The endocrine system

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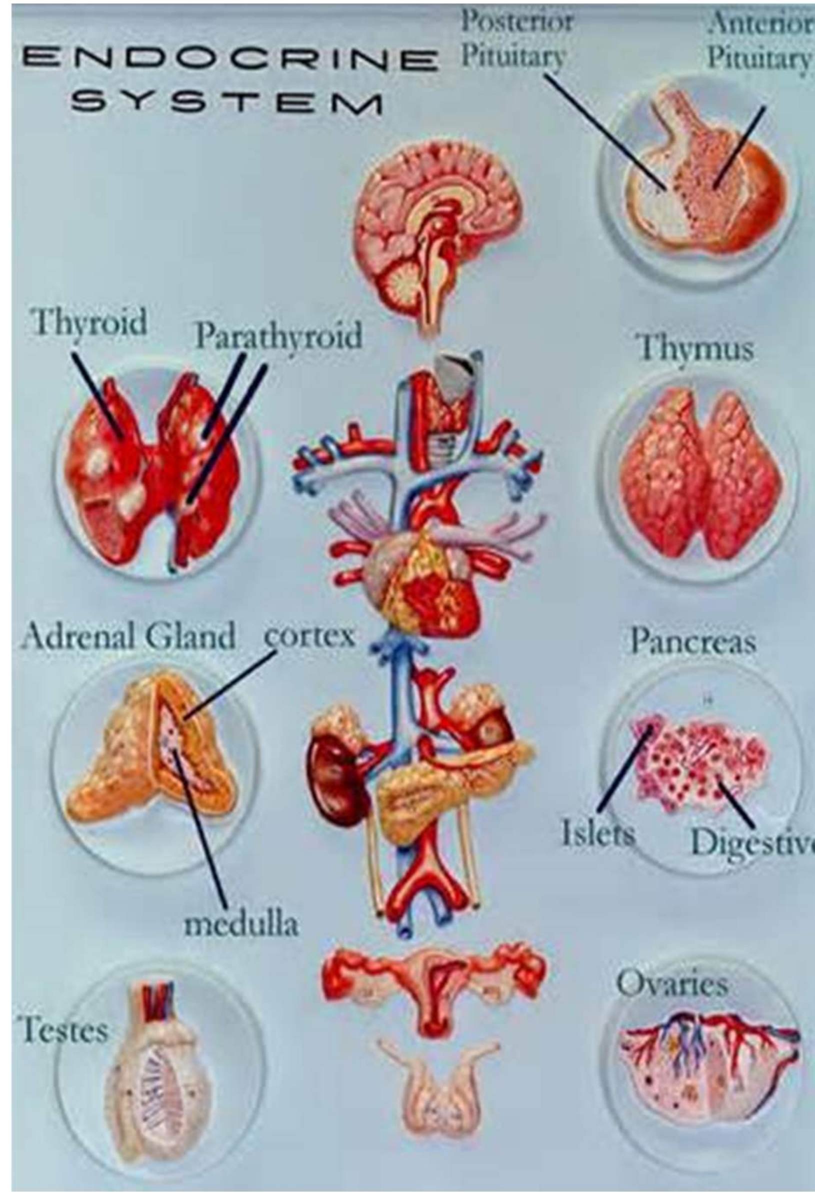
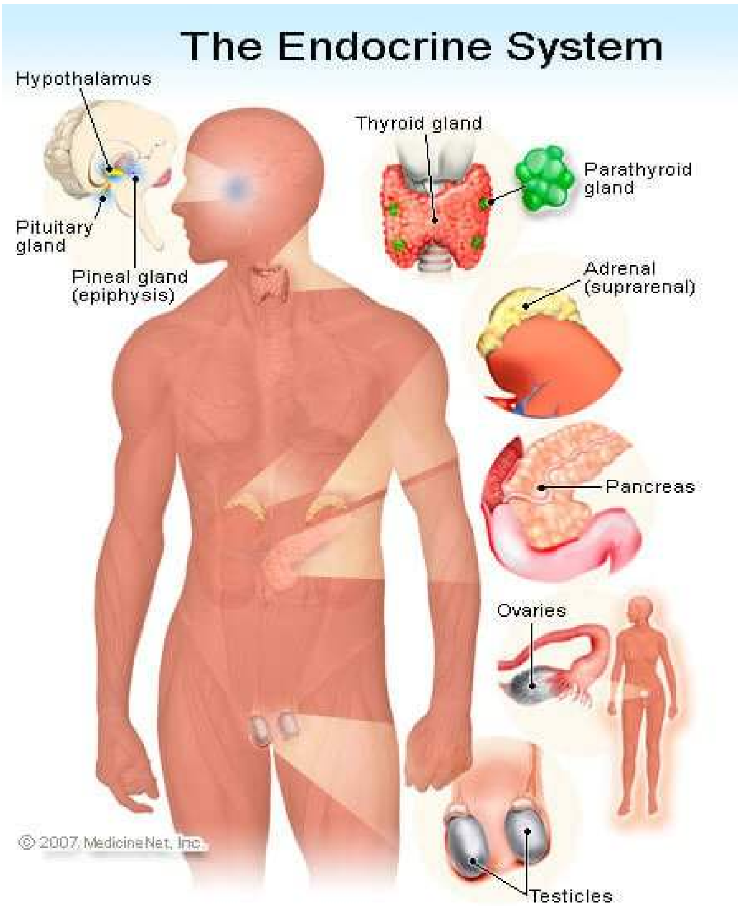


GENERALITY



The Endocrine System
Hypothalamus
Pituitary gland
Pineal gland (epiphysis)
Thyroid gland
Parathyroid gland
Adrenal (suprarenal)
Pancreas
Ovaries
Testicles
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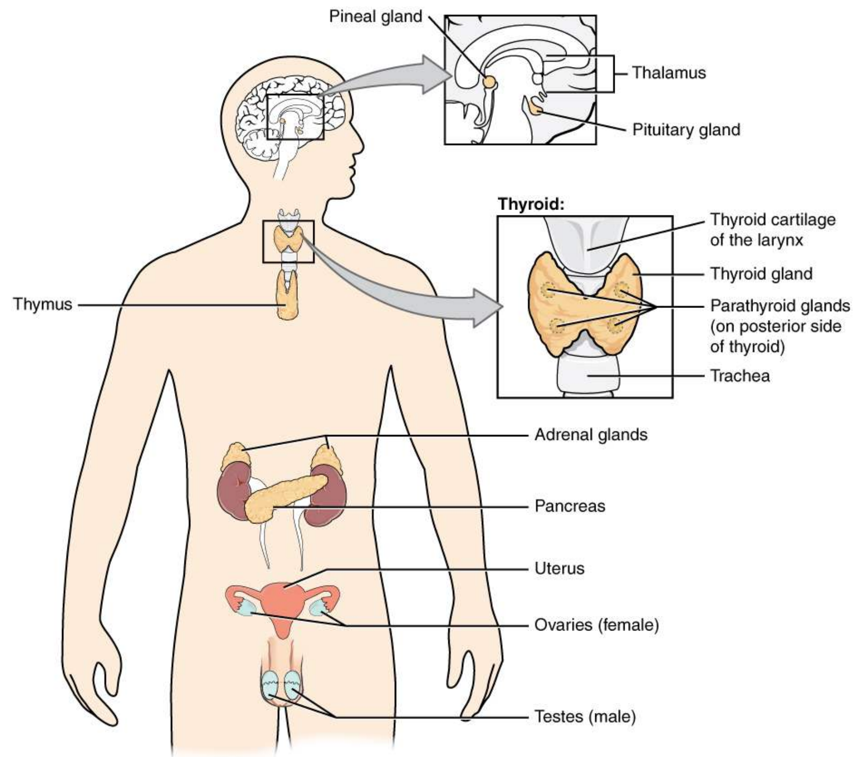


Pineal gland
Thalamus
Pituitary gland
Thyroid:
Thyroid cartilage of the larynx
Thyroid gland
Parathyroid glands (on posterior side of thyroid)
Trachea
Thymus
Adrenal glands
Pancreas
Uterus
Ovaries (female)
Testes (male)

What are endocrine systems for?

Endocrine Functions

- Maintain Internal Homeostasis
- Support Cell Growth
- Coordinate Development
- Coordinate Reproduction
- Facilitate Responses to External Stimuli

What are the elements of an endocrine system?

- *Sender* = Sending Cell
- *Signal* = Hormone
- *Nondestructive Medium* = Serum & Hormone Binders
- *Selective Receiver* = Receptor Protein
- *Transducer* = Transducer Proteins & 2º Messengers
- *Amplifier* = Transducer/Effector Enzymes
- *Effector* = Effector Proteins
- *Response* = Cellular Response (2º Hormones)

General Functions of the Endocrine System

Regulating development, growth, and metabolism

- Hormones help regulate embryonic cell division and differentiation
- Hormones regulate metabolism (both anabolism and catabolism)

Maintaining homeostasis of blood composition and volume

- Hormones regulate blood solute concentrations (e.g., glucose, ions)
- Hormones regulate blood volume, cellular concentration, and platelet number

Controlling digestive processes

- Hormones influence secretory processes and movement of materials in digestive tract

Controlling reproductive activities

- Hormones affect development and function of reproductive systems and the expression of sexual behaviors

Functions

Maintenance of growth & development

- **– Growth hormone,**
- **Thyroxine,**
- **insulin,**
- **Glucocorticoid,**
- **Gonadal hormones**
- **Maintenance of internal environment**

– ADH,

- **Mineralocorticoids,**
- **PTH**
- **Regulation of energy balance and metabolism –**
- **Insulin,**
- **glucagon ,**
- **Leptin & Ghrelin**
- **Reproduction & species propagation – Gonadal & Pituitary hormones**

When two or more hormones work together to produce particular result their effects are said to be **synergistic**.

- These effects may be additive or complementary.
- Additive: Same effect of the hormones on one target organ, for example, epinephrine and norepinephrine on heart rate
- Complementary: Work on different stages of a physiological procedure, for example, FSH (initiation) and testosterone (maintenance) on spermatogenesis

Stimulation of Hormone Synthesis and Release

Hormone release is regulated by reflexes to stimuli

Hormonal, humoral, or nervous stimuli can initiate hormone release

- **Hormonal stimulation**
  - A gland cell releases its hormone when some other hormone binds to it
- **Humoral stimulation**
  - A gland cell releases its hormone when there is a certain change in levels of a nutrient or ion in the blood
- **Nervous stimulation**
  - A gland cell releases its hormone when a neuron stimulates it

Types of Endocrine Stimulation

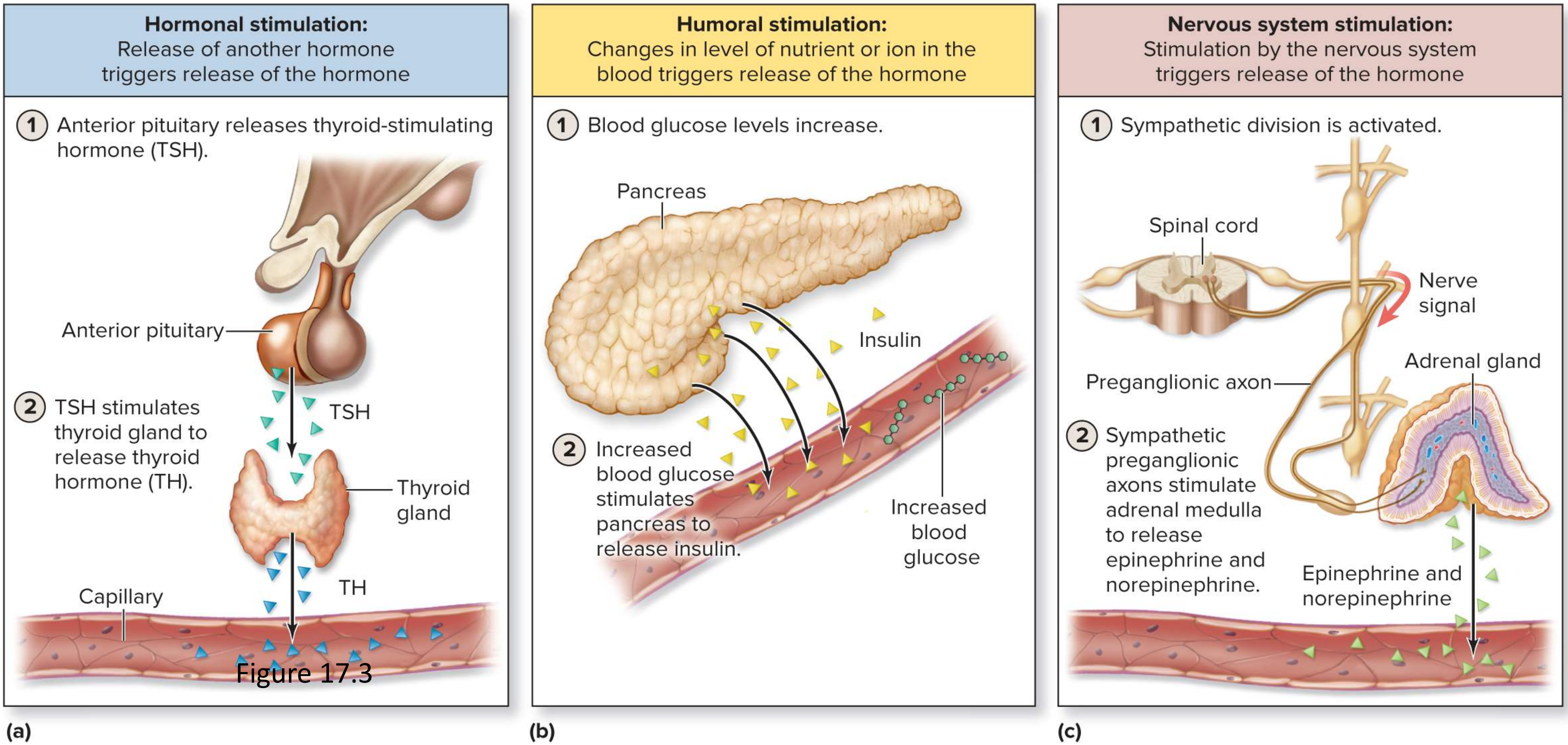


Figure 17.3

Levels of Circulating Hormone [1]

A hormone's blood concentration depends on how fast it is synthesized and eliminated

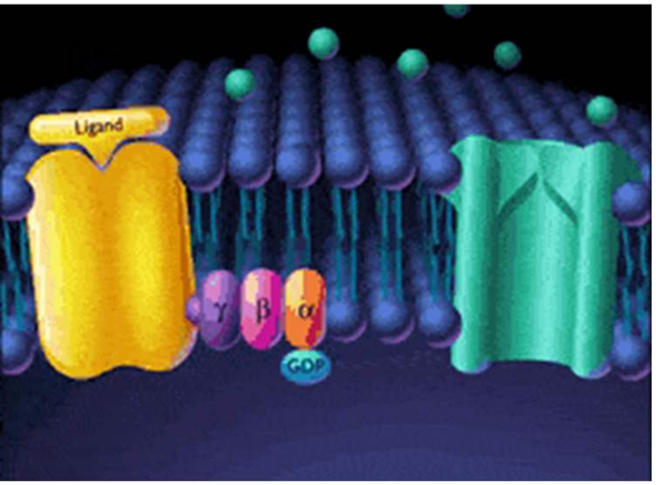
- **Hormone release** and its concentration in blood are positively correlated
  - An increase in release results in higher the blood concentration and vice versa
- **Hormone elimination** occurs in multiple ways
  - ***Enzymatic degradation in liver cells***
  - Removal from blood via kidney excretion or target cell uptake
  - The faster the elimination rate, the lower the blood concentration and vice versa

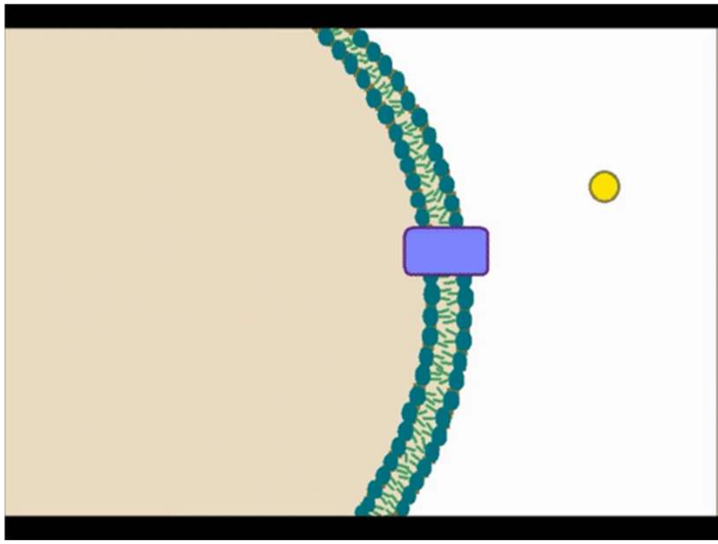
Half-Life—time necessary to reduce a hormone's concentration to half of its original level

- Depends on how efficiently it is eliminated
- **Hormones with short half-life must be secreted frequently to maintain normal concentration**
- **<u>Water-soluble hormones generally have short half-life</u>**
  - E.g., half-life of a few minutes for small peptide hormones
- **<u>Steroid hormones generally have a long half-life</u>**
  - Carrier proteins protect them
  - E.g., testosterone half-life is 12 days

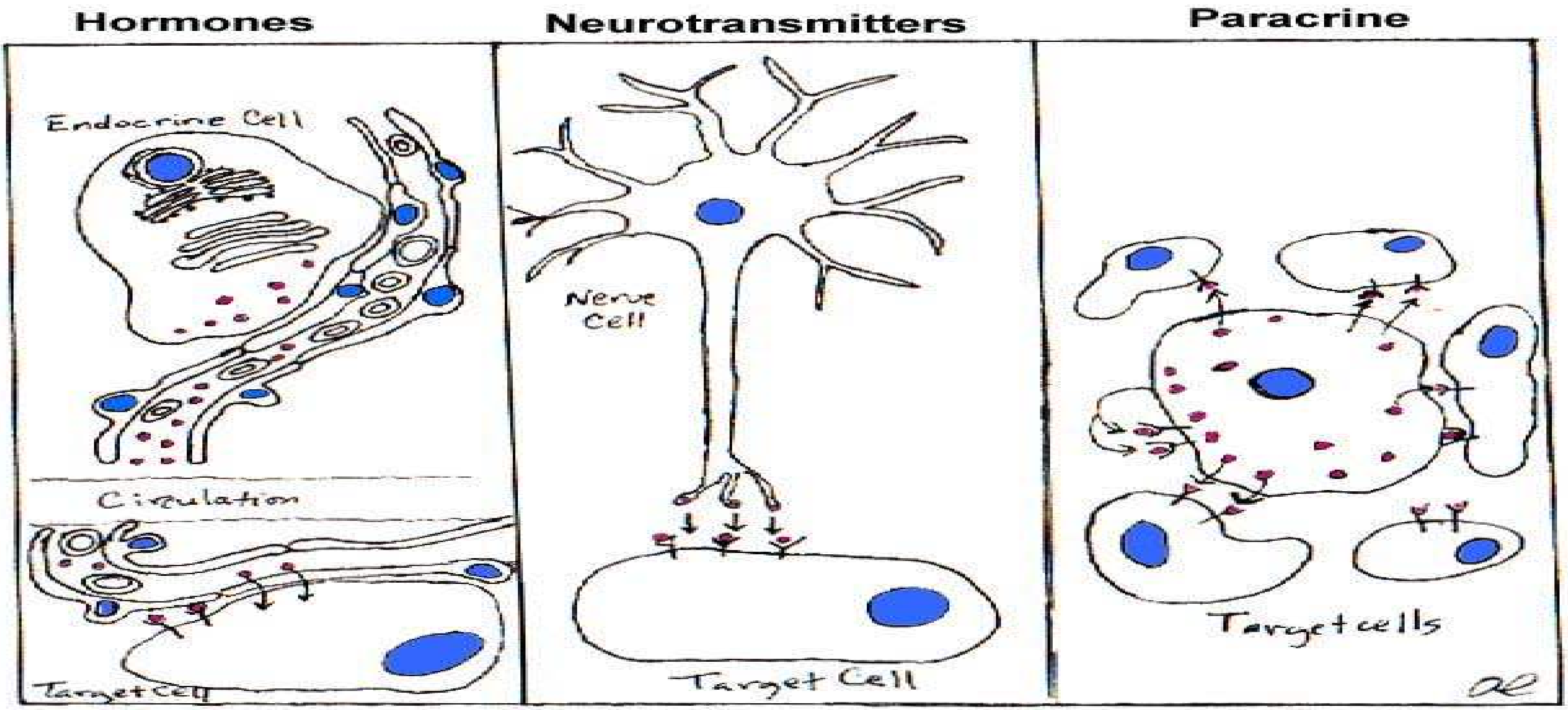
Major Mechanisms for Signaling

- **Endocrine hormones** - small molecules released into the circulation to effect target cells at distant sites from the original release point.
- **Paracrine hormones** - small molecules released in **a local area** which has an effect only on cells within that local area of the body
- **Neurotransmission** - synaptic transmission





Comparison of the three



Endocrine Glands Defined

- Exocrine glands

– secrete products into ducts which empty into body cavities or body surface
– sweat, oil, mucous, & digestive glands

- Endocrine glands

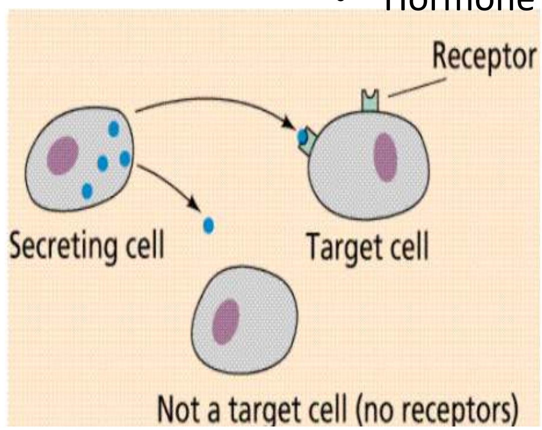
Composed of ductless glands that synthesize and secrete hormones

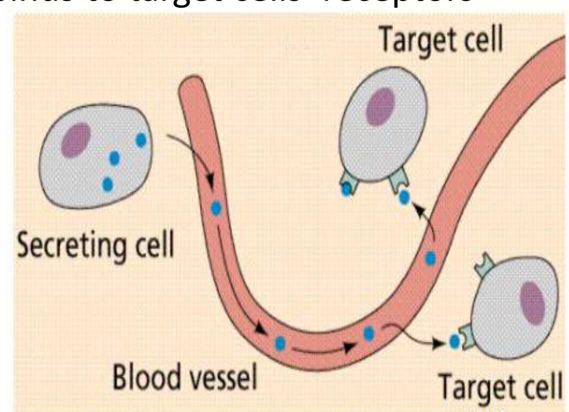
– secrete products (hormones) into bloodstream
– pituitary, thyroid, parathyroid, adrenal, pineal
– other organs secrete hormones as a 2nd function
- hypothalamus, thymus, pancreas,ovaries,testes, kidneys, stomach, liver, small intestine, skin, heart & placenta

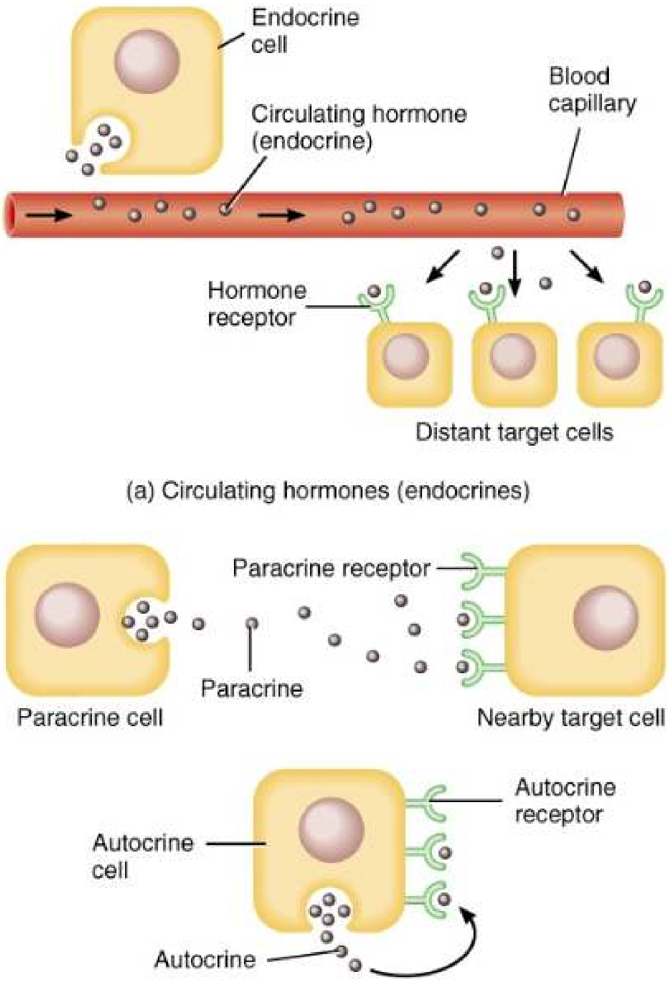
Hormone transport to target cells:

- Hormones released into interstitial fluid and then enter blood
- Transported within blood
- Randomly leave blood and enter interstitial fluid
- Hormone binds to target cells’ receptors

- The endocrine system is a collection of glands that secrete chemical messages we call hormones.
- These signals are passed through the blood to arrive at a target organ, which has cells possessing the appropriate receptor.







(a) Circulating hormones (endocrines)

(b) Local hormones (paracrines and autocrines)

Circulating & Local Hormones

- Circulating hormones
  - act on distant targets
  - travel in blood
- Local hormones
  - paracrines act on neighboring cells
  - autocrines act on same cell that secreted them

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
  - **liver cells---insulin stimulates glycogen synthesis**
  - **adipose---insulin stimulates triglyceride synthesis**

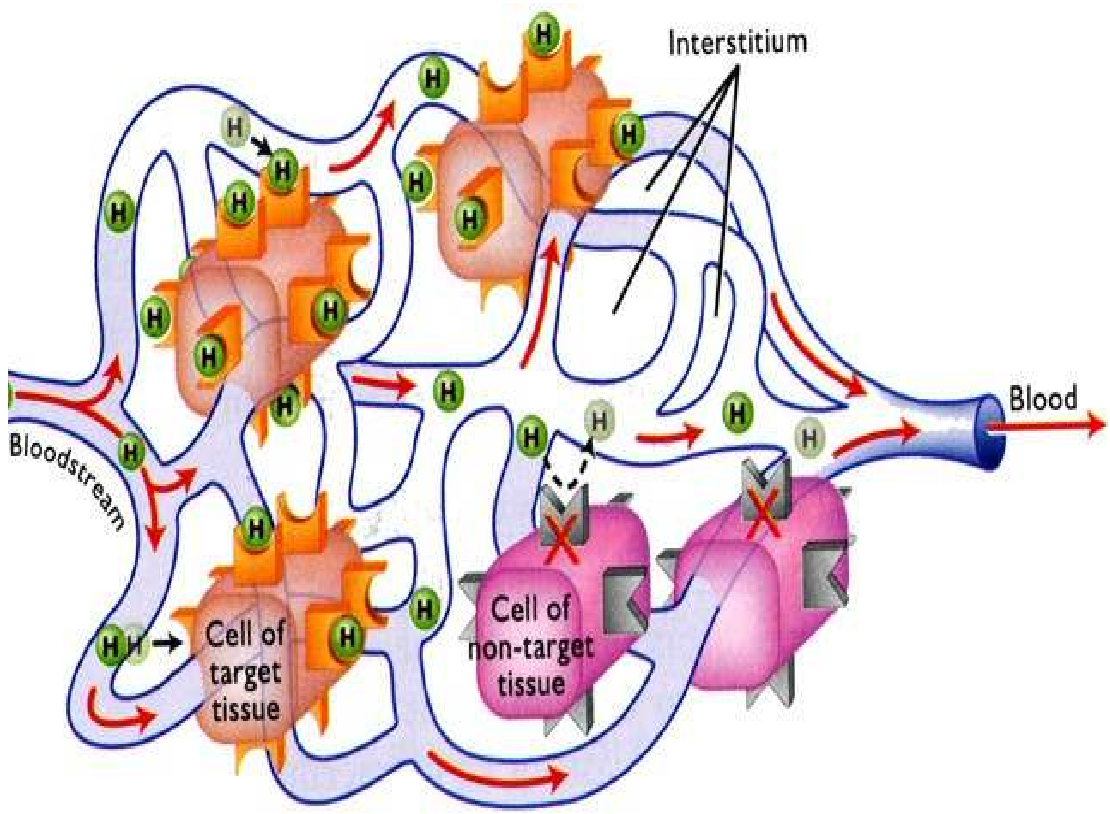
Control of Hormone Secretion

• 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

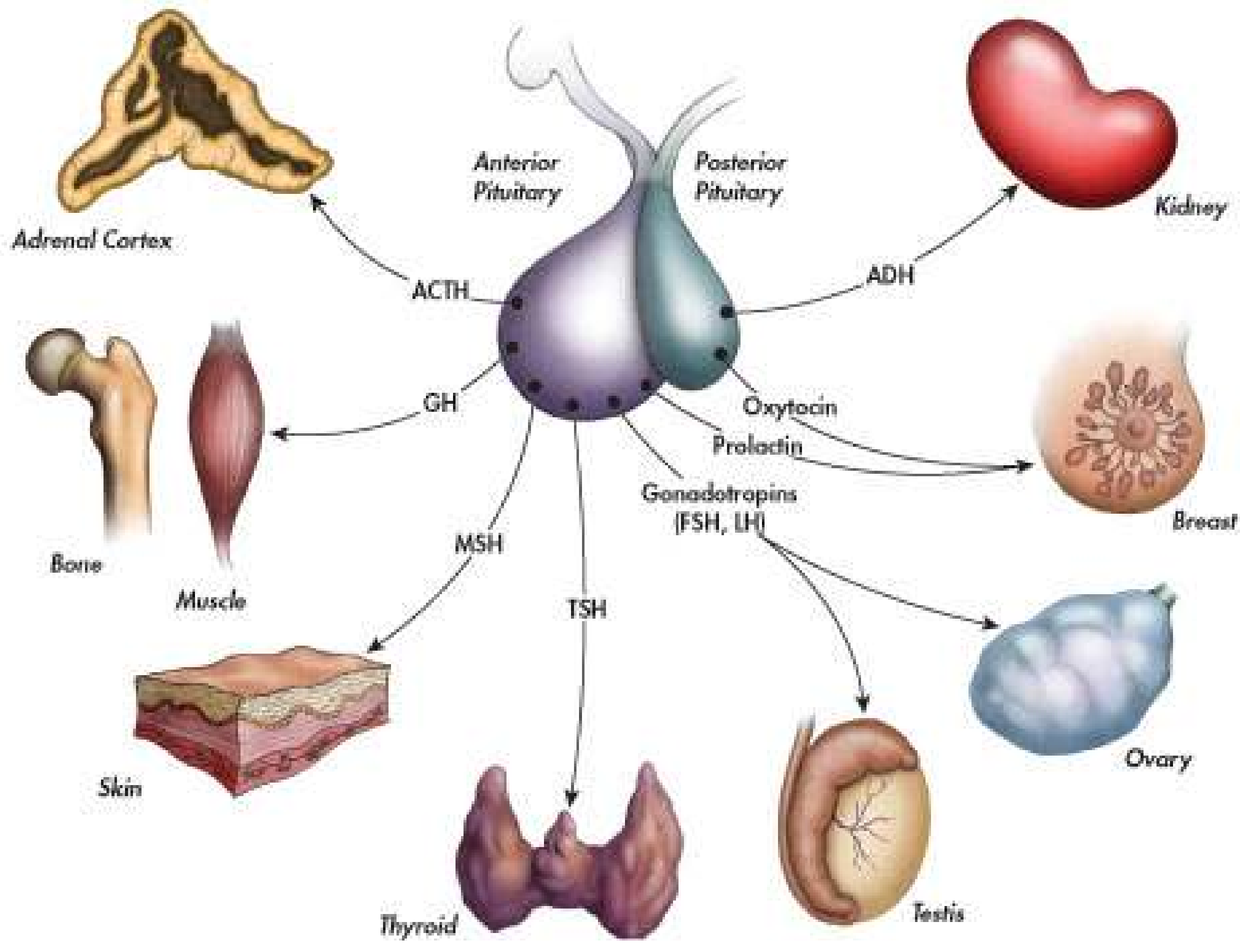


Endocrine-related Problems

- Overproduction of a hormone
- Underproduction of a hormone
- Nonfunctional receptors that cause target cells to become insensitive to hormones

FEEDBACK SYSTEMS

- **CORTEX, SUBCORTEX?→**
- **HYPOTHALAMUS →**
- **ANTERIOR PITUITARY →**
- **ENDOCRINE GLAND →**
- **END ORGAN →**
- **HYPOTHALAMUS →**



Examples of Negative Feedback in the Endocrine System

1. Regulation of Blood Glucose Levels

High Blood Glucose:

•**Stimulus:** Blood glucose levels rise after eating.
•**Sensor:** Pancreatic beta cells detect the increase in blood glucose.
•**Control Center:** Beta cells in the pancreas release insulin.
•**Effector:** Insulin promotes glucose uptake by cells and stimulates the liver to convert glucose to glycogen.
•**Response:** Blood glucose levels decrease, reducing the initial stimulus.

Low Blood Glucose:

•**Stimulus:** Blood glucose levels drop, such as between meals.
•**Sensor:** Pancreatic alpha cells detect the decrease in blood glucose.
•**Control Center:** Alpha cells in the pancreas release glucagon.
•**Effector:** Glucagon stimulates the liver to break down glycogen into glucose and release it into the blood.
•**Response:** Blood glucose levels increase, reducing the initial stimulus.

Regulation of Thyroid Hormones

•**Stimulus:** Low levels of thyroid hormones (T3 and T4) in the blood.
•**Sensor:** Hypothalamus detects low levels of T3 and T4.
•**Control Center:** Hypothalamus releases thyrotropin-releasing hormone (TRH).
•**Effector:** TRH stimulates the anterior pituitary gland to release thyroid-stimulating hormone (TSH), which then stimulates the thyroid gland to produce and release T3 and T4.
•**Response:** Levels of T3 and T4 increase in the blood, inhibiting further release of TRH and TSH.

Regulation of Cortisol Levels

•**Stimulus:** Low levels of cortisol or stress.
•**Sensor:** Hypothalamus detects low cortisol levels or stress.
•**Control Center:** Hypothalamus releases corticotropin-releasing hormone (CRH).
•**Effector:** CRH stimulates the anterior pituitary gland to release adrenocorticotropic hormone (ACTH), which then stimulates the adrenal cortex to release cortisol.
•**Response:** Cortisol levels increase in the blood, inhibiting further release of CRH and ACTH.

Hormones

5 major classes

1. *Amino acid derivatives* → dopamine, catecholamine, and thyroid hormone;
2. *Small neuropeptides* → gonadotropin-releasing hormone (GnRH), thyrotropin-releasing hormone (TRH), somatostatin, and vasopressin;
3. *Large proteins* → insulin, luteinizing hormone (LH), and PTH produced by classic endocrine glands;
4. *Steroid hormones* such as cortisol and estrogen;
5. *Vitamin derivatives* such as retinoids (vitamin A) and vitamin D.

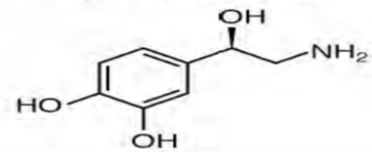
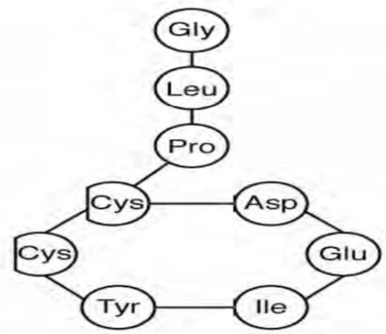
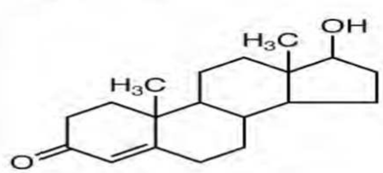
As a rule – protein based hormones act on the 'cell surface receptors' and steroid based hormones act on 'intracellular nuclear proteins'

- **<u>A steroid hormone directly initiates the production of proteins</u>** within a target cell.

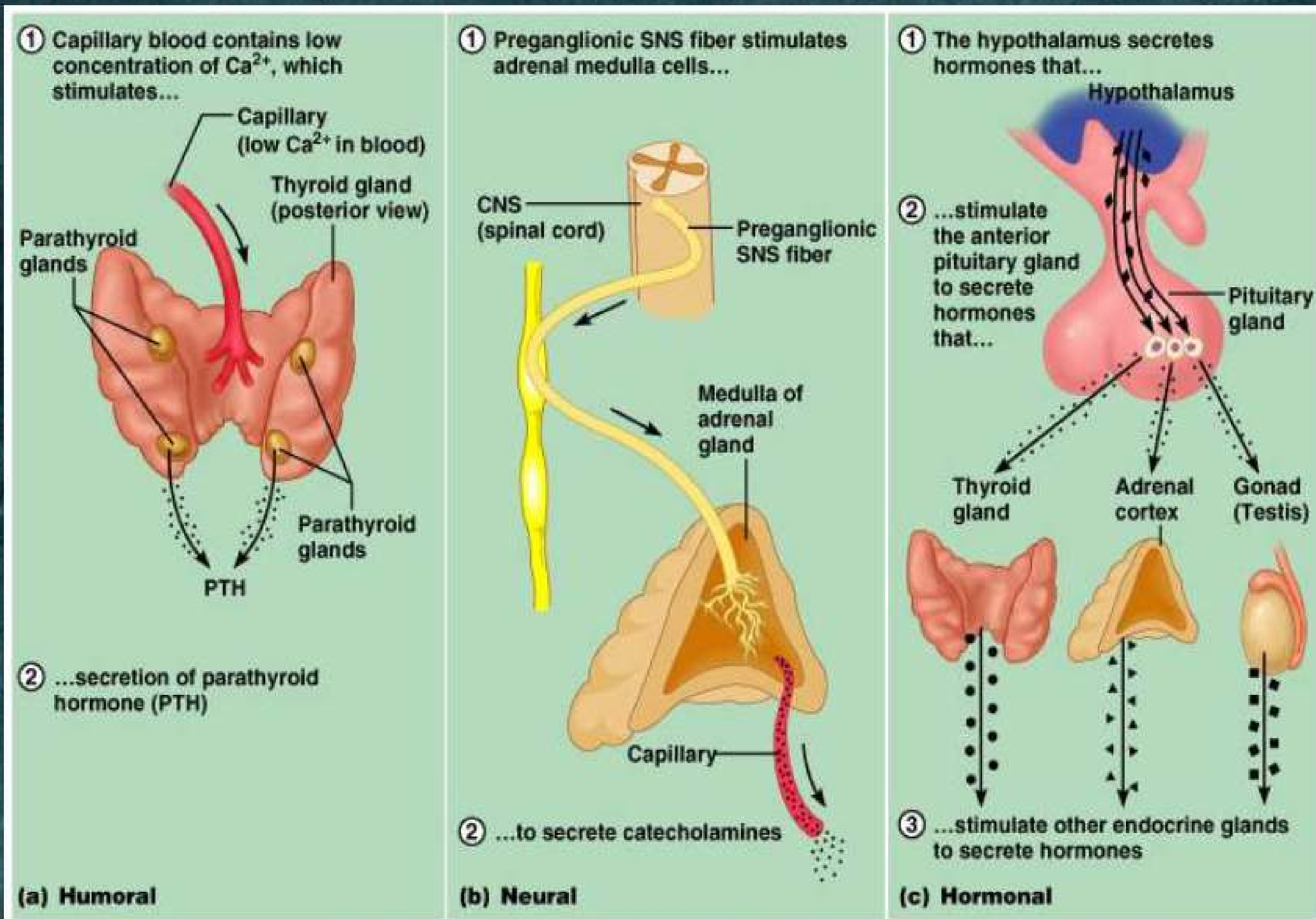
- Steroid hormones easily diffuse through the cell membrane.
- The hormone binds to its receptor in the cytosol, forming a receptor–hormone complex.

