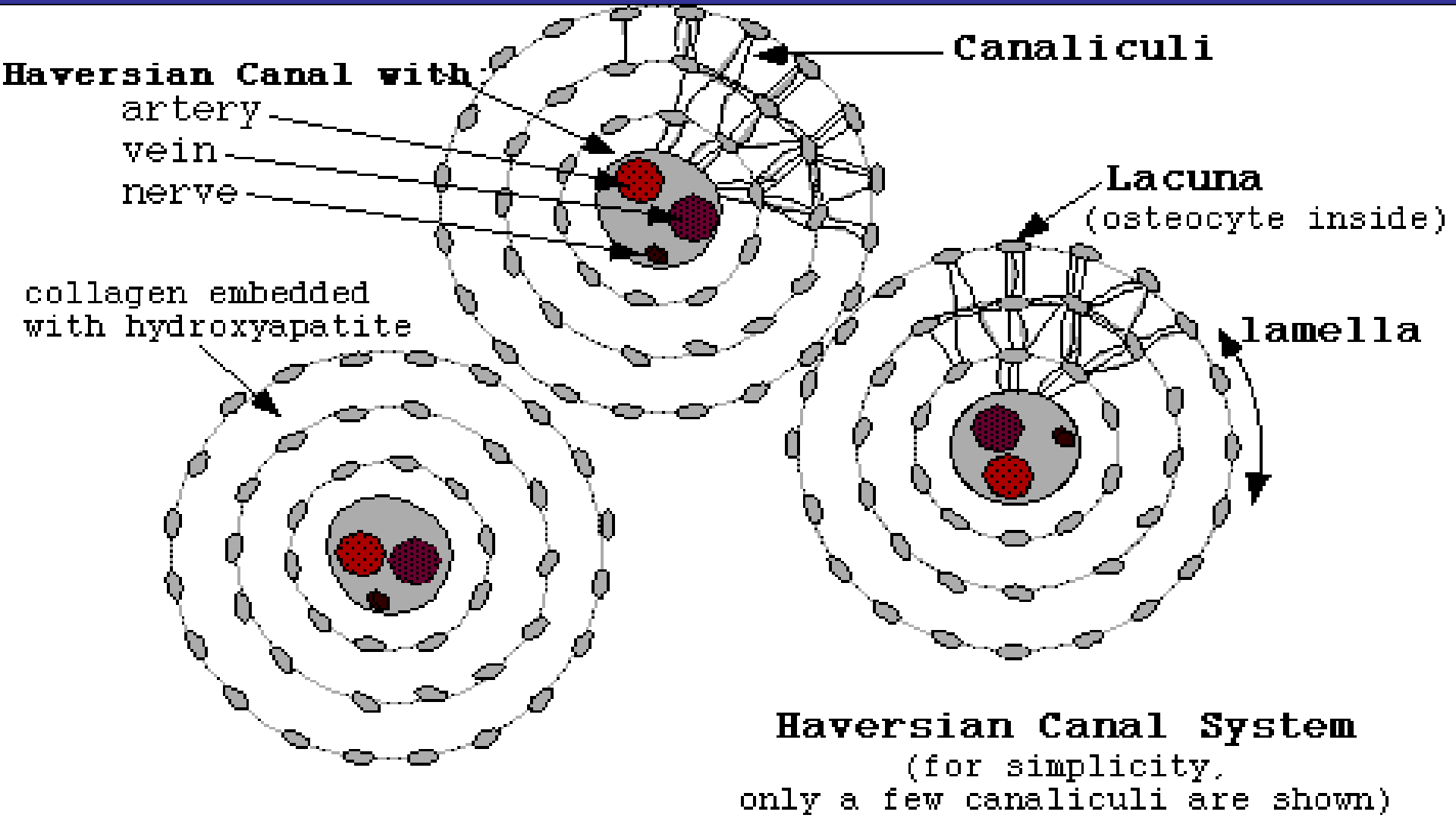
Microscopic Structure of Compact Bone

- Contains many cylinder-shaped structural units called *osteons*, or *Haversian systems*
- Four types of structures make up each osteon:

- Lamella—concentric, cylinder-shaped layers of calcified matrix
- Lacunae—small spaces containing tissue fluid in which bone cells are located between hard layers of the lamella

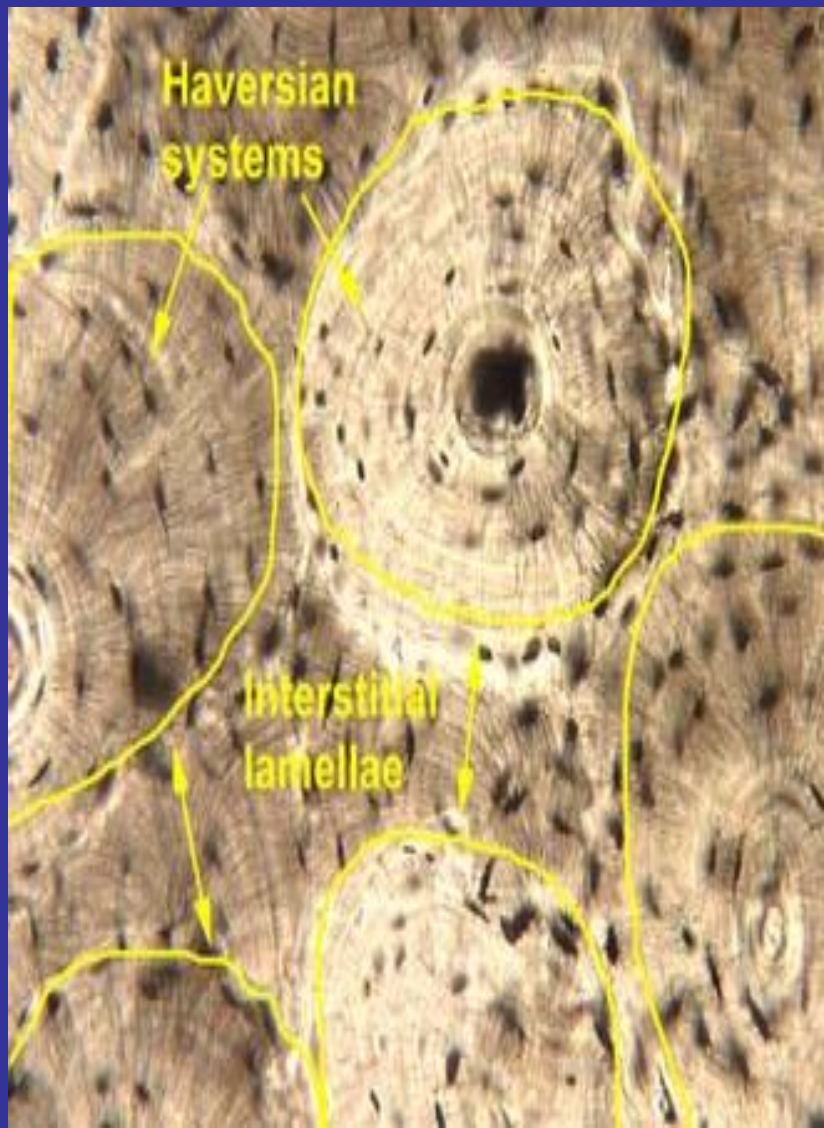


Microscopic Structure of Compact Bone



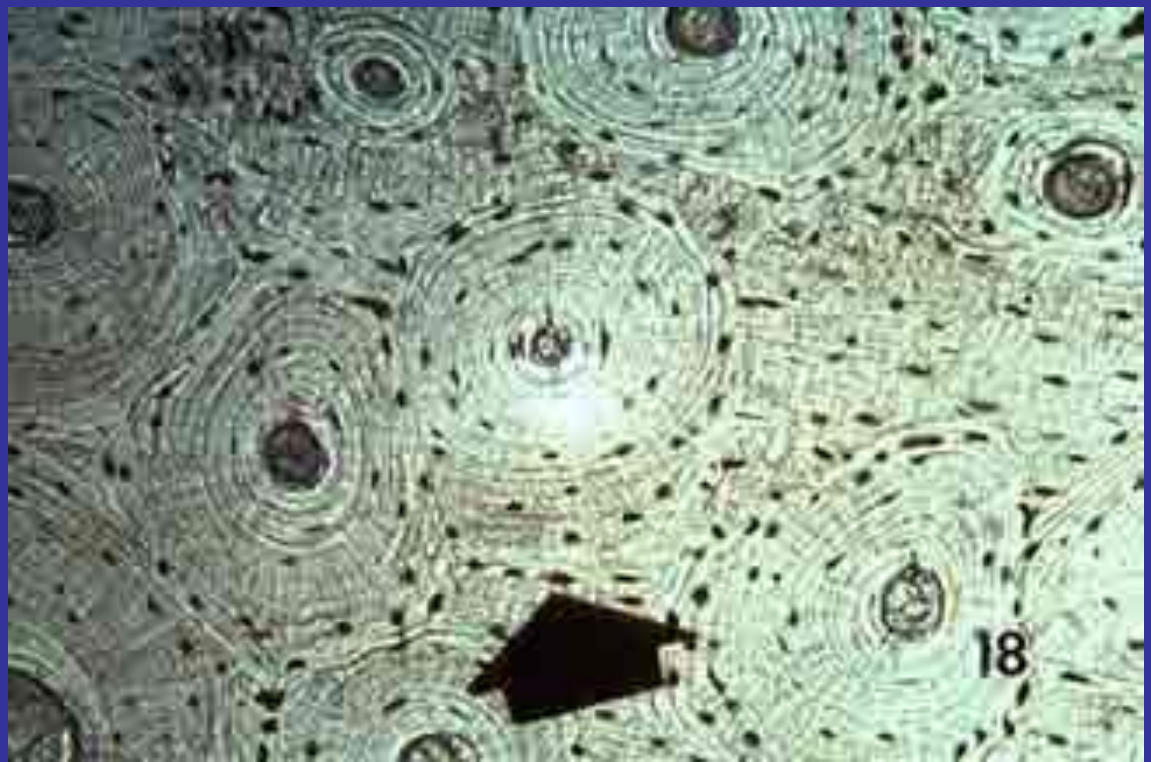
Microscopic Structure of Compact Bone

- Canaliculi—ultrasmall canals radiating in all directions from the lacunae and connecting them to each other and to the Haversian canal
- Haversian canal—extends lengthwise through the center of each osteon and contains blood vessels and lymphatic vessels

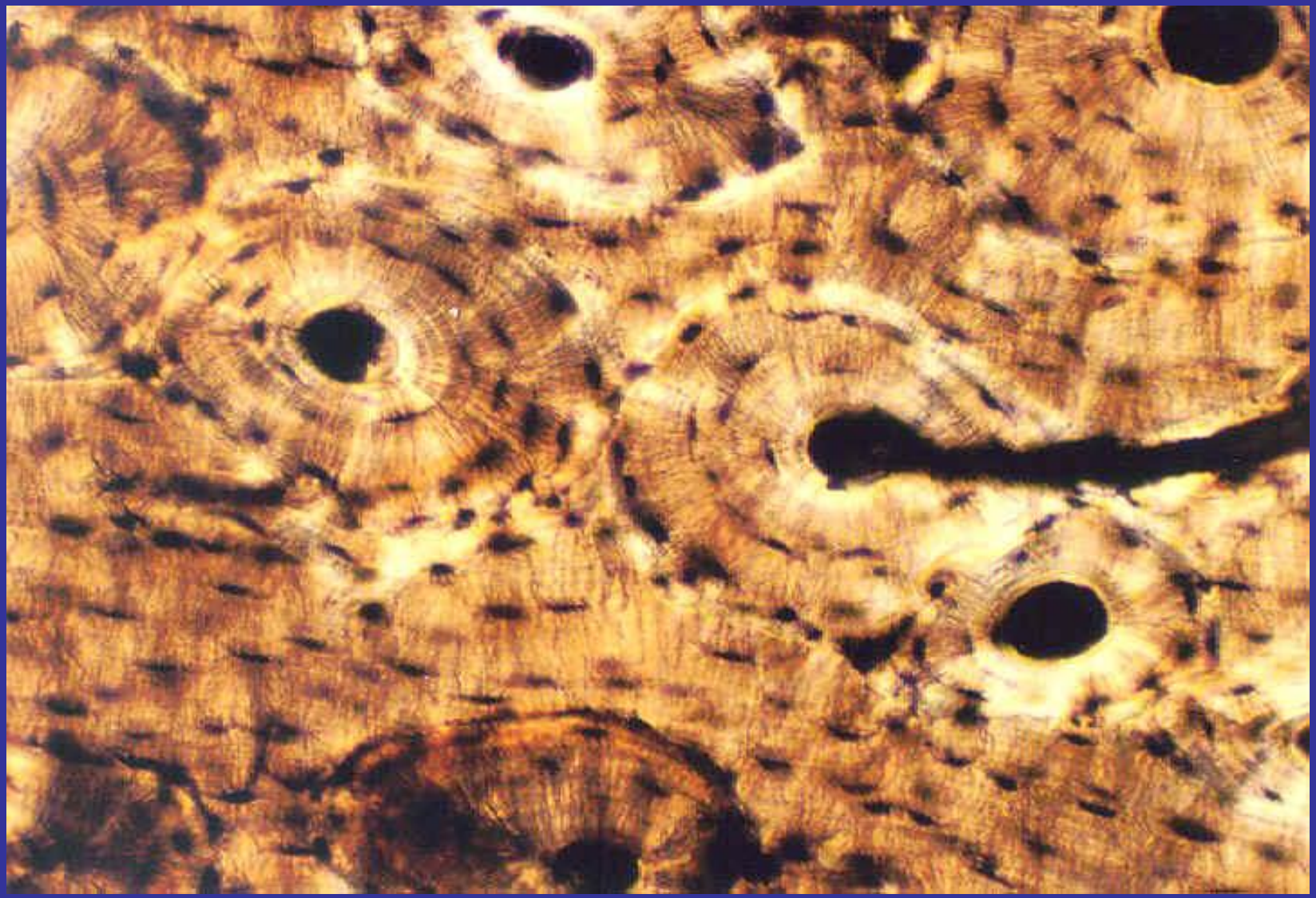


Haversian System

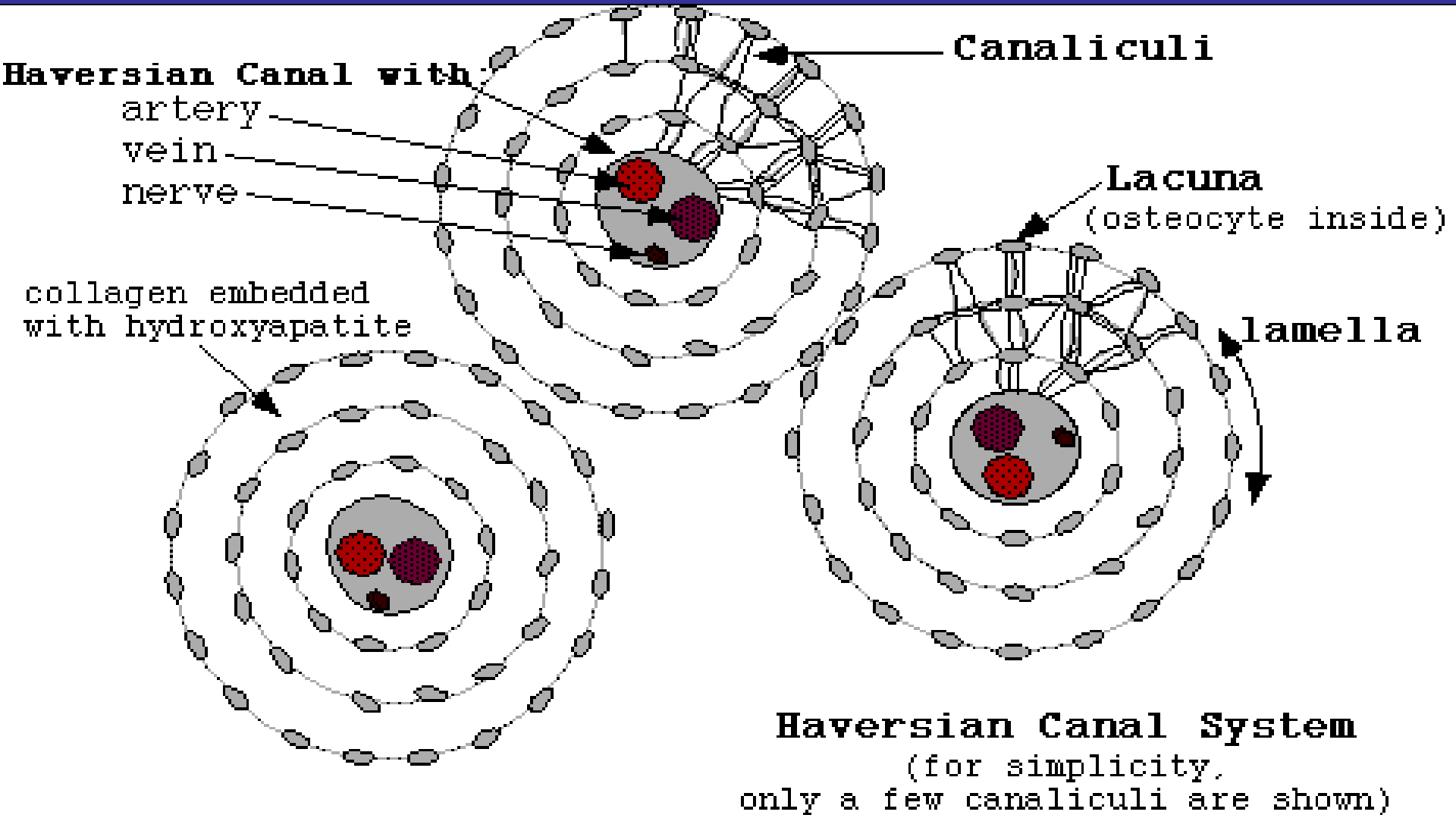
- Structure of compact bone
- Rings of bone tissue with blood vessels and nerves in the center



Haversian System



Microscopic Structure of Compact Bone



Bone Development

- Initial skeleton of cartilage in infants
- Replaced with bone by osteoblasts
- More than 300 bones at birth – fuse to 206
- Always growing and breaking down
  - ✓ Osteoblasts – form new bone cells
  - ✓ Osteoclasts – break bone cells down
  - ✓ Osteocytes – mature bone cells

Bones – reservoir of calcium

- 99% of skeletal calcium forms stable bone (not exchangeable with the Ca in extracellular fluid)
- 1% is in the form of releasable pool of Ca
- Balance of deposition and resorption
- **Osteoblasts** – bone-forming cells responsible for bone deposition
  - Secrete type I collagen
  - Differentiate into osteosytes
- **Osteoclasts –** “bone-eating” cells that resorb the previously formed bone

Regulation of osteoblasts function

- **Stimulation**
  - ✓ PTH (fast reaction - activation of calcium pump ? – pumping Ca to ECF)
  - ✓ 1,25 Dihydrocholecalciferol
  - ✓ IL-1
  - ✓ T3, T4
  - ✓ hGH, IGF-1 (insuline-like growth factor)
  - ✓ PGE_2 (prostaglandine)
  - ✓ TNF (tumor necrosis factor)
  - ✓ Estrogens ?
- **Inhibition**
  - ✓ Corticosteroids

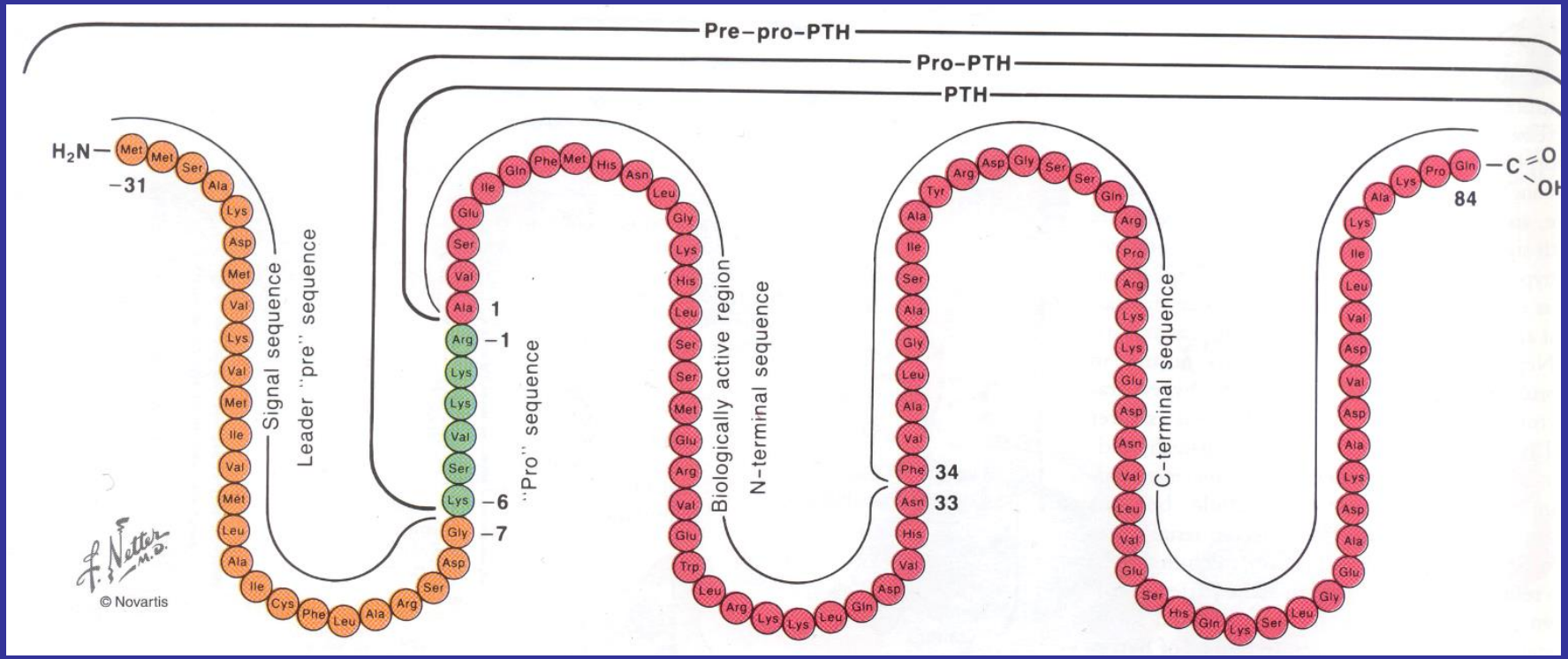
Regulation of osteoclasts function

- **Stimulation**
  - ✓PTH (not directly – through stimulation of osteoblasts)
  - ✓1,25 Dihydrocholecalciferol (not directly – through stimulation of osteoblasts)
  - ✓IL-6, IL-11
- **Inhibition**
  - ✓Calcitonin (directly – receptors)
  - ✓Estrogens (by inhibiting production of certain cytokines)
  - ✓TGF-β (tranforming growth factor)
  - ✓PGE_2(prostaglandine)