- The receptor–hormone complex then enters the nucleus and binds to the target gene on the DNA.

- Transcription of the gene creates a messenger RNA that is translated into the desired protein within the cytoplasm.

Hormone Class	Components	Example(s)
Amine Hormone	Amino acids with modified groups (e.g. norepinephrine's carboxyl group is replaced with a benzene ring)	**Norepinephrine** 
Peptide Hormone	Short chains of linked amino acids	**Oxytocin** 
Protein Hormone	Long chains of linked amino acids	**Human Growth Hormone** 
Steroid Hormones	Derived from the lipid cholesterol	**Testosterone**  **Progesterone** 

Types of Hormones



- **(a) Humoral**: in response to changing levels of ions or nutrients in the blood
- **(b) Neural**: stimulation by nerves
- **(c) Hormonal**: stimulation received from other hormones

Sites of hormone action

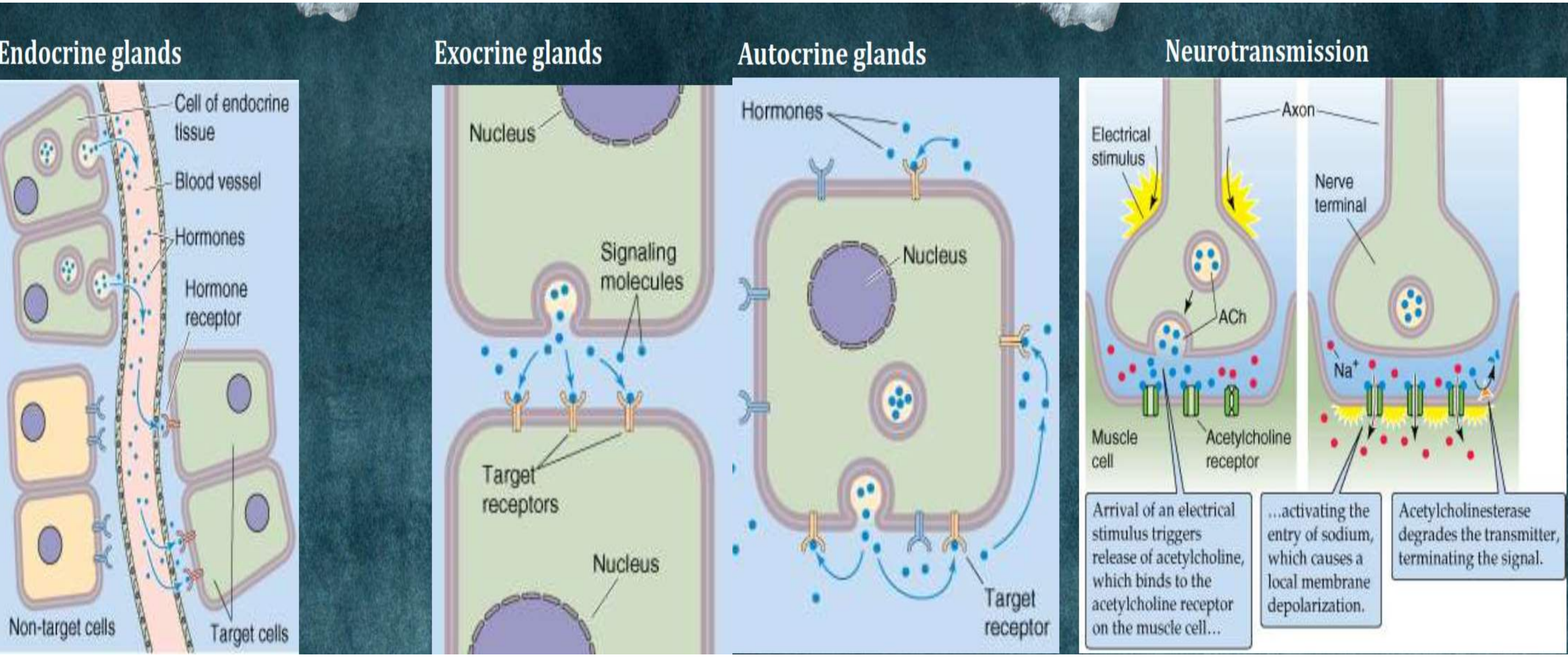


TABLE 50.1: Mechanism of action of hormones (for expansions or abbreviations, see Appendix No.I)

Group	*Mechanism of action*	*Examples of hormone*
I A	Hormones bind with cell surface receptors with cAMP as the second messenger	ACTH, ADH, FSH HCG, LH, TSH MSH, PTH, CRH Glucagon, Calcitonin Catecholamines Retinoic acid
I B	Hormones having cell surface receptors; cGMP as second messenger	ANF (atrial natriuretic factor), NO (nitric oxide)
I C	Hormones having cell surface receptors; second messenger is calcium or phosphatidyl inositol (PIP2)	TRH, GnRH catecholamines Acetylcholine CCK, Gastrin Vasopressin Oxytocin, PDGF
I D	Hormones having cell surface receptors and mediated through tyrosine kinase	Insulin Somatomedin EGF, FGF PDGF, CGSF NGF, IGF
I E	Hormones having cell surface receptors, but intracellular messenger is a kinase or utilize phosphatase cascade	IL, GH, PRL, TNF, Adiponectin, Leptin, Resistin, Erythropoietin
I I	Hormones that bind to intracellular receptors	Glucocorticoids Mineralocorticoids Estrogens, Progesterone Androgens Calcitriol, Thyroxine

There are two types of cells in signal transduction

- the **sender cell where the signal originates**
- the **target cell that receives the signal.**

- **The signal alters** or modulates the activity/function of the cell.

- **Autocrine signaling occurs when same cell acts as** sender and recipient, e.g. growth, differentiation, immune and inflammatory response.

- **Paracrine signaling is** effected by local mediators which have their effect nearthe site of secretion without entering the circulation.
- The effect is rapid and transient.

- **Juxtacrine signaling occurs when the two type of cells are adjacent to each other so that contact is established through gap junctions or through protein molecules on the surface of the two cells.**

- **Endocrine signaling is between cells which are located at a distance from each other and the signal may be hormones or chemical messengers secreted into circulation.**

Once they reach the target cell, they bind to specific target cell receptors with high affinity.

List three kinds of interaction of different hormones acting on the same target cell.

- • **Permissiveness** – one **hormone cannot exert its full effects without another hormone being present** (ex. Reproductive system hormones regulate the development of the reproductive system.
- However thyroid hormone is also necessary for normal timely development of reproductive structures. Lack of thyroid hormone delays reproductive development.

  • **Synergism** – occurs when more than one **hormone produces the same effect at the target cell and their combined effects are amplified.** (ex. both glucagon (pancreas) and epinephrine causes the liver to release glucose into the blood. When they act together, the amount of glucose released is about 150% of what is released when each hormone acts alone

  • **Antagonism** – occurs when **one hormones opposes the action of another hormone**. (ex. insulin which lowers blood glucose levels, is antagonized by glucagon, which raises blood glucose levels.

- **Antagonists may:**
  ? compete for the same receptor
  ? Act through different metabolic pathways
  ? Cause down-regulation of the receptors for the antagonistic hormone.

Endocrine Physiology: Hormone Receptors and Effects

- Cyclic AMP
  - Made by removing two phosphates from ATP
  - Activates or reactivates cytoplasmic enzymes
  - Leads to various metabolic effects
    - e.g., wake up certain genes, producing new enzymes
    - e.g., change permeability of plasma membrane
    - e.g., glucagon activating certain metabolic pathways

- Steroid hormones
  - – Hydrophobic, readily pass into cell
  - – Bind receptor associated with DNA
  - – Causes gene to be transcribed
  - – Specific protein produced
    - alters metabolism in various ways

Hormones stimulate adenyl cyclase: ACTH, ADH, Calcitonin, CRH, FSH, Glucagon, epinephrine, hCG, LH, LPH, MSH, PTH and TSH.

Hormones inhibit adenyl cyclase: Acetylcholine, angiotensin II and somatostatin.

Signaling pathways of endocrine hormones

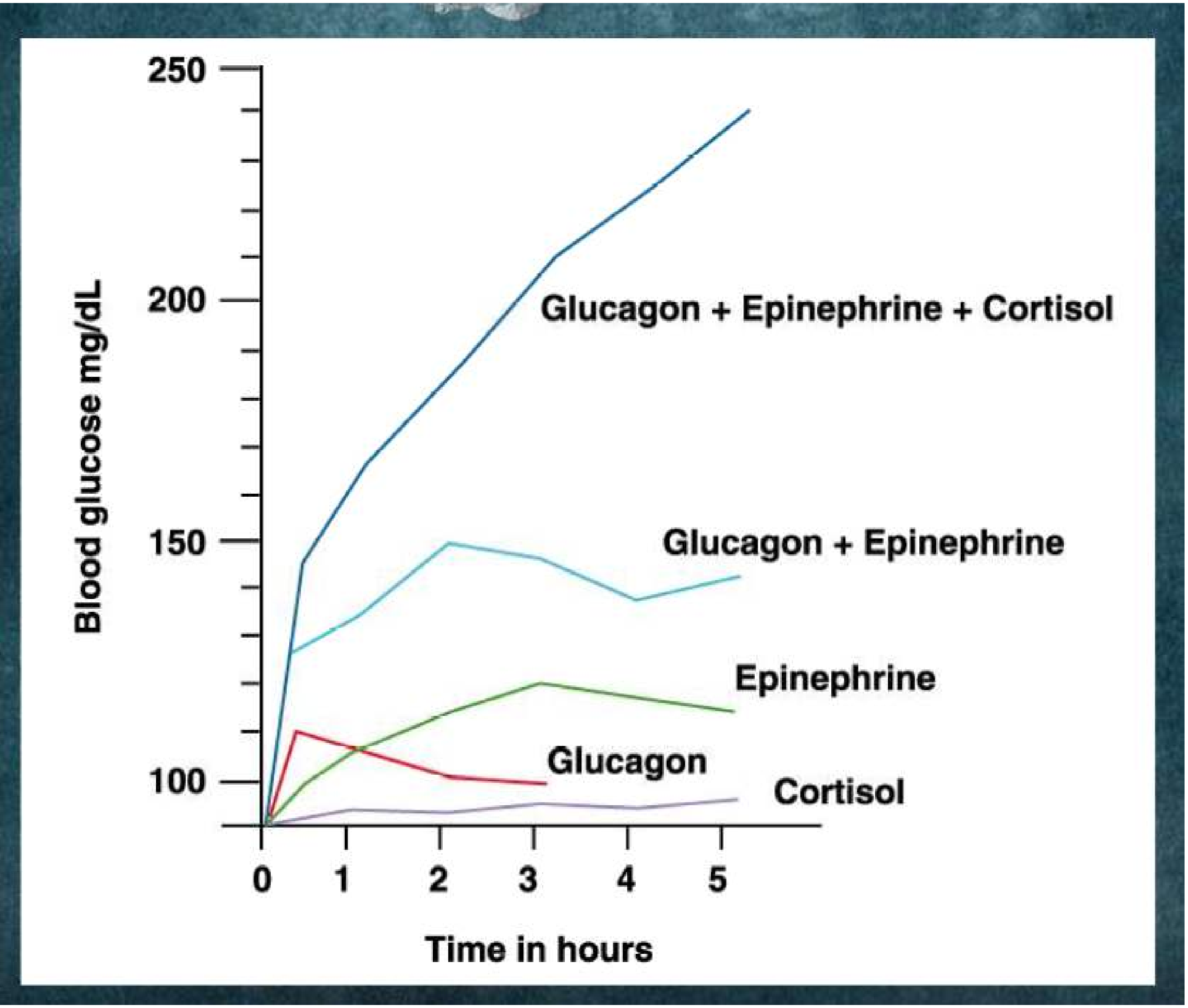
cAMP	FSH, LH, ACTH, TSH, CRH, hCG, ADH (V_2-receptor), MSH, PTH, calcitonin, GHRH, glucagon, histamine (H_2-receptor)	FLAT ChAMP
cGMP	BNP, ANP, EDRF (NO)	BAD GraMPa Think vasodilators
IP_3	GnRH, Oxytocin, ADH (V_1-receptor), TRH, Histamine (H_1-receptor), Angiotensin II, Gastrin	GOAT HAG
Intracellular receptor	Progesterone, Estrogen, Testosterone, Cortisol, Aldosterone, T_3/T_4, Vitamin D	PET CAT on TV
Receptor tyrosine kinase	Insulin, IGF-1, FGF, PDGF, EGF	MAP kinase pathway Think Growth Factors
Nonreceptor tyrosine kinase	Prolactin, Immunomodulators (eg, cytokines IL-2, IL-6, IFN), GH, G-CSF, Erythropoietin, Thrombopoietin	JAK/STAT pathway Think acidophils and cytokines PIGGLET

Signaling Pathways of Endocrine Hormones

General mechanism

- **releasing hormone (IP_3) → pituitary hormone (cAMP) → systemic hormone (steroid)**
    - **GnRH → FSH/LH → estrogen/testosterone/progesterone**
    - **TRH → TSH → T_3/T_4**
- **vasoactive hormones**
    - cGMP
- **growth factors**
    - tyrosine kinase
- **growth hormone, cytokines, hormones**
    - receptor tyrosine kinase

IP_3	cAMP	cGMP	Tyrosine kinase - intrinsic	Tyrosine kinase - receptor associated	Steroid
GnRH	FSH	ANP	Insulin	Prolactin	Glucocorticoid
Gastrin	LH	NO (EDRF)	IGF-1	Cytokines (IL-2,6,8)	Estrogen
Oxytocin	ACTH		FGF	GH	Progesterone
TRH	TSH		PDGF		Testosterone
ADH (V_1)	CRH				Aldosterone
Histamine (H_1)	hCG				Vitamin D
Angiotensin II	PTH				T_3/T_4
	Calcitonin				Cortisol
	Glucagon				
	GHRH (can act via IP_3 as well)				



Synergistic effects

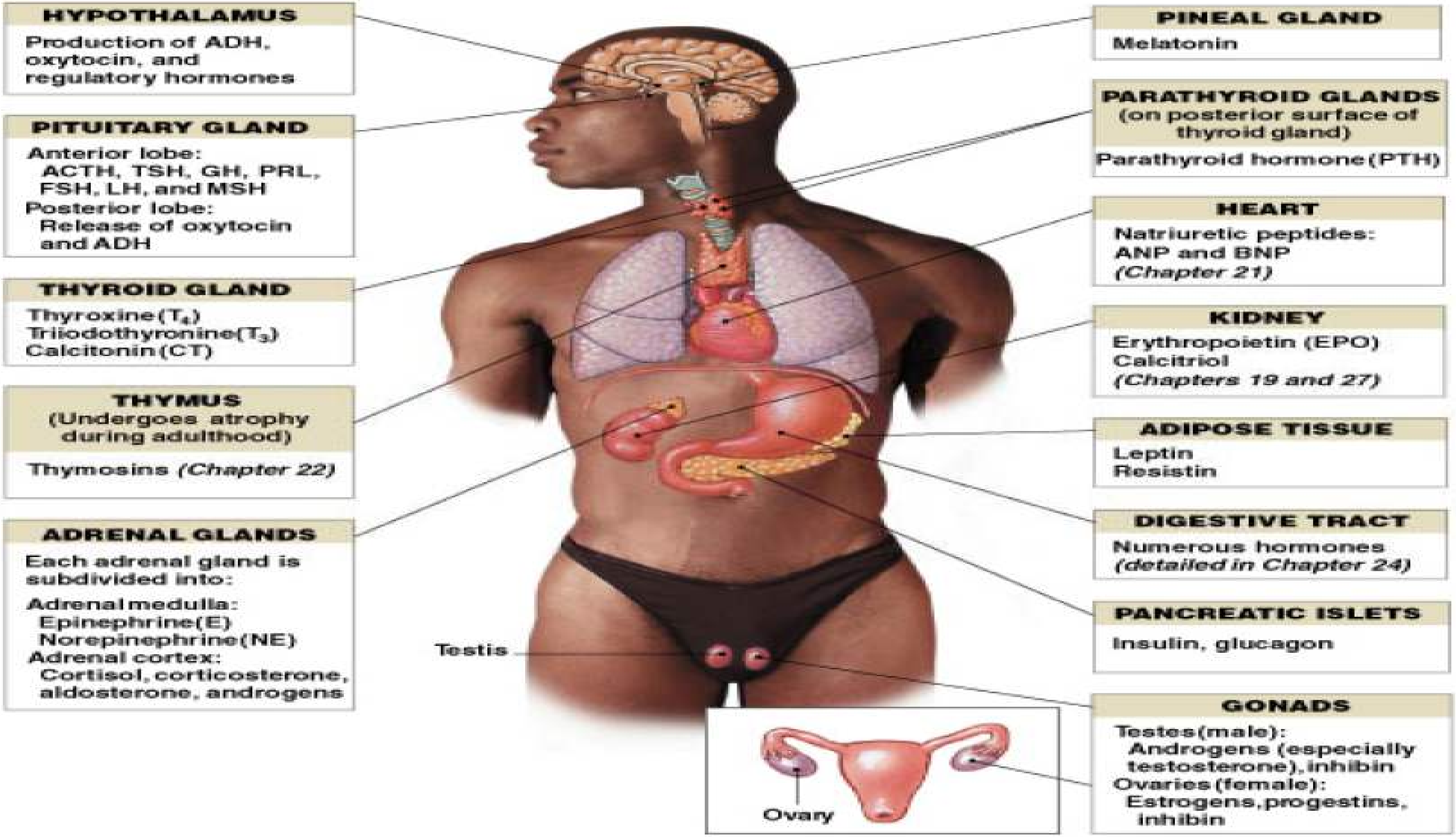
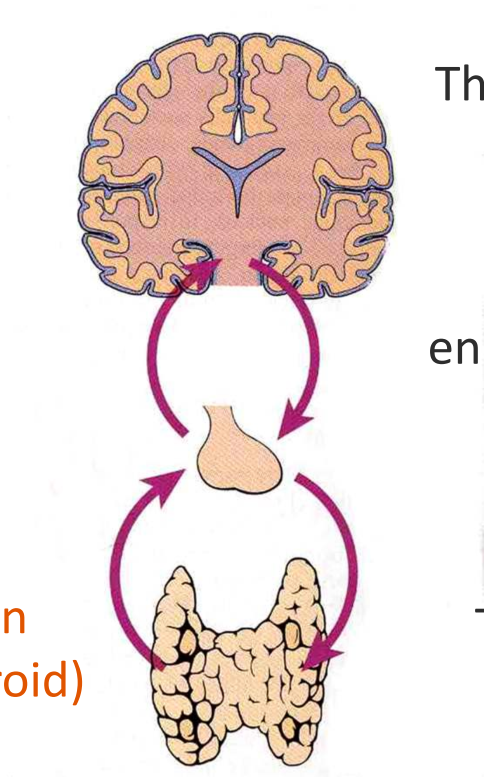

HYPOTHALAMUS
Production of ADH, oxytocin, and regulatory hormones
PITUITARY GLAND
Anterior lobe: ACTH, TSH, GH, PRL, FSH, LH, and MSH
Posterior lobe: Release of oxytocin and ADH
THYROID GLAND
Thyroxine(T_4)
Triiodothyronine(T_3)
Calcitonin(CT)
THYMUS
(Undergoes atrophy during adulthood)
Thymosins (Chapter 22)
ADRENAL GLANDS
Each adrenal gland is subdivided into:
Adrenal medulla: Epinephrine(E) Norepinephrine(NE)
Adrenal cortex: Cortisol, corticosterone, aldosterone, androgens
Testis
Ovary
PINEAL GLAND
Melatonin
PARATHYROID GLANDS
(on posterior surface of thyroid gland)
Parathyroid hormone(PTH)
HEART
Natriuretic peptides: ANP and BNP
(Chapter 21)
KIDNEY
Erythropoietin (EPO)
Calcitriol
(Chapters 19 and 27)
ADIPOSE TISSUE
Leptin
Resistin
DIGESTIVE TRACT
Numerous hormones
(detailed in Chapter 24)
PANCREATIC ISLETS
Insulin, glucagon
GONADS
Testes(male): Androgens (especially testosterone), inhibin
Ovaries(female): Estrogens, progestins, inhibin

Table 37-1. Hormones and Their Sites of Production in Nonpregnant Adults

Gland	Hormone
Hormones Synthesized and Secreted by Dedicated Endocrine Glands	
Pituitary gland	Growth hormone (GH) Prolactin Adrenocorticotropic hormone (ACTH) Thyroid-stimulating hormone (TSH) Follicle-stimulating hormone (FSH) Luteinizing hormone (LH)
Thyroid gland	Tetraiodothyronine (T_4; thyroxine) Triiodothyronine (T_3) Calcitonin
Parathyroid glands	Parathyroid hormone (PTH)
Islets of Langerhans (endocrine pancreas)	Insulin Glucagon Somatostatin
Adrenal gland	Epinephrine Norepinephrine Cortisol Aldosterone Dehydroepiandrosterone sulfate (DHEAS)
Ovaries	Estradiol-17β Progesterone Inhibin
Testes	Testosterone Antimüllerian hormone (AMH) Inhibin
Hormones Synthesized in Organs with a Primary Function Other Than Endocrine	
Brain (hypothalamus)	Antidiuretic hormone (ADH; vasopressin) Oxytocin Corticotropin-releasing hormone (CRH) Thyrotropin-releasing hormone (TRH) Gonadotropin-releasing hormone (GnRH) Growth hormone-releasing hormone (GHRH) Somatostatin Dopamine
Brain (pineal gland)	Melatonin
Heart	Atrial natriuretic peptide (ANP)
Kidney	Erythropoietin
Adipose tissue	Leptin Adiponectin
Stomach	Gastrin Somatostatin Ghrelin
Intestines	Secretin Cholecystokinin Glucagon-like peptide-1 (GLP-1) Glucagon-like peptide-2 (GLP-2) Glucose-dependent insulinotropic peptide (GIP; gastrin inhibitory peptide) Motilin
Liver	Insulin-like growth factor type I (IGF-I)

Endocrine System in a Nutshell



Hypothalamus

The hypothalamus tells the pituitary what to do

The hypothalamus is like a CEO but we don’t talk about it much (not many diseases there)

Pituitary

The pituitary tells the endocrine organ what to do

The pituitary is like a COO. It basically tells everyone what to do.

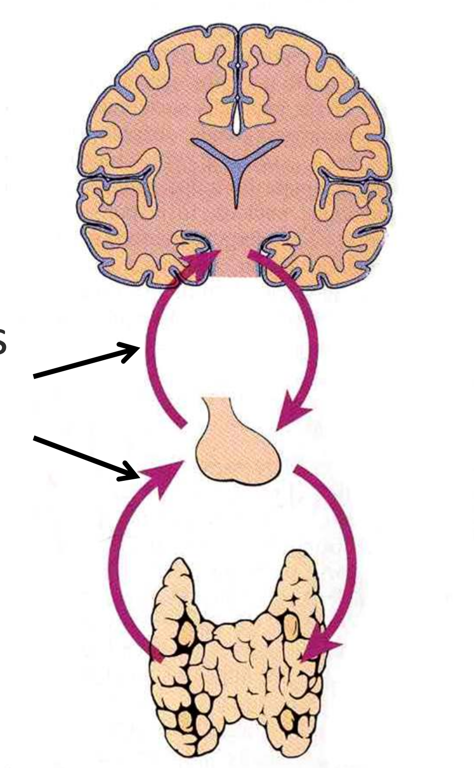
Endocrine organ (for example, thyroid)

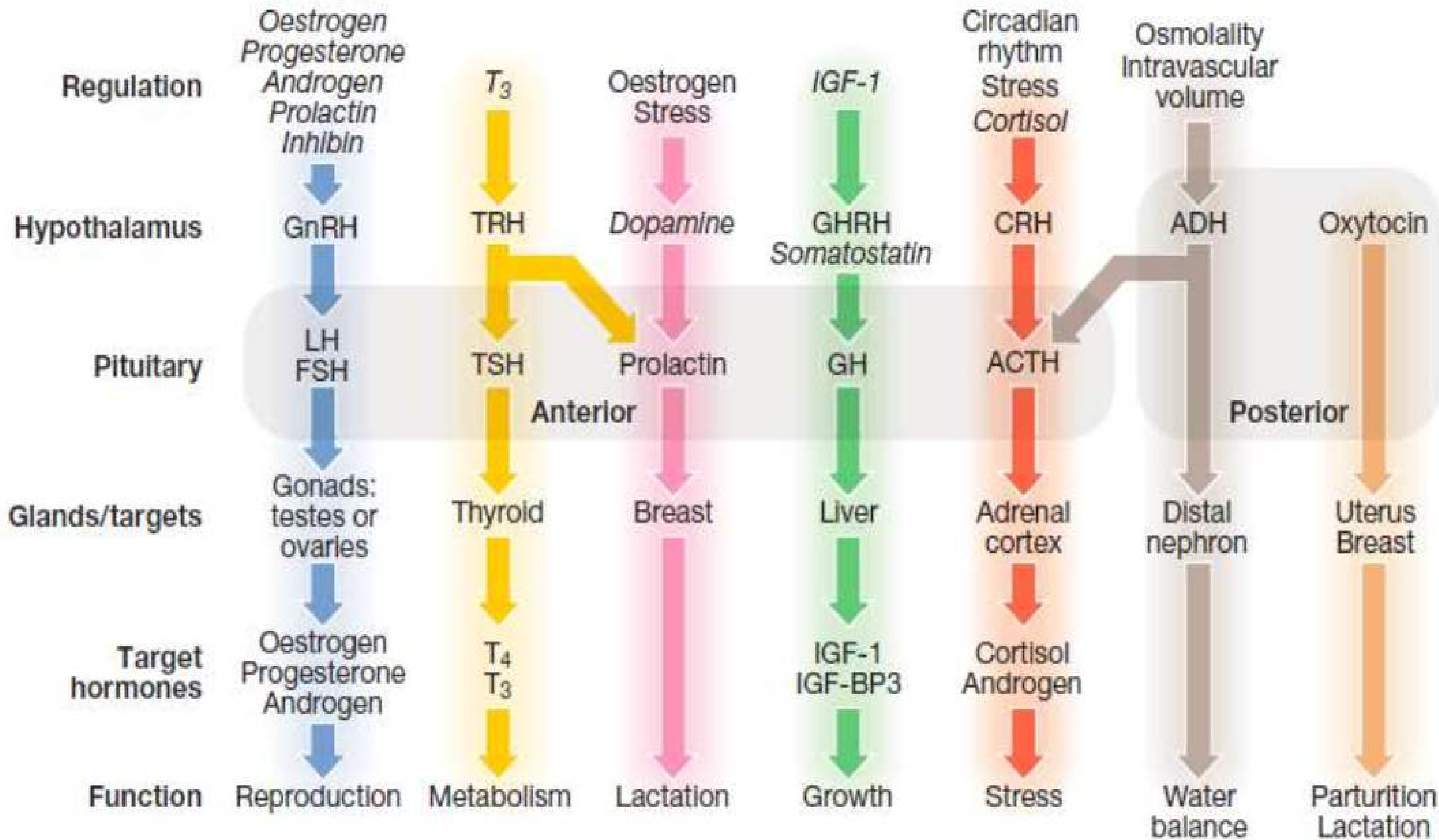
The endocrine organ releases hormone

The endocrine organ is the worker drone. Poor guy.

Endocrine System in a Nutshell

There are negative feedback loops that tell the system when to stop producing hormone.




Regulation
Hypothalamus
Pituitary
Glands/targets
Target hormones
Function
Oestrogen Progesterone Androgen Prolactin Inhibin
GnRH
LH FSH
Gonads: testes or ovaries
Oestrogen Progesterone Androgen
Reproduction
T3
TRH
TSH
Thyroid
T4 T3
Metabolism
Oestrogen Stress
Dopamine
Prolactin
Breast
Lactation
IGF-1
GHRH Somatostatin
GH
Liver
IGF-1 IGF-BP3
Growth
Circadian rhythm Stress Cortisol
CRH
ACTH
Adrenal cortex
Cortisol Androgen
Stress
Osmolality Intravascular volume
ADH
Distal nephron
Water balance
Oxytocin
Uterus Breast
Parturition Lactation
Anterior
Posterior

Hormones Produced to a Significant Degree by Peripheral Conversion	
Lungs	Angiotensin II
Kidney	1,25-Dihydroxyvitamin D (vitamin D)
Adipose, mammary glands, other organs	Estradiol-17β
Liver, sebaceous gland, other organs	Testosterone
Genital skin, prostate, other organs	5-Dihydrotestosterone (DHT)
Many organs	T_3

Table 37-2. Steroid Hormones

Family	Number of Carbons	Specific Hormone	Primary Site of Synthesis	Primary Receptor
Progestin	21	Progesterone	Ovary Placenta	Progesterone receptor (PR)
Glucocorticoid	21	Cortisol Corticosterone	Adrenal cortex	Glucocorticoid receptor (GR)
Mineralocorticoid	21	Aldosterone 11-Deoxycorticosterone	Adrenal cortex	Mineralocorticoid receptor (MR)
Androgen	19	Testosterone Dihydrotestosterone	Testis	Androgen receptor (AR)
Estrogen	18	Estradiol-17β Estriol	Ovary Placenta	Estrogen receptor (ER)

Transport in the Blood

Lipid-soluble hormones use carrier molecules

Lipid-soluble hormones, also known as steroid hormones and thyroid hormones

- ***Do not dissolve readily in blood***
- ***can diffuse through cell membranes due to their lipid-soluble nature***
- ***Carriers are water-soluble proteins made by the liver***
- ***Carriers protect hormones from early destruction***
- ***Binding between hormone and carrier is temporary***
  - Attachment, detachment, reattachment are common
  - Most of the hormone (90% or more) is **bound hormone**
  - Only **unbound (free) hormone** is able to exit blood and bind to target cell receptors

Most water-soluble hormones travel freely through blood

- A few use carrier proteins to prolong their life

Examples of Lipid-Soluble Hormones

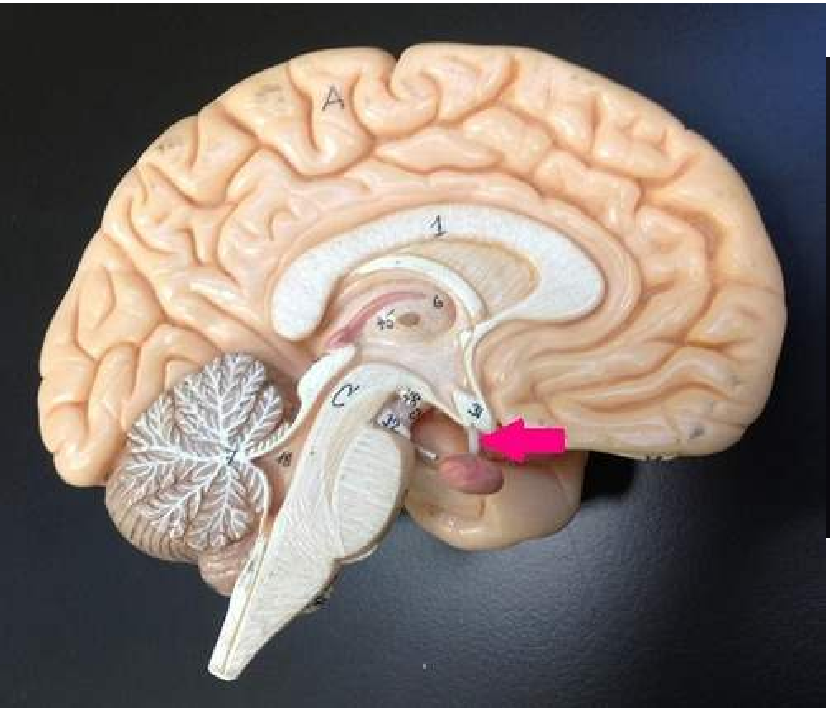
Steroid Hormones

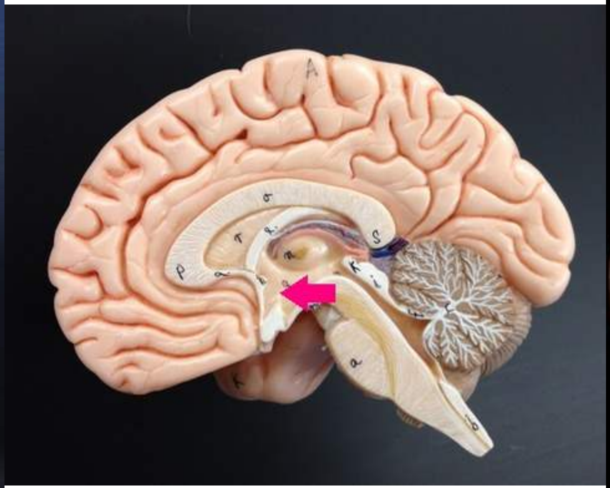
1. **Glucocorticoids (e.g., Cortisol)**
   1. **Produced By:** Adrenal cortex.
   2. **Functions:** Regulate metabolism, immune response, and stress response.
2. **Mineralocorticoids (e.g., Aldosterone)**
   1. **Produced By:** Adrenal cortex.
   2. **Functions:** Regulate sodium and potassium balance and blood pressure.
3. **Sex Hormones (e.g., Estrogens, Progesterone, Testosterone)**
   1. **Produced By:** Gonads (ovaries and testes).
   2. **Functions:** Regulate reproductive functions, secondary sexual characteristics, and other physiological processes.
4. **Androgens (e.g., DHEA)**
   1. **Produced By:** Adrenal cortex.
   2. **Functions:** Serve as precursors to sex hormones and have anabolic effects.

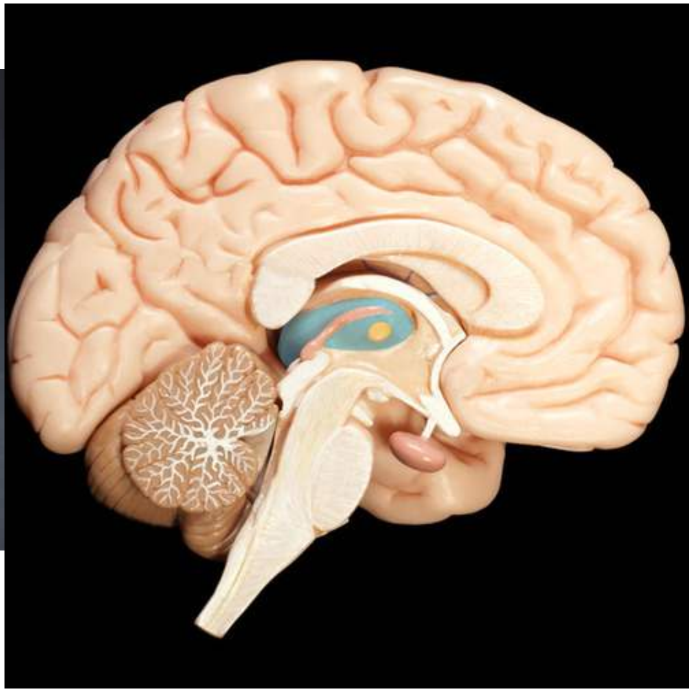
Thyroid Hormones

1. **Triiodothyronine (T3)**
   1. **Produced By:** Thyroid gland.
   2. **Functions:** Regulates metabolism, growth, and development.
2. **Thyroxine (T4)**
   1. **Produced By:** Thyroid gland.
   2. **Functions:** Serves as a precursor to T3 and helps regulate metabolism.

NEURO- ENDOCRINE

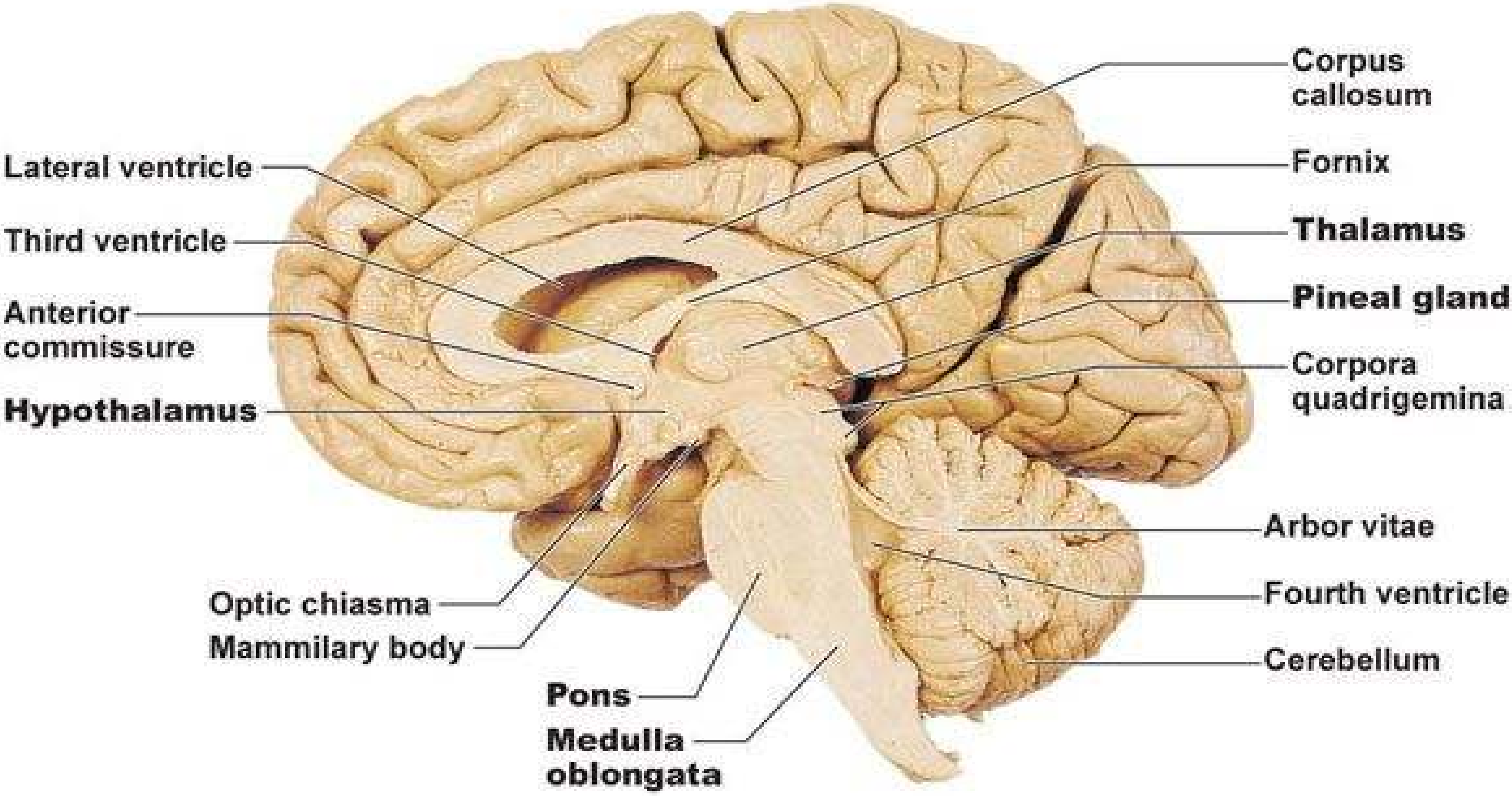






Overview of the Endocrine System: Comparison of the Nervous and Endocrine Systems

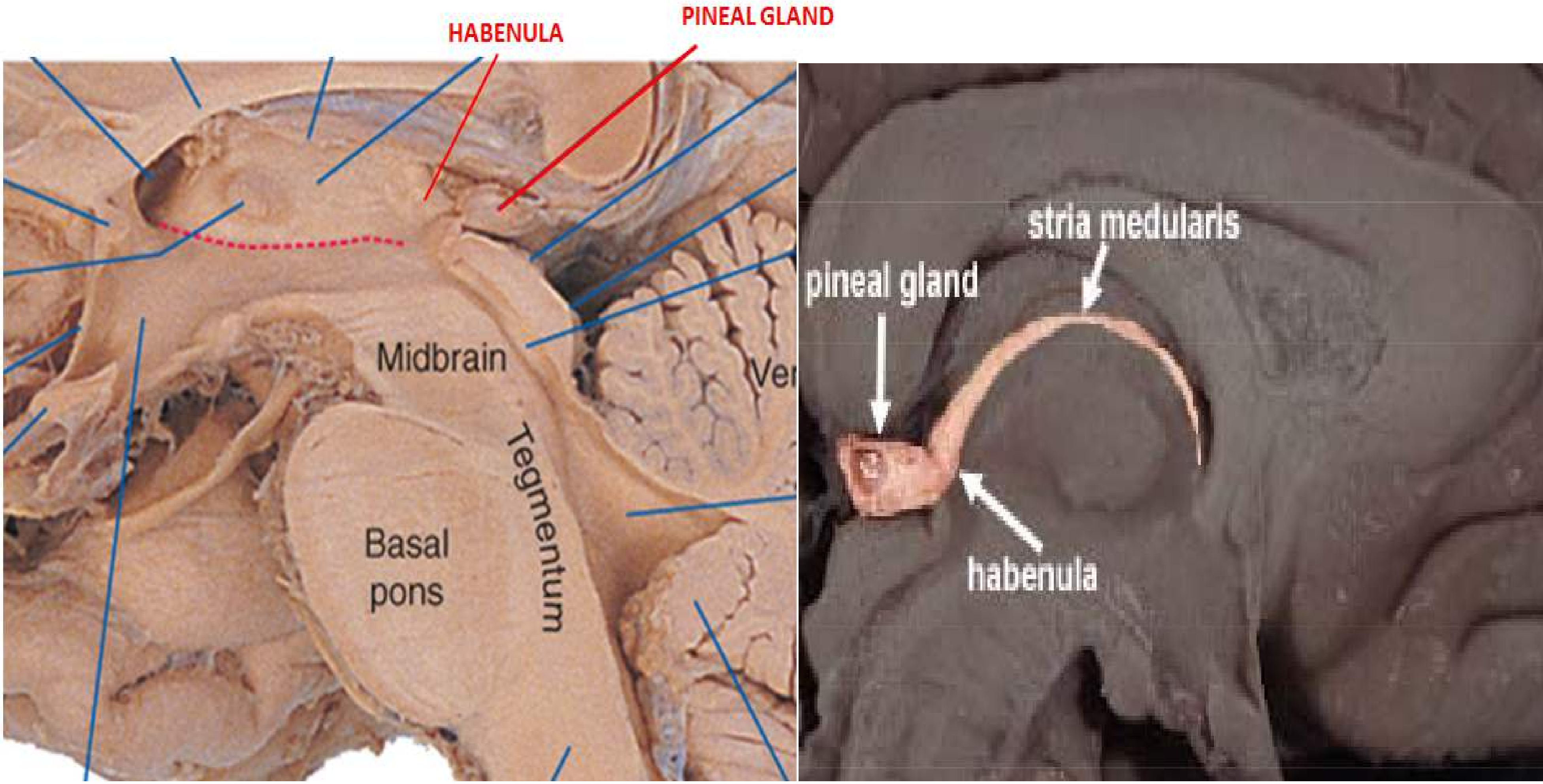
- Endocrine System
  - Chemical signals only
  - Slower to respond and stop
  - Hormones go everywhere
  - Adapts relatively slowly
  - Sometimes widespread effects
- Nervous System
  - Chemical and electrical signals
  - Responds and stops quickly
  - Targets specific organ
  - Adapts quickly
  - Usually local effects


Corpus callosum
Lateral ventricle
Fornix
Third ventricle
Thalamus
Anterior commissure
Pineal gland
Corpora quadrigemina
Hypothalamus
Arbor vitae
Optic chiasma
Fourth ventricle
Mammilary body
Cerebellum
Pons
Medulla oblongata

EPITHALAMUS

MADE UP OF PINEAL GLAND AND HABENULA

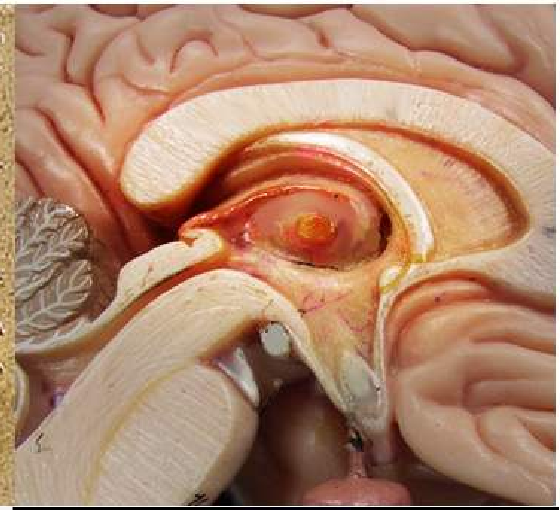
- Habenula involved in food and water intake

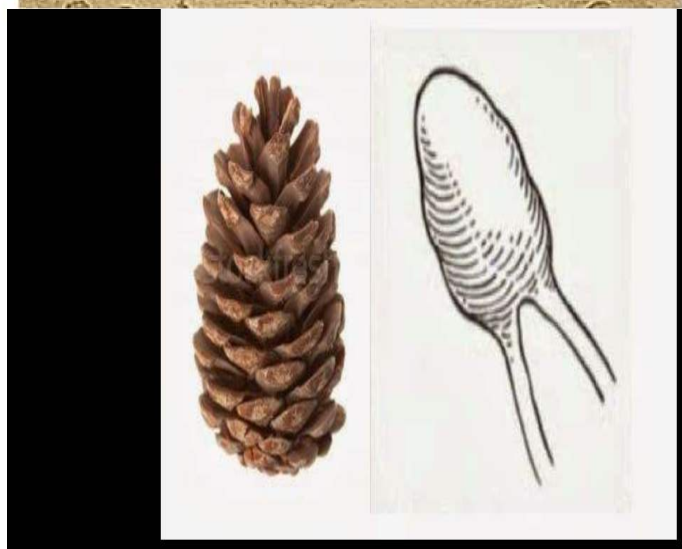


Pineal Gland

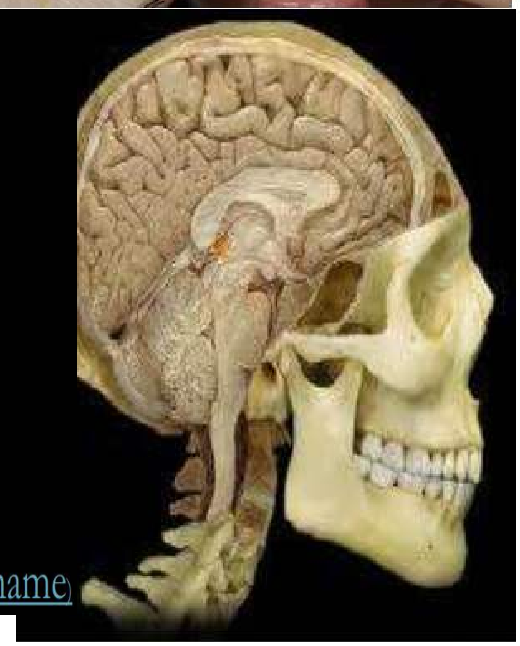
The 3rd eye of anubis

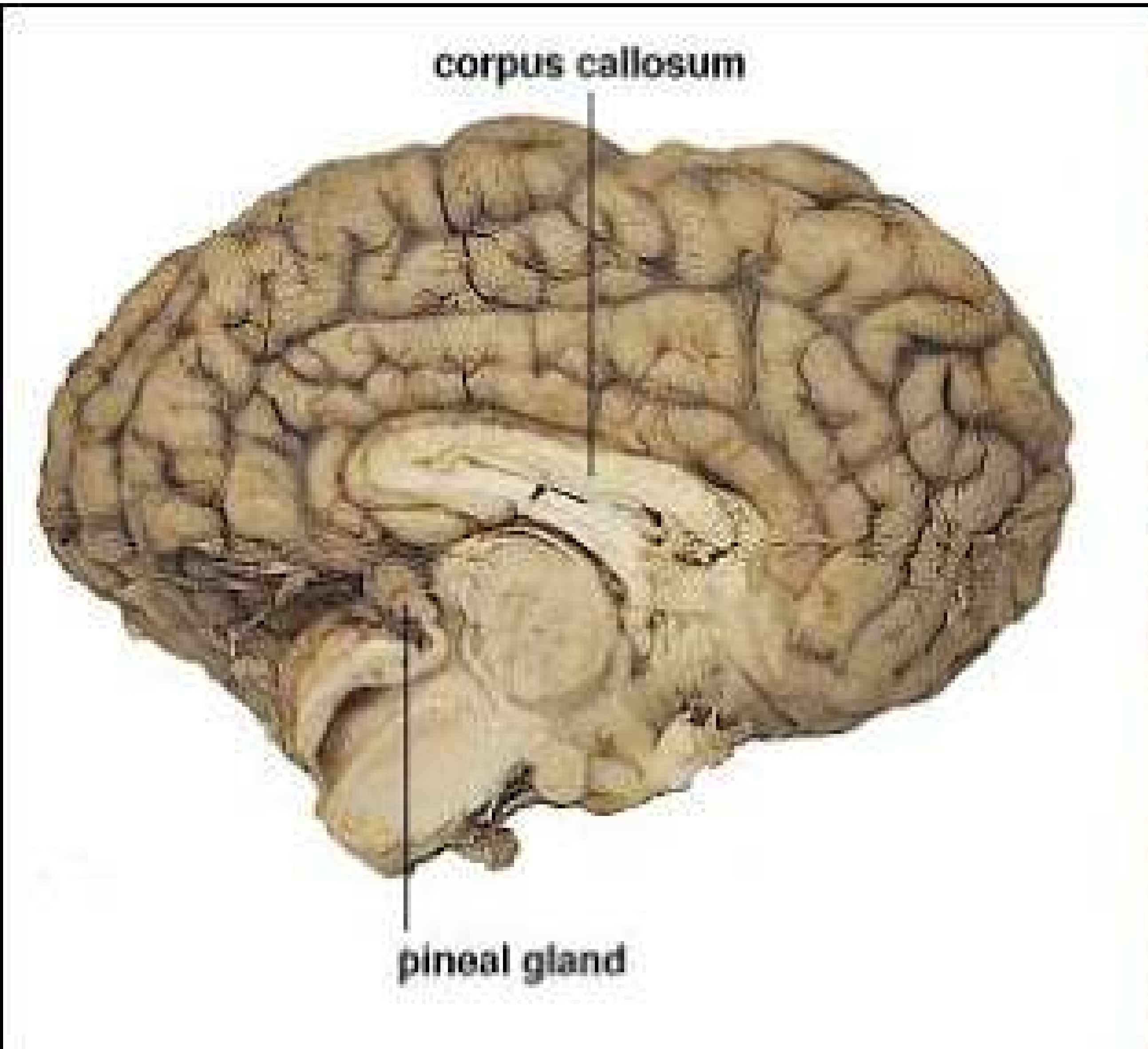
- AKA epiphysis cerebi
- **Pinealocytes secrete melato**
  - **Involved in diurnal rhythms**
  - **Innervated by neurons of the ANS**
- Brain Sand
  - Crystallized deposits of calcium carbonates and calcium phosphates

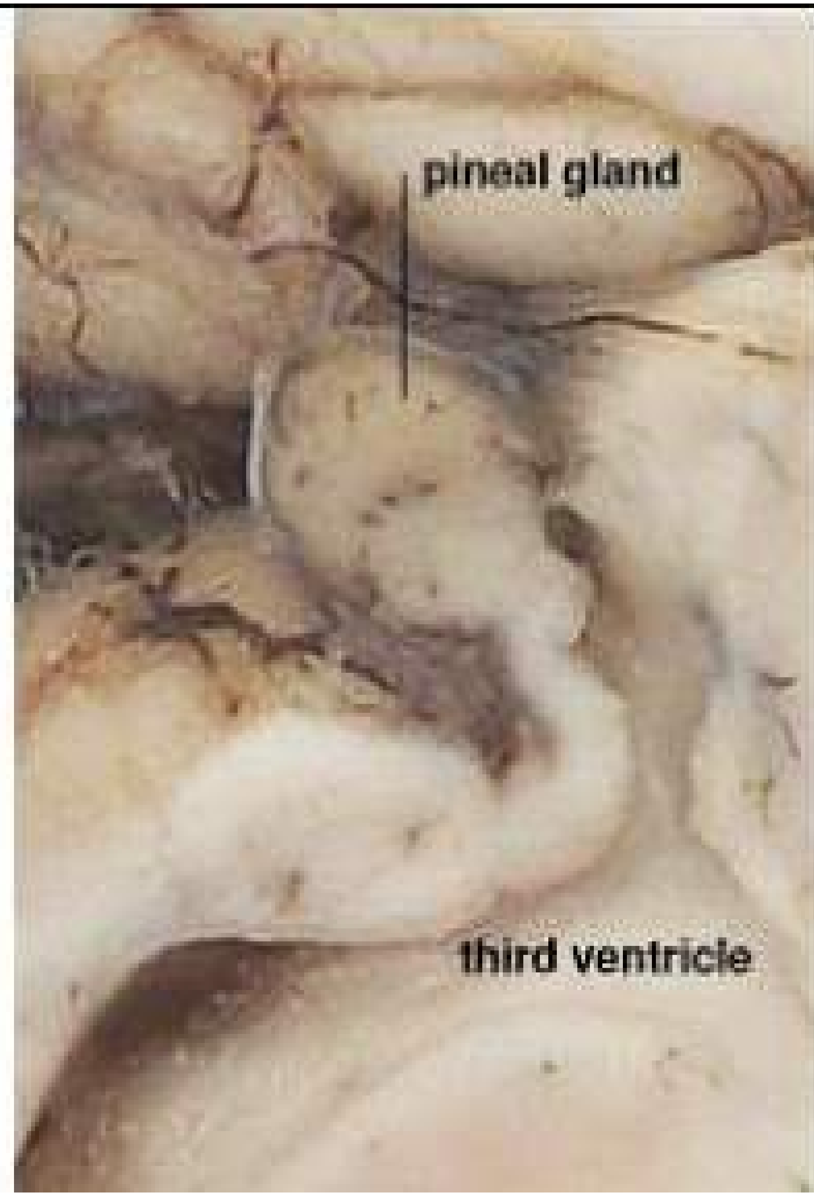




Its shape resembles a tiny pine cone (hence its name)




corpus callosum
pineal gland


pineal gland
third ventricle

- The pineal body is surrounded by pia mater, which functions as its capsule and which sends connective tissue septa into the pineal body, subdividing it into lobules.

- **In the pineal we find two cell types:**
    - **pinealocytes** (about 95% of the cells; large, light and round nuclei)
    - **astrocytes** (glial cells; dark, elongated nuclei).

- Aside from the cells the pineal gland also contains ..... sand - well - **brain sand (or acervuli cerebri or - just for good measure - corpora arenacea)**. These are calcium-containing concretions in the pineal parenchyma, which increase in size and number with age.

- The most prominent secretory product of the pineal body is melatonin.
    - they may "delay" puberty through anti-gonadotrophic effects.
- blocks the secretion of gonadotropins (LH & FSH) from anterior pituitary gland. inhibit ovarian activity
- • These hormones aid in the proper development and functioning of the ovaries and testes

- Secretory activity in the pineal gland is stimulated by **darkness and inhibited by light.**
- Via the effects of pineal hormones on the adenohypophysis and sex hormones it is likely that the pineal body is involved in phenomena associated with **the circadian rhythm and seasonal phenomena** (e.g. seasonal affective disorder, SAD).

- The pineal body is innervated by **postganglionic sympathetic fibres derived from the superior cervical ganglion**.
- **serotonin** serotonin -neuro transmitter , vasoconstrictor
    - stimulates smooth muscles and inhibits gastric secretion

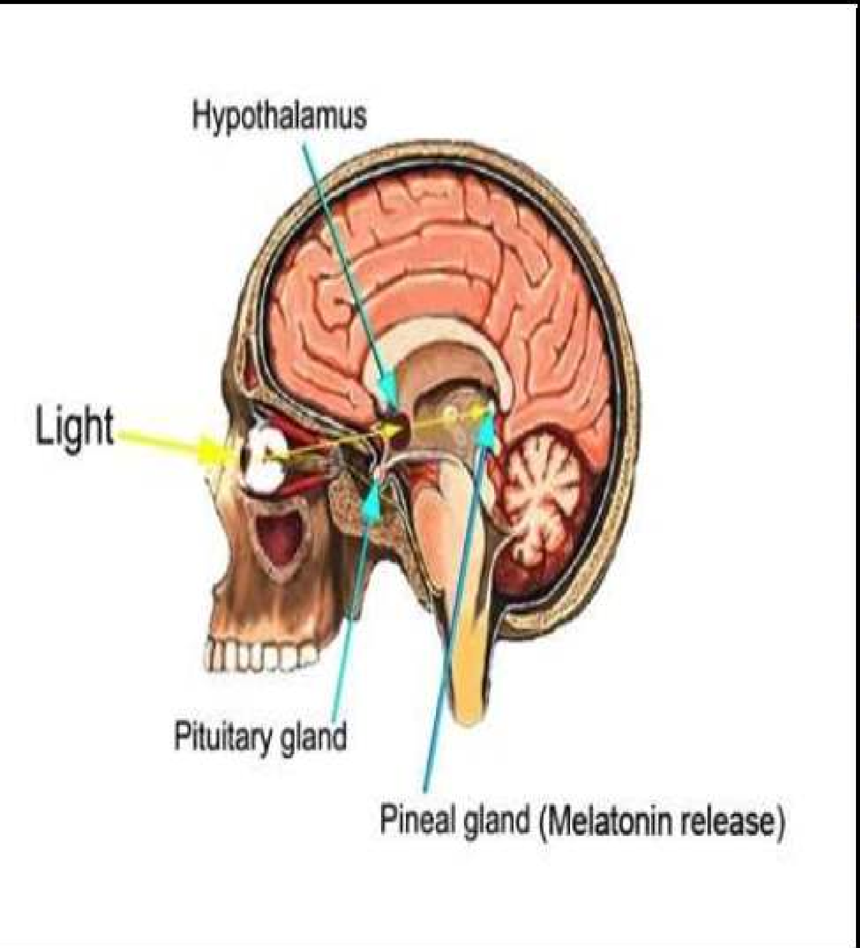
Melatonin effects :

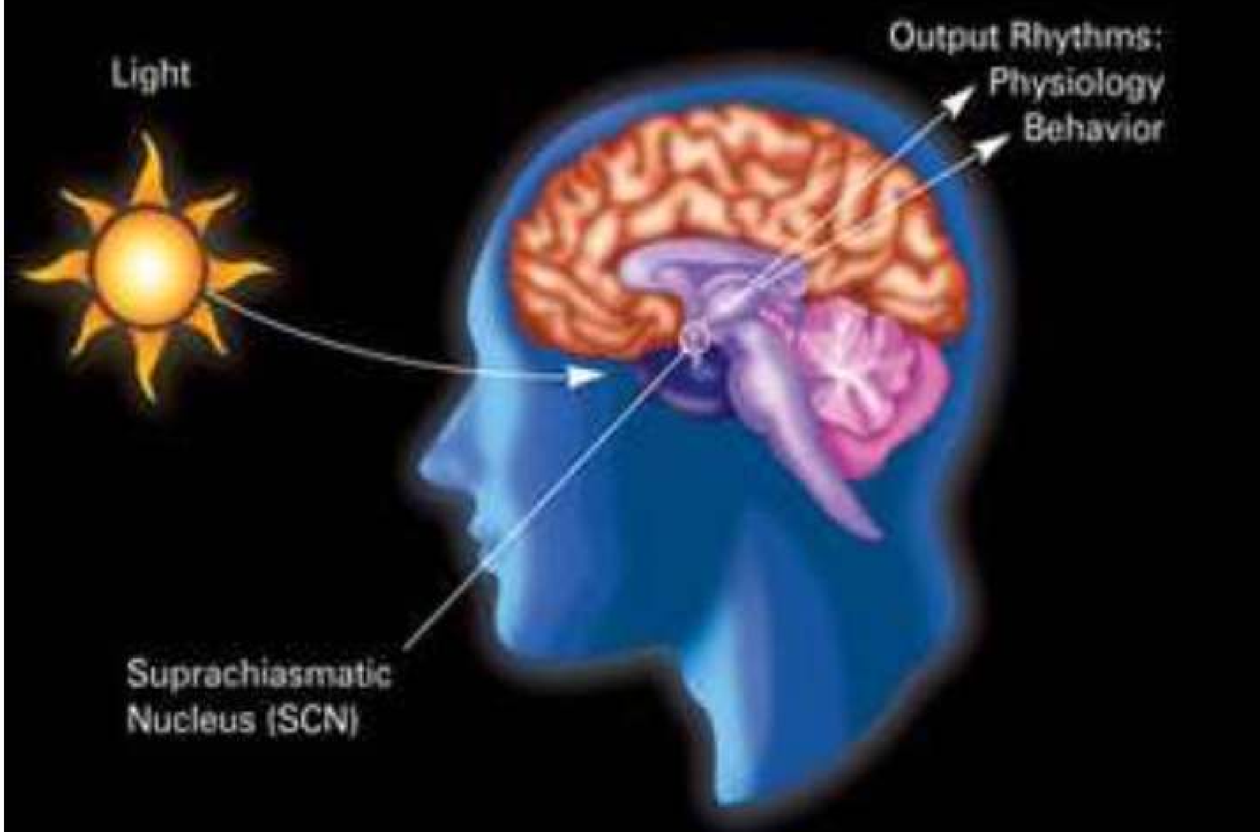
- **Dreaming: Some supplemental melatonin users report an increase in vivid dreaming .**

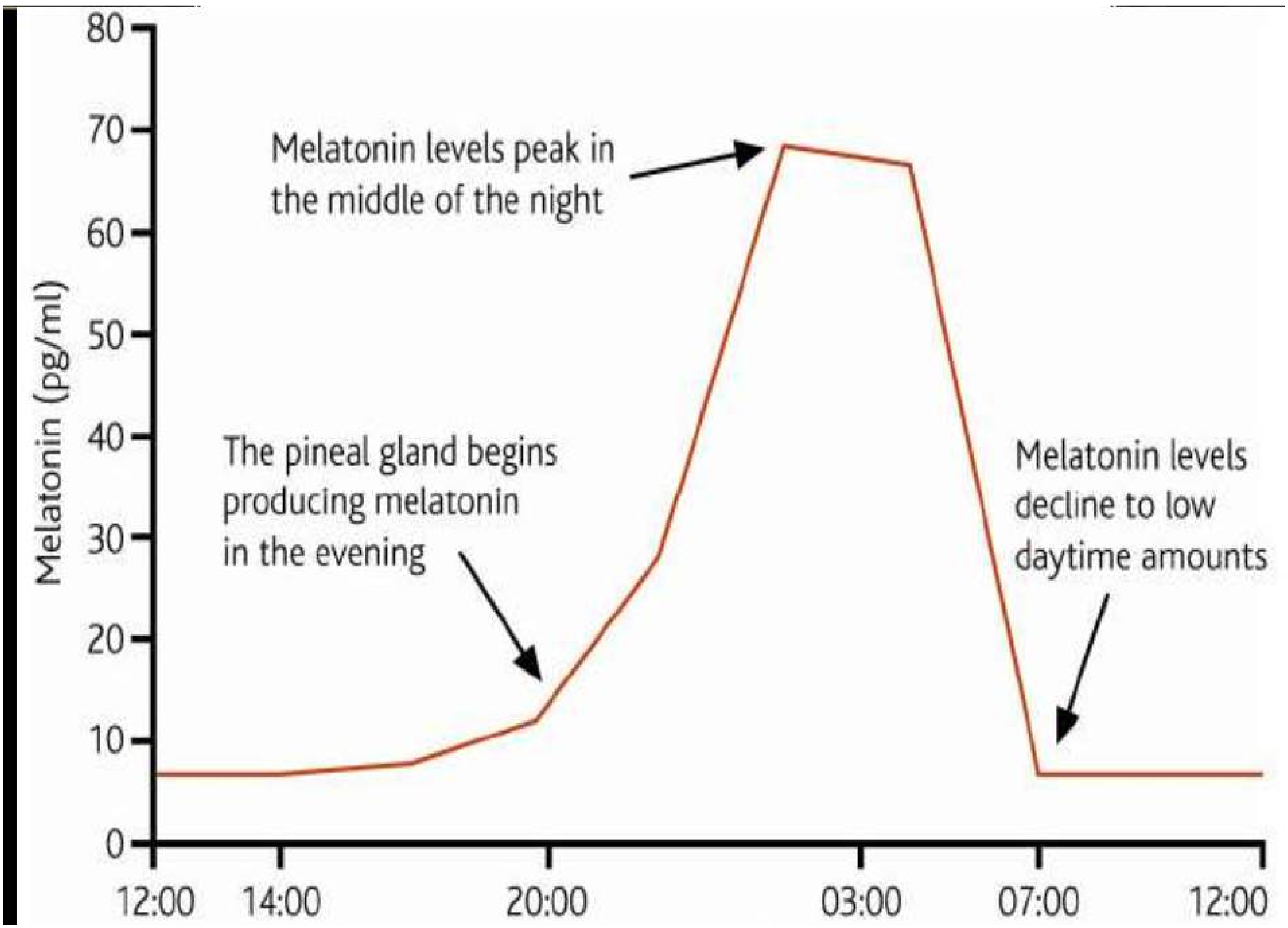
Extremely high doses of melatonin (50m g) dramatically increased REM sleep time and dream activity in both people with and people without narcolepsy .

- **Autism Individuals with autism spectrum disorders (ASD) may have lower than normal** levels of melatonin

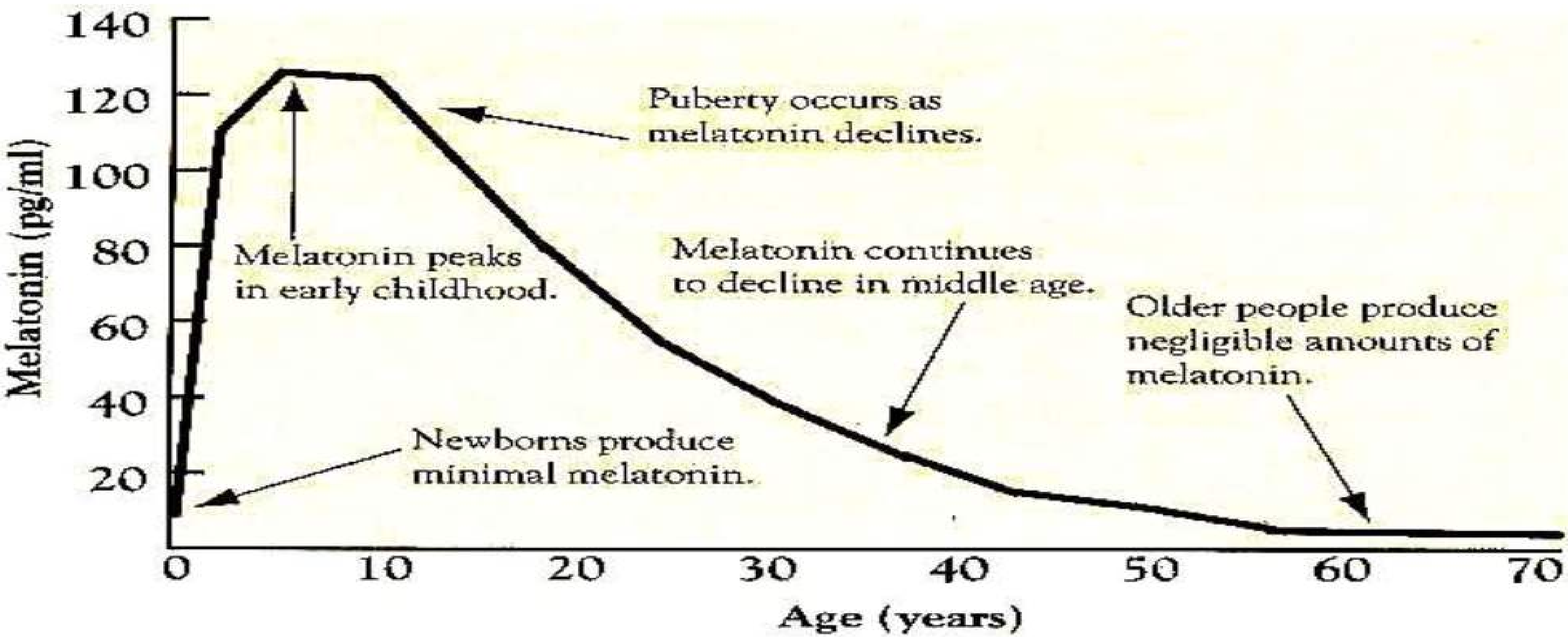
- <u>Natural Sleeping Tablet</u>

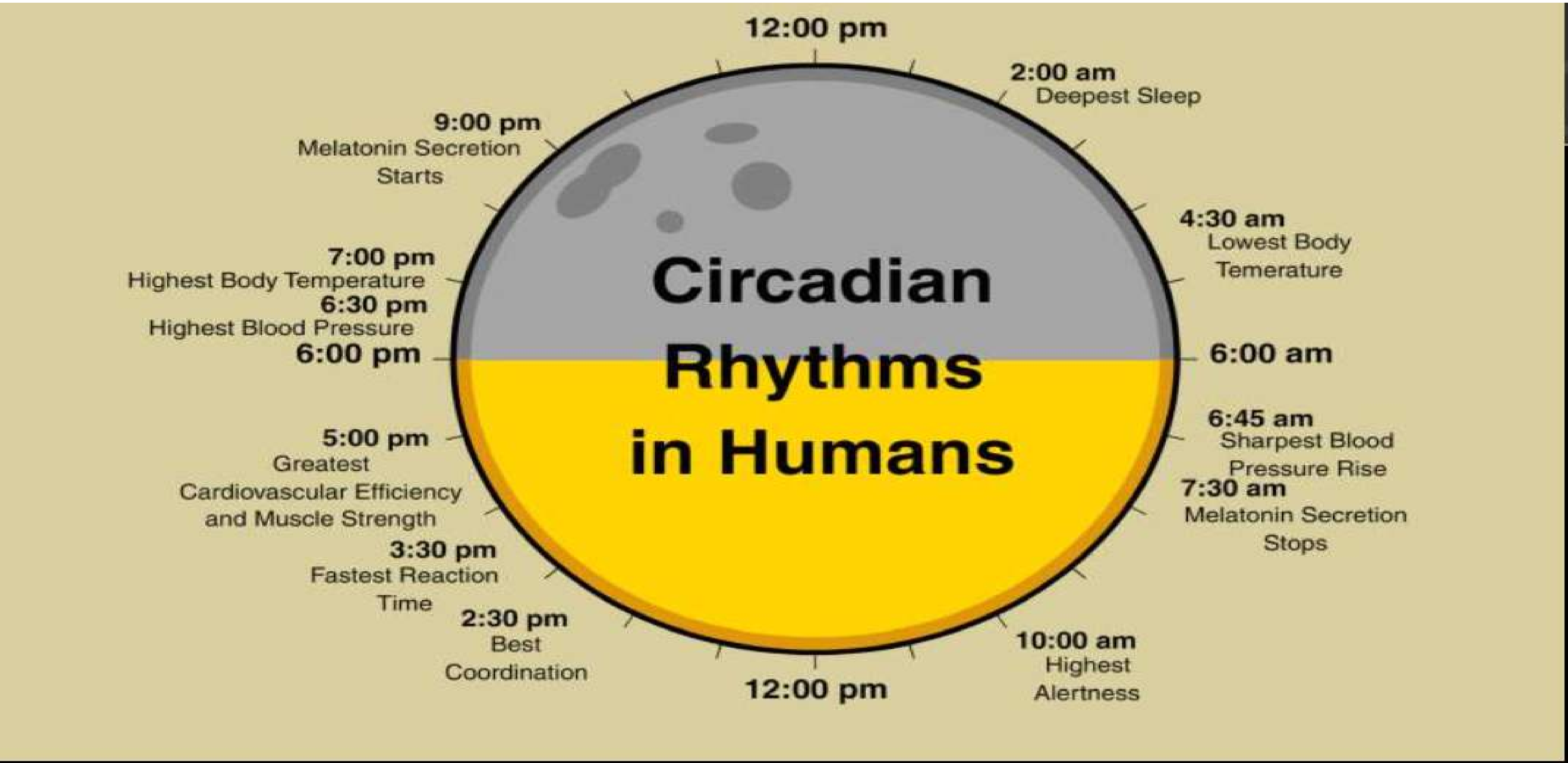




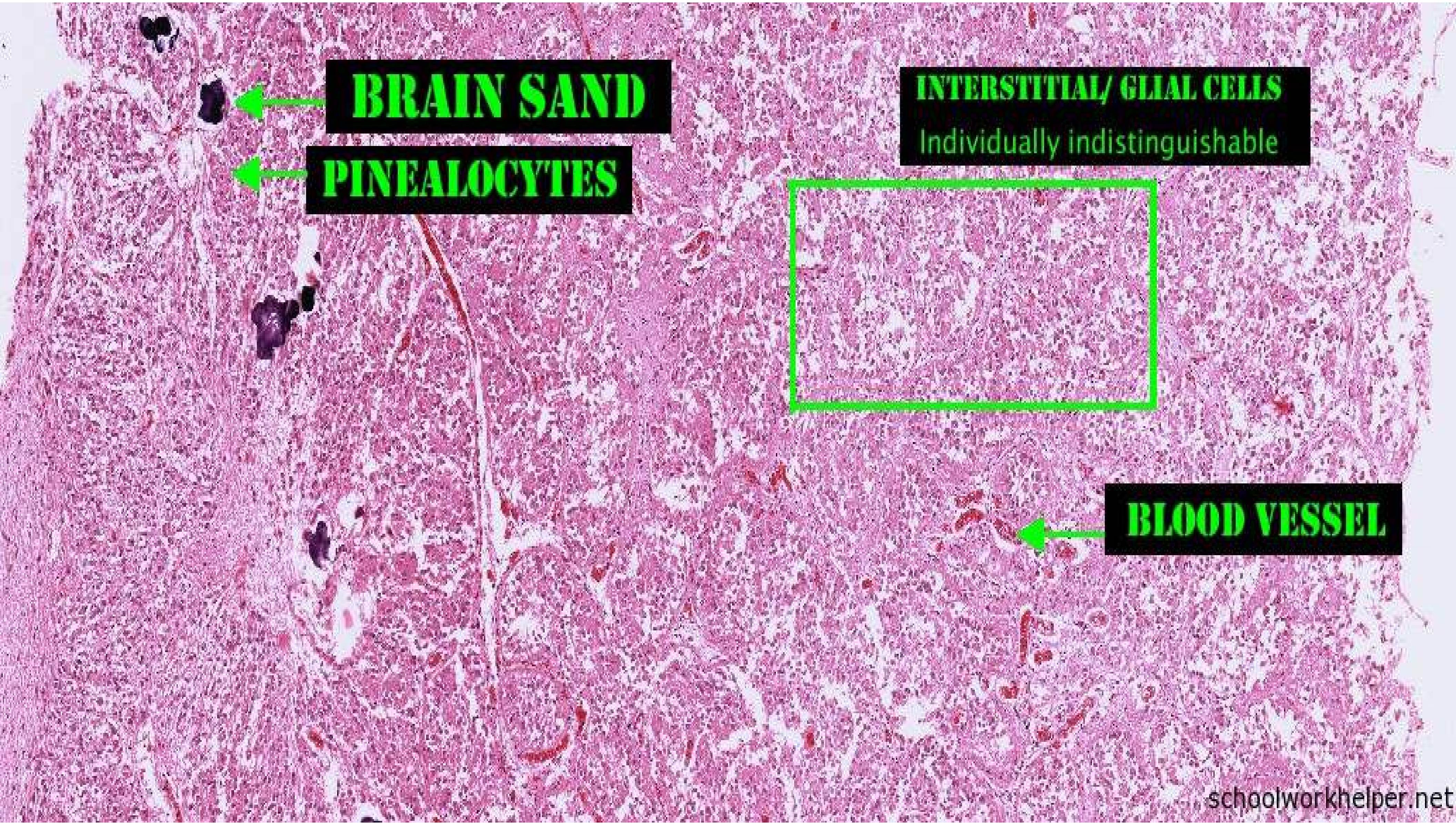

Melatonin (pg/ml)
80
70
60
50
40
30
20
10
0
12:00
14:00
20:00
03:00
07:00
12:00
Melatonin levels peak in the middle of the night
The pineal gland begins producing melatonin in the evening
Melatonin levels decline to low daytime amounts