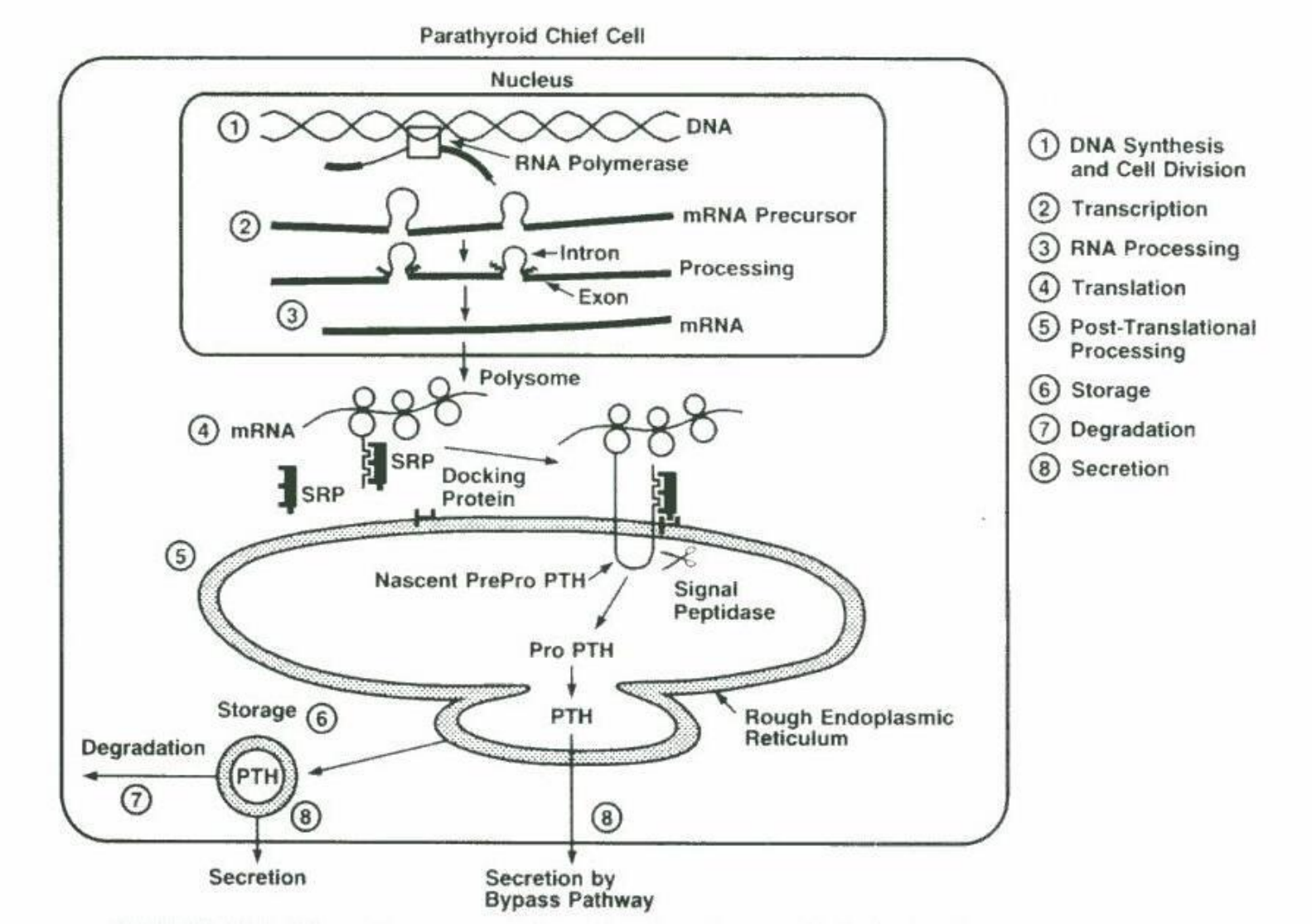
Parathyroid Hormone

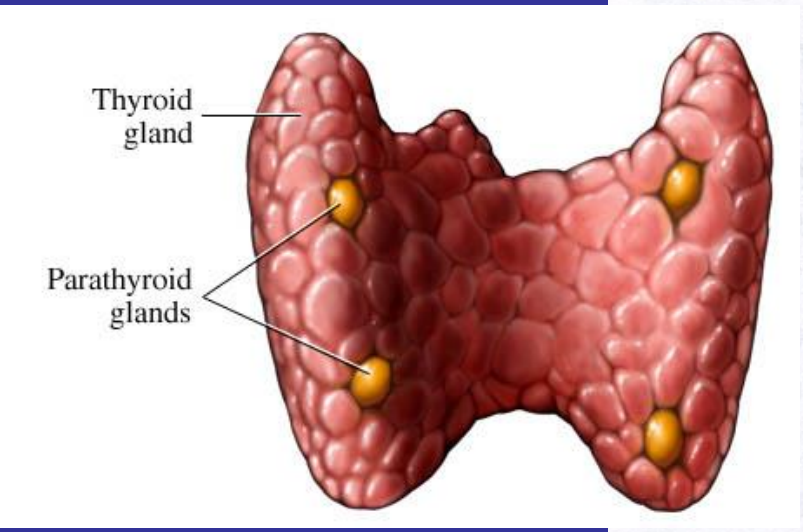
- Secreted by parathyroid glands
  - Rapid response to reduced calcium (minutes)
- Polypeptide
  - 84 amino acid residues
  - 9,500 daltons M.W.
- Peptide fragments can be active for periods measured in hours
- Operates in tissues via cAMP second messenger

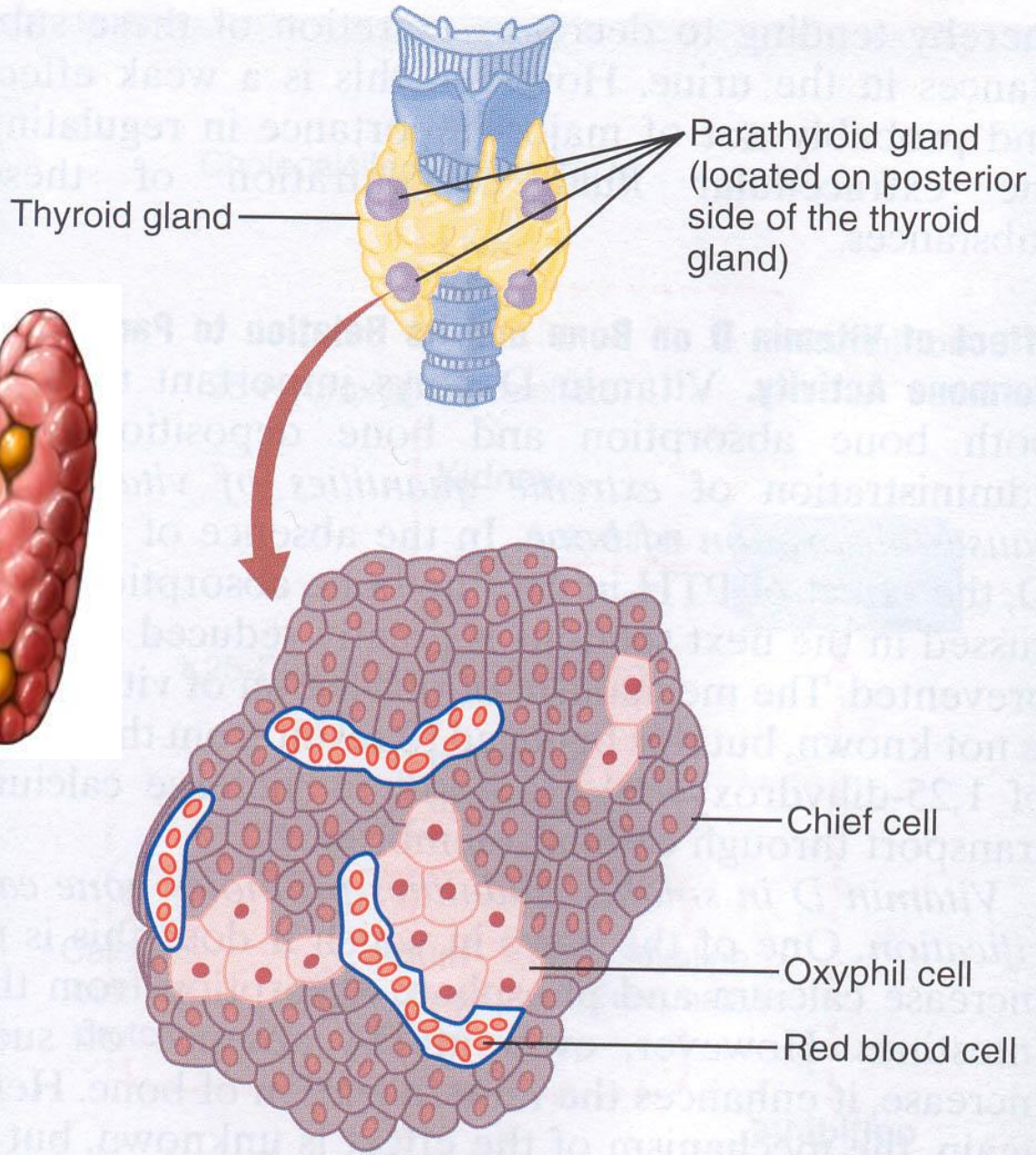
Parathyroid Hormone



Parathyroid Hormone Biosynthesis



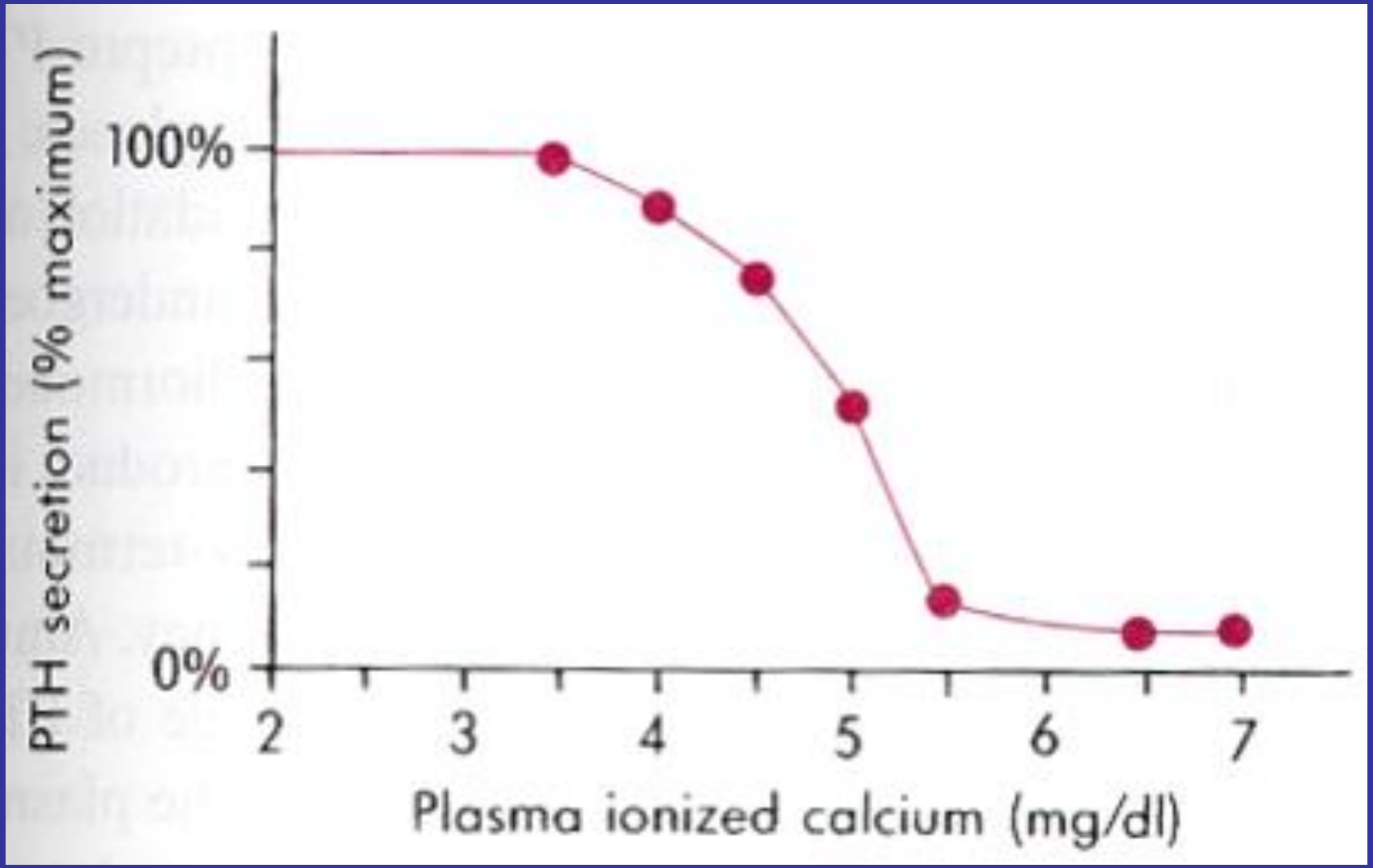

Thyroid gland
Parathyroid glands


Thyroid gland
Parathyroid gland (located on posterior side of the thyroid gland)
Chief cell
Oxyphil cell
Red blood cell

Regulation of PTH

- The dominant regulator of PTH is plasma Ca^{2+}
- Secretion of PTH is inversely related to [Ca^{2+}]
- Maximum secretion of PTH occurs at plasma Ca^{2+} below 3.5 mg/dL
- At Ca^{2+} above 5.5 mg/dL, PTH secretion is maximally inhibited.

Calcium regulates PTH

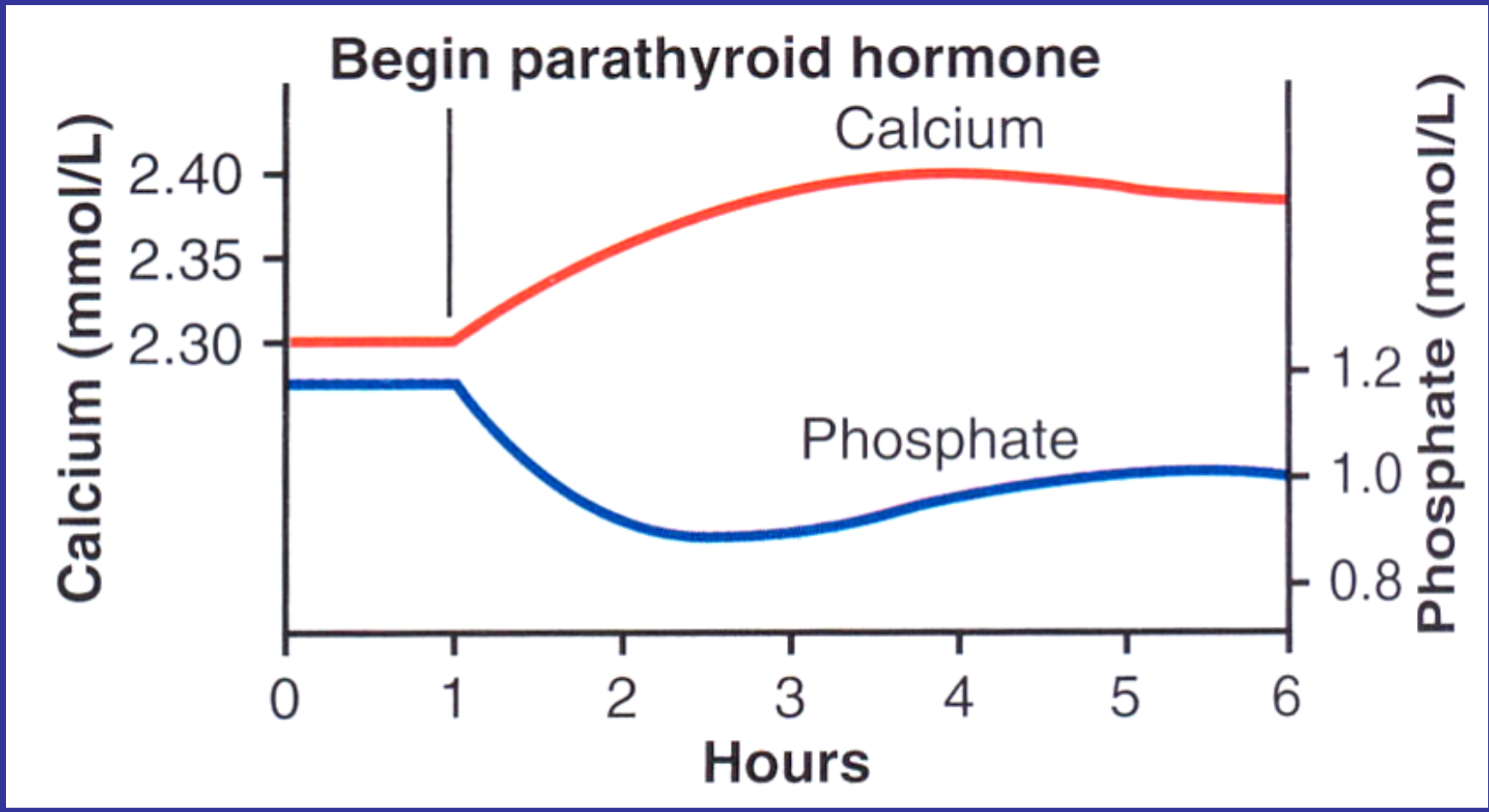


Regulation of PTH

- When Ca^{2+} falls, cAMP rises and PTH is secreted
- 1,25-$(OH)_2$-D inhibits PTH gene expression, providing another level of feedback control of PTH
- Despite close connection between Ca^{2+} and PO_4, no direct control of PTH is exerted by phosphate levels

Effects of PTH

- Increases calcium absorption from bone
  - ✓ Existing osteocytes stimulated (minutes to hours) to transport calcium – calcium pumps
  - ✓ Existing osteoclasts activated and new osteoclasts formed (days to weeks) to digest bone and release calcium
    - Stimulated indirectly by osteoblasts


Begin parathyroid hormone
Calcium
Phosphate
Calcium (mmol/L)
2.40
2.35
2.30
1.2
1.0
0.8
Phosphate (mmol/L)
0
1
2
3
4
5
6
Hours

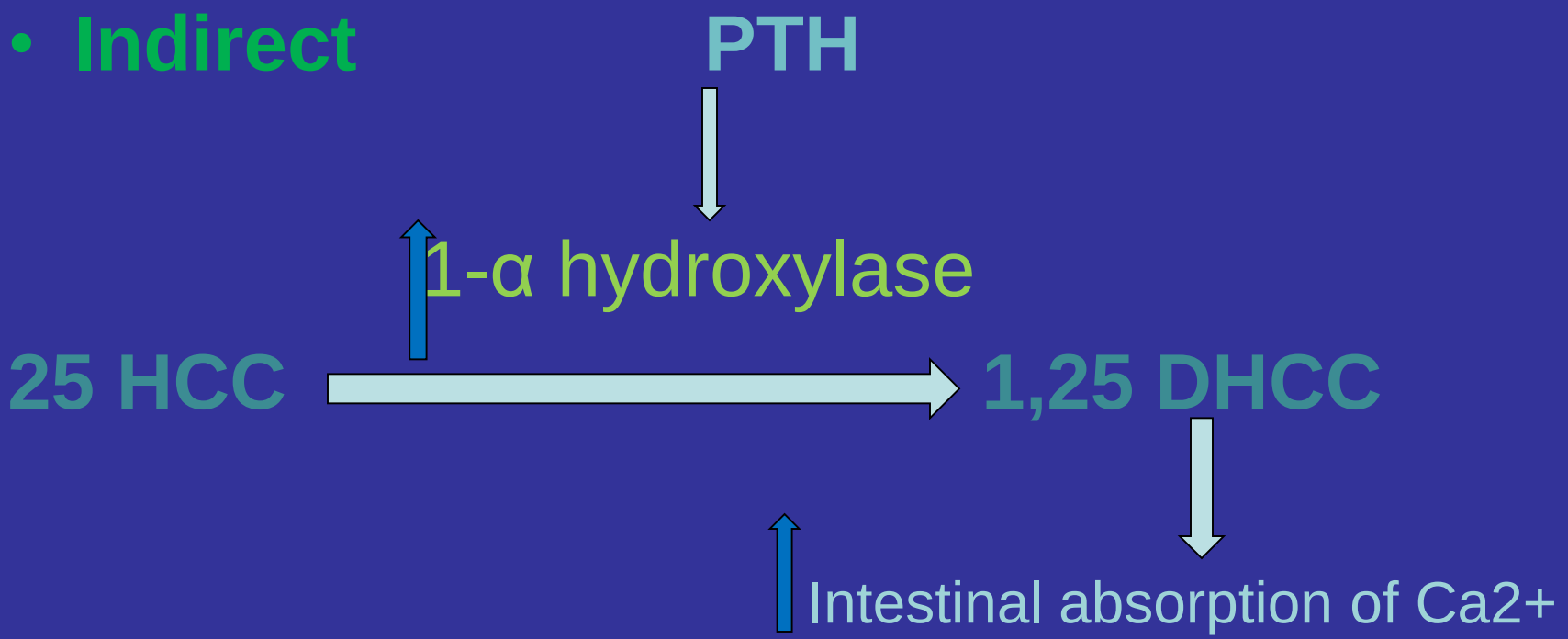
PTH actions (Kidney)

- **Direct**

  - ✓ PTH increases resorption of Ca^{2+} in the distal tubules
  - ✓ PTH increases PO_4 3- and HCO_3- excretion in the urine

PTH actions (Kidney)

- **Indirect**



Actions of PTH: Kidney

- PTH acts on the kidney to increase the reabsorption of calcium (decreased excretion) Also get increased excretion of phosphate (other component of bone mineralization), and decreased excretion of hydrogen ions (more acidic environment favors dimineralization of bone)
- ALSO, get increased production of the active metabolite of vitamin D3 (required for calcium absorption from the small intestine, bone demineralization).

- NET RESULT: increased plasma calcium levels

PTH actions (Bone)

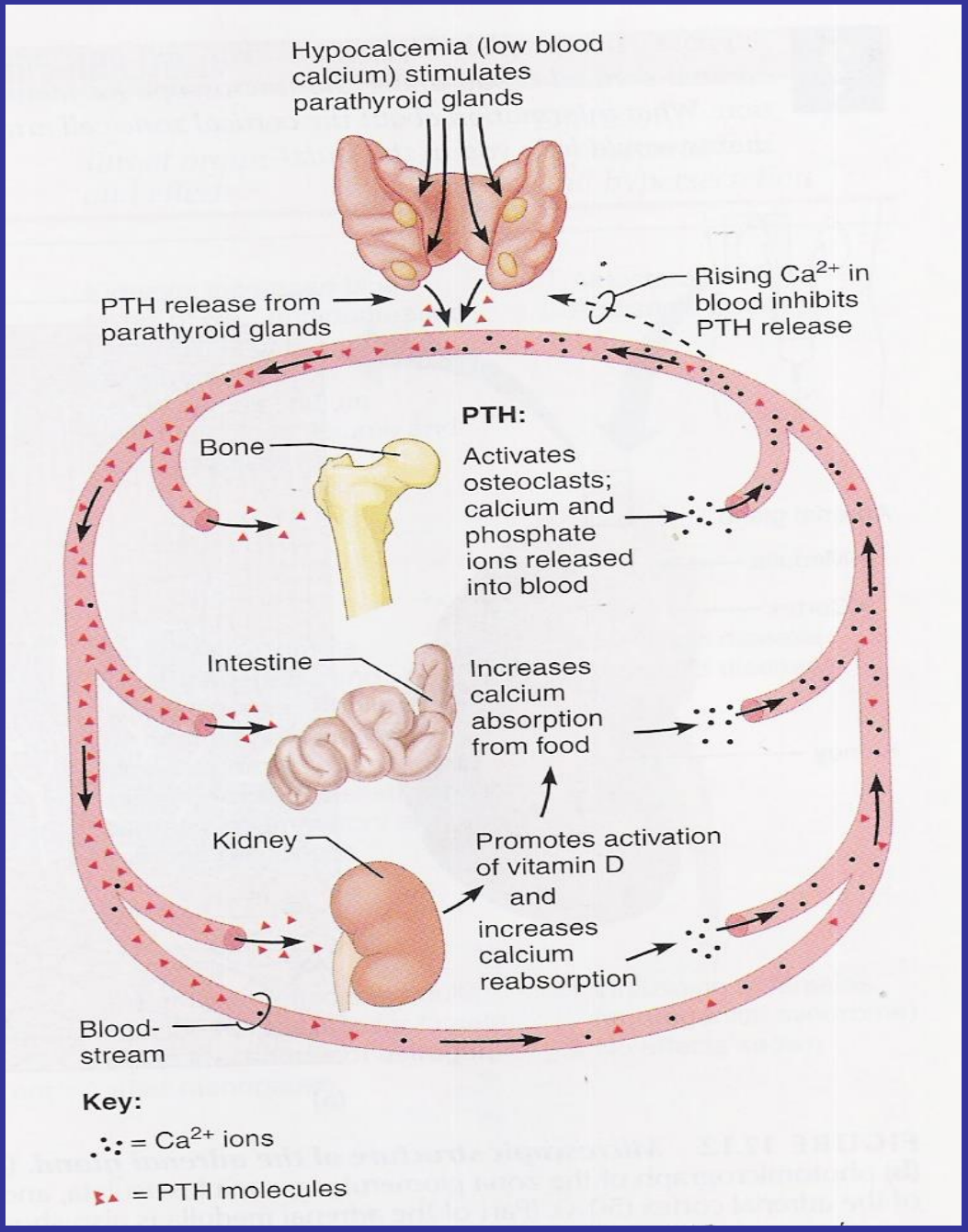
- PTH acts on osteoblasts to inhibit the synthesis of collagen (inhibition of bone formation)
- PTH acts on osteoblasts to stimulate secretion of cytokines, which acts on the osteoclasts to promote demineralization and Ca2+ release (osteoclastic bone resorption)
- PTH also activates Ca^{2+} pumps within the surface osteoblasts to move Ca^{2+} out of bone fluid and into the extracellular fluid (ECF)