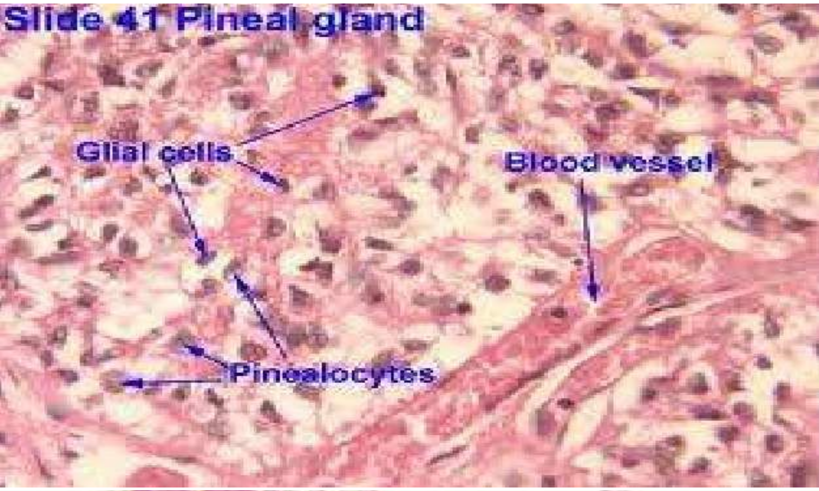
MELATONIN VS AGE

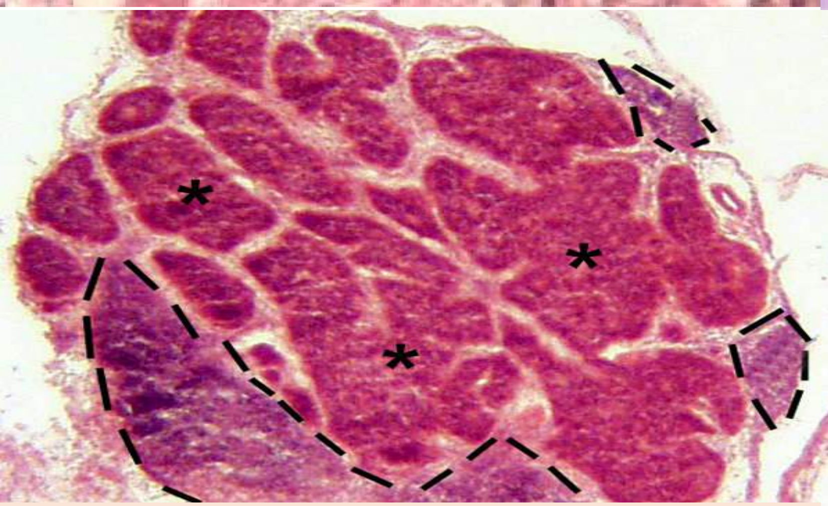




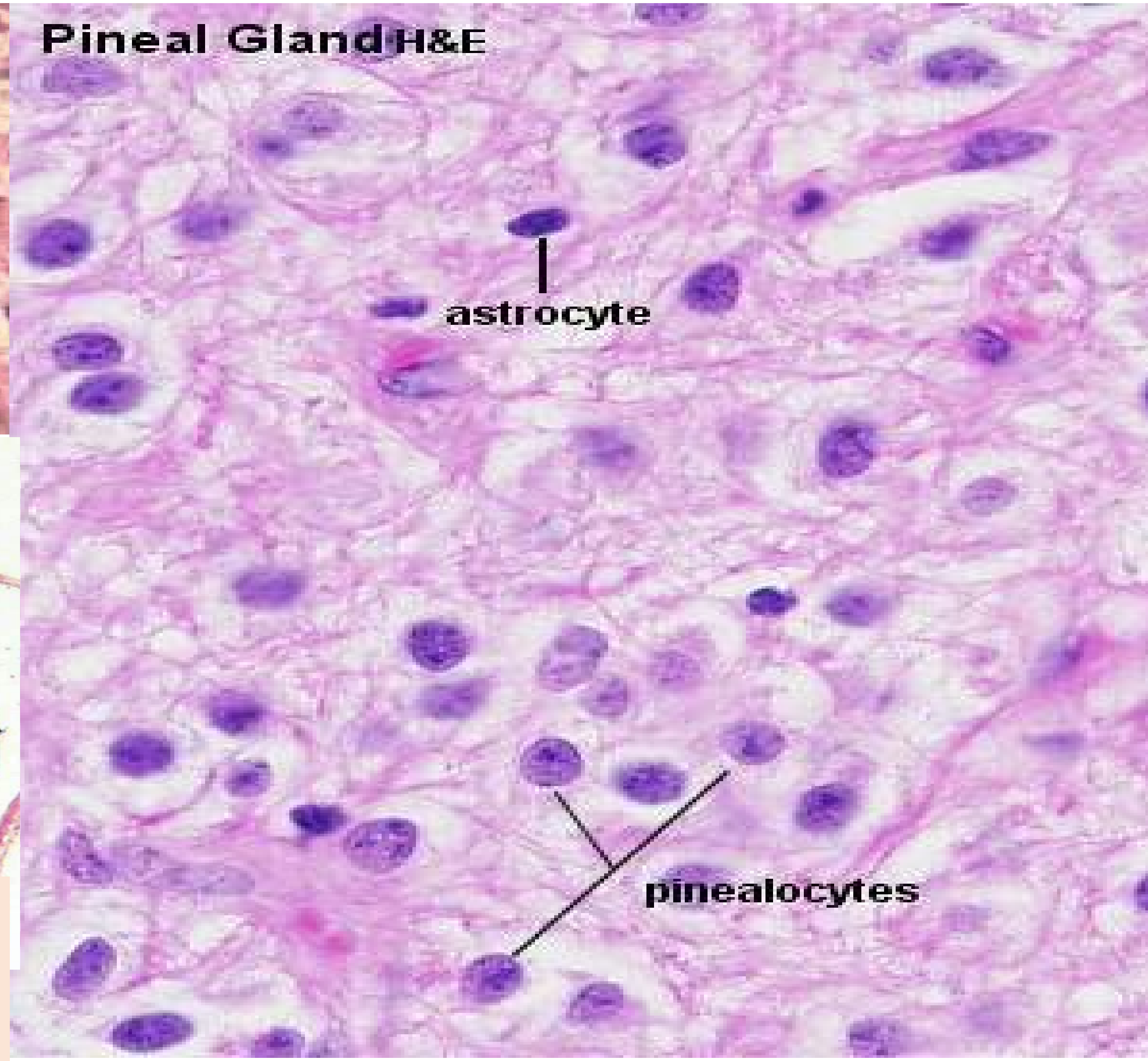
Circadian rhythms are physical, mental and behavioral changes that follow a roughly 24-hour cycle, responding primarily to light and darkness in an organism's environment.


BRAIN SAND
PINEALOCYTES
INTERSTITIAL/ GLIAL CELLS
Individually indistinguishable
BLOOD VESSEL
schoolworkhelper.net





The pineal follicles (*) comprise pinealocytes and supportive cells arranged as epithelium. Prominent interstitial septa separate individual follicles.



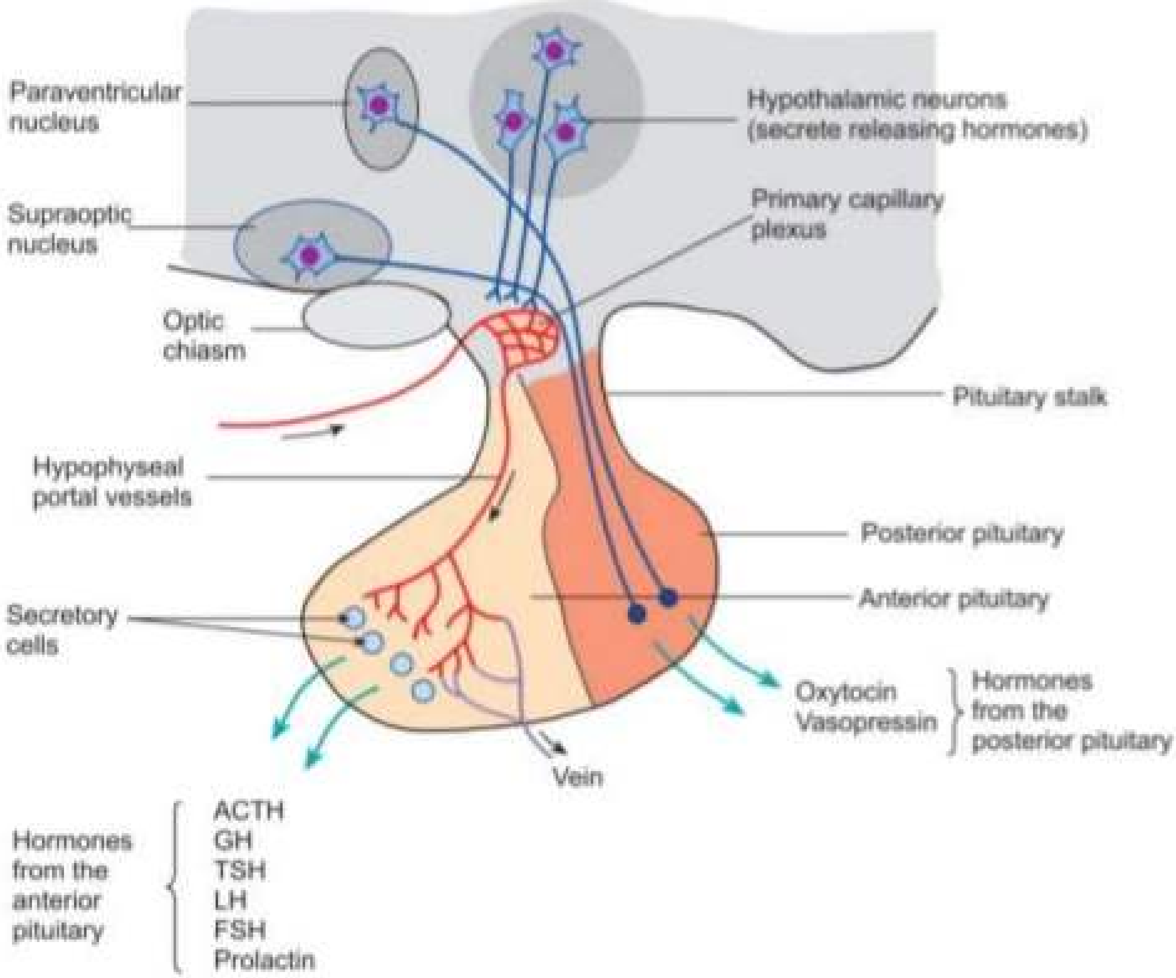
FUNCTIONS OF THE NEUROENDOCRINE SYSTEM

Along with the nervous system, hormones provide the necessary communication between all the cells that constitute a multicellular animal

Nervous system-Is involved in rapid transfer of short-term events and coordination of short-term events. Electrochemical information involving neurons.

Neurosecretory cells-Neurons have electrical activity but involved in the production and release of neurosecretion that produces their effect as chemicals.

Endocrine system-Is involved in the integration and coordination of long-term events through chemicals called hormones.



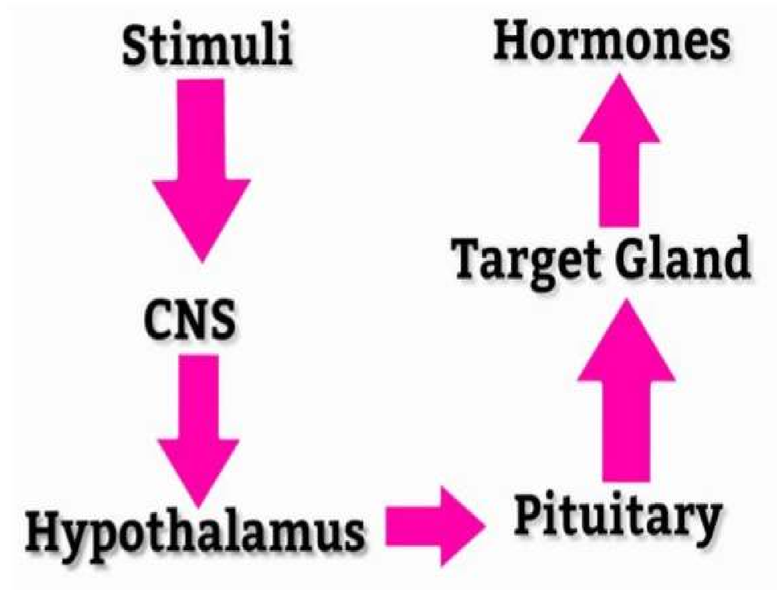
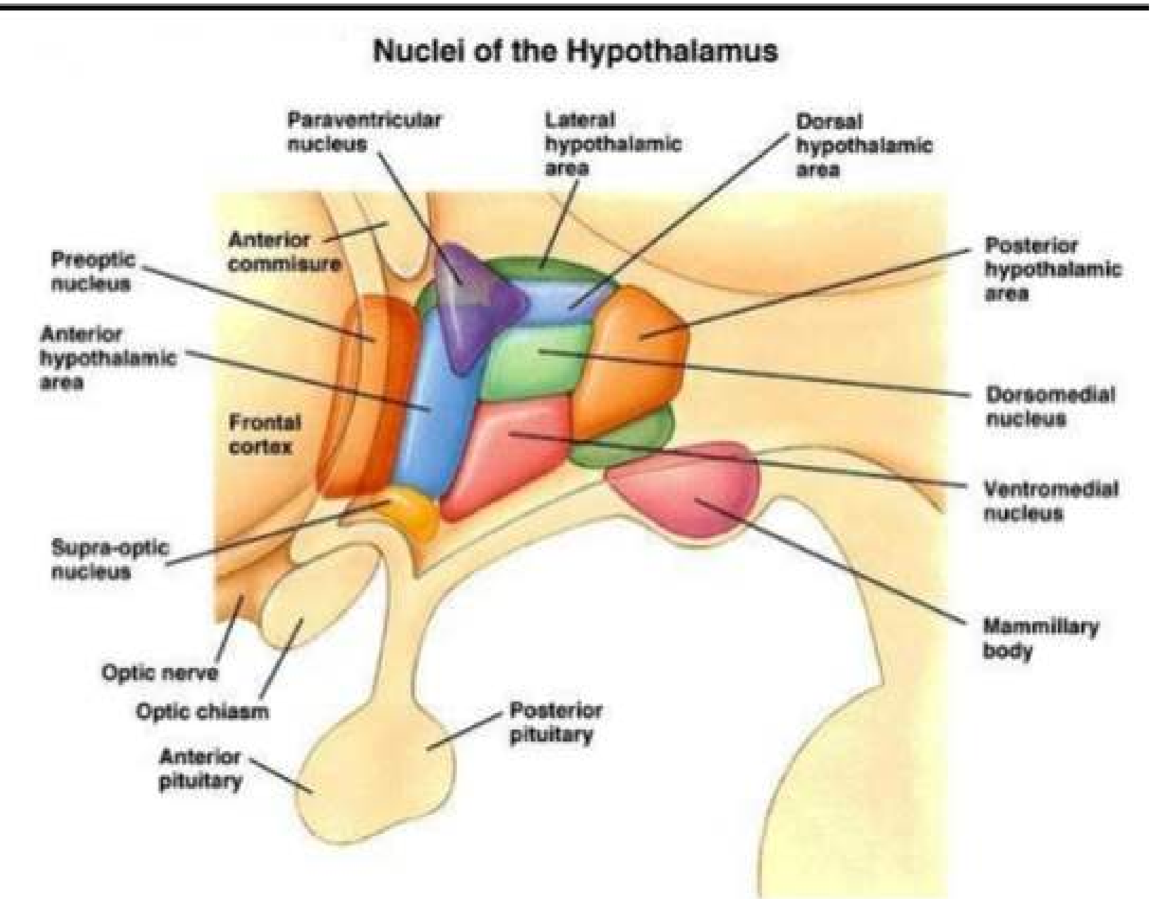


Fig.Showing ,The secretory activity of many endocrine glands is controlled by the nervous system.

Hypothalamus



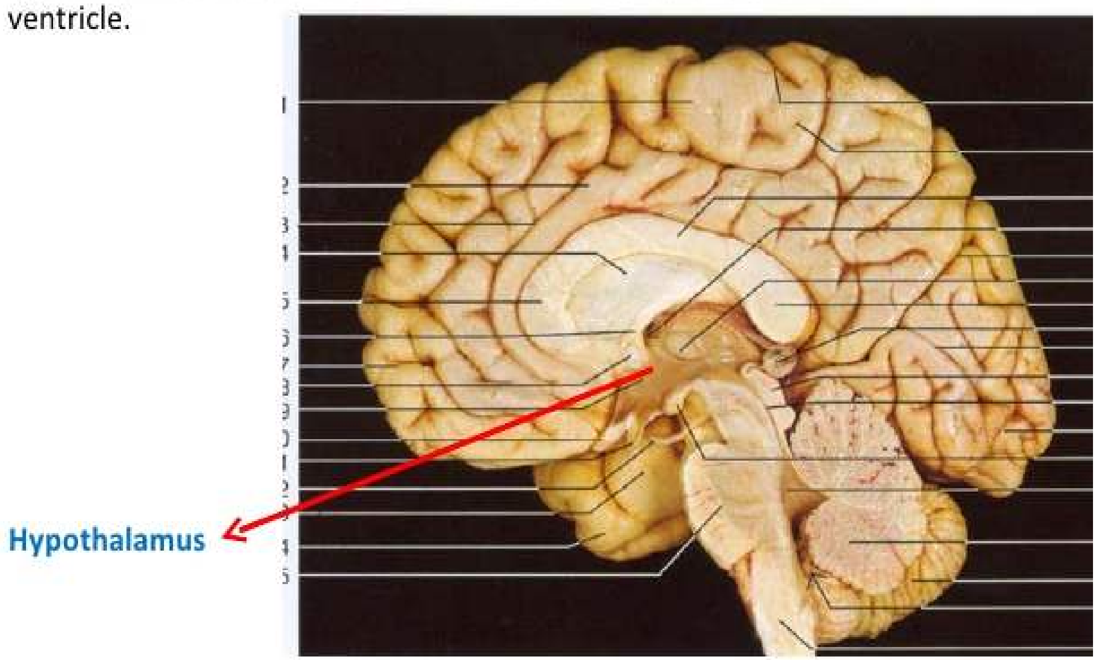
Functions of Hypothalamus. (AS-RESPECT)

- Autonomic functions.
- Sleep –wake cycle.
- Reward & punishment centre.
- Endocrinal functions.
- Sexual behaviour & reproduction.
- Ph(F)ood intake regulation.
- Emotional & Instinctual behaviour.
- Circadian Rhythm control.
- Temperature regulation.

Hypothalamus

The hypothalamus consists of only 4 cm^3 of neural tissue, or 0.3% of the total brain.

The hypothalamus extends from the lamina terminalis to a vertical plane posterior to the mammillary bodies, and from the hypothalamic sulcus to the base of the brain beneath the third ventricle.



- The hypothalamus contains neurons that control releases from the anterior pituitary.
- Seven hypothalamic hormones are released into a portal system connecting the hypothalamus and pituitary, and cause targets in the pituitary to release eight hormones.

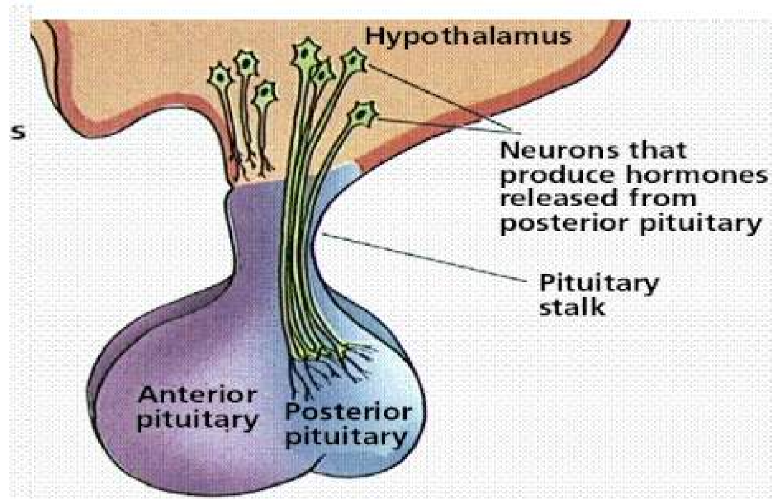
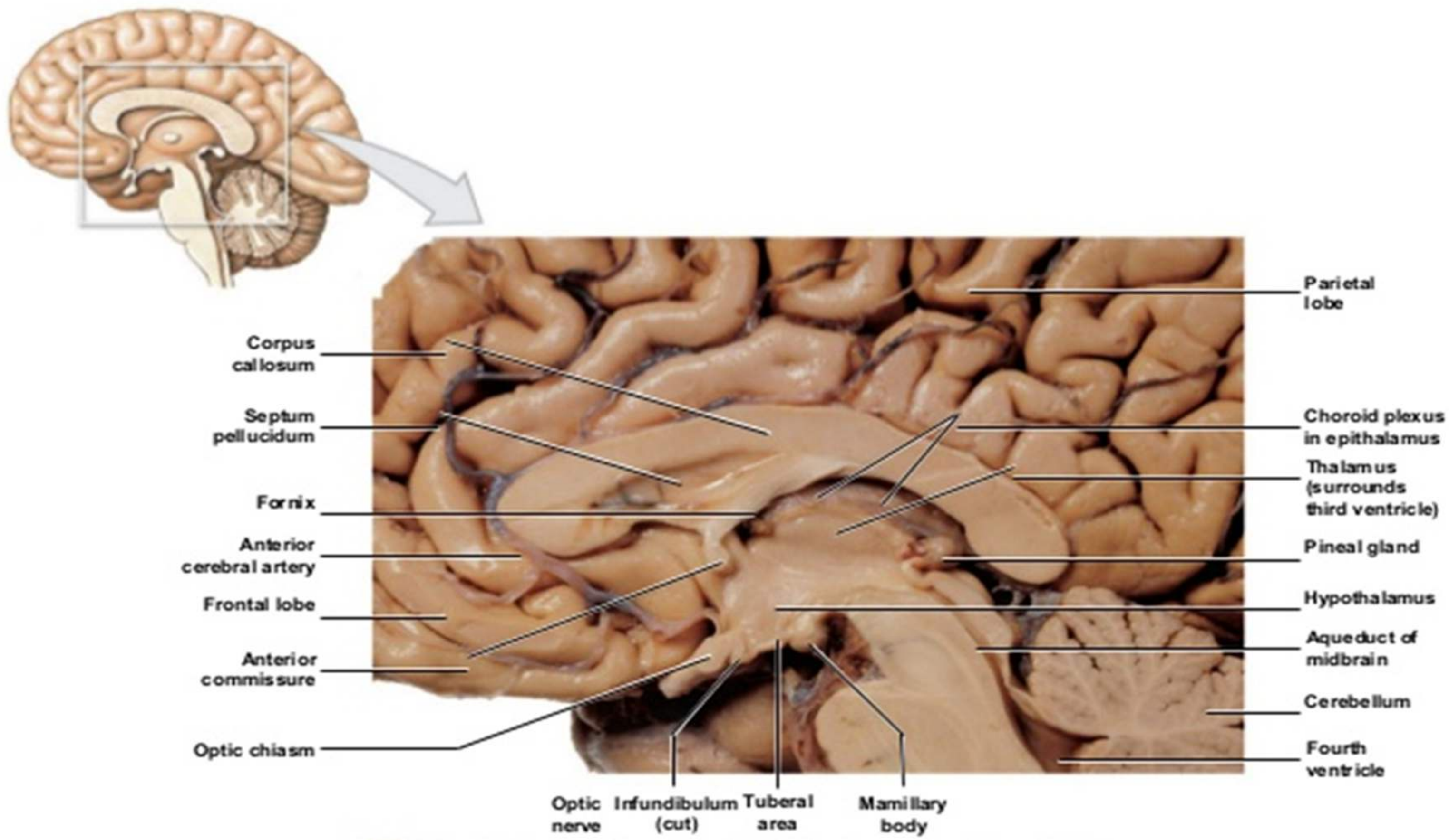


Figure 16.12a The Hypothalamus



a Midsagittal section through the brain. This view shows the major features of the diencephalon and adjacent portions of the brain stem.

PRINCIPAL HYPOTHALAMIC POLYPEPTIDE.

- **Food intake increased by**
  - Neuropeptide Y.
  - Orexin – A
  - Orexin –B
  - Melanin concentrating hormone. (MCH)
  - Ghrelin.
- **Food intake decreased by**
  - Cocacine & amphetamine regulated transcript. (CART)
  - CRH.

Endocrinal functions.

- Anterior Pituitary.(through Tubero-infundibular tract & hypophyseal portal system)
- Controls Thyroid G.
- Controls Metabolism through adrenal gland.
- Keep gonads inhibited.
- Control formation of milk by prolactin secretion.

- Posterior Pituitary regulate water balance through ADH.
- Regulation Of Uterine Contractility & regulation of Milk Ejection from breast through oxytocin.

RAGE

- **Rage** – violent & aggressive emotional state by strong stimulation of **Punishment Centre**.
- Kept in check by counterbalancing activity of Ventromedial N of hypothalamus, hippocampus, amygdala & ant portion of limbic cortex.

- **Characterized by –**
  - Development of defense posture.
  - Extension of limbs
  - Lifting of tail.
  - Hissing & splitting
  - Piloerection.
  - Wide openings of eye.
  - Pupil dilation.

Hypothalamic control of Anterior pituitary gland secretion

- **Hypothalamus controls the hormonal secretions of the anterior pituitary**, which in turn regulates other endocrine glands.
- Neurons in the hypothalamus secrete releasing hormones and inhibiting hormones into blood capillaries at the base of the hypothalamus.
- Reasing & inhibiting hormones released by Paravocellular Neurosecretory cells of the hypothalamus.

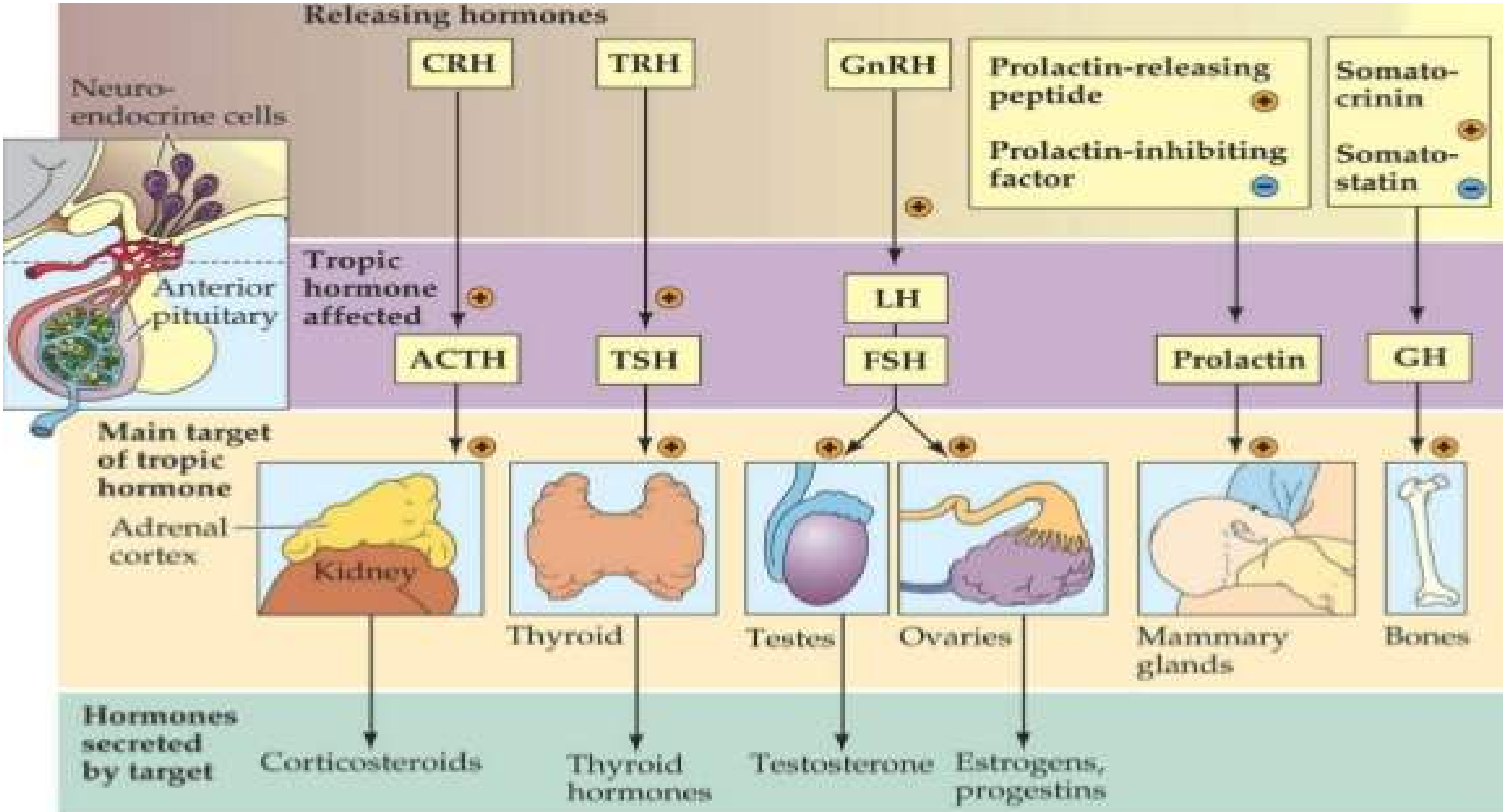
Releasing and Inhibiting hormones

Hypothalamic -Releasing hormones :

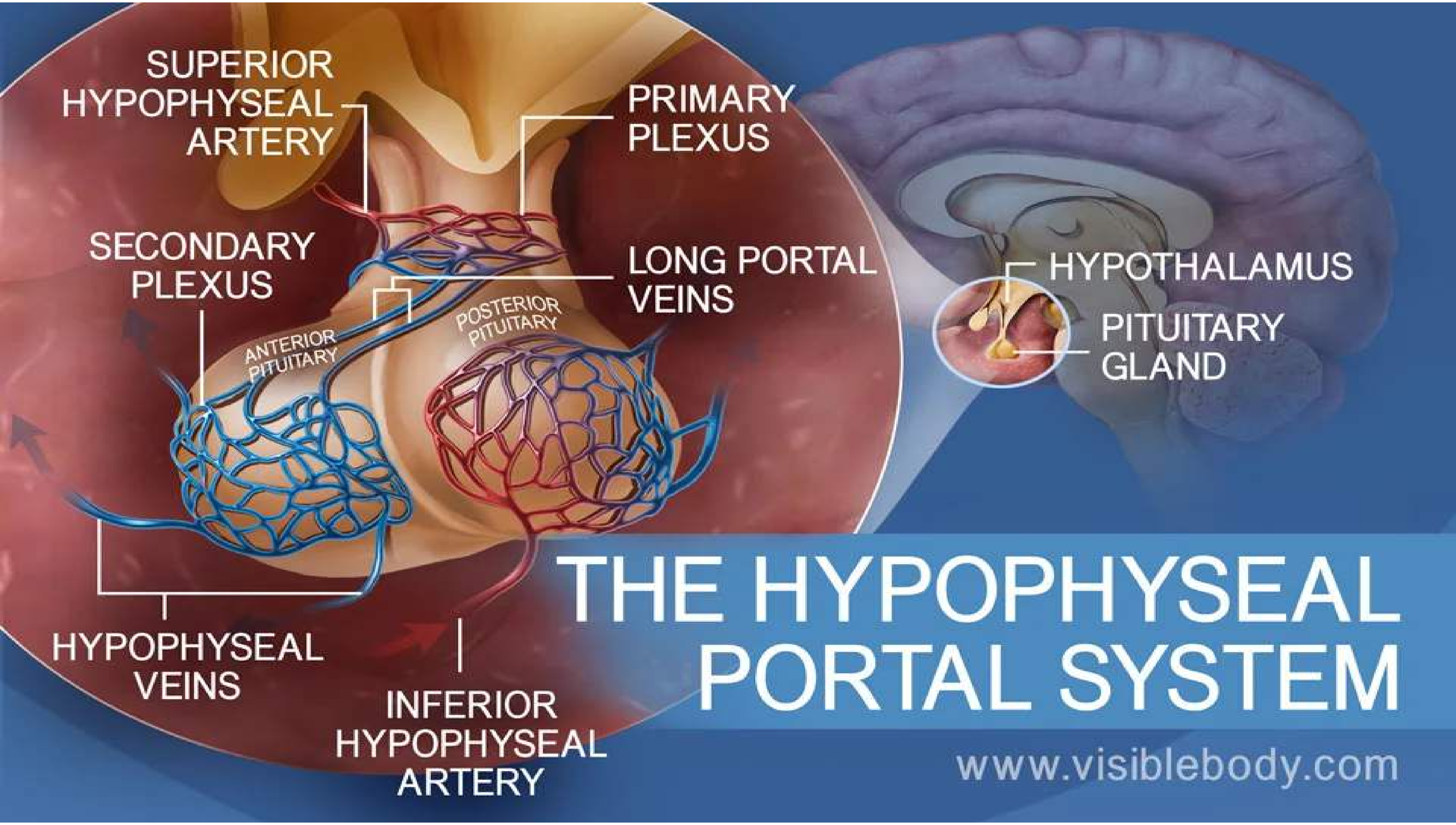
- **CRH (Corticotropn releasing Hormone) =➔Stimulates the release of ACTH**
- **TRH (Thyrotropin-Releasing Hormone) =➔ Stimulates the release of TSH**
- **GnRH (Gonadotropin-Releasing Hormone) =➔stimulates the release of FSH& LH**
- **GHRH(Growth Hormone Releasing Hormone) ==➔Stimulates the release of GH**

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)	Stimulates LH and FSH secretion
Prolactin releasing hormone (PRH)	Stimulates PRL secretion
Prolactin inhibiting hormone (dopamine)	Inhibits PRL secretion



Releasing hormones
CRH
TRH
GnRH
Prolactin-releasing peptide
Prolactin-inhibiting factor
Somato-crinin
Somato-statin
Neuro-endocrine cells
Anterior pituitary
Tropic hormone affected
LH
ACTH
TSH
FSH
Prolactin
GH
Main target of tropic hormone
Adrenal cortex
Kidney
Thyroid
Testes
Ovaries
Mammary glands
Bones
Hormones secreted by target
Corticosteroids
Thyroid hormones
Testosterone
Estrogens, progestins


SUPERIOR HYPOPHYSEAL ARTERY
PRIMARY PLEXUS
SECONDARY PLEXUS
LONG PORTAL VEINS
POSTERIOR PITUITARY
ANTERIOR PITUITARY
HYPOTHALAMUS
PITUITARY GLAND
HYPOPHYSEAL VEINS
INFERIOR HYPOPHYSEAL ARTERY
THE HYPOPHYSEAL PORTAL SYSTEM
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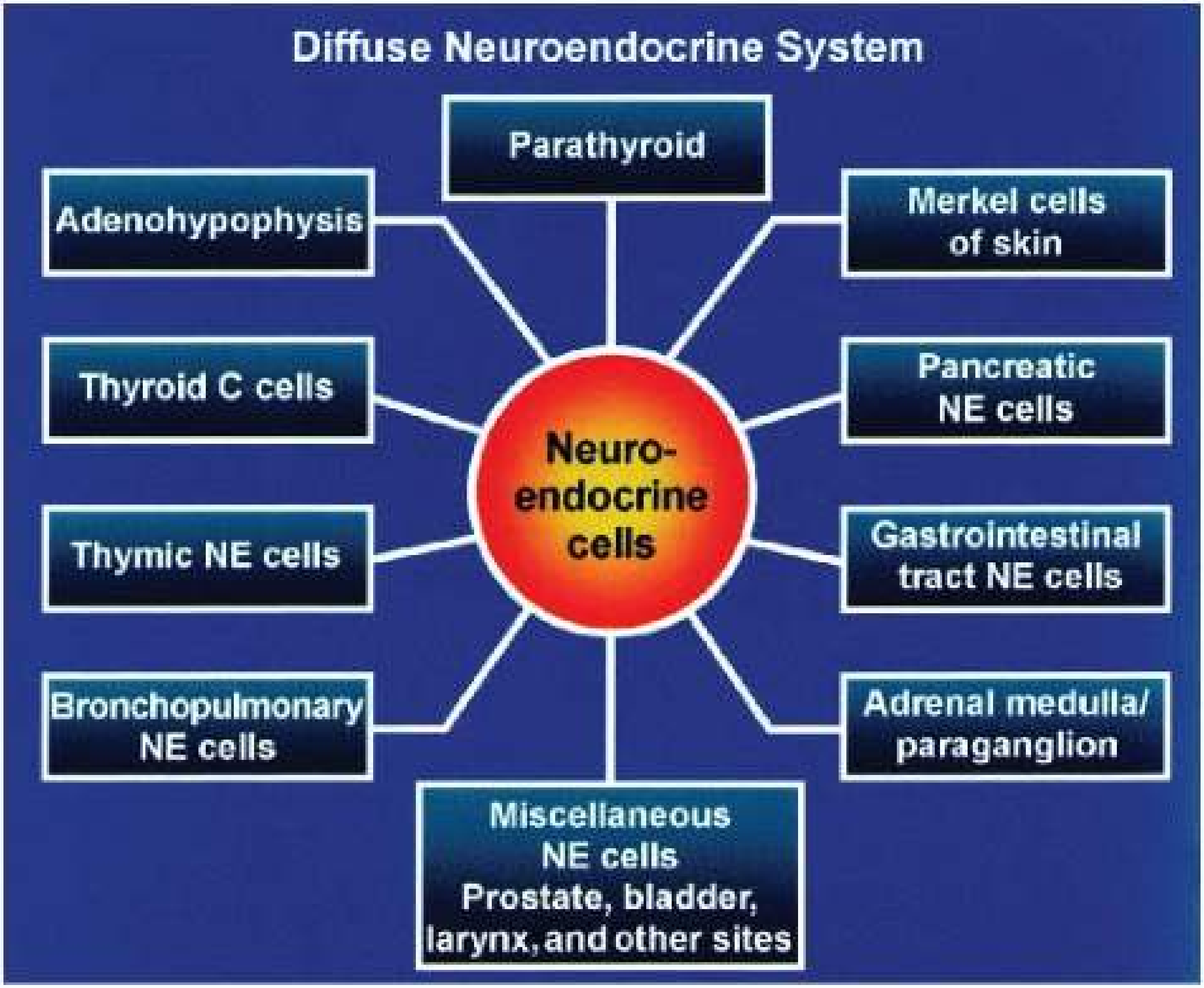


diffuse neuroendocrine system, which is composed of classic endocrine organs as well as scattered neuroendocrine cells in various organs and tissues.