Actions of PTH: Bone

- PTH acts to increase degradation of bone (release of calcium).
  - ✓ Causes osteoblasts to release cytokines, which stimulate osteoclast activity
  - ✓ Stimulates bone stem cells to develop into osteoclasts
  - ✓ Net result: increased release of calcium from bone
  - ✓ Effects on bone are dependent upon presence of vitamin D

PTH action

- The overall action of PTH is to increase plasma Ca^{2+} levels and decrease plasma phosphate levels
- PTH acts directly on the bones to stimulate Ca^{2+} resorption and kidney to stimulate Ca^{2+} reabsorption in the distal tubule of the kidney and to inhibit reabosorptioin of phosphate (thereby stimulating its excretion)
- PTH also acts indirectly on intestine by stimulating 1,25-$(OH)_2$-D synthesis

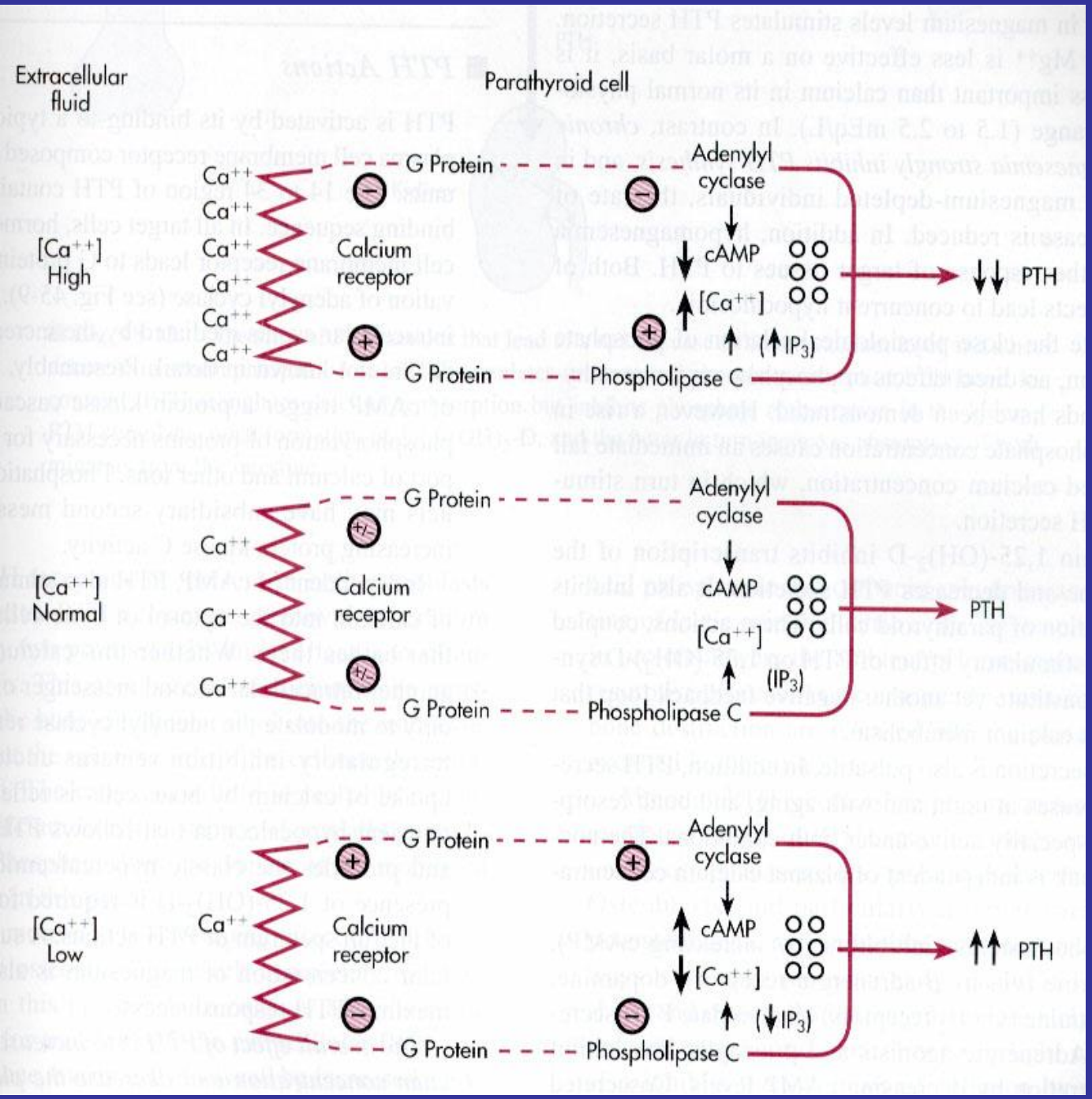

Hypocalcemia (low blood calcium) stimulates parathyroid glands
PTH release from parathyroid glands
Rising Ca^{2+} in blood inhibits PTH release
PTH:
Bone
Activates osteoclasts; calcium and phosphate ions released into blood
Intestine
Increases calcium absorption from food
Kidney
Promotes activation of vitamin D and increases calcium reabsorption
Blood-stream
Key:
= Ca^{2+} ions
= PTH molecules

Mechanism of Action of PTH

- PTH binds to a G protein-coupled receptor
- Binding of PTH to its receptor activates 2 signaling pathways:
  - ✓ increased cyclic AMP
  - ✓ increased phospholipase C
- Activation of PKA appears to be sufficient to decrease bone mineralization
- Both PKA and PKC activity appear to be required for increased resorption of calcium by the kidneys

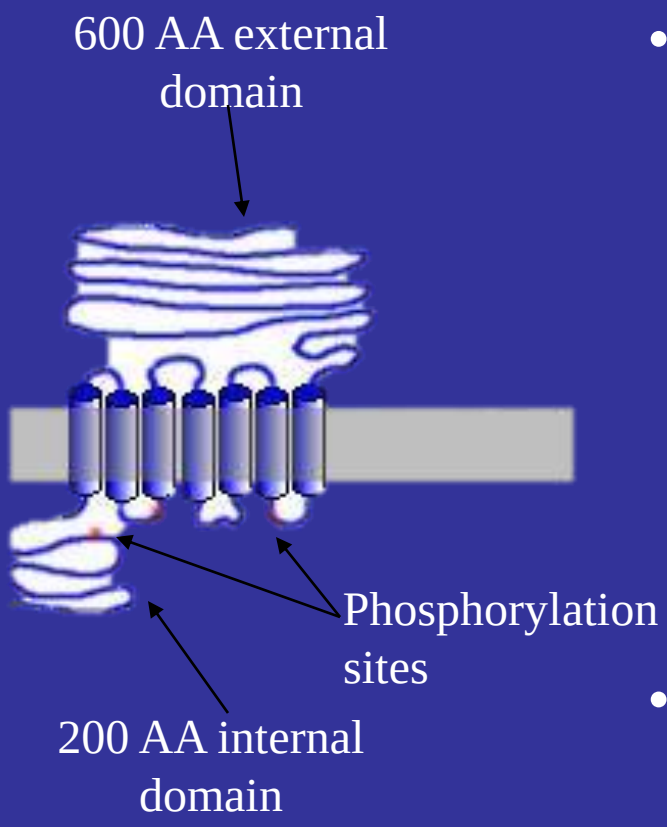
Regulation of PTH Secretion

- PTH is released in response to changes in plasma calcium levels.
  - ✓ Low calcium results in high PTH release
  - ✓ High calcium results in low PTH release
- PTH cells contain a receptor for calcium, coupled to a G protein.
- Result of calcium binding: increased phospholipase C, decreased cyclic AMP
- Low calcium results in higher cAMP, PTH release
- Also, vitamin D inhibits PTH release (negative feedback).



Calcium regulates PTH secretion

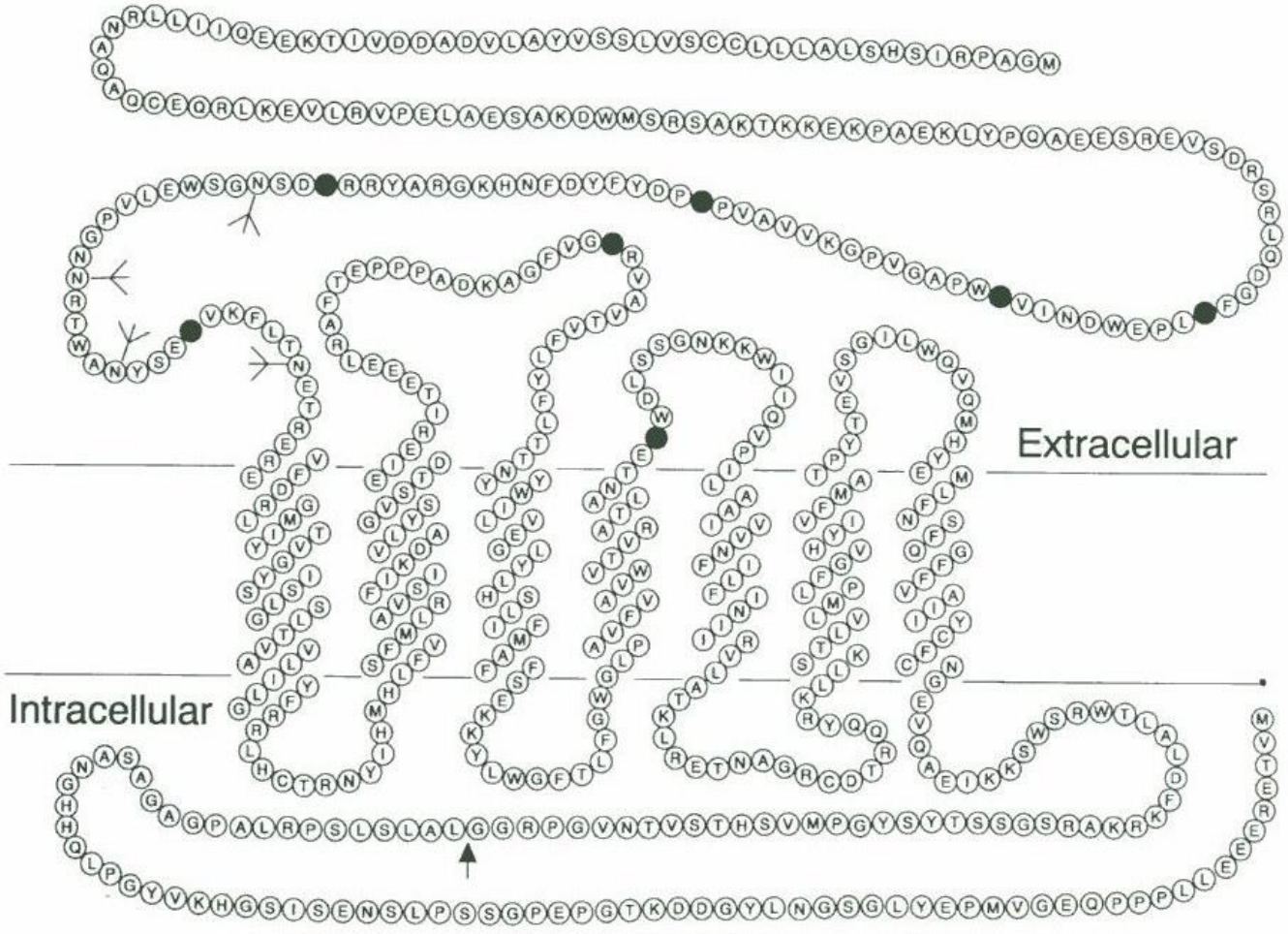
Calcium Signal Transduction in Parathyroid Gland