Pituitary Gland

MASTER GLAND

- Also known as Hypophysis Cerebri
- Situated in the hypophyseal fossa in middle cranial fossa
- Histologically it shows two parts-

  Adenohypophysis and Neurohypophysis

  Adenohypophysis shows presence of chromophobes & chromophils

  Chromophils are of two types- Acidophils & Basophils.

- **Neurohypophysis-** It shows presence of axons of neuron , cell bodies of which are situated in hypothalamus. Interspersed among the nerve fibre few neuroglial cells called as pituicytes.

Anterior Pituitary: Hormones

- **Anterior pituitary hormones**
  - FLAT PiG
    - FSH (follicle-stimulating hormone)
    - LH (luteinizing hormone)
    - ACTH (adrenocorticotropic hormone)
    - TSH (thyroid-stimulating hormone)
    - Prolactin
    - Growth hormone (somatotropin)
  - **categories of hormones**
    - corticolipotropins
      - ACTH and MSH (melanocyte-stimulating hormone)
    - glycoprotein hormones
      - FSH, LH, TSH
    - somatomammotropins
      - prolactin and growth hormone

ACIDOPHILS (growth)

- **GROWTH HORMONE**
- **PROLACTIN**

BASOPHILS (trophs)

- **TSH**
- **ACTH**
- **LH, FSH**

- **Cortiolipotropins**
  - **synthesis**
    - corticolipotropins are derived from a single precursor, POMC
      - POMC = pro-opiomelanocortin
  - pathway details
  - **MSH**
    - corticolipotropin synthesis products (aka fragments) contain MSH
    - increased MSH levels → skin pigmentation
    - e.g., Addison's disease
      - **↑ ACTH → ↑ MSH → skin pigmentation**
- **Glycoprotein hormones**
  - subunits of peptide hormones
    - glycoprotein hormones contain 2 subunits: **α and β subunit**
      - α subunits identical, β subunits non-identical
        - hormone specificity determined by β subunit
  - human chorionic gonadotropin (hCG) structurally related to glycoprotein hormone
    - **hCG contains identical α subunit**

- **Somatomammotropins**
  - **prolactin**
  - **growth hormone**
    - **secretion**
      - pulsatile secretory pattern
        - secretory **bursts approximately every 2 hours**
        - ↑ in secretory bursts during exercise and sleep
    - **functions**
      - ↑ linear growth and muscle mass
        - **growth mediated by production of somatomedins**
        - **aka insulin-like growth factors (IGFs)**
      - **diabetogenic effect**
        - insulin resistance
          - decreases glucose uptake and utilization
        - "diabetogenic"
          - growth hormone produces increases in blood glucose

Hormones secreted by anterior pituitary

1. **FSH** (follicle stimulating hormone)
1. **LH** (luteinizing hormone)

The above two are called **gonadotropins**

3. **TSH** (thyroid stimulating hormone, thyrotropin)
4. **ACTH** (adrenocorticotropic hormone)
5. **GH** (growth hormone; somatotropin or somatotropic hormone)
6. **PRL** (prolactin)

- **Tropic (trophic) hormones-**- target other endocrine glands to release their own hormones.

Hormones from basophils :go to other endocrine glands, thyroid, adrenal cortex, ovary, testis. Cells from acidophils do NOT.

Acidophils make GROWTH related hormones.
Basophils make hormones which STIMULATE OTHER endocrine glands.
Chromophobes make NOTHING.

- When stained with the PAS reaction all three types of basophils appear reddish

Chromophobe cells

anterior pituitary cells that lack granules and that do not react with acidophilic/basophilic stains
e.g., stromal cells and degranulated chromophils

- **Chromophobe cells are unstained or weakly stained cells. appears relatively pale under the microscope**
- EM and immunocytochemistry are used.
- They are now thought to represent acidophil and basophilic cells in a dormant or recently degranulated stage (degranulation = release of most of the secretory vesicles), but may also include stem cells of the secretory cells.

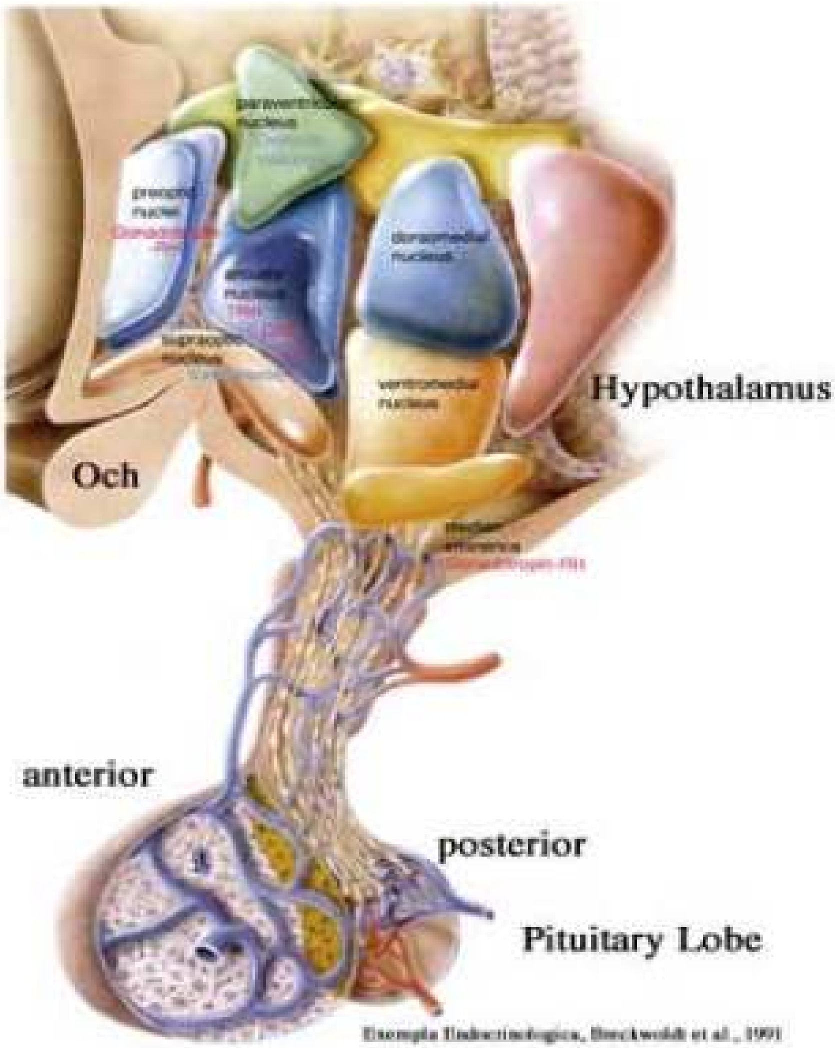
One type of chromophobe cell is known as amphophils.

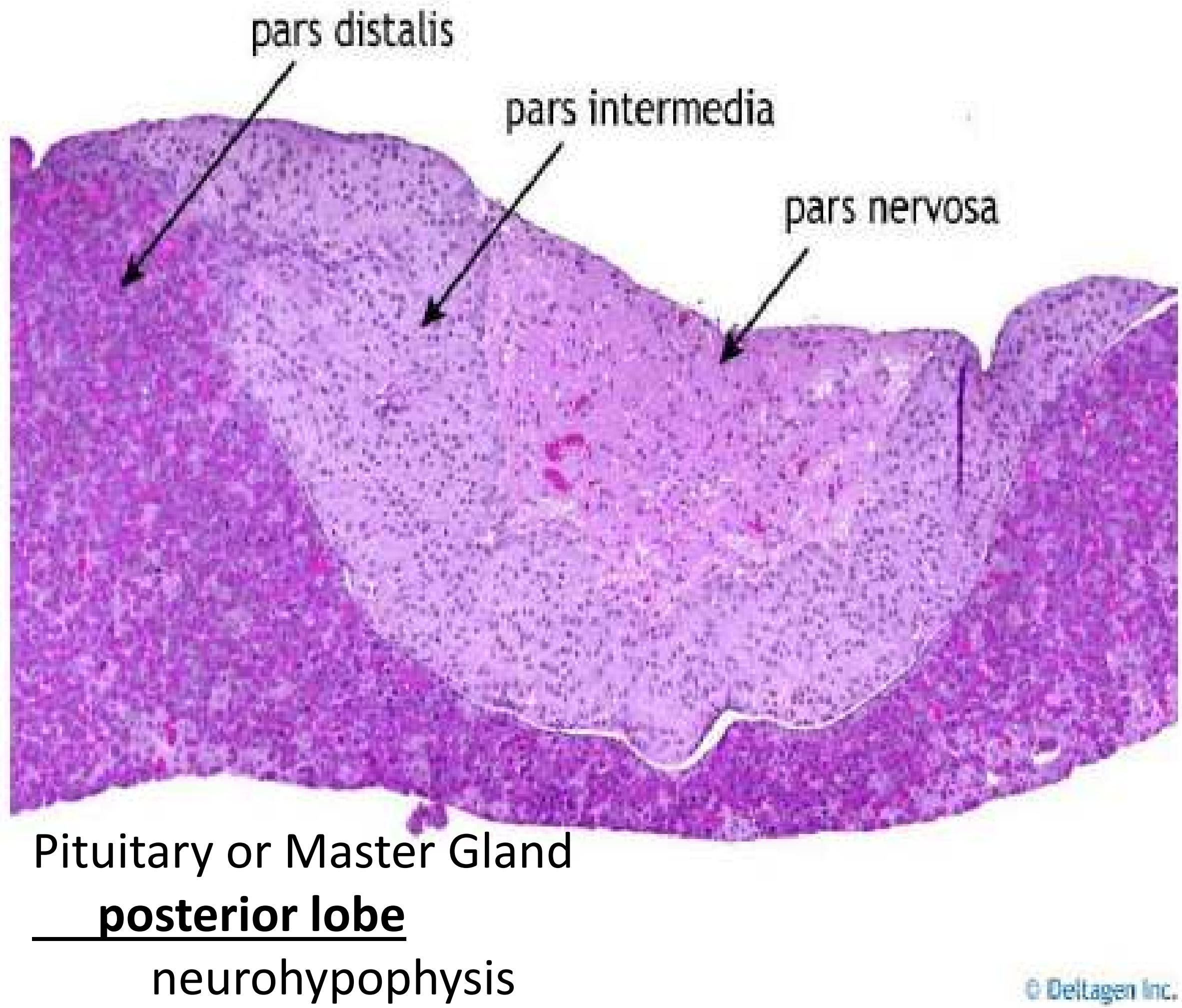
- **Amphophils are epithelial cells found in the anterior and intermediate lobes of the pituitary.**
    - **Together, these epithelial cells are responsible for producing the hormones of the anterior pituitary and releasing them into the bloodstream.**
- **Melanotrophs (also, Melanotropes) are another type of chromophobe which secrete melanocyte stimulating hormone (MSH).**

Chromophobe" also refers to a type of renal cell carcinoma (distinct from "clear cell")
30% of patients with Birt-Hogg-Dubé syndrome will also develop chromophobe renal cancer.

Table 20.3 Pituitary Gland Hormones

Hormone	Target Cells	Effects of Hormone
HORMONES OF THE ANTERIOR PITUITARY		
Adrenocorticotropic hormone (ACTH)	Adrenal cortex	Stimulates production of corticosteroid hormones
Follicle-stimulating hormone (FSH)	Female: Ovaries Male: Testes	Female: Stimulates growth of ovarian follicles Male: Stimulates sperm production
Luteinizing hormone (LH)	Female: Ovaries Male: Testes	Female: Stimulates ovulation, estrogen and progesterone synthesis in ovary Male: Stimulates androgen synthesis in testes
Thyroid-stimulating hormone (TSH)	Thyroid gland	Stimulates thyroid hormone synthesis and secretion
Prolactin (PRL)	Female: Mammary glands Male: Not known	Female: Stimulates milk production in mammary glands Male: May play a role in the sensitivity of the testes interstitial cells to LH
Growth hormone (GH)	Almost every cell in the body	Increased growth and metabolism in target cells; synthesis of somatomedin in the liver to stimulate growth at epiphyseal plate
Melanocyte-stimulating hormone (MSH)	Melanocytes	Stimulates synthesis of melanin and dispersion of melanin granules in epidermal cells
HORMONES STORED IN THE POSTERIOR PITUITARY		
Antidiuretic hormone (ADH) (also called vasopressin)	Kidney Smooth muscle in arteriole walls	Stimulates reabsorption of water from urine in kidneys Stimulates vasoconstriction in arterioles of body, thereby raising blood pressure
Oxytocin (OT)	Female: Uterus, mammary glands Male: Smooth muscle of male reproductive tract	Female: Stimulates smooth muscle contraction in uterine wall; stimulates milk ejection from mammary glands Male: Stimulates contraction of smooth muscle of male reproductive tract





Pituitary or Master Gland

posterior lobe

neurohypophysis

anterior lobe

adenohypophysis

Acidophil cells (or acidophils)

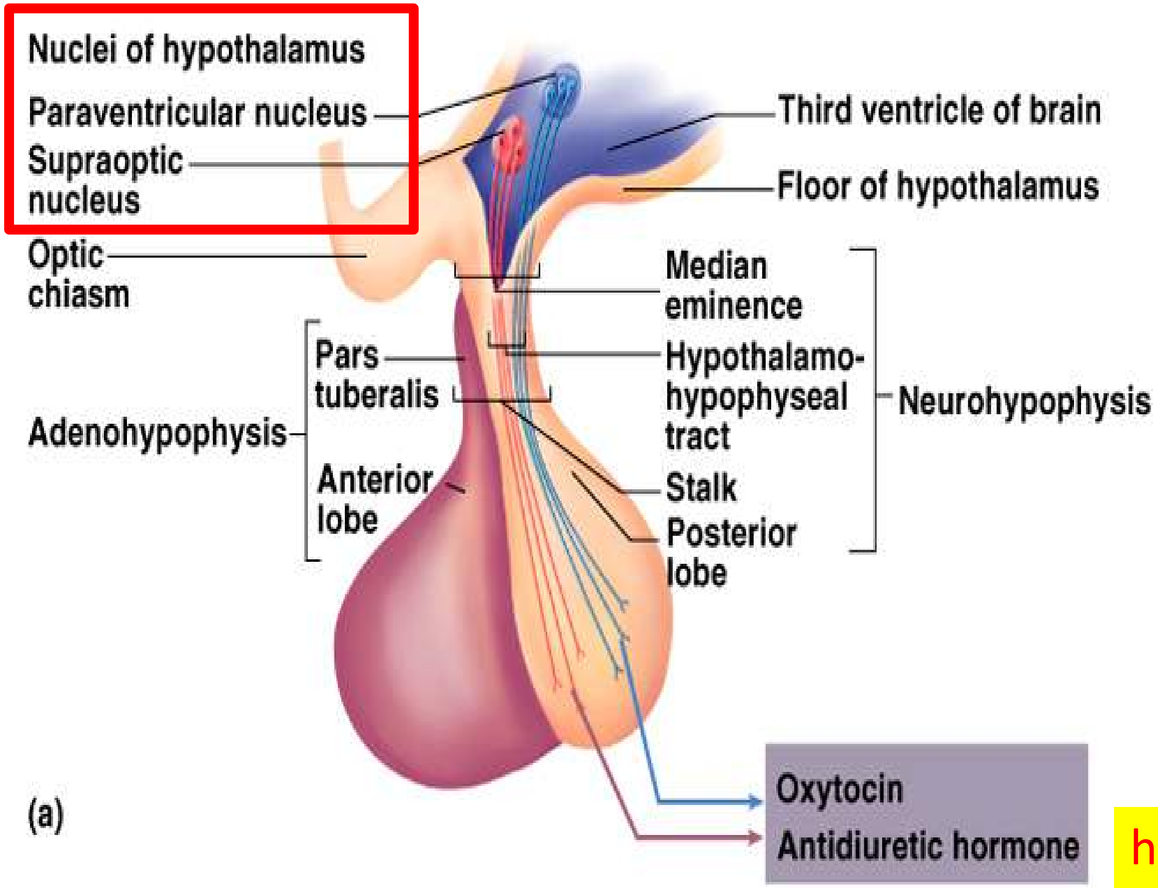
- Acidophils are rounded cells and typically smaller than basophil cells.
- Acidophils account for roughly 65% of the cells in the adenohypophysis.
- **The most frequent subtype of acidophils are the somatotrophs** (which can be stained with the dye orange G).
- **Somatotrophs produce growth hormone** (GH or somatotropin), which e.g. stimulates liver cells to produce polypeptide growth factors which stimulate growth (e.g. somatomedin which stimulates epiphyseal cartilage - overproduction of this hormone may result in gigantism or acromegaly).
- **Mammotrophs (or lactotrophs),** the second group of acidophils, secrete prolactin.
    - **Their number increases significantly in late pregnancy and the early months of lactation.**

Basophil cells (or basophils)

Based on their hormone products basophils are divided into three subtypes.

- **Thyrotrophs produce thyroid stimulating hormone (TSH or thyrotropin).**
- **Gonadotrophs**
    - **produce follicle stimulating hormone (FSH),** which **stimulates the seminiferous epithelium in males in addition to early follicular growth in females.**
    - **Gonadotrophs also produce luteinizing hormone (LH), which stimulates production of testosterone by Leydig cells in males in addition to late follicular maturation, oestrogen secretion and formation of corpus luteum in females.**
- **Corticotrophs (or adrenocorticolipotrophs)**
    - **secrete adrenocorticotropic hormone (ACTH or corticotropin) and lipotropin (LPH, no known function in humans).**
        - **Corticotropes are the most frequent cell type in the pars intermedia.**
        - **In the pars intermedia, the precursor of ACTH and LPH undergoes further hydrolysis into melanocyte stimulating hormone (MSH, increased pigmentation in patients with Addison's disease) and a number of other peptides (among them endogenous opioids).**

The Posterior Pituitary



•<u>posterior pituitary, or neurohypophysis =</u> is the <u>**neural portion of the pituitary**</u>

- a <u>collection of unmyelinated axons</u>
  - axons **extend from cell bodies in hypothalamus**

•consists of:

- **pars nervosa,**
- **infundibular stalk,**
- **median eminence**

•neurophysins carry hormones made in the hypothalamus (ADH and oxytocin) from the hypothalamus to the posterior pituitary

•<u>embryological origin</u>

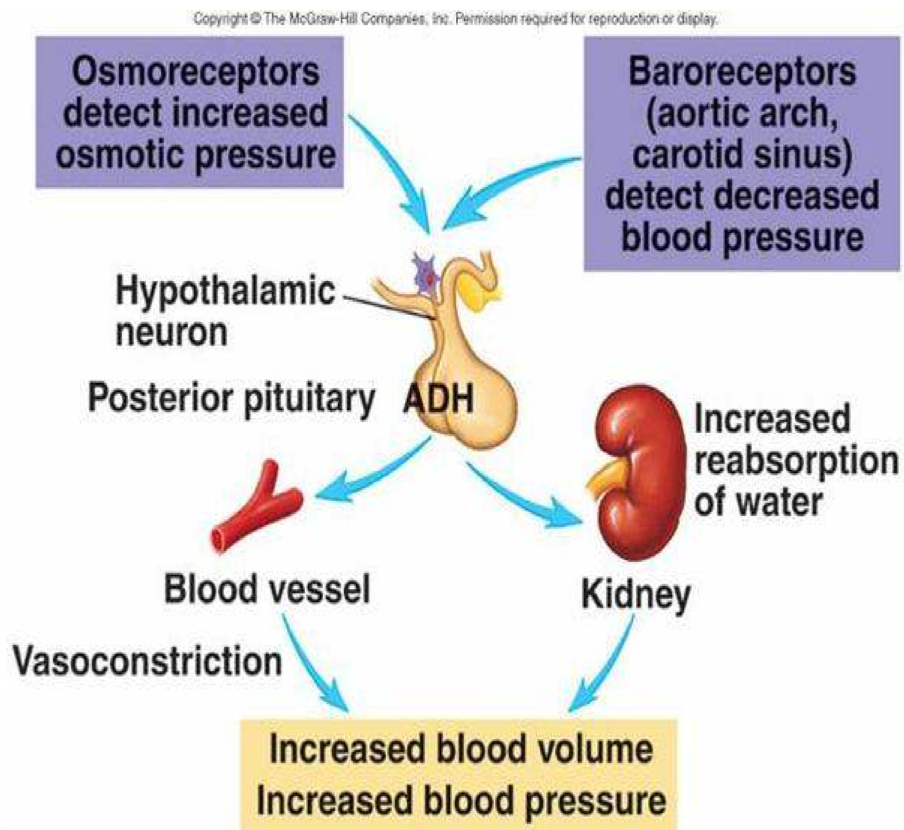
- **neural ectoderm**
  - **downgrowth of neural ectoderm (diencephalon)**

hormones are secreted by magnocellular neurons located in the supraoptic and paraventricular nucleus of hypothalamus

The Posterior Pituitary

Antidiuretic hormone (ADH; vasopressin)

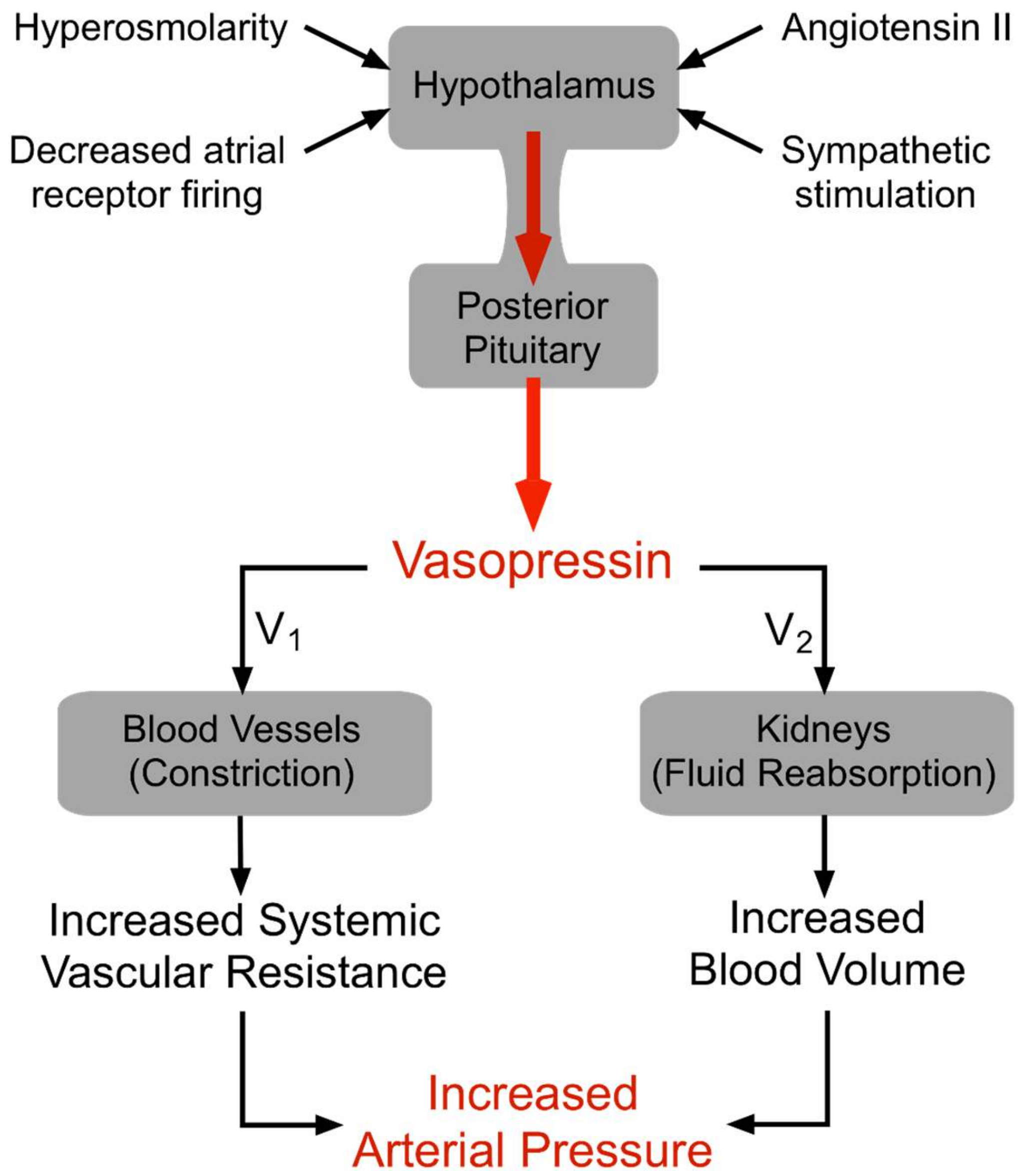
- **synthesis**
  - **hypothalamic supraoptic nucleus neuronal cell bodies synthesize ADH pro-hormone**
    - **ADH pro-hormone contains ADH and neurophysin II**
  - **ADH pro-hormones are packaged in secretory vesicles**
    - secretory vesicles are transported via axonal transport to nerve terminals
      - **nerve terminals** in pars nervosa of posterior pituitary
  - **ADH pro-hormone processing occurs in secretory vesicles during axonal transport**
    - **cleavage of neurophysin II and release of ADH hormone**
- **secretion**
  - **action potential depolarizes nerve terminals**
    - neurosecretory vesicles fuse with plasma membrane
      - **releases ADH and neurophysin II into perivascular space of highly fenestrated capillaries by which ADH enters systemic circulation**



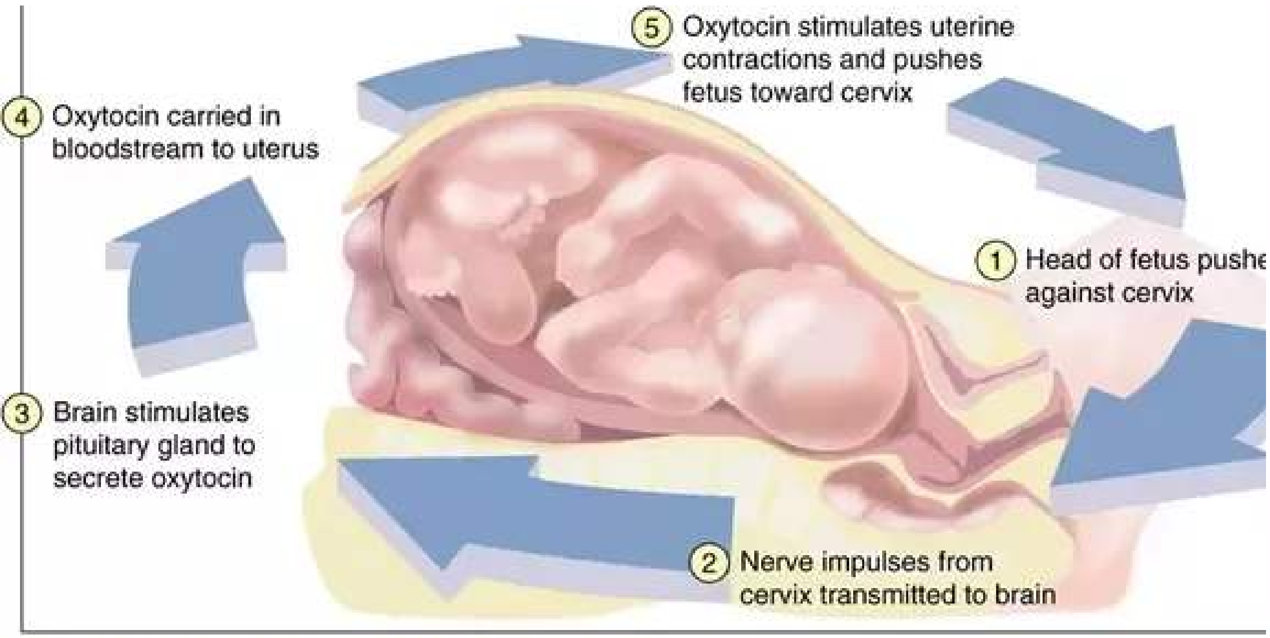
POSTERIOR PITUITARY

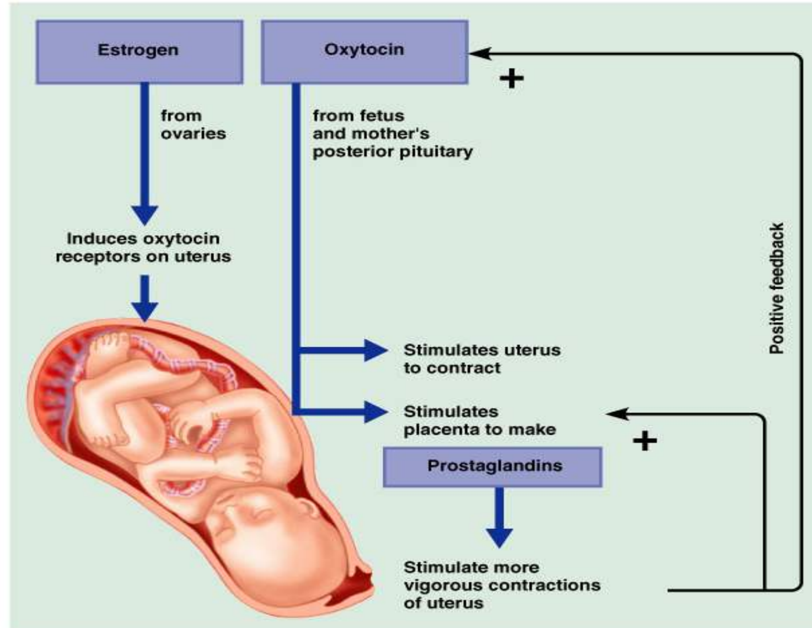
- **OXYTOCIN (contracts uterine smooth muscle)**
- **VASOPRESSIN (ADH)**
  - **vasoconstriction,**
  - **gluconeogenesis,**
  - **platelet aggregation,**
  - **release of Factor-VIII and vWb factor,**
  - **concentrates urine, main effects on kidney and brain)**

- The posterior pituitary does not make these hormones, it just releases them.
- The hypothalamus actually makes the hormones and transfers it down the stalk to the neurohypophysis.



Hyperosmolarity
Hypothalamus
Angiotensin II
Decreased atrial receptor firing
Sympathetic stimulation
Posterior Pituitary
Vasopressin
V1
V2
Blood Vessels (Constriction)
Kidneys (Fluid Reabsorption)
Increased Systemic Vascular Resistance
Increased Blood Volume
Increased Arterial Pressure





INCREASING OXYTOCIN

- LIGHT TOUCH
- SUCKING
- FOOD INTAKE
- WARMTH
- LIGHT PRESSURE
- MASSAGE-LIKE STROKING
- SEXUAL STIMULATION
- CALM & SUPPORTIVE ENVIRONMENT

Increases Oxytocin Release	Inhibits Oxytocin Release
feeling secure	feeling frightened
privacy	feeling watched
dim lighting	bright lights
people you know	strangers
touch	questions
comfortable environment	uncomfortable environment
relaxation	thinking

BAHS* of Posterior Pituitary Hormones

Hormone	Stimulates
Antidiuretic hormone	Water reabsorption in the kidney
Oxytocin	Contraction of uterine smooth muscle in labor. Contraction of breast cells to allow milk let down.

* Boring as heck summary

VIS* of Oxytocin

Situation	**Stimulates**
Interpersonal connection	Trust
Orgasm	Pleasure AND connection with that particular person
Intimate relationship	Monogamy
Sports teams	Better performance

* Very interesting summary

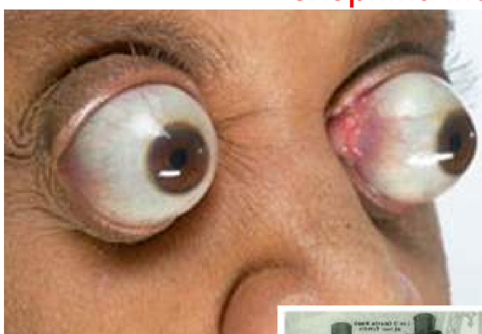
Normal pituitary.
With Turkish saddle,
i.e., sella turcica.

Pituitary Pathology

- Growth Hormone GH
  - dwarfism -hyposecretion
  - giantism, acromegaly-hypersecretion
- Thyroid Stimulating Hormone TSH
  - cretinism (infants) -hyposecretion
  - myxedema(adults) -hyposecretion
  - Toxic goiter (adults -hypersecretion
    - exophthalmos



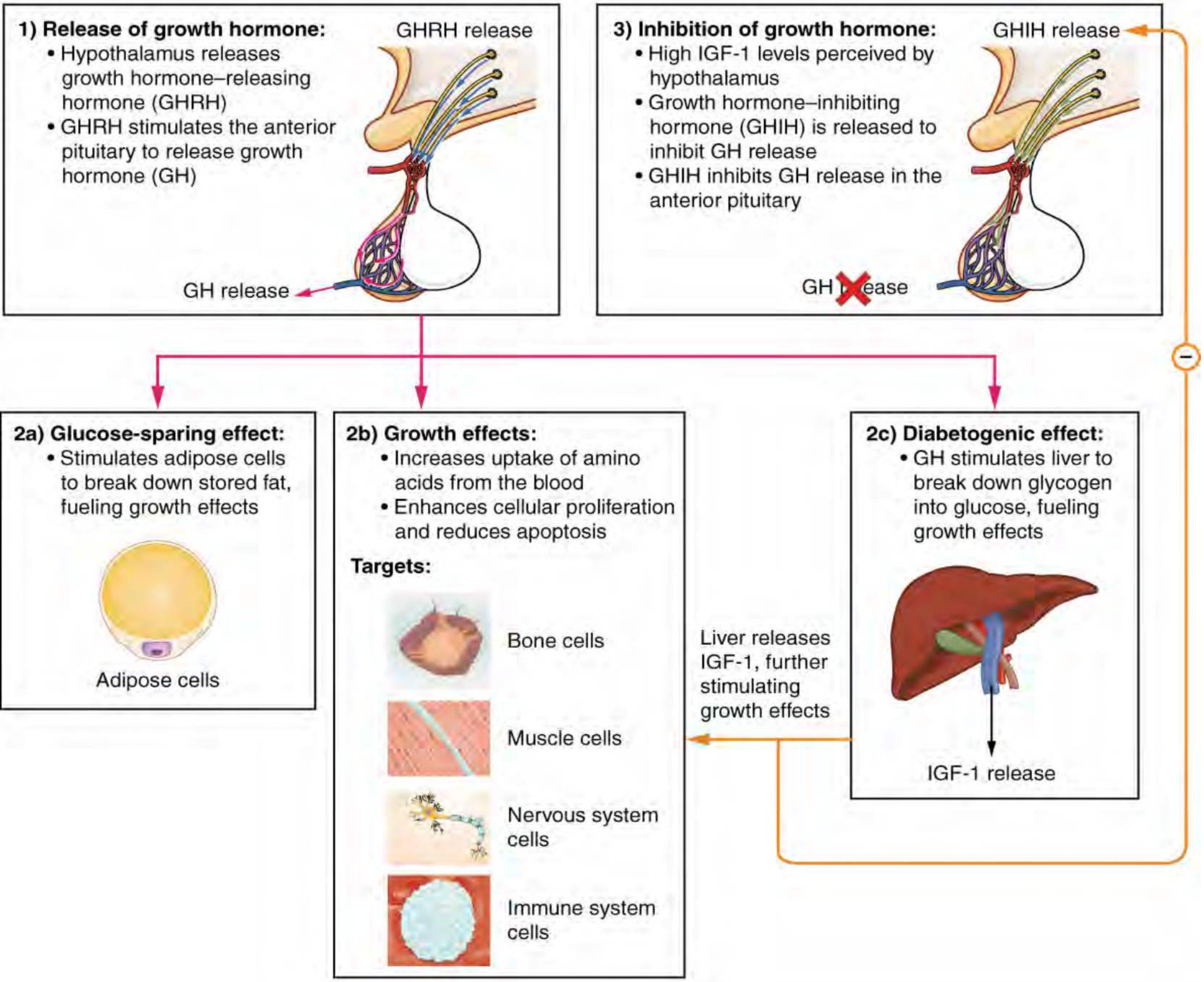




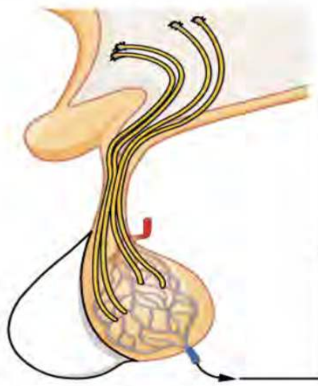






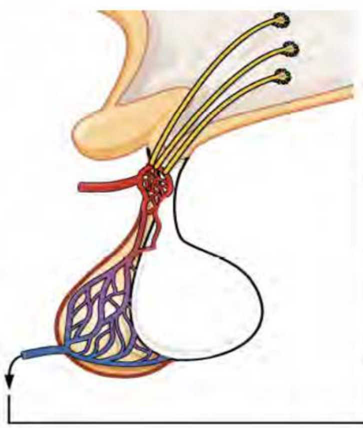


Growth hormone (GH) directly accelerates the rate of protein synthesis in skeletal muscle and bones. Insulin-like growth factor 1 (IGF-1) is activated by growth hormone and
indirectly supports the formation of new proteins in muscle cells and bone.