- G-Protein Coupled Receptor
- Activates Phospholipase C
  - Leads to increased Diacylglycerol (DG) and Inositol trisphosphate (IP3) as secondary messengers
  - Inhibits adenylate cyclase to reduce cAMP
- Present in C cells of Thyroid Gland
  - Regulates calcitonin secretion

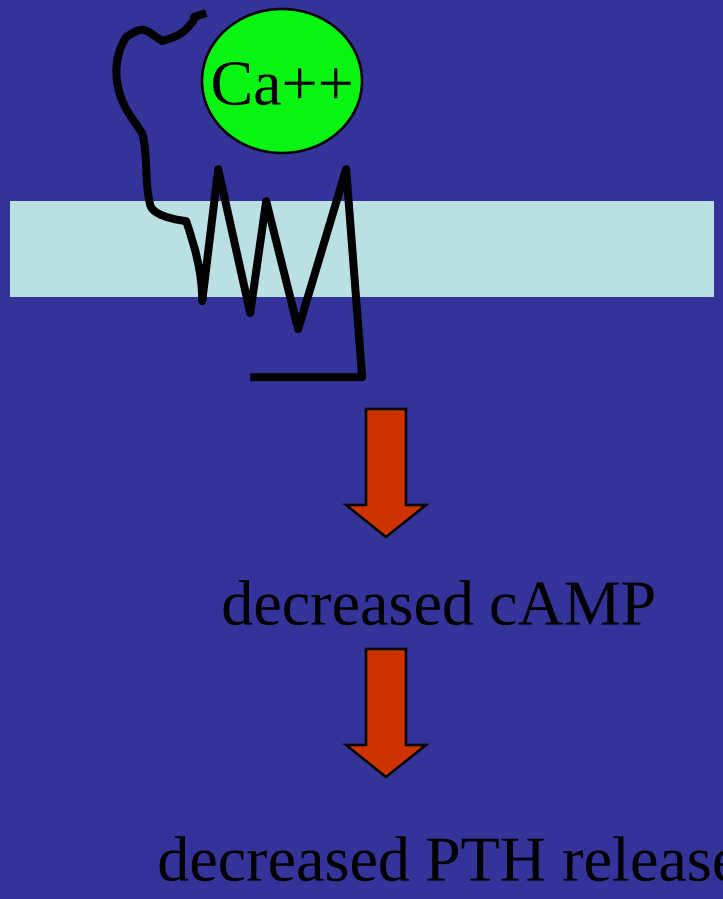
Parathyroid Hormone Receptor

- 7 TM
- GPCR

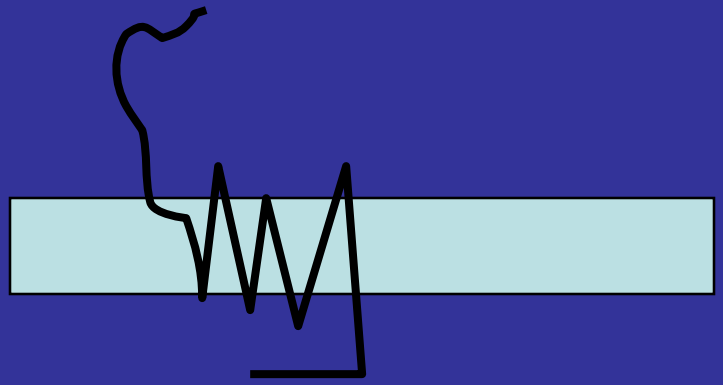


Schematic representation of the PTH/PTHrP receptor (NH_2 terminus at top) from kidney cells, potential N-glycosylation sites (⅄), and cysteine residues that are conserved in the calcitonin receptor (●). In OK-H, residues 508 to 515 (to the left of the arrow) are WPCSALD. The peptide ends eight residues after the arrow.

Calcium Receptor, cAMP, and PTH Release



Calcium Receptor, cAMP, and PTH Release



increased cAMP

increased PTH release

PTH-Related Peptide

- Has high degree of homology to PTH, but is not from the same gene.
- Can activate the PTH receptor.
- In certain cancer patients with high PTH-related peptide levels, this peptide causes hypercalcemia.
- But, its normal physiological role is not clear.
  - ✓ mammary gland development/lactation?
  - ✓ kidney glomerular function?
  - ✓growth and development?

PTHrP

- Three forms of PTHrP identified, all about twice the size of native PTH
- Marked structural homology with PTH
- PTHrP and PTH bind to the same receptor
- PTHrP reproduce full spectrum of PTH activities

Vitamin D

- Vitamin D, after its activation to the hormone 1,25-dihydroxy Vitamin D3 is a principal regulator of Ca^{2+}
- Vitamin D increases Ca^{2+} absorption from the intestine and Ca^{2+} resorption from the bone

Synthesis of Vitamin D

- Humans acquire vitamin D from two sources
- Vitamin D is produced in the skin by ultraviolet radiation and ingested in the diet
- Vitamin D is not a classic hormone because it is not produce and secreted by an endocrine “gland.” Nor is it a true “vitamin” since it can be synthesized *de novo*
- Vitamin D is a true hormone that acts on distant target cells to evoke responses after binding to high affinity receptors

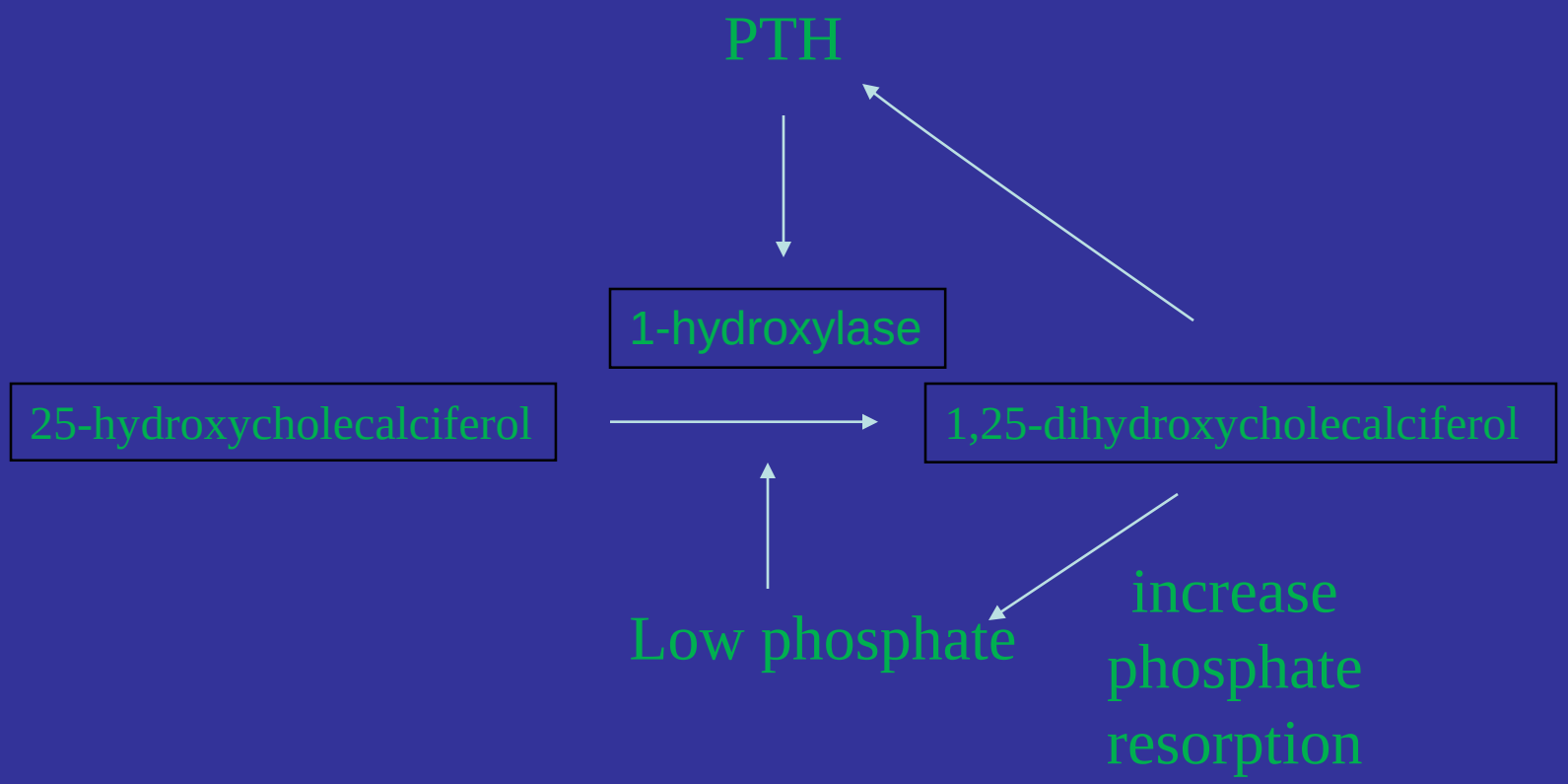
Synthesis of Vitamin D

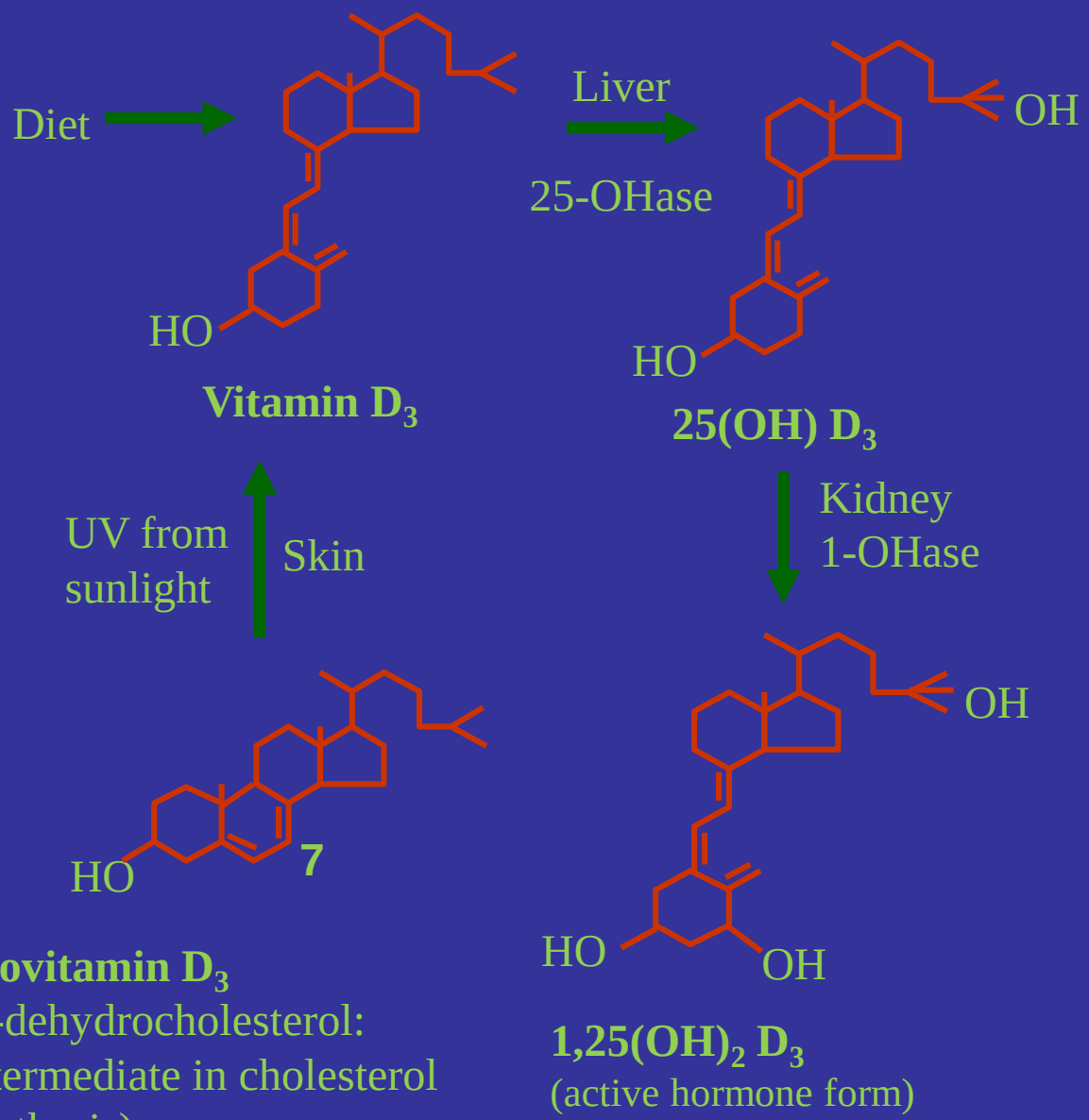
- Vitamin D3 synthesis occurs in keratinocytes in the skin
- 7-dehydrocholesterol is photoconverted to previtamin D3, then spontaneously converts to vitamin D3
- Previtamin D3 will become degraded by over exposure to UV light and thus is not overproduced
- Also 1,25-dihydroxy-D (the end product of vitamin D synthesis) feeds back to inhibit its production