Posterior Pituitary Hormones

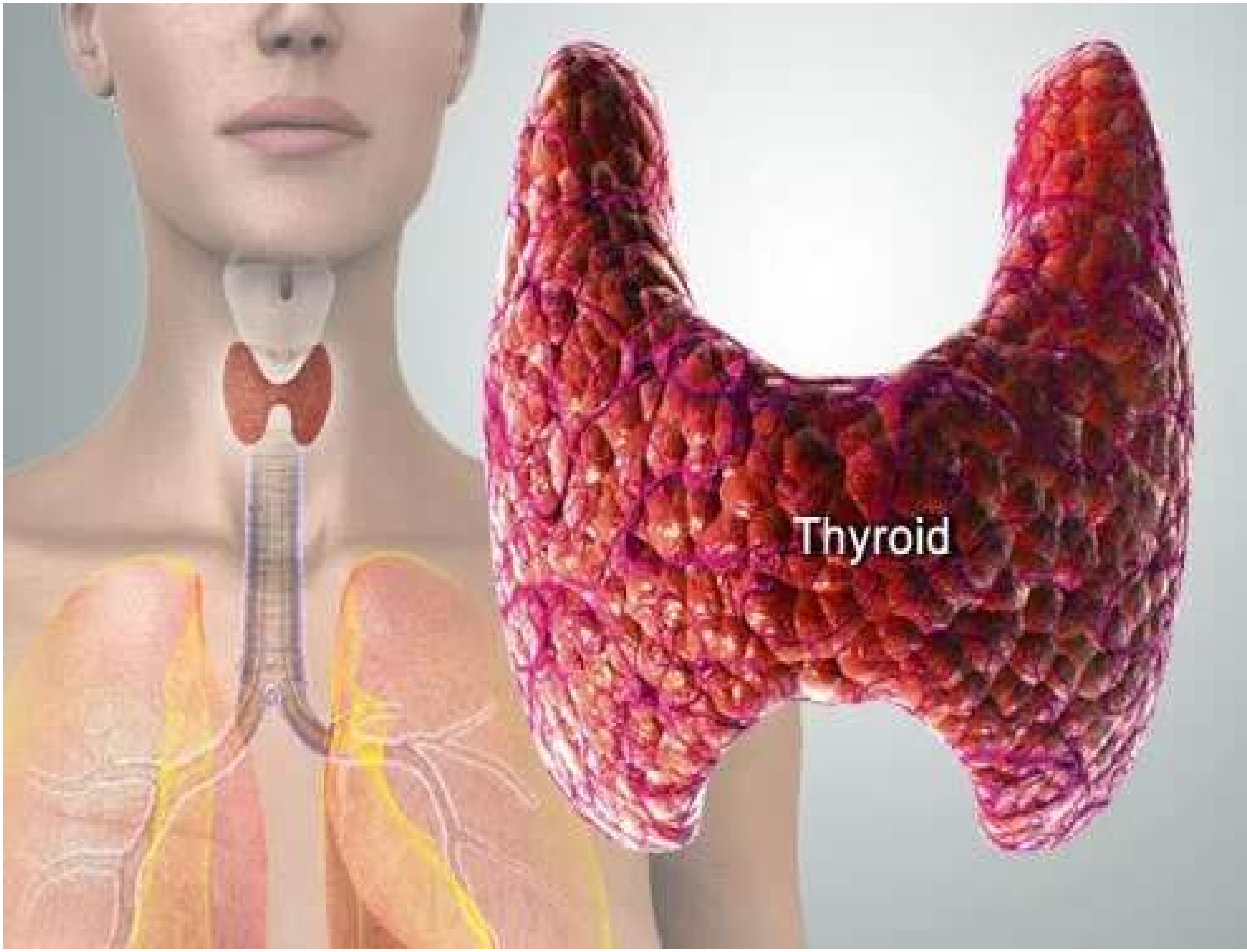
Releasing hormone (hypothalamus)	Pituitary hormone	Target	Effects
ADH	Stores ADH	Kidneys, sweat glands, circulatory system	Water balance
–	OT	Female reproductive system	Triggers uterine contractions during childbirth



Anterior Pituitary Hormones

Releasing hormone (hypothalamus)	Pituitary hormone	Target	Effects
GnRH	LH	Reproductive system	Stimulates production of sex hormones by gonads
GnRH	FSH	Reproductive system	Stimulates production of sperm and eggs
TRH	TSH	Thyroid gland	Stimulates the release of thyroid hormone (TH). TH regulates metabolism.
PRH (inhibited by PIH)	PRL	Mammary glands	Promotes milk production
GHRH (inhibited by GHIH)	GH	Liver, bone, muscles	Induces targets to produce insulin-like growth factors (IGF). IGFs stimulate body growth and a higher metabolic rate.
CRH	ACTH	Adrenal glands	Induces targets to produce glucocorticoids, which regulate metabolism and the stress response

Thyroid



What Does Thyroid Hormone Do?

- **Quick answer: increase growth and metabolism.**
- **More detailed answer:**
  - stimulate mitochondrial protein synthesis
  - increase absorption of carbohydrates
  - regulate fat metabolism
  - promote cell growth.
- **Bottom line: it increases basal metabolic rate and revs up most bodily functions** (increases heart rate, raises body temperature, increases nervous reactivity, increases GI motility…the list goes on).

Iodine Metabolism

i. Daily requirement of iodine is 150–200 mg/day.

- **Its** sources are drinking water, fish, cereals, vegetables and iodinated salt.

ii. Total body contains 25–30 mg of iodine.

- **All cells do contain iodine**
- **but 80% of the total is stored in the thyroid gland.**
- **Iodine level in blood is 5–10 µg/dL.**

iii. In most parts of the world, iodine is a scarce component of the soil.

- Upper regions of mountains generally contain less iodine.
- Such areas are called **goitrous belts, e.g. Himalayan region.**

i v. Commercial source of iodine is seaweeds.

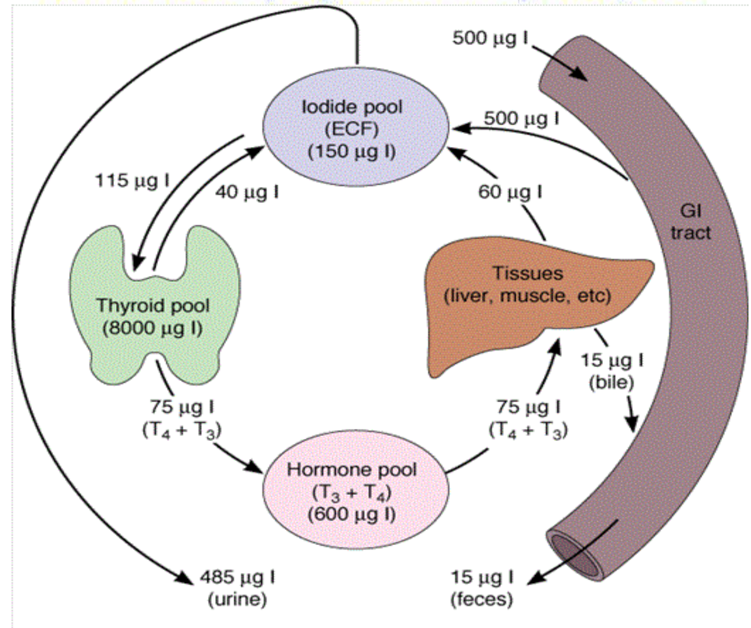
The program of iodination of common salt has resulted in increased availability of iodine.

v. Ingredients in foodstuffs, which prevent utilization of iodine are called **goitrogens.**

- **Goitrogens are seen in cassava, maize, millet, bamboo shoots, sweet potatoes and beans.**
- **Cabbage and tapioca contain thiocyanate**, **which inhibits iodine uptake by thyroid**.
- Mustard seed contains **thiourea, which inhibits iodination of** thyroglobulin.

vi. The only biological role of iodine is in formation of thyroid hormones, thyroxine (T4) and tri-iodo thyronine (T3).

- **Iodine is absorbed from upper small intestine.**
- **Iodine is transported in plasma by loosely binding to plasma proteins.**
- **Iodine absorption also occurs through skin & lungs.**
- **80% of body's iodine is stored in the organic form as iodothyroglobulin in thyroid gland.**



Source: Gardner DG, Shoback D: *Greenspan's Basic & Clinical Endocrinology, 9th Edition:* www.accessmedicine.com

Thyroid Hormones

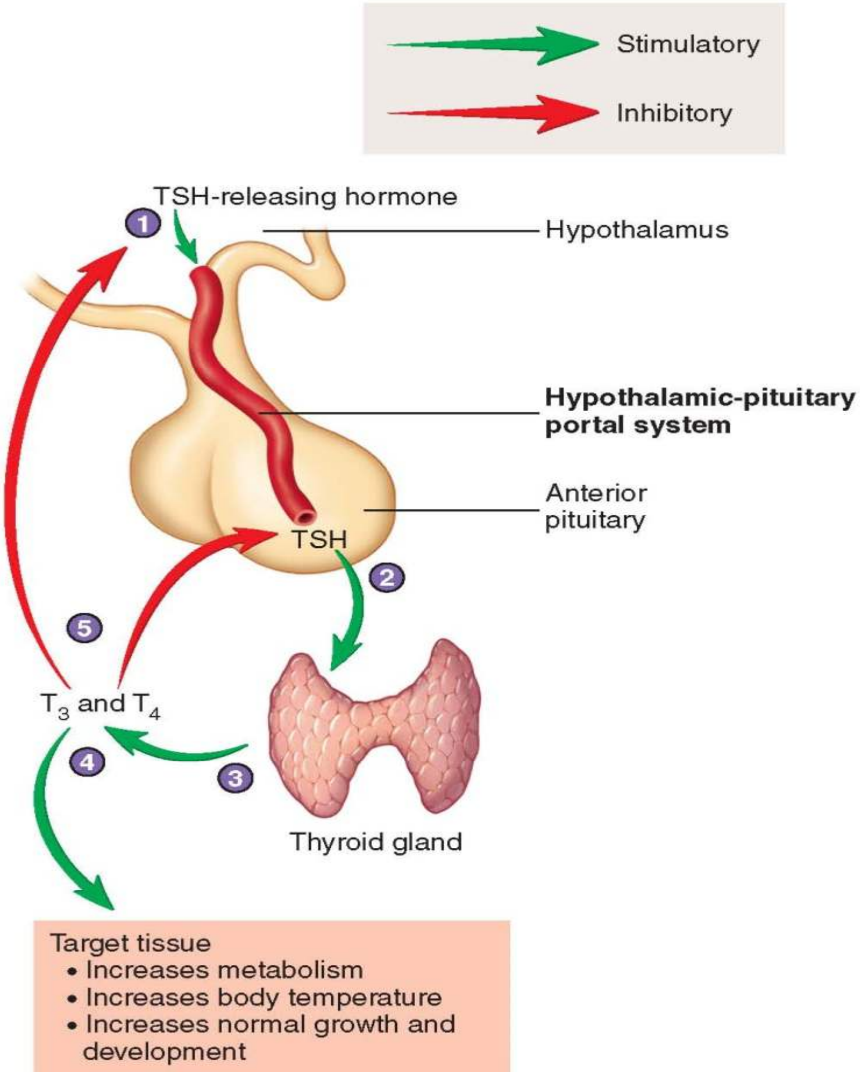
- **Thyroxine (T4) and Triiodothyronine (T3)-**
  - increases rate of energy release from carbohydrates
  - increases rate of protein synthesis
  - accelerates growth
  - stimulates activity in the nervous system
  - **controlled by TSH**
- **Calcitonin-**
  - **lowers blood calcium and phosphate ion concentrations by inhibiting release of calcium and phosphate from bones**
  - increases rate at which calcium and phosphate are deposited in bones

Thyroid Gland

- Follicular cells synthesize **thyroglobulin** (a protein backbone) and secrete it into the colloid.
- Follicular cells take up iodide from the blood and attach it to tyrosine residues on thyroglobulin, forming T3 and T4 (thyroid hormones), which stay attached to thyroglobulin until needed.
- When stimulated by TSH, follicular cells eat a bit of colloid, digest it in a vesicle, cleave off the T3 and T4 and release it into the blood.

There are two groups of hormones derived from the amino acid tyrosine: Thyroid hormones are basically a "double" tyrosine with the critical incorporation of 3 or 4 iodine atoms. Catecholamines include epinephrine and norepinephrine, which are used as both hormones and neurotransmitters.

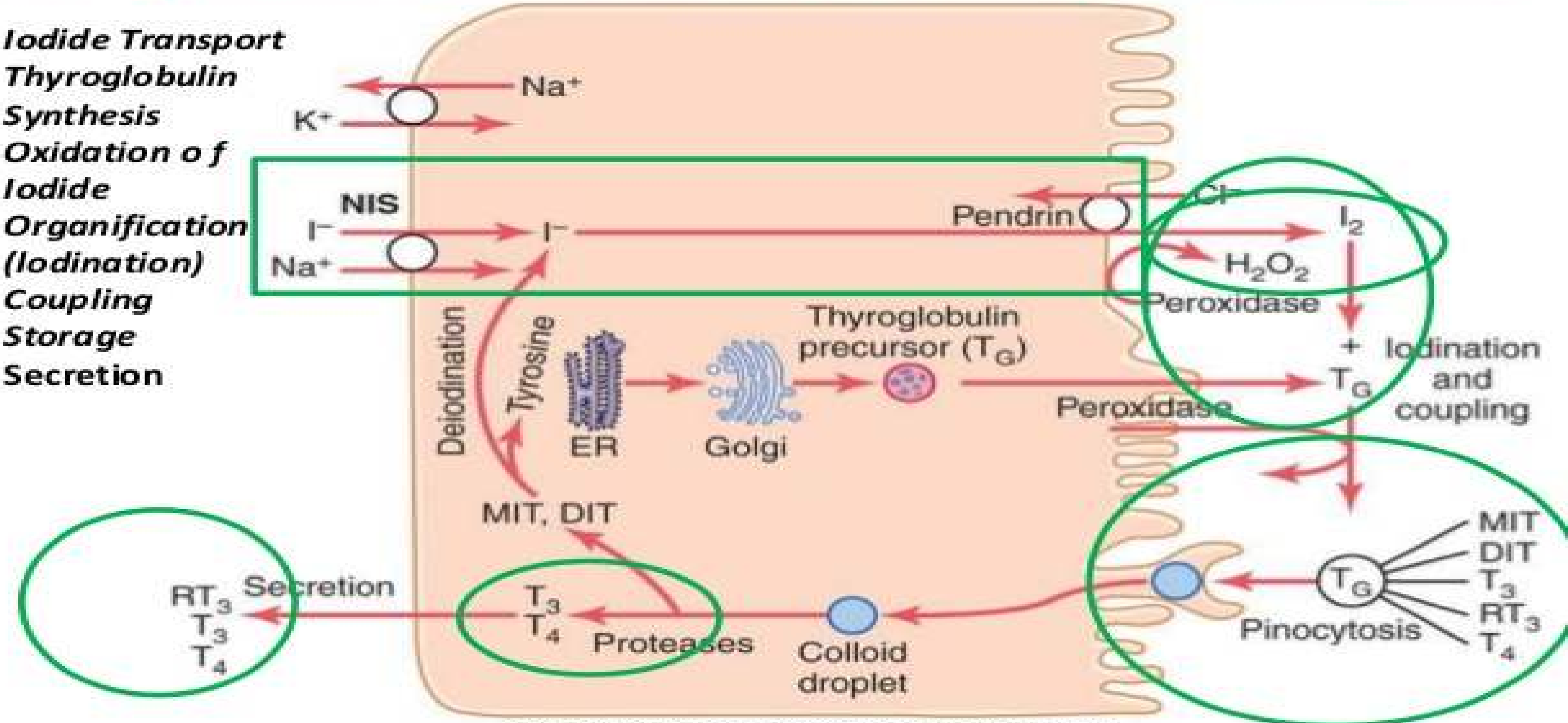
1. Neurons within the hypothalamus release TSH-releasing hormone into the blood. It passes through the hypothalamic-pituitary portal system to the anterior pituitary.
2. TSH-releasing hormone causes cells of the anterior pituitary to secrete TSH, which passes through the general circulation to the thyroid gland.
3. TSH causes increased release of thyroid hormones (T_3 and T_4) into the general circulation.
4. T_3 and T_4 act on target tissues to produce a response.
5. T_3 and T_4 also have an inhibitory effect on the secretion of TSH-releasing hormone from the hypothalamus and TSH from the anterior pituitary.



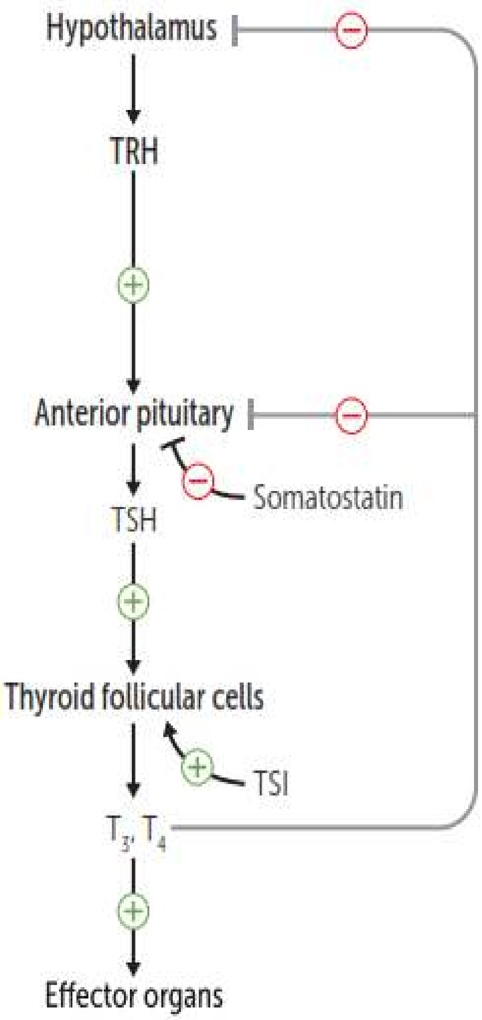
Regulation of Thyroid Hormone (T_3 and T_4) Secretion

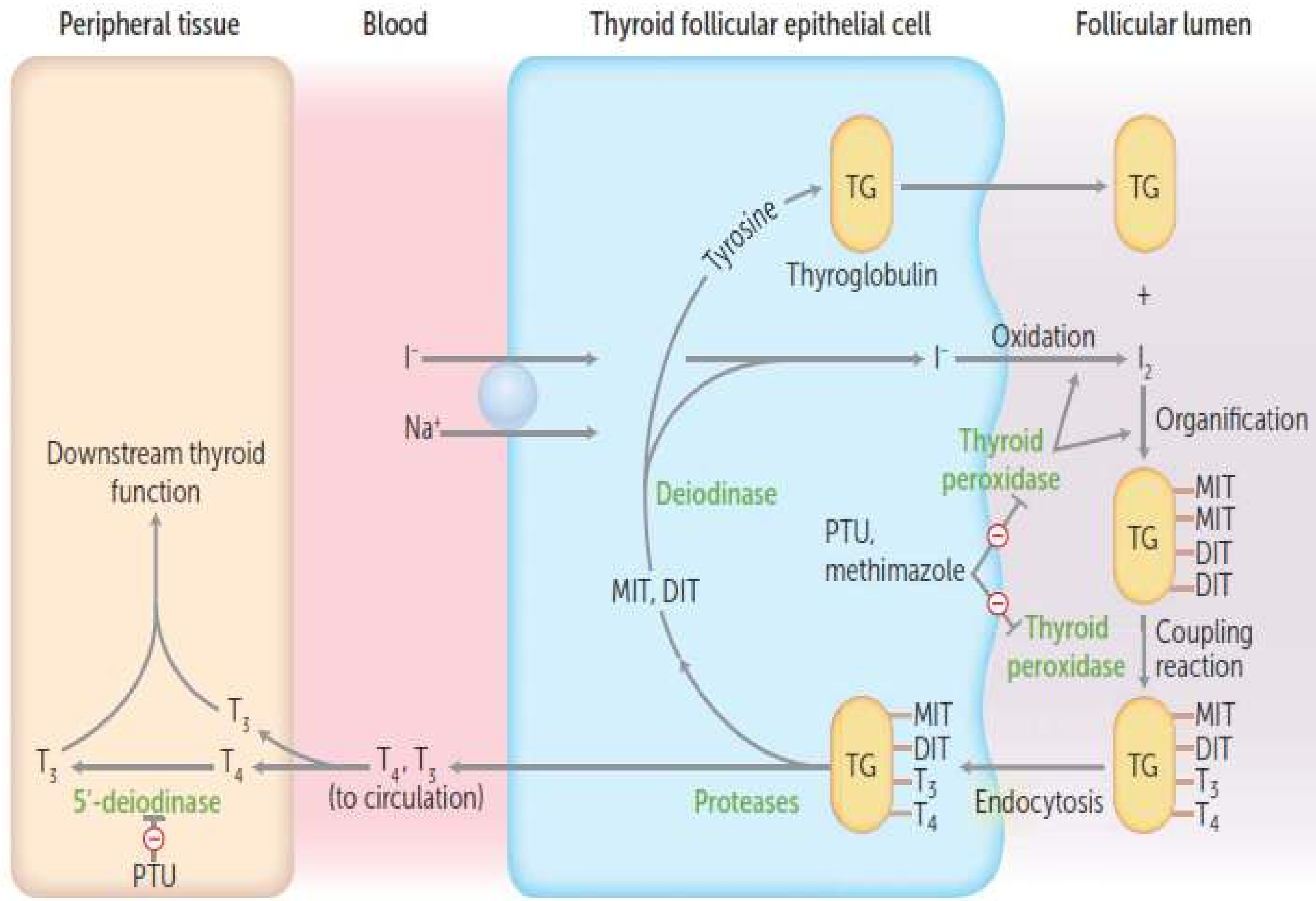
Bio-synthesis and Secretion of Thyroid Hormone

1. ***Iodide Transport***
2. ***Thyroglobulin Synthesis***
3. ***Oxidation o f Iodide***
4. ***Organification (Iodination)***
5. ***Coupling***
6. ***Storage***
7. ***Secretion***

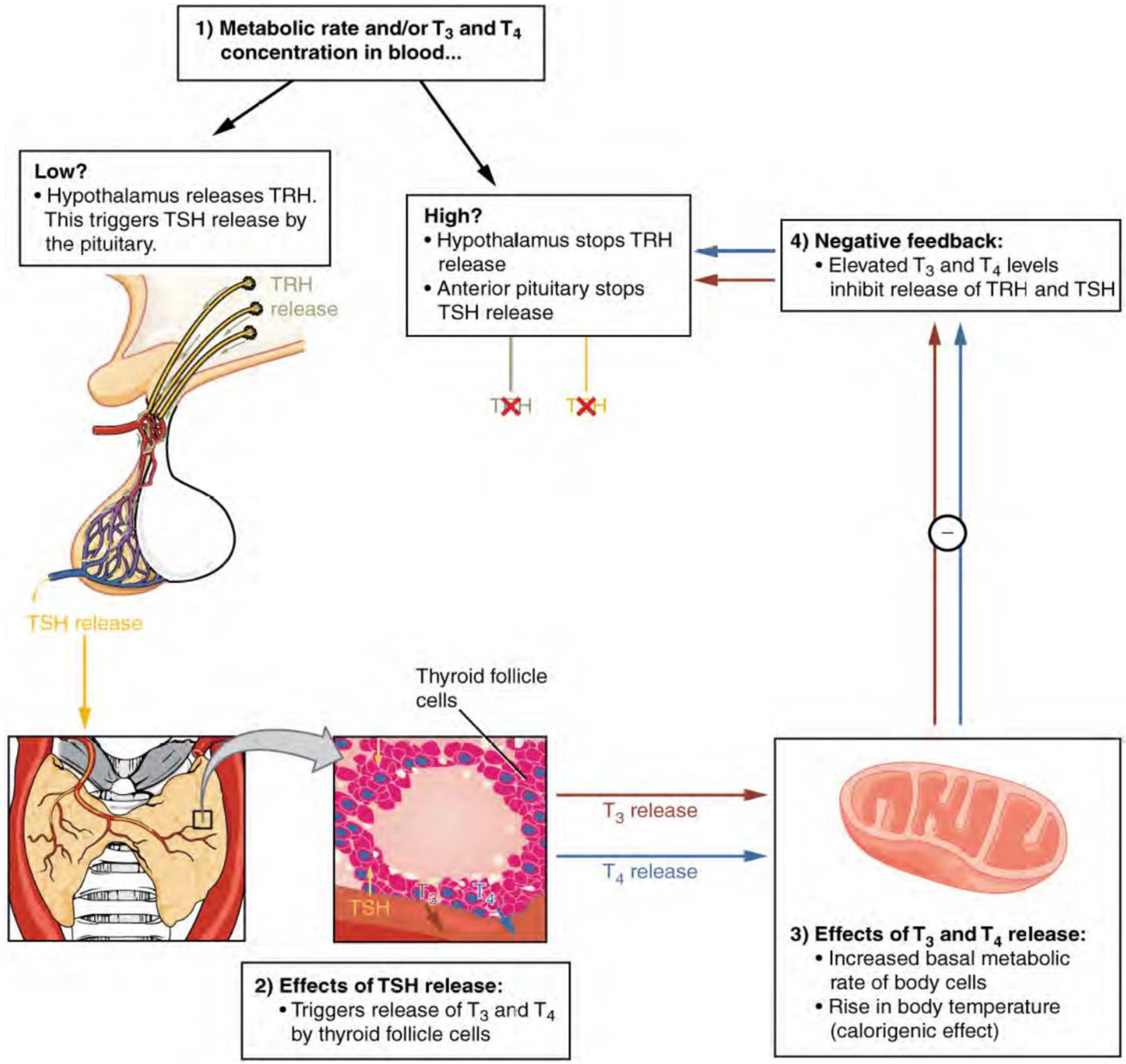


monoiodotyrosine (MIT) and diiodotyrosine (DIT)





monoiodotyrosine (MIT) and diiodotyrosine (DIT)


1) Metabolic rate and/or T_3 and T_4 concentration in blood...
Low?
• Hypothalamus releases TRH. This triggers TSH release by the pituitary.
High?
• Hypothalamus stops TRH release
• Anterior pituitary stops TSH release
4) Negative feedback:
• Elevated T_3 and T_4 levels inhibit release of TRH and TSH
TRH release
TSH release
Thyroid follicle cells
TSH
T_3
T_4
T_3 release
T_4 release
–
2) Effects of TSH release:
• Triggers release of T_3 and T_4 by thyroid follicle cells
3) Effects of T_3 and T_4 release:
• Increased basal metabolic rate of body cells
• Rise in body temperature (calorigenic effect)

Synthesis of T4 and T3 by the thyroid gland involves six major steps:

(1) active transport of iodide across the basement membrane into the thyroid cell (trapping)

(2) oxidation of iodide and iodination of tyrosyl residues in thyroglobulin (organification)

(3) linking pairs of iodotyrosine molecules within thyroglobulin to form the iodothyronines T3 and T4 (coupling)

(4) pinocytosis and then proteolysis of thyroglobulin with release of free iodothyronines and iodotyrosines into the circulation

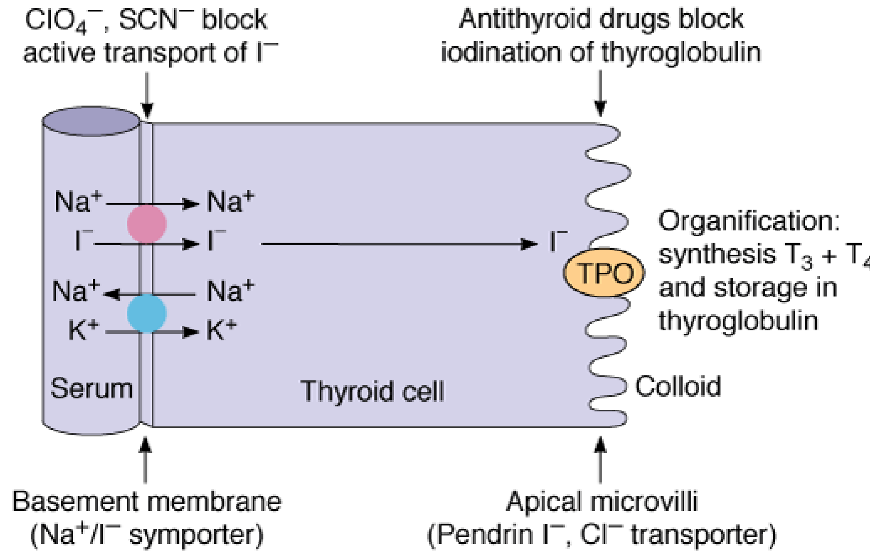
(5) deiodination of iodotyrosines within the thyroid cell, with conservation and reuse of the liberated iodide

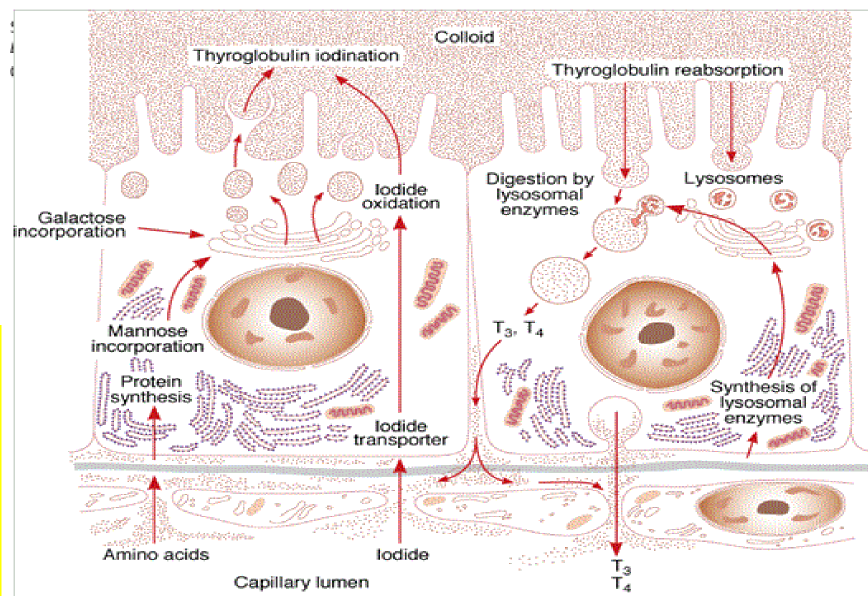
(6) intrathyroidal 5′-deiodination of T4 to T3.

Thyroid hormone synthesis requires that NIS, thyroglobulin, and the enzyme thyroid peroxidase (TPO) all be present, functional, and uninhibited

The thiocarbamide drugs, including

- **methimazole,**
- **carbimazole,**
- **propylthiouracil (PTU)**
- are competitive inhibitors of TPO. Their resulting ability to block thyroid hormone synthesis

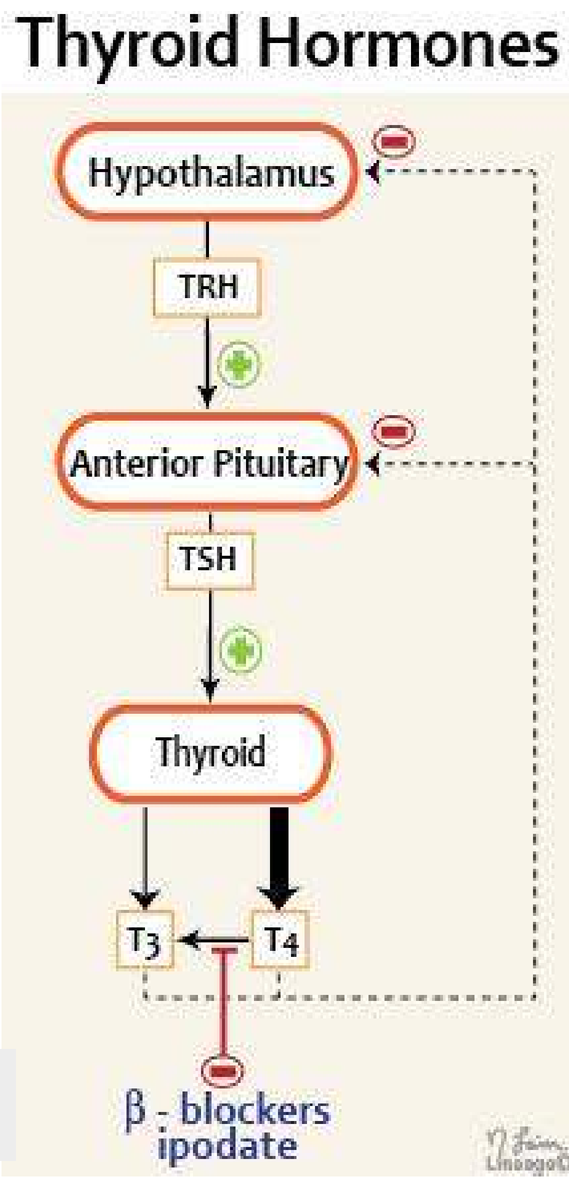




Source: Gardner DG, Shoback D: *Greenspan's Basic & Clinical Endocrinology, 9th Edition*: www.accessmedicine.com

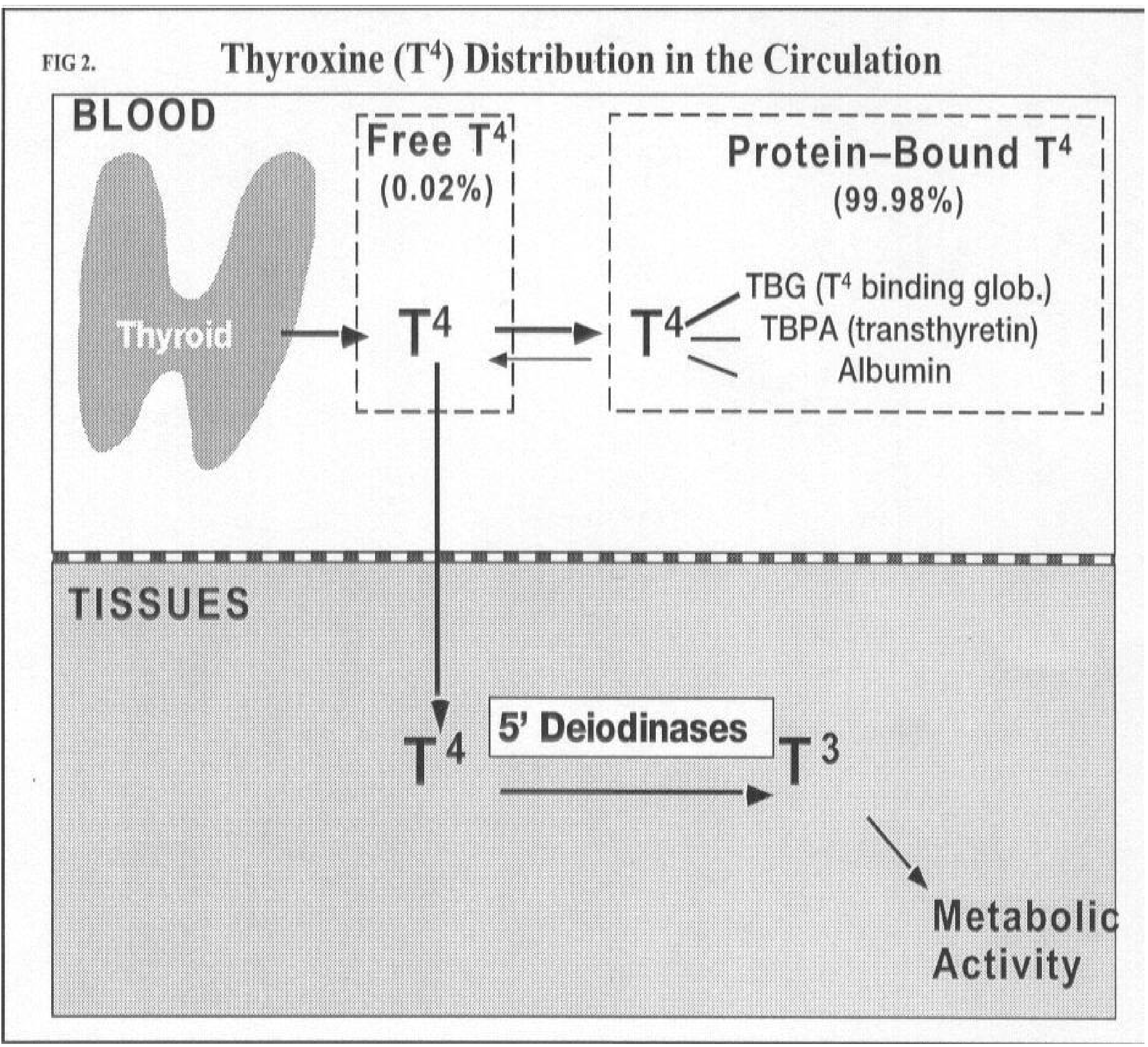
- **Synthesis**
  - created in the thyroid gland
  - stored in thyroid follicles
  - **thyroid peroxidase responsible for oxidation, organification, and coupling**
    - **forms I_2 via oxidation of I-**
    - **forms thyroglobulin via organification of I_2**
  - **T_4 converted to T_3 in peripheral tissues by outer ring deiodinase**
  - **T_4 converted to rT_3 by inner ring deiodinase**

- **Regulation**
  - **TRH released from the hypothalamus to stimulates TSH release from the pituitary**
    - **TSH stimulates follicular cells to produce T_3 and T_4**



Abnormally low levels of T4 may indicate: dietary issues, such as fasting, malnutrition, or an iodine deficiency. medications that affect protein levels. hypothyroidism.

FIG 2.



Function

- bone growth
- CNS maturation
  - recall cretinism involves short stature and mental retardation
- increase the basal metabolic rate
  - via ↑ Na^+/K^+-ATPase activity
  - results in ↑ O2 consumption, RR, and body temperature
- ↑ β_1 receptors in heart
  - results in ↑ CO, HR, SV, and contractility
    - recall the importance of treating hyperthyroidism with β-blockers
- **↑ glycogenolysis, gluconeogenesis, and lipolysis**

Thyroid hormones (T_3/T_4)

Iodine-containing hormones that control the body's metabolic rate.

SOURCE

Follicles of thyroid. Most T_3 formed in target tissues.

FUNCTION

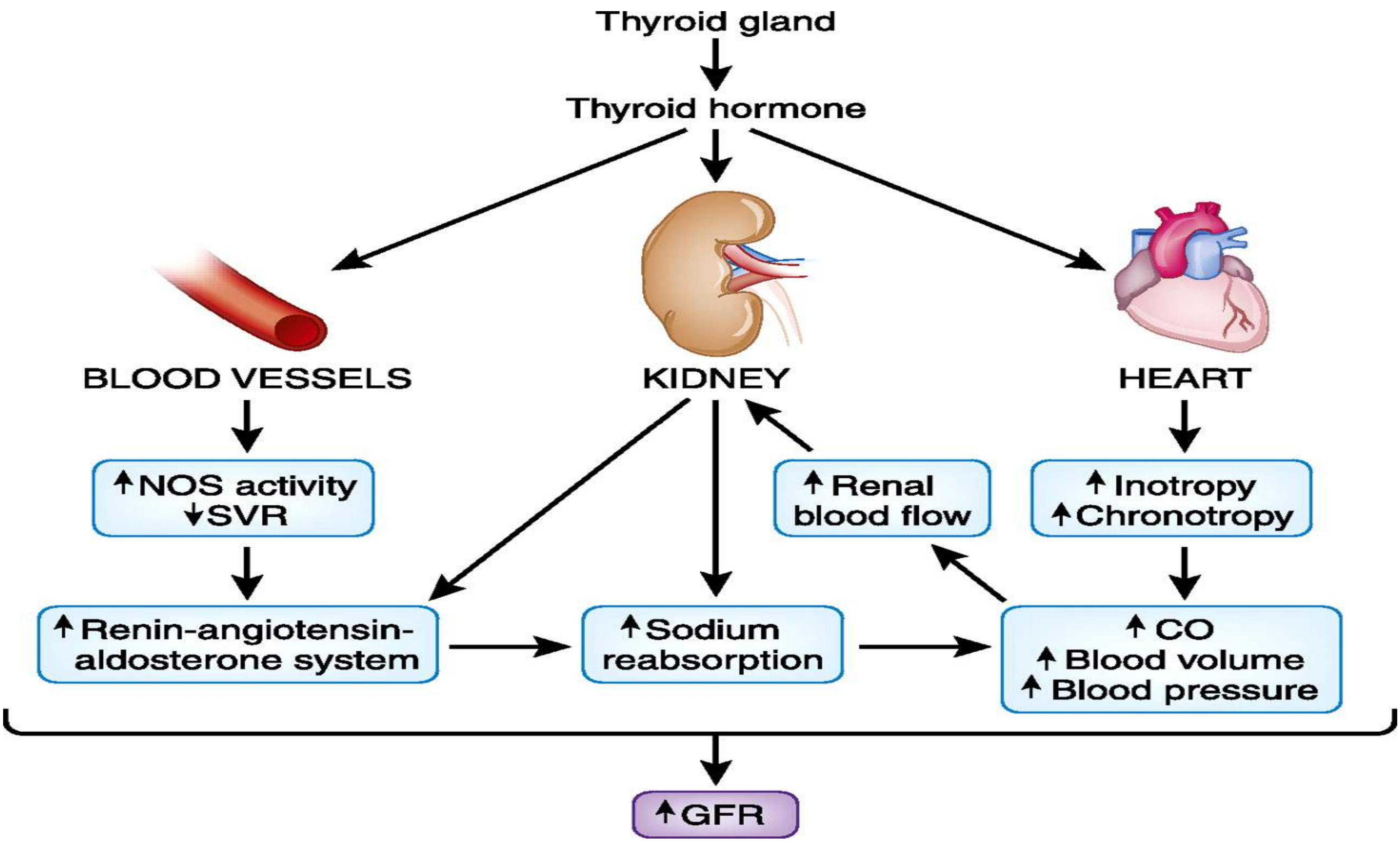
Bone growth (synergism with GH)
CNS maturation
↑ β_1 receptors in heart = ↑ CO, HR, SV, contractility
↑ basal metabolic rate via ↑ Na^+/K^+-ATPase activity → ↑ O_2 consumption, RR, body temperature
↑ glycogenolysis, gluconeogenesis, lipolysis

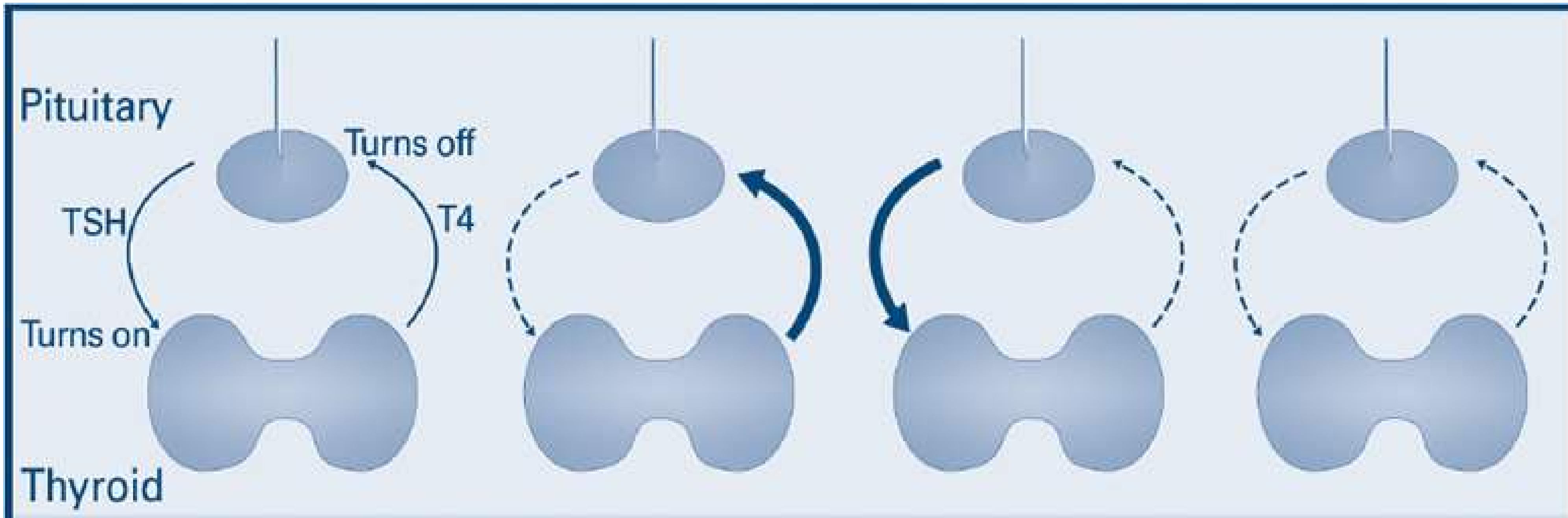
REGULATION

TRH (hypothalamus) stimulates TSH (pituitary), which stimulates follicular cells. May also be stimulated by thyroid-stimulating immunoglobulin (TSI) in Graves disease.
Negative feedback primarily by free T_3/T_4 to anterior pituitary (↓ sensitivity to TRH) and hypothalamus (↓ TRH secretion).
Wolff-Chaikoff effect—excess iodine temporarily inhibits thyroid peroxidase → ↓ iodine organification → ↓ T_3/T_4 production.

T_3 functions—**4 B's**:
- **B**rain maturation
- **B**one growth
- **β**-adrenergic effects
- **B**asal metabolic rate ↑

Thyroxine-binding globulin (TBG) binds most T_3/T_4 in blood; only free hormone is active. ↓ TBG in hepatic failure, steroids; ↑ TBG in pregnancy or OCP use (estrogen ↑ TBG).
T_4 is major thyroid product; converted to T_3 in peripheral tissue by 5′-deiodinase.
T_3 binds nuclear receptor with greater affinity than T_4.
Thyroid peroxidase is the enzyme responsible for oxidation and organification of iodide as well as coupling of monoiodotyrosine (MIT) and di-iodotyrosine (DIT). DIT + DIT = T_4. DIT + MIT = T_3.
Propylthiouracil (PTU) inhibits both thyroid peroxidase and 5′-deiodinase. Methimazole inhibits thyroid peroxidase only. Glucocorticoids inhibit peripheral conversion of T_4 to T_3.


Thyroid gland
Thyroid hormone
BLOOD VESSELS
KIDNEY
HEART
↑NOS activity
↓SVR
↑Renal blood flow
↑Inotropy
↑Chronotropy
↑Renin-angiotensin-aldosterone system
↑Sodium reabsorption
↑CO
↑Blood volume
↑Blood pressure
↑GFR



CONDITION:	Normal	Hyperthyroidism	Hypothyroidism Primary	Hypothyroidism Secondary
TSH	Normal	Low	High	Low
T4	Normal	High	Low	Low

Parafollicular Cells (C Cells)

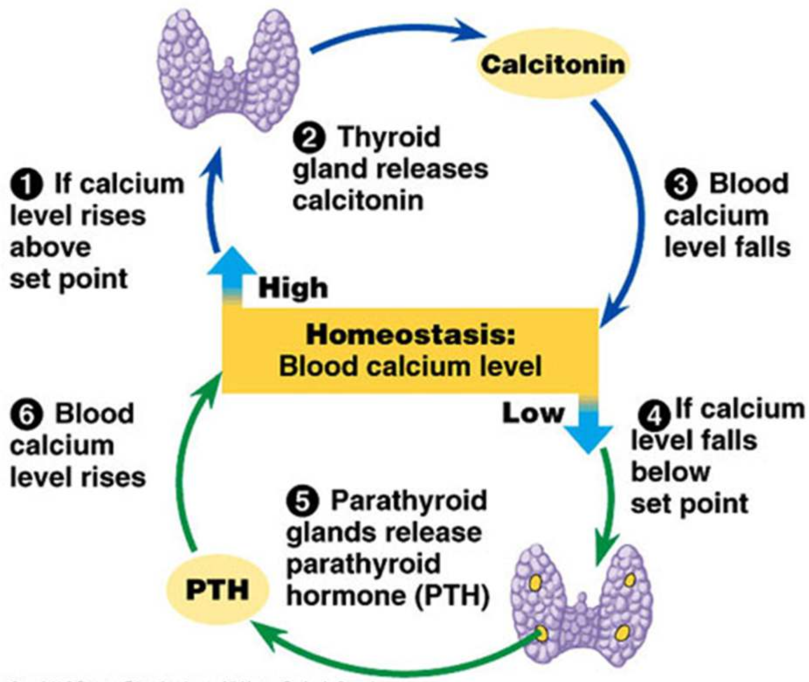
- Derived from neural crest ectoderm.
- Located between follicular cells and between follicles.
- Parafollicular cells are larger cells with clear cytoplasm and small secretory granules containing calcitonin.
- Calcitonin is made in response to high blood calcium (it’s not affected by a pituitary hormone!).
- Calcitonin lowers blood calcium levels by inhibiting osteoclastic resorption.

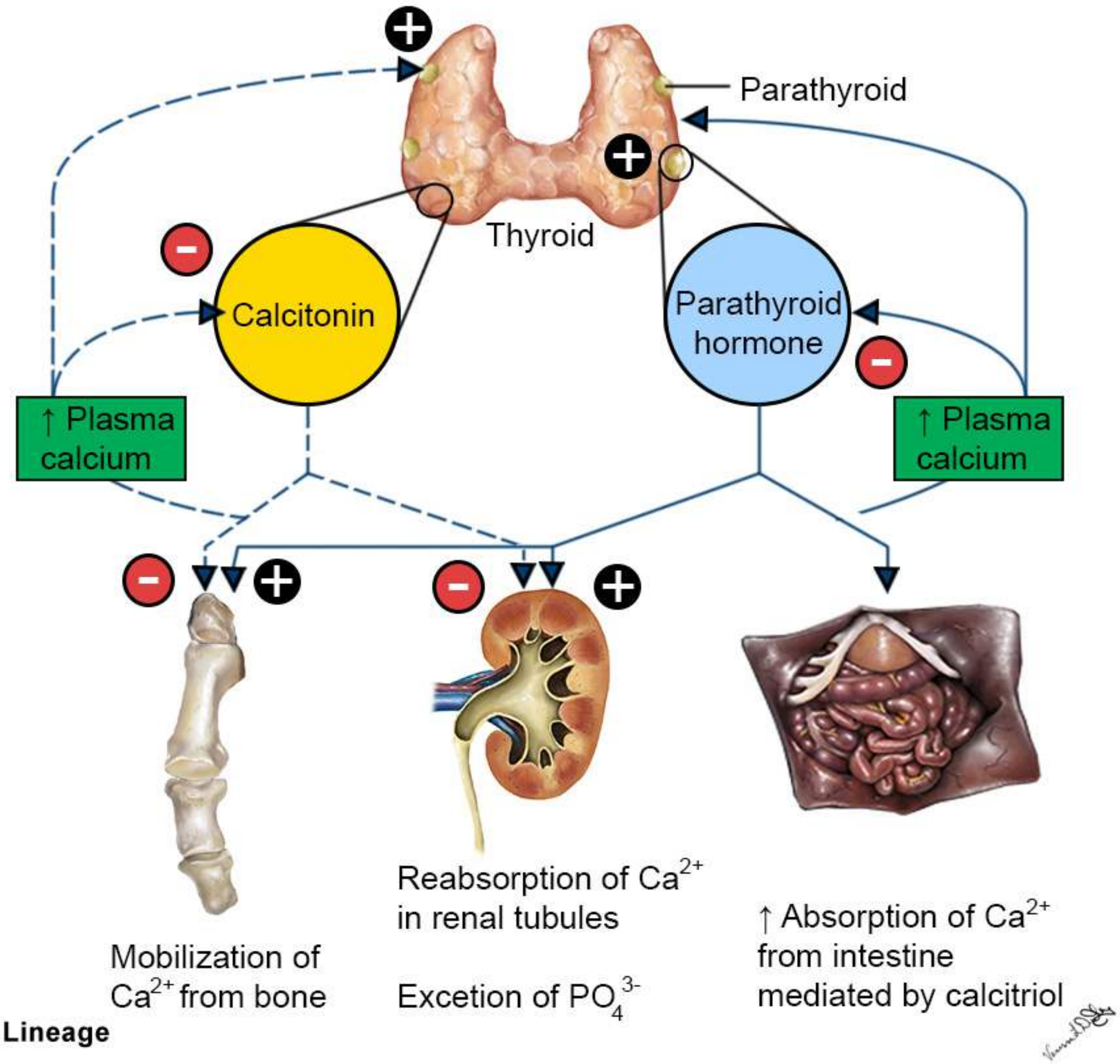
Calcitonin

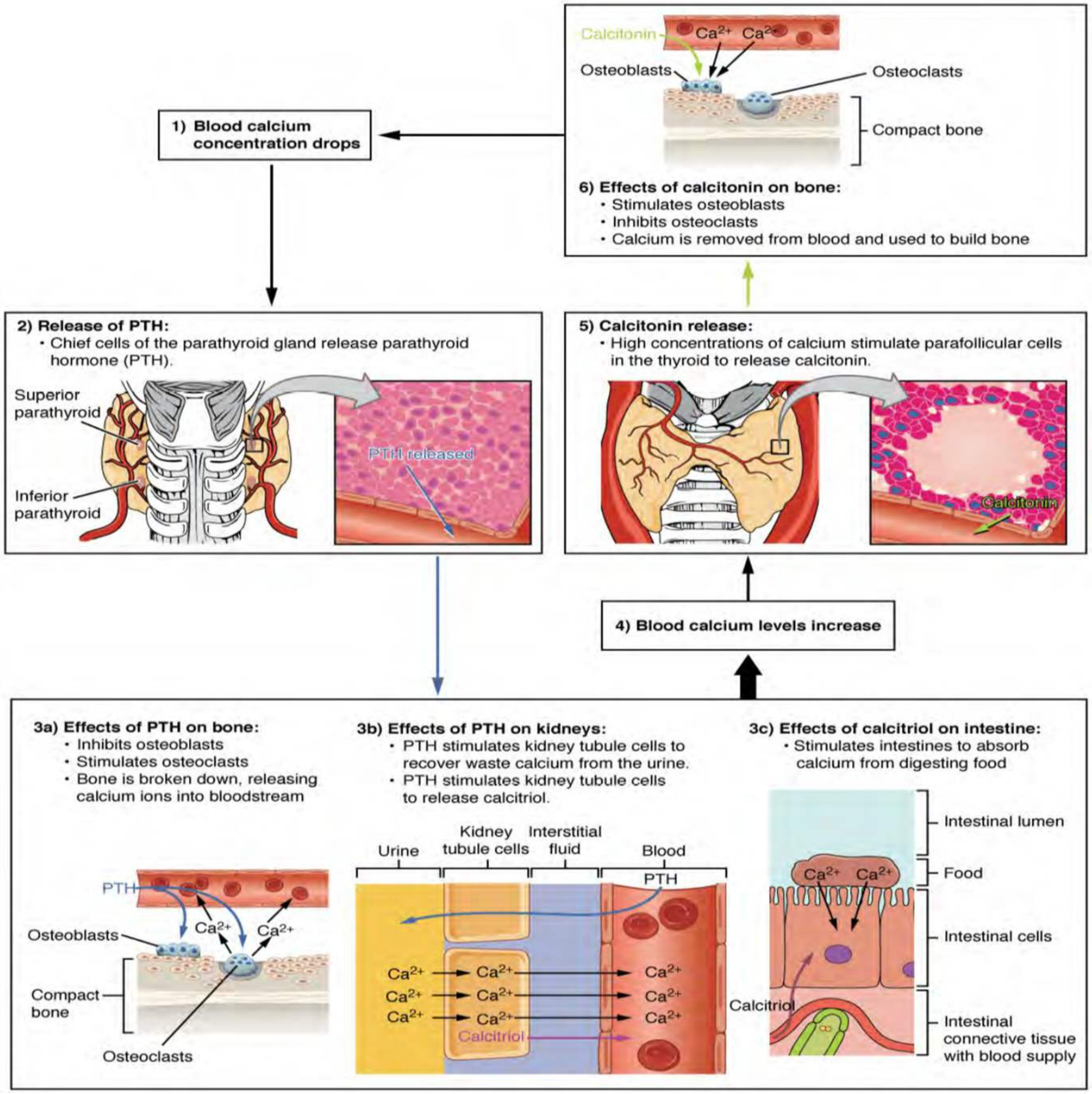
SOURCE	Parafollicular cells (C cells) of thyroid.
FUNCTION	↓ bone resorption of Ca^{2+}.
REGULATION	↑ serum Ca^{2+} → calcitonin secretion.

Calcitonin opposes actions of PTH. Not important in normal Ca^{2+} homeostasis.

Calcitonin tones down serum Ca^{2+} levels and keeps it in bones.



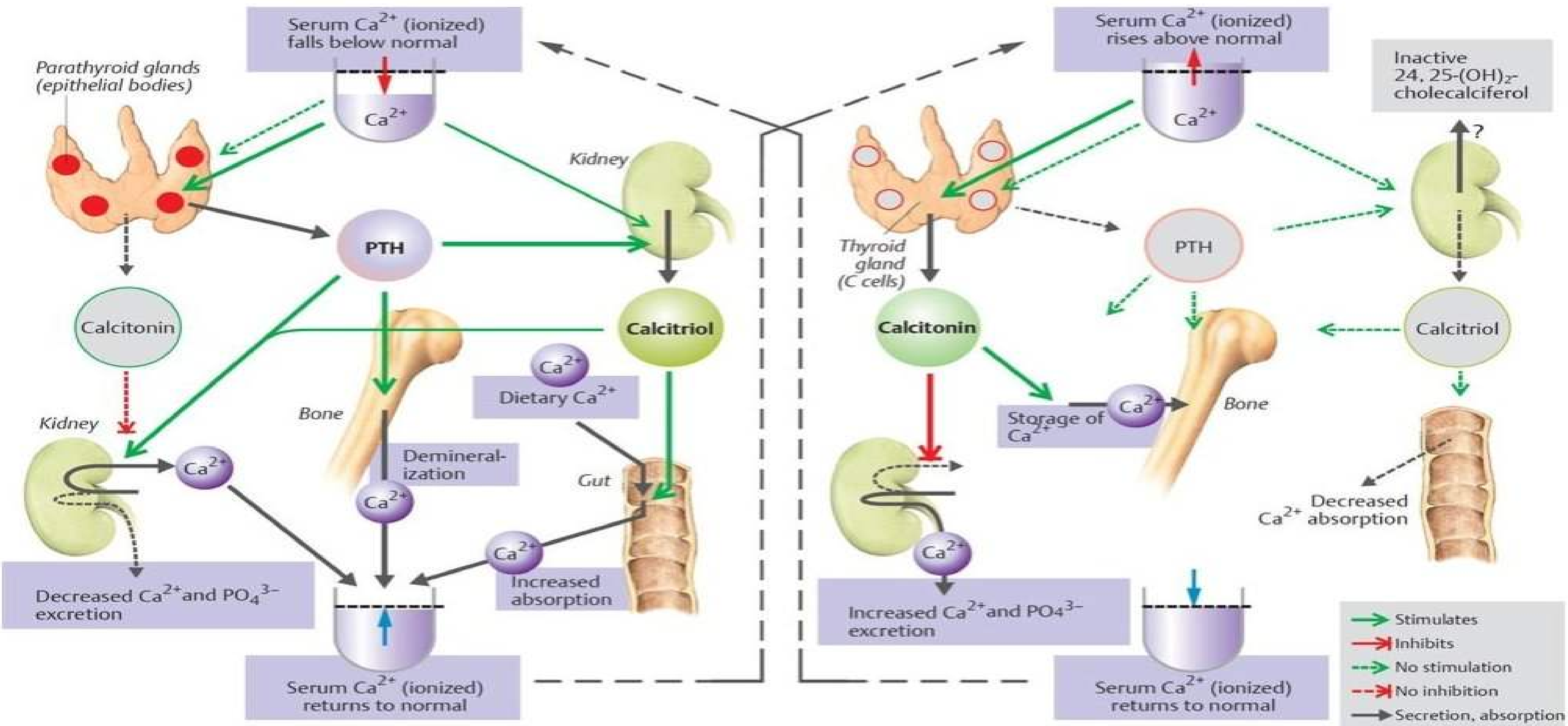

Parathyroid
Thyroid
Calcitonin
Parathyroid hormone
↑ Plasma calcium
↑ Plasma calcium
Mobilization of Ca^{2+} from bone
Reabsorption of Ca^{2+} in renal tubules
Excetion of PO_4^{3-}
↑ Absorption of Ca^{2+} from intestine mediated by calcitriol



Calcitonin
Ca2+ Ca2+
Osteoblasts
Osteoclasts
Compact bone
6) Effects of calcitonin on bone:
• Stimulates osteoblasts
• Inhibits osteoclasts
• Calcium is removed from blood and used to build bone
1) Blood calcium concentration drops
2) Release of PTH:
• Chief cells of the parathyroid gland release parathyroid hormone (PTH).
Superior parathyroid
Inferior parathyroid
PTH released
5) Calcitonin release:
• High concentrations of calcium stimulate parafollicular cells in the thyroid to release calcitonin.
Calcitonin
4) Blood calcium levels increase
3a) Effects of PTH on bone:
• Inhibits osteoblasts
• Stimulates osteoclasts
• Bone is broken down, releasing calcium ions into bloodstream
PTH
Ca2+
Ca2+
Osteoblasts
Compact bone
Osteoclasts
3b) Effects of PTH on kidneys:
• PTH stimulates kidney tubule cells to recover waste calcium from the urine.
• PTH stimulates kidney tubule cells to release calcitriol.
Urine
Kidney tubule cells
Interstitial fluid
Blood
PTH
Ca2+
Ca2+
Ca2+
Ca2+
Ca2+
Ca2+
Ca2+
Ca2+
Ca2+
Calcitriol
3c) Effects of calcitriol on intestine:
• Stimulates intestines to absorb calcium from digesting food
Intestinal lumen
Ca2+ Ca2+
Food
Intestinal cells
Calcitriol
Intestinal connective tissue with blood supply

Hormonal regulation of the blood Ca^{2+} concentration.

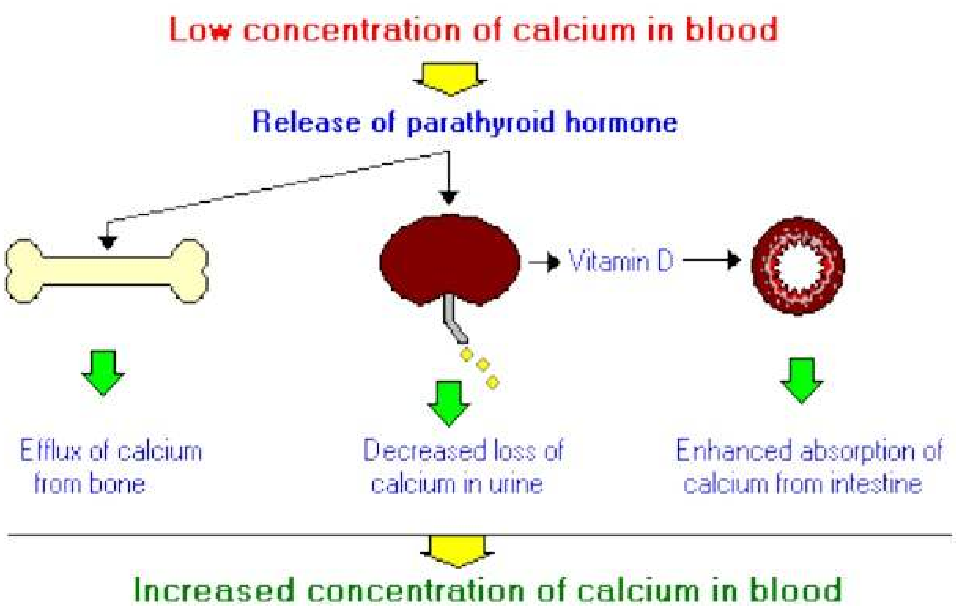
Ca^{2+} homeostasis is achieved by three main hormones: parathyroid hormone (PTH, from parathyroid gland), calcitonin (from parafollicular cells of the thyroid gland), and calcitriol (mainly produced in the kidney). In low serum Ca^{2+} states, the actions of parathyroid hormone and calcitriol predominate, causing increased Ca^{2+} uptake from the gut and bone and decreased renal excretion. In high serum Ca^{2+} states, the action of calcitonin predominates, causing decreased Ca^{2+} uptake from the gut, increased renal excretion, and storage of excess Ca^{2+} in bone.



Source : Pharmacology - An Illustrated Review (Thieme Illustrated Review Series) - Simmons, Mark

	PTH	Vitamin D	Calcitonin
Bone:	↑ resorption.	↑ resorption & formation.	↓ resorption.
Kidney:	↑ tubular Ca^{++} reabsorption. ↑ tubular PO_4^{-} excretion.	↑ tubular Ca^{++}& PO_4^{-} reabsorptn	↓ tubular Ca^{++} & PO_4^{-} reabsorptn.
G.I.T.	Indirect through calcitriol (↑ Ca^{++}&PO_4^{-} reabsorption).	↑ Ca^{++} &PO_4^{-} reabsorption.	
Serum Ca^{++}	↑	↑	↓
PO_4^{-}	↓	↑	↓

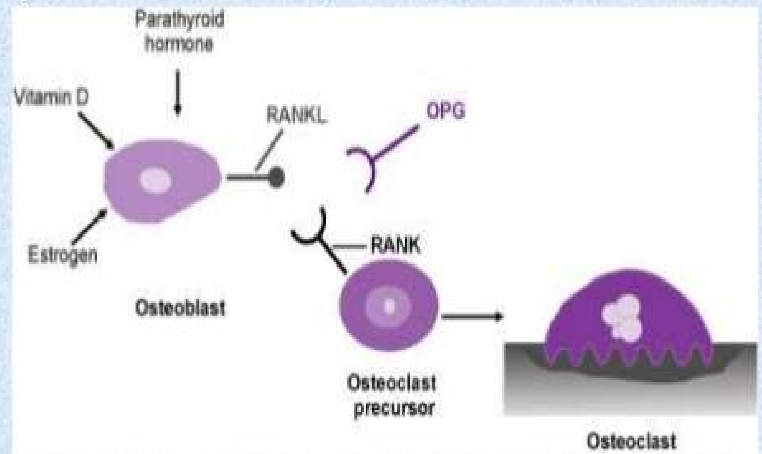
Parathyroid



PTH binds to **osteoblasts**.

Osteoblasts **increase expression of RANK-L** and inhibits their expression of Osteoprotegerin (OPG). *(OPG blocks RANK-L)*

RANK-L **binds RANK** on **osteoclast precursors**, and they form new osteoclasts. And osteoclasts **enhance bone resorption** thus increasing Blood Calcium and Decreasing Bone Calcium

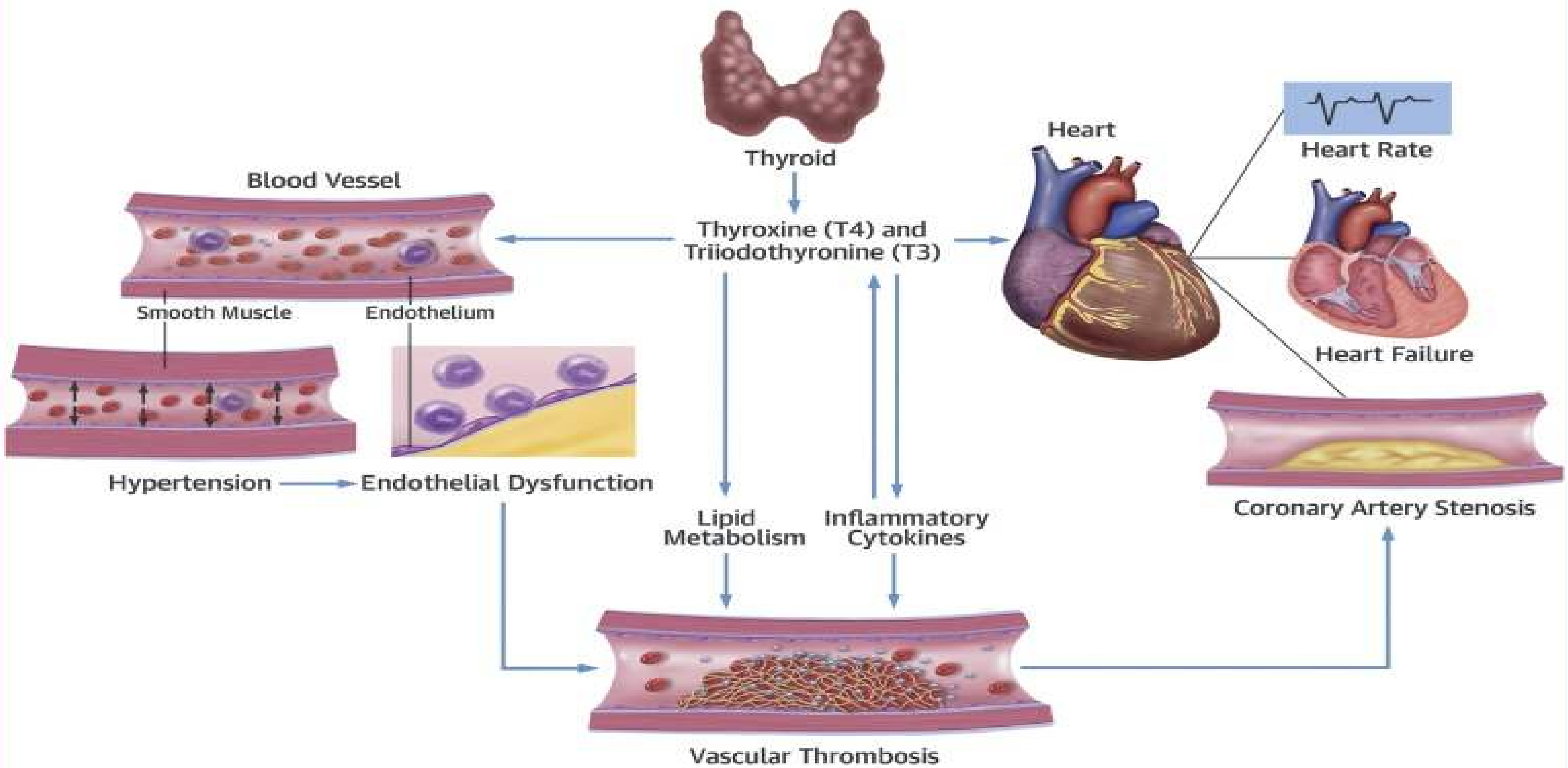


Heart

- The natriuretic peptide family consists of three biologically active peptides: (will be discussing this in cardiovascular)
  - **atrial natriuretic peptide (ANP),**
  - **brain (or B-type) natriuretic peptide (BNP),**
  - **and C-type natriuretic peptide (CNP).**

  - Among these, ANP and BNP are secreted by the heart and act as cardiac hormones.

CENTRAL ILLUSTRATION: The Interactions Between Thyroid Hormones and the Cardiovascular System

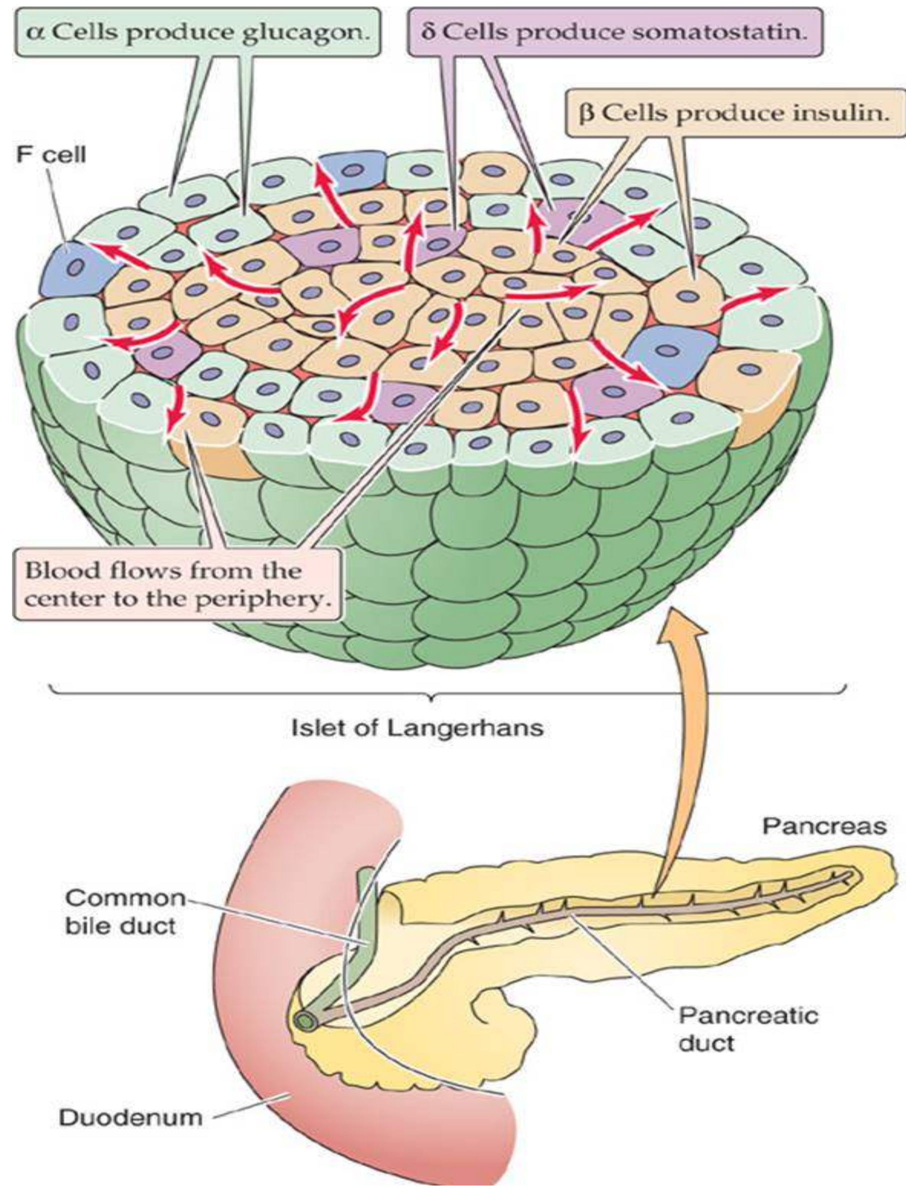


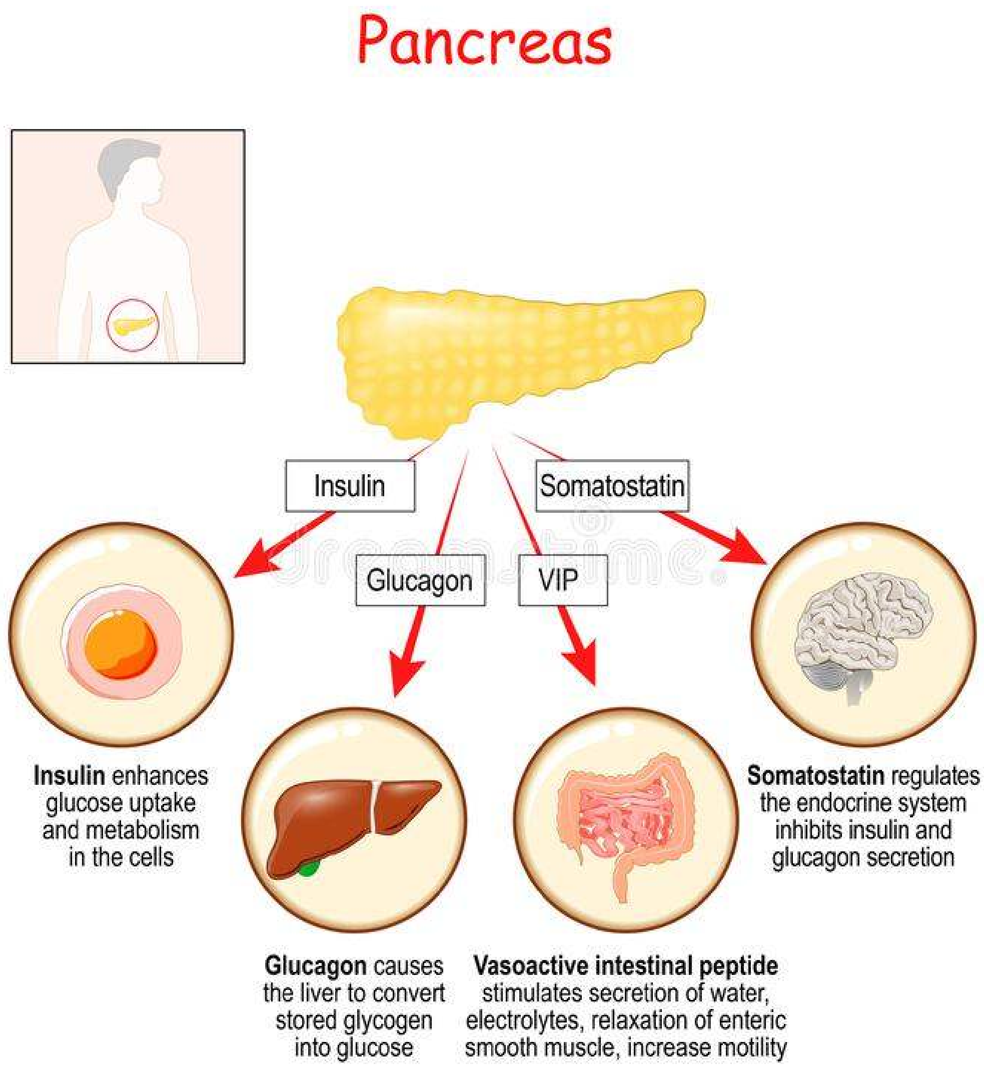
Razvi, S. et al. J Am Coll Cardiol. 2018;71(16):1781–96.