Synthesis of Vitamin D

- PTH stimulates vitamin D synthesis. In the winter or if exposure to sunlight is limited (indoor jobs!), then dietary vitamin D is essential
- Vitamin D itself is inactive, it requires modification to the active metabolite, 1,25-dihydroxy-D
- The first hydroxylation reaction takes place in the liver yielding 25-hydroxy D
- Then 25-hydroxy D is transported to the kidney where the second hydroxylation reaction takes place

Regulation of Vitamin D by PTH and Phosphate Levels





OHase = hydroxylase

Specific receptors in intestine, bone, kidney

Ca:
Intestinal absorption
Renal reabsorption

PO_4:
Intestinal absorption
Renal reabsorption

Photobiosynthesis of vitamin D_3 and its metabolism

Vitamin D

- Vitamin D is a lipid soluble hormone that binds to a typical nuclear receptor, analogous to steroid hormones
- Because it is lipid soluble, it travels in the blood bound to hydroxylated α-globulin
- There are many target genes for Vitamin D

Vitamin D action

- The main action of 1,25-$(OH)_2$-D is to stimulate absorption of Ca^{2+} from the intestine
- 1,25-$(OH)_2$-D induces the production of calcium binding proteins which sequester Ca^{2+} , buffer high Ca^{2+} concentrations that arise during initial absorption and allow Ca^{2+} to be absorbed against a high Ca^{2+} gradient

Vitamin D promotes intestinal calcium absorption

- Vitamin D acts via steroid hormone like receptor to increase transcriptional and translational activity
- One gene product is calcium-binding protein (CaBP)
- CaBP facilitates calcium uptake by intestinal cells

Vitamin D Actions on Bones

- Another important target for 1,25-$(OH)_2$-D is the bone
- Osteoblasts, but not osteoclasts have vitamin D receptors
- 1,25-$(OH)_2$-D acts on osteoblasts which produce a paracrine signal that activates osteoclasts to resorb Ca^{2+} from the bone matrix.
- 1,25-$(OH)_2$-D also stimulates osteocytic osteolysis.

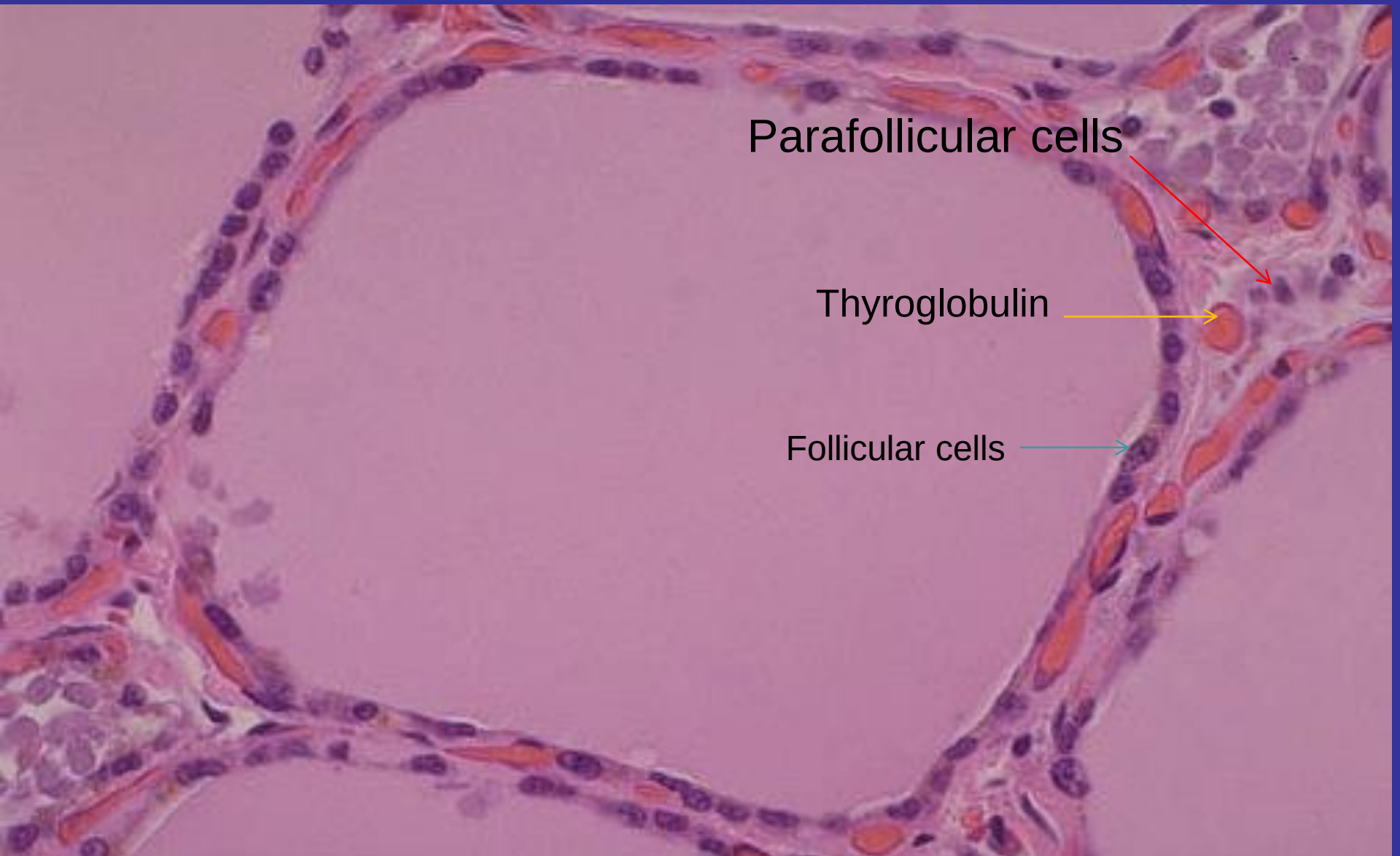
Vitamin D and Bones

- Proper bone formation is stimulated by 1,25-$(OH)_2$-D
- In its absence, excess osteoid accumulates from lack of 1,25-$(OH)_2$-D repression of osteoblastic collagen synthesis
- Inadequate supply of vitamin D results in **rickets**, a disease of bone deformation

Calcitonin

- Calcitonin acts to decrease plasma Ca^{2+} levels
- Calcitonin is synthesized and secreted by the parafollicular cells of the thyroid gland
- They are distinct from thyroid follicular cells by their large size, pale cytoplasm, and small secretory granules

Parafollicular cells



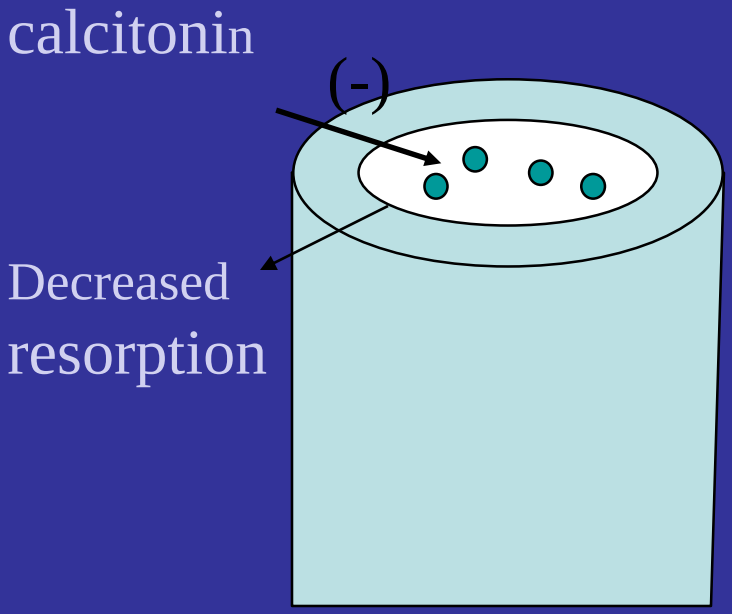
Calcitonin

- The major stimulus of calcitonin secretion is a rise in plasma Ca^{2+} levels

- Calcitonin is a physiological antagonist to PTH with regard to Ca^{2+} homeostasis

Actions of Calcitonin

- The major action of calcitonin is on bone metabolism
- Calcitonin inhibits activity of osteoclasts, resulting in decreased bone resorption (and decreased plasma Ca^{2+} a levels)



osteoclasts: destroy bone to release Ca

Calcitonin

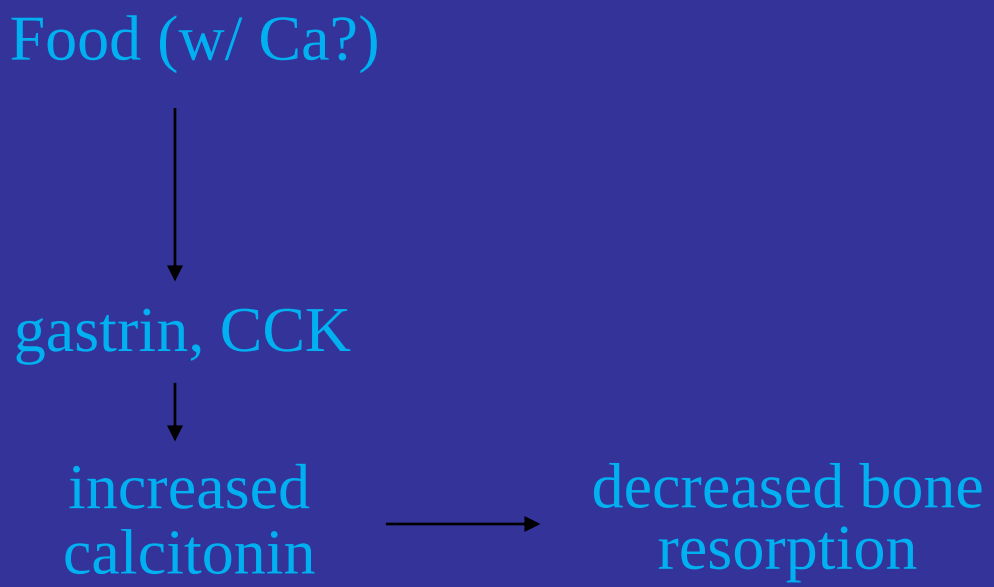
- The target cell for calcitonin is the osteoclast
- Calcitonin acts via increased cAMP concentrations to inhibit osteoclast motility and cell shape and inactivates them
- The major effect of calcitonin administration is a rapid fall in Ca^{2+} caused by inhibition of bone resorption

Calcitonin

- Role of calcitonin in normal Ca^{2+} control is not understood—may be more important in control of bone remodeling
- Used clinically in treatment of hypercalcelmia and in certain bone diseases in which sustained reduction of osteoclastic resorption is therapeutically advantageous.
- Chronic excess of calcitonin does not produce hypocalcemia and removal of parafollicular cells does not cause hypercalcemia. PTH and Vitamin D3 regulation dominate
- May be more important in regulating bone remodeling than in Ca^{2+} homeostasis.

Regulation of Calcitonin Release

- Calcitonin release is stimulated by increased circulating plasma calcium levels
- Calcitonin release is also caused by the gastrointestinal hormones gastrin and cholecystokinin (CCK), whose levels increase during digestion of food.



What is the Role of Calcitonin in Humans?

- Removal of the thyroid gland has no effect on plasma Ca levels!
- Excessive calcitonin release does not affect bone metabolism!
- Other mechanisms are more important in regulating calcium metabolism (*i.e.*, PTH and vitamin D)

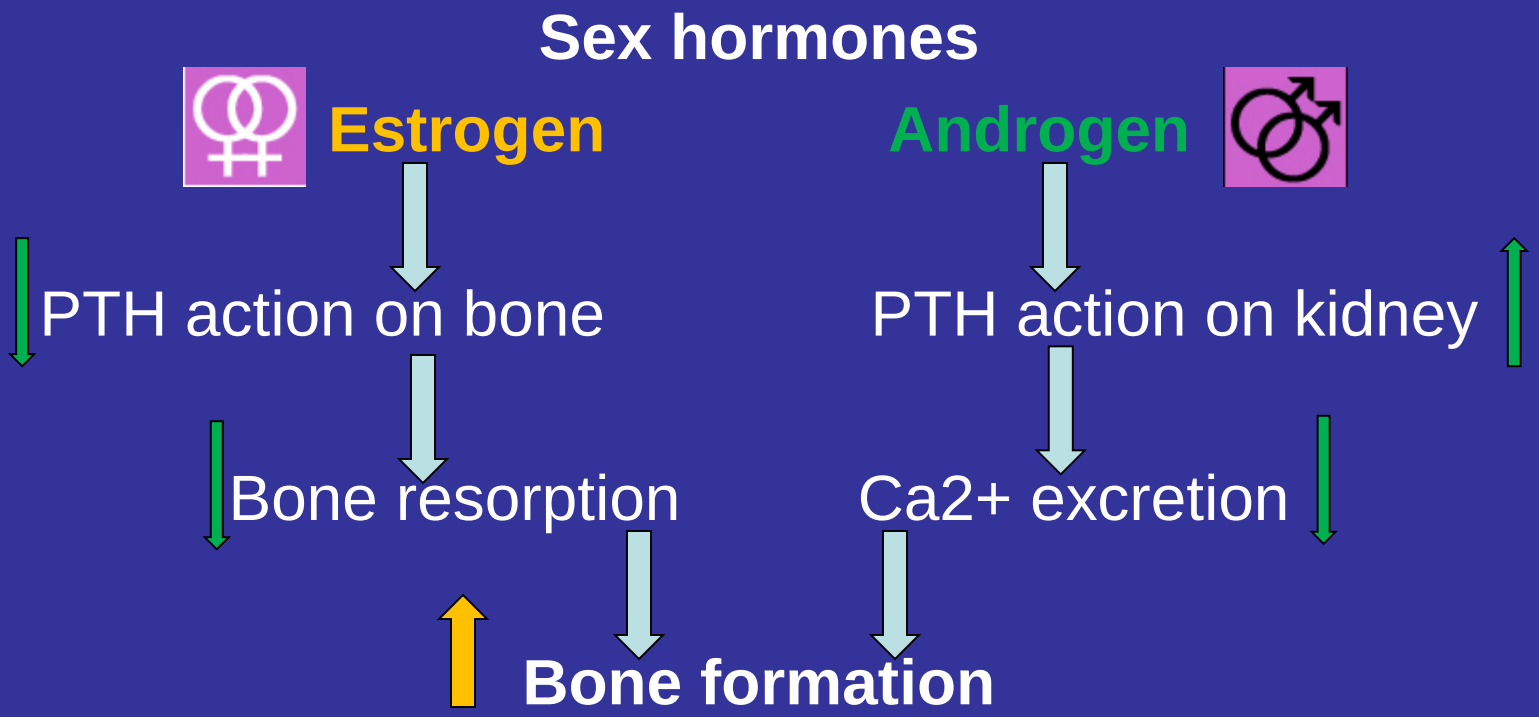
Calcitonin Gene-Related Peptide (CGRP)

- The calcitonin gene produces several products due to alternative splicing of the RNA.
- CGRP is an alternative product of the calcitonin gene.
- CGRP does NOT bind to the calcitonin receptor.
- CGRP is expressed in thyroid, heart, lungs, GI tract, and nervous tissue.
- It is believed to function as a neurotransmitter, not as a regulator of Ca.

Other Hormones

- **GH, IGFs**
  - ✓Activate chondrocytes
  - ✓ intestinal Ca2+absorption
  - ✓renal PO4 3 – reabsorption
- **Thyroid hormone**
  - ✓Physiological level: Increase bone formation
  - ✓Excess : Increase bone resorption by decrease1,25 DHCC and increase renal Ca2+excretion

Sex hormones



Glucocorticoids

- **Osteoporosis**
  - ✓ ⇩ GI Ca2+absorption.
  - ✓ ⇧ Renal Ca2+excretion
  - ✓ ⇧ PTH

Hypoparathyroidism

- Hypocalcemia occurs when there is inadequate response of the Vitamin D-PTH axis to hypocalcemic stimuli
- Hypocalcemia is often multifactorial
- Hypocalcemia is invariably associated with hypoparathyroidism
- Bihormonal—concomitant decrease in 1,25-(OH)2-D

Hypoparathyroidism

- PTH-deficient hypoparathyroidism
  - ✓ Reduced or absent synthesis of PTH
  - ✓ Often due to inadvertent removal of excessive parathyroid tissue during thyroid or parathyroid surgery
- PTH-ineffective hypoparathyroidism
  - ✓ Synthesis of biologically inactive PTH

Pseudohypoparathyroidism

- PTH-resistant hypoparathyroidism
  - ✓ Due to defect in PTH receptor-adenylate cyclase complex
- Mutation in Gαs subunit
- Patients are also resistant to TSH, glucagon and gonadotropins

Pseudohypoparathyroidism

- Symptoms and signs
  - ✓Hypocalcaemia
  - ✓Hyperphosphatemia
  - ✓Characteristic physical appearance: short stature, round face, short thick neck, obesity, shortening of the metacarpals
  - ✓Autosomal dominant

Primary Hyperparathyroidism

- Etiology
  - ✓Solitary Adenoma (80-85%)
  - ✓Double Adenomas (2-4%)
  - ✓Muliple Gland Hyperplasia (10-30%)
  - ✓Parathyroid Carcinoma (0.5%)
  - ✓MEN syndromes (10% of MGH have MEN 1)
- Diagnosis
  - ✓Signs & Symptoms
  - ✓Elevated serum calcium
  - ✓Elevated PTH

Homeostatic Imbalances

Rickets

- Disease of children due to a lack of vitamin D
- Calcium is not deposited in bones
- Bones become soft
- Bowing of the bones, and other deformities occur

Homeostatic Imbalances

Osteomalacia

- “Rickets” of adults
- Due to a lack of vitamin D
- Calcium is not deposited in the bones
- Bones become brittle

Homeostatic Imbalances

Osteoporosis

Bone reabsorption is greater than bone deposition

Due to any of the following

- ✓ Lack of estrogen in women.
- ✓ Lack of exercise to stress the bones
- ✓ Inadequate intake of calcium and phosphorus
- ✓ Abnormalities of vitamin D metabolism.
- ✓ Loss of muscle mass

Age Related Dysfunctions

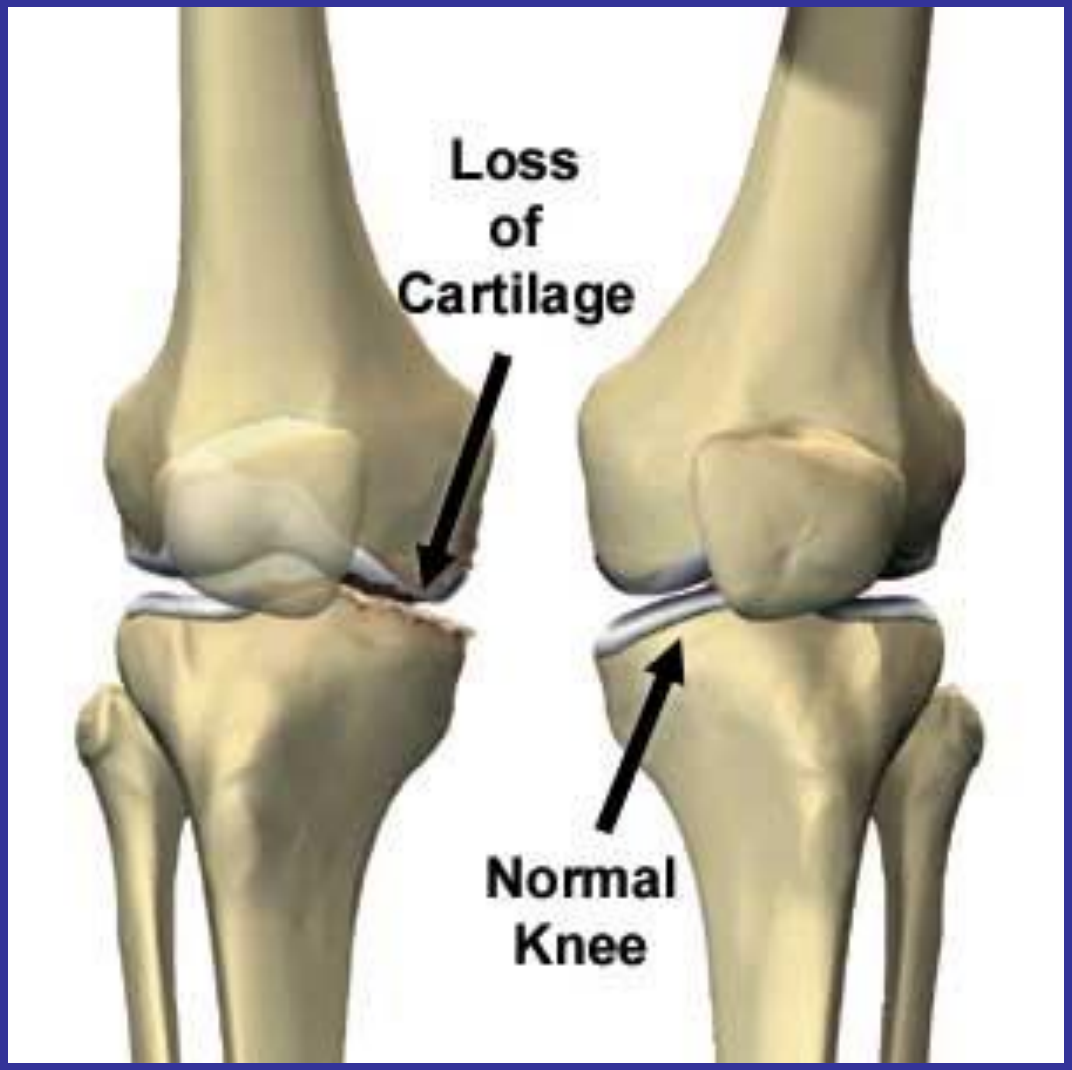
Arthritis

Osteoarthritis - 90% of pop. By age 40

Chronic inflammation of articular cartilage

- ✓ Can be normal age-dependent change
- ✓ Can also be pathology due to ?
- ✓ Age-related changes
- ✓ Decrease blood supply
- ✓ Trauma

Osteoarthritis



Osteoporosis

Decline in Bone Density

Bone Resorption > Bone Deposition

Increase Risk for Fracture

compression fractures of vertebrae hip fractures

Role of calcium, vitamin D, estrogen, exercise

Calcitonin vs. Parathyroid Hormone

Osteoporosis