Pancreas

- Pancreas is having both Endocrine and Exocrine parts.
- The Endocrine part is made up of Islet of Langerhans which are aggregated in tail part of pancreas.
- Islet of Langerhans is an encapsulated structure bounded by thin capsule of reticular fibres.
- In the islet, following three different types of cells are mainly found. Alpha, Beta and D cells.

Beta (ß) cells produce INSULIN
- Alpha (a) cells produce GLUCAGON
- Delta (d) cells produce SOMATOSTATIN
- F cells produce PANCREATIC POLYPEPTIDE



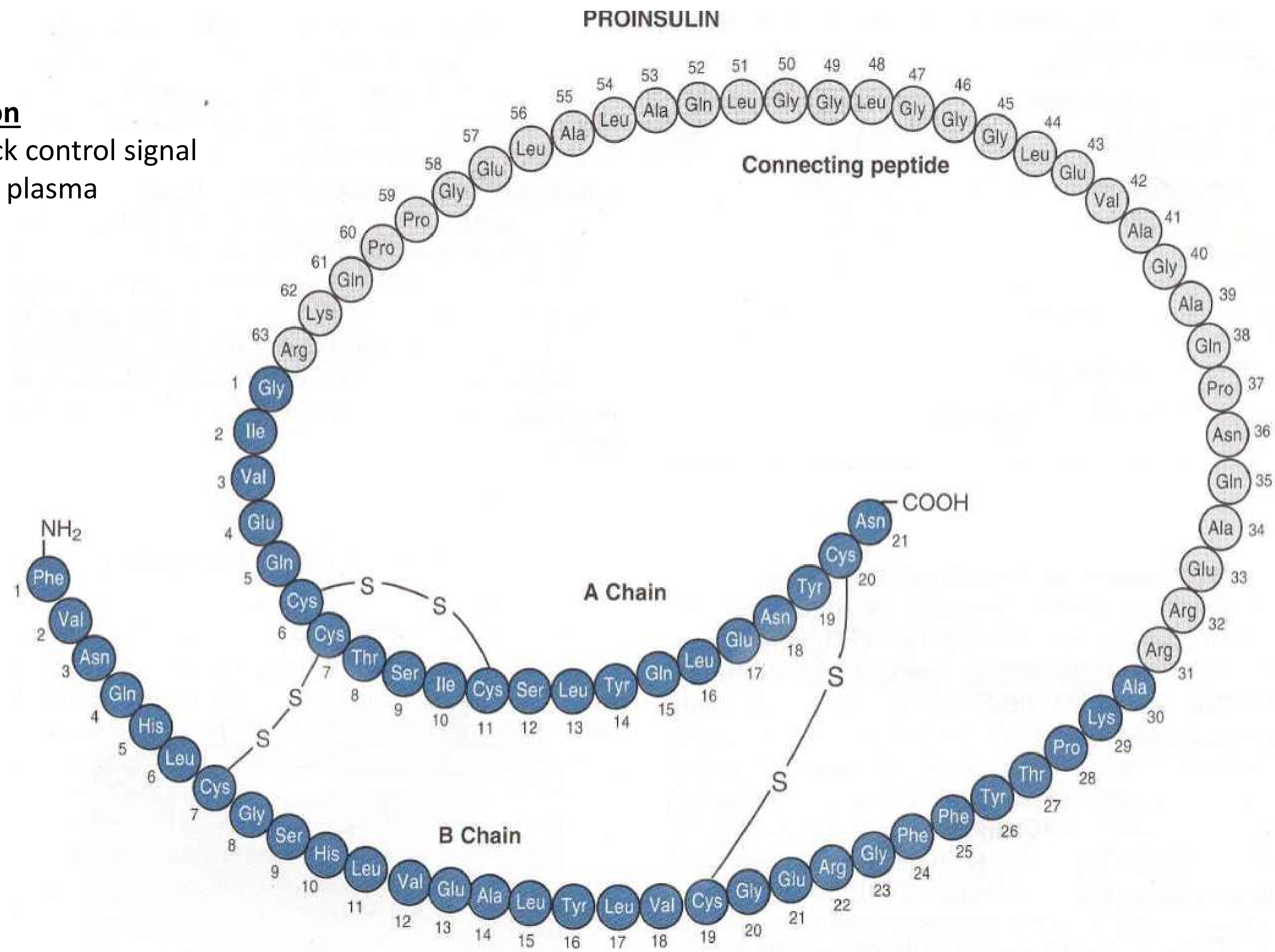

Pancreas
Insulin
Somatostatin
Glucagon
VIP
Insulin enhances glucose uptake and metabolism in the cells
Somatostatin regulates the endocrine system inhibits insulin and glucagon secretion
Glucagon causes the liver to convert stored glycogen into glucose
Vasoactive intestinal peptide stimulates secretion of water, electrolytes, relaxation of enteric smooth muscle, increase motility

Insulin

Regulation of insulin secretion

Mainly regulated by feed back control signal provided by nutrients level in plasma

" Hormone of Abundancy"



Regulators of 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	
Cholecystokinin (CCK)	
Secretin	
Vasoactive intestinal peptide (VIP)	
Epinephrine (β-receptor)	
Parasympathetic nervous system	Sympathetic nervous system stimulation

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

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

"ANTI-DIABETOGENIC"

facilitates amino acids entry into muscle cells
- Facilitates protein synthesis in ribosomes by induction of gene transcription
- Inhibits proteolysis by decreasing lysosomal activity

"**ANABOLIC HORMONE**"

INSULIN ACTION ON FAT METABOLISM

LIVER

- Anti ketogenic & Lipogenic
- Stimulates HMG-CoA reductase

ADIPOSE TISSUE

- Promotes storage of fat
- Inhibits lipolysis by inhibiting Hormone sensitive lipase
- Promotes lipogenesis by stimulating lipoprotein lipase

"ANTI-KETOGENIC"

The absorptive state, or the fed state, occurs after a meal when your body is digesting the food and absorbing the nutrients (catabolism exceeds anabolism). Digestion begins the moment you put food into your mouth, as the food is broken down into its constituent parts to be absorbed through the intestine.

INSULIN ACTION ON PLASMA K+ CONCENTRATION

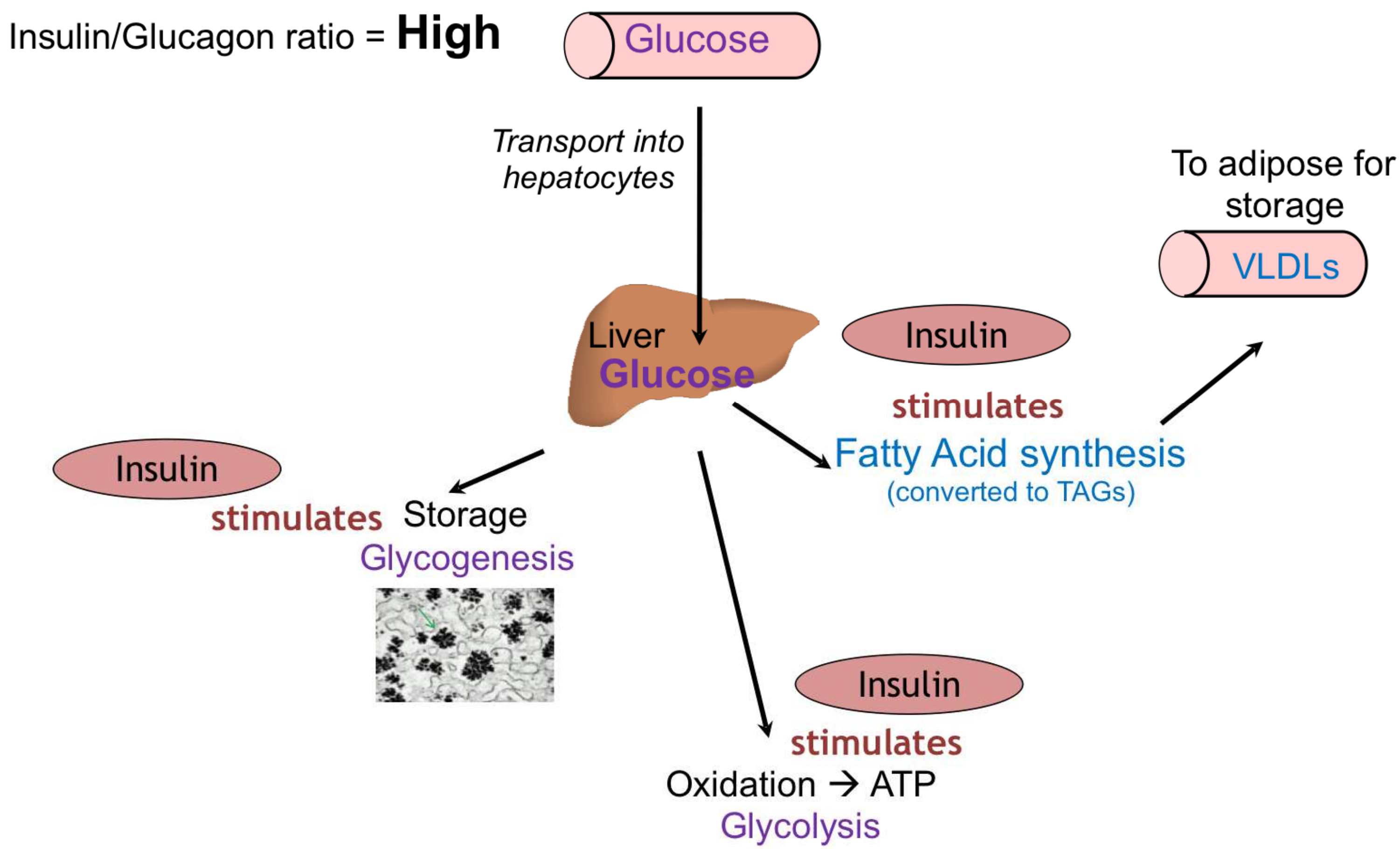
- Facilitates rapid entry of K+ into cell by simulating Na-K ATPase activity
- Thus decreases plasma concentration of K+
- APPLIED: Insulin is given along with glucose in the treatment of Hyperkalemia that occurs in Acute Renal Failure

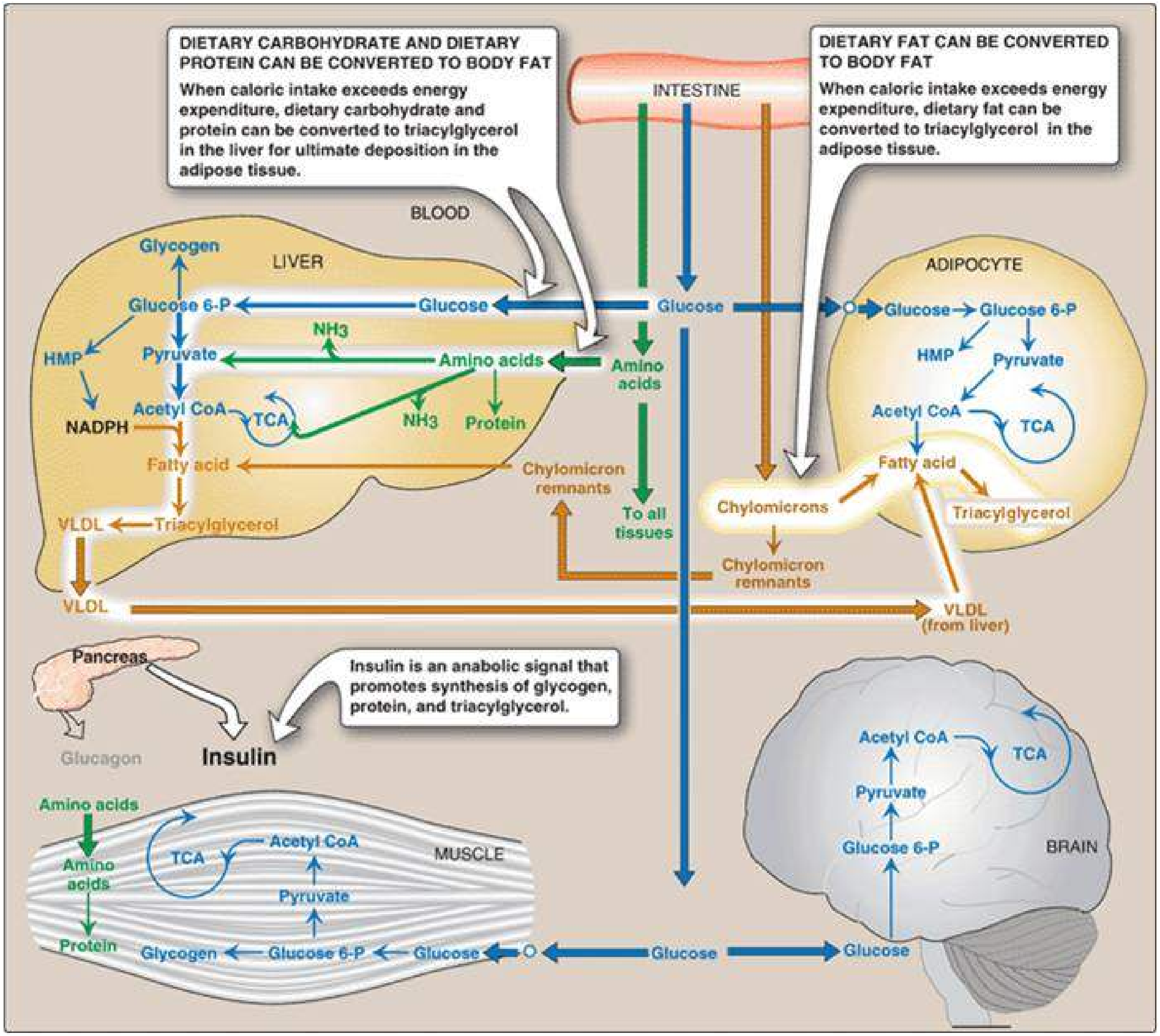
"PHYSIOLGICAL REGULATOR OF PLASMA K+ CONCENTRATION"

Dominates in Fed State Metabolism

- **INCREASE GLUCOSE UPTAKE IN MOST CELLS =➔Anti-Diabetogenic**
- **INCREASE GLUCOSE USE & STORAGE=➔Anabolic**
- **INCREASE PROTEIN SYNTHESIS=➔Anti-ketogenic**
- **INCREASE FAT SYNTHESIS=➔Lipogenic**

Metabolism in Fed State: Liver





DIETARY CARBOHYDRATE AND DIETARY PROTEIN CAN BE CONVERTED TO BODY FAT
When caloric intake exceeds energy expenditure, dietary carbohydrate and protein can be converted to triacylglycerol in the liver for ultimate deposition in the adipose tissue.
INTESTINE
DIETARY FAT CAN BE CONVERTED TO BODY FAT
When caloric intake exceeds energy expenditure, dietary fat can be converted to triacylglycerol in the adipose tissue.
BLOOD
LIVER
Glycogen
Glucose 6-P
Glucose
HMP
Pyruvate
NH3
Amino acids
NADPH
Acetyl CoA
TCA
NH3
Protein
Fatty acid
Chylomicron remnants
VLDL
Triacylglycerol
VLDL
Glucose
Amino acids
To all tissues
ADIPOCYTE
Glucose
Glucose 6-P
HMP
Pyruvate
Acetyl CoA
TCA
Fatty acid
Chylomicrons
Triacylglycerol
Chylomicron remnants
VLDL (from liver)
Pancreas
Glucagon
Insulin
Insulin is an anabolic signal that promotes synthesis of glycogen, protein, and triacylglycerol.
Amino acids
Amino acids
Protein
TCA
Acetyl CoA
Pyruvate
MUSCLE
Glycogen
Glucose 6-P
Glucose
Glucose
Glucose
BRAIN
Acetyl CoA
TCA
Pyruvate
Glucose 6-P

GLUCAGON

Produced by alpha 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 non carbohydrates
  - Release of glucose to the blood from liver cells

Stimulates glycogenolysis, gluconeogenesis & inhibits glycogenesis
- Promotes lipolysis & ketogenesis
- Increases calorigenesis

"Prodiabetogenic and Ketogenic"

INSULIN–GLUCAGON RATIO

- **Insulin** is hormone of **energy storage**
- **Glucagon** is hormone of **energy release**
- A balance should be maintained for normal metabolic functions
- After a normal balance diet is 3
- After overnight fasting decreases to 1, may decrease to as low as 0.4 after prolonged fasting
- Physiological significance – during neonatal period a low I/G ratio is critical for survival

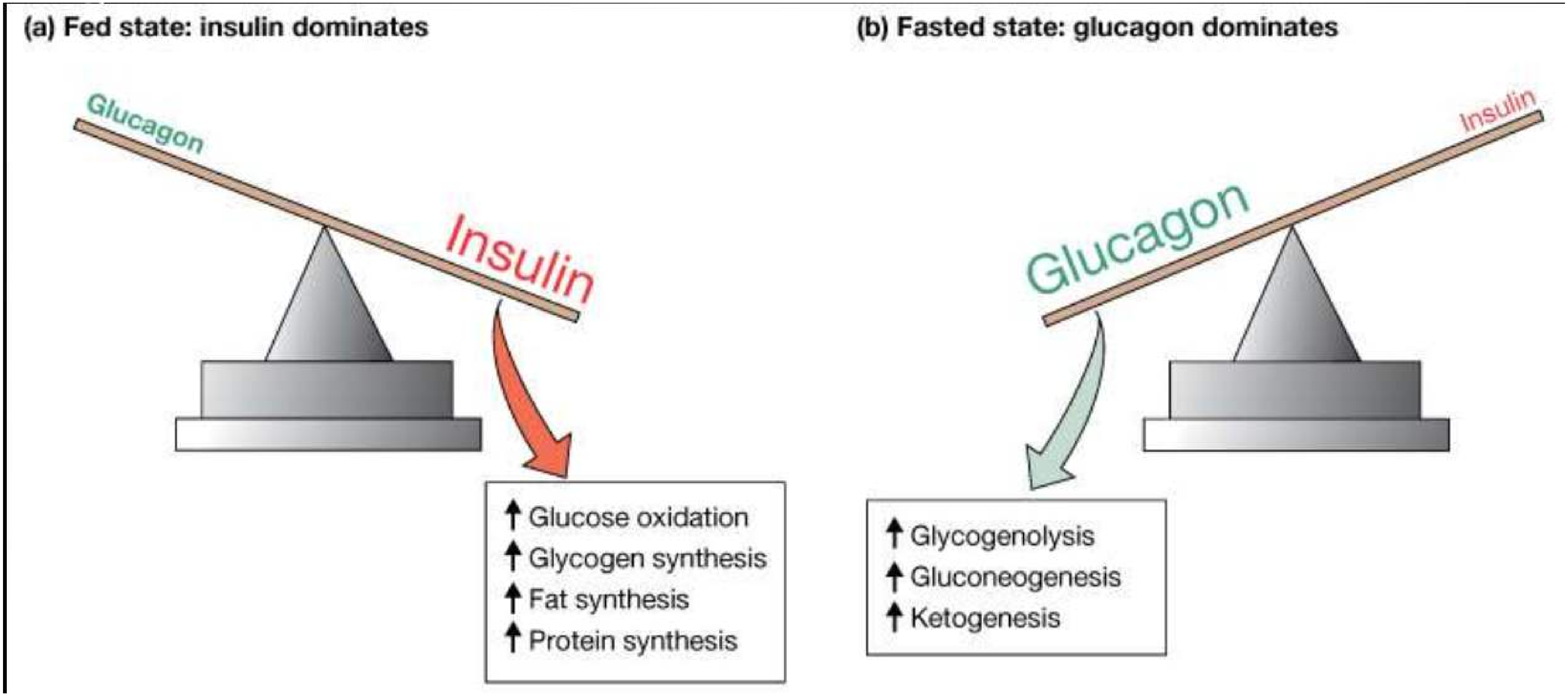
Effects on Glucagon Secretion

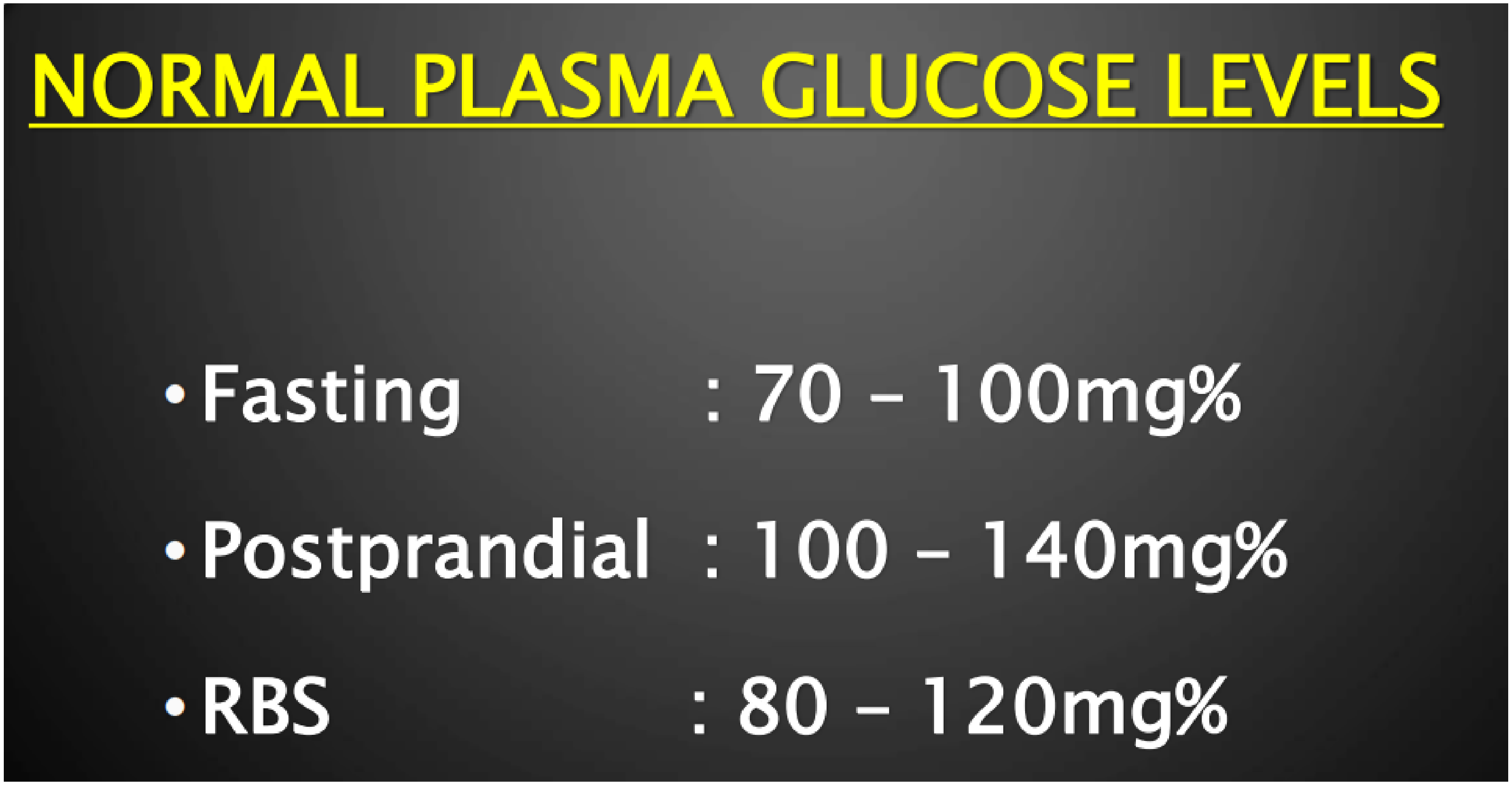
Stimuli for Glucagon Secretion

↓ Blood glucose
↑ Serum amino acids (arginine, alanine)
Sympathetic nervous system stimulation
Stress
Exercise

Inhibitors of Glucagon Secretion

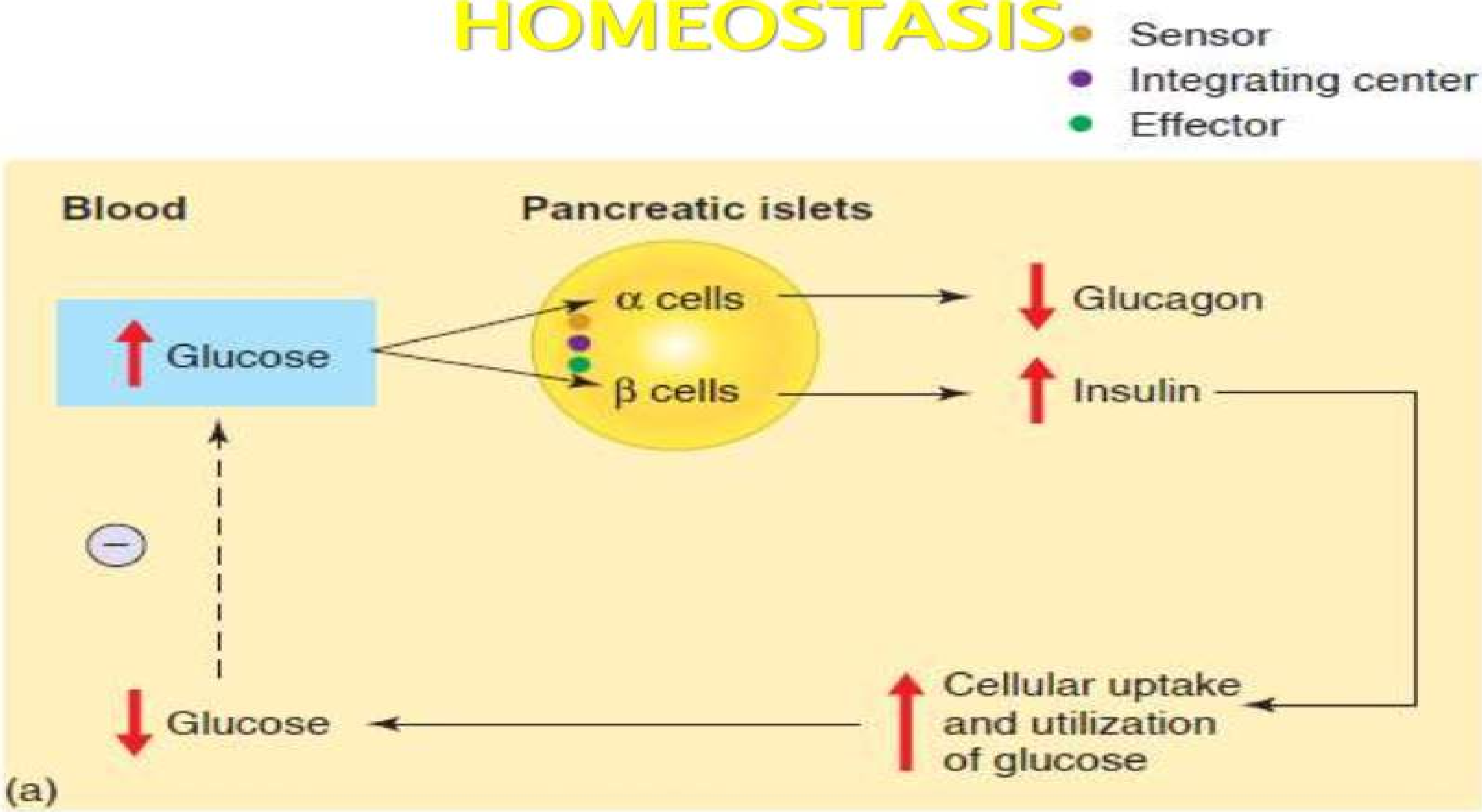
Somatostatin
Insulin
↑ Blood glucose


(a) Fed state: insulin dominates
Glucagon
Insulin
↑ Glucose oxidation
↑ Glycogen synthesis
↑ Fat synthesis
↑ Protein synthesis
(b) Fasted state: glucagon dominates
Insulin
Glucagon
↑ Glycogenolysis
↑ Gluconeogenesis
↑ Ketogenesis



Rbs = random blood sugar

GLUCOSE HOMEOSTASIS



GLUCOSE HOMEOSTASIS

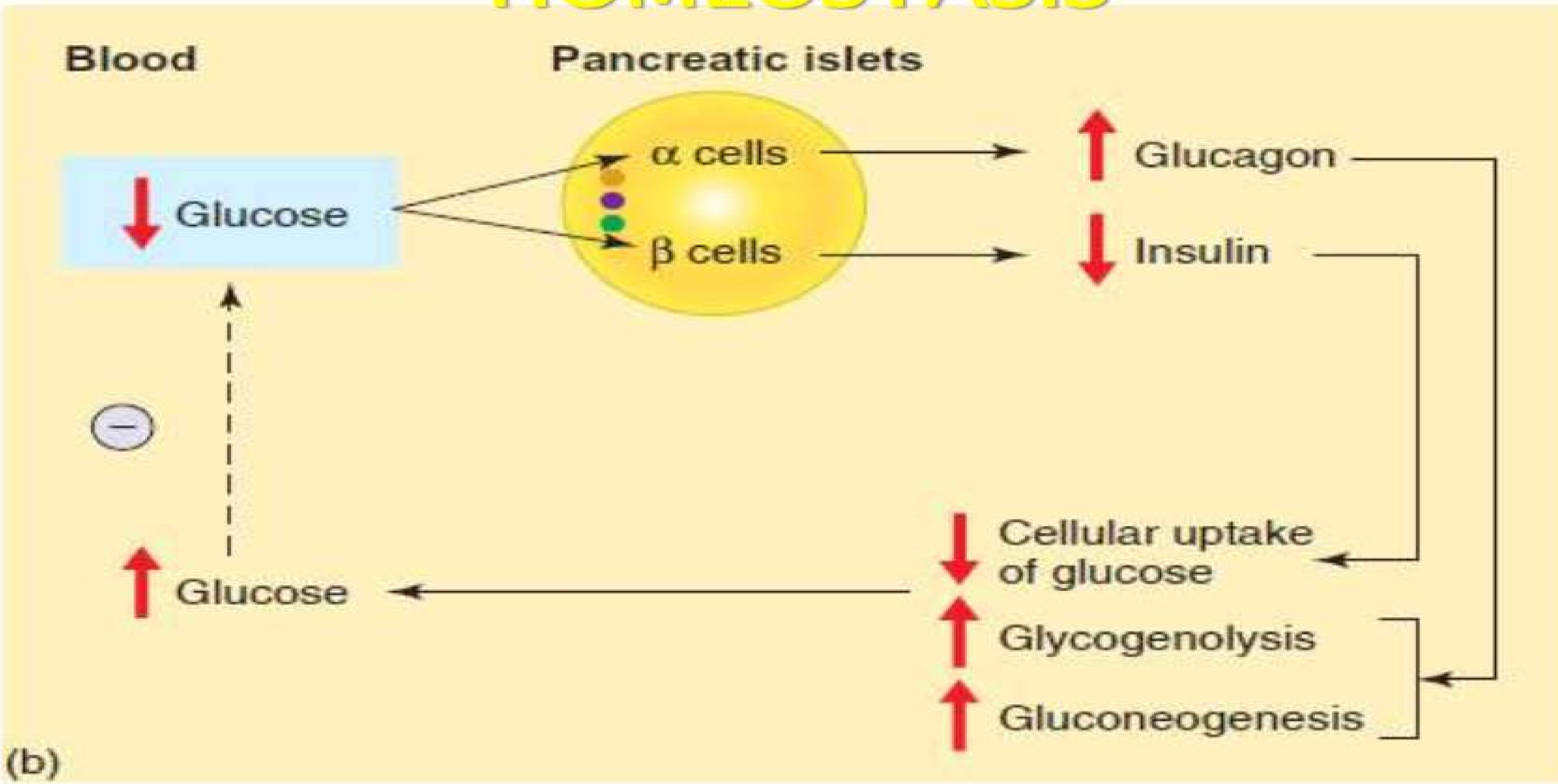


Table: 49.4 Major differences between Type 1 and Type 2 diabetes mellitus.

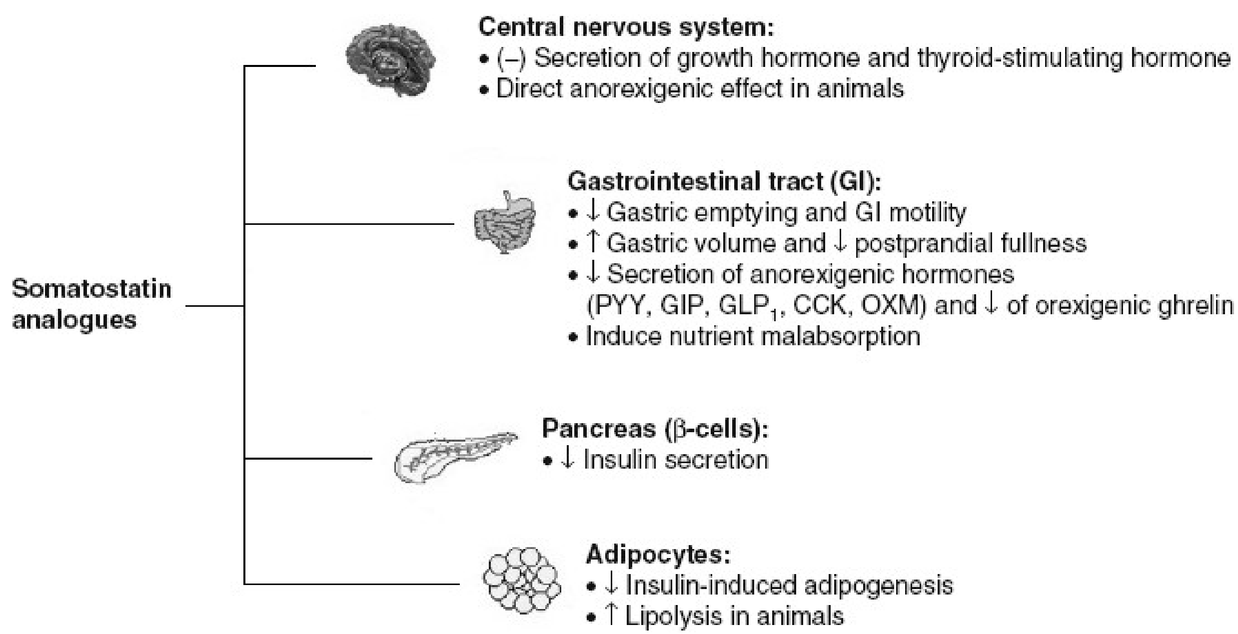
	Type I	Type II
1. Age of onset	Before the age of 40 (Juvenile onset diabetes)	After the age of 40 (Maturity onset diabetes)
2. Body fat mass	Not obese	Obese
3. Incidence	10% of the total diabetes	90% of the total diabetes
4. Genetic susceptibility	Concordance rate is < 50%	Concordance rate is > 50%
5. Incidence of ketoacidosis	High	Low
6. B cell mass of pancreas	B cells destroyed	B cells morphology is normal.
7. Nature of onset	Rapid	Gradual
8. Usual complication	Ketoacidotic coma	Hyperosmolal coma

SOMATOSTATIN

Secreted from D cells of pancreas

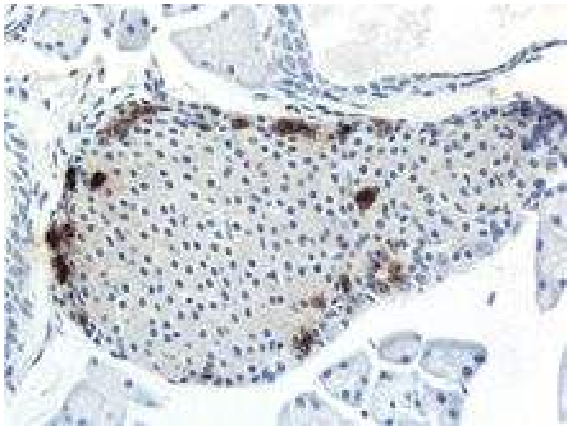
- Also secreted in SOMATOSTATIN hypothalamus & GIT

- Inhibits secretion of insulin & glucagon
- Inhibits GI motility* & GI secretions
- Regulates feedback control of gastric emptying



PANCREATIC POLYPEPTIDE

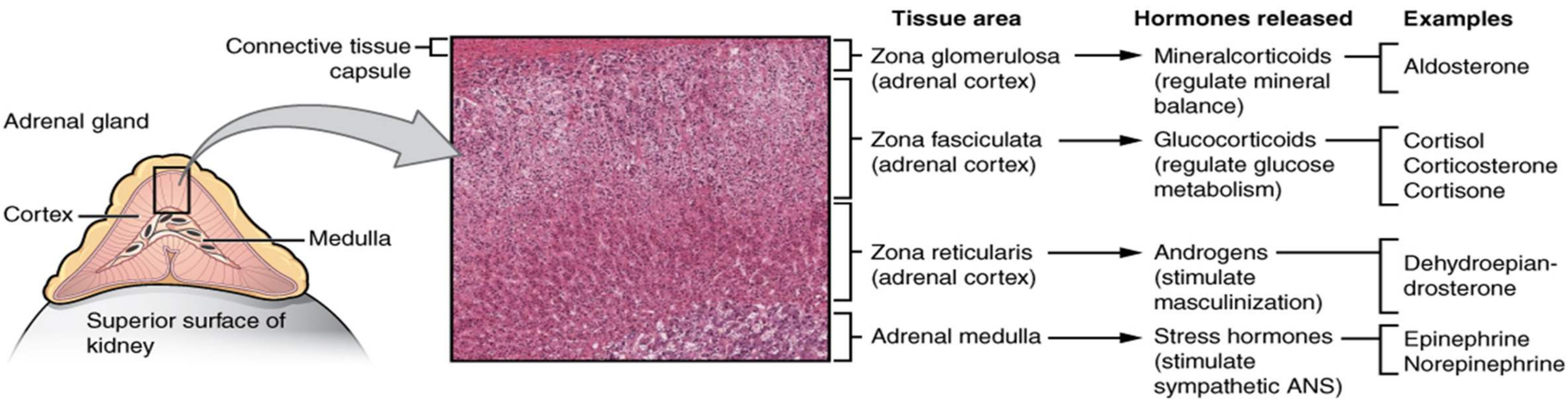
•Pancreatic polypeptide (PP) is a polypeptide secreted Secreted from F cells of pancreas or PP Cells = predominantly in the head of the pancreas.



- Structurally similar to Neuropeptide Y secreted from hypothalamus
- •Secreted in response to food intake
- Inhibits exocrine pancreatic secretion
- Slows the absorption of food from the GI tract

- The function of PP is to self-regulate pancreatic secretion activities (endocrine and exocrine).
- It also has effects on hepatic glycogen levels and gastrointestinal secretions.
- Its secretion in humans is increased after a protein meal, fasting, exercise, and acute hypoglycemia, and is decreased by somatostatin and intravenous glucose.
- Plasma PP has been shown to be reduced in conditions associated with increased food intake and elevated in anorexia nervosa. In addition, peripheral administration of PP has been shown to decrease food intake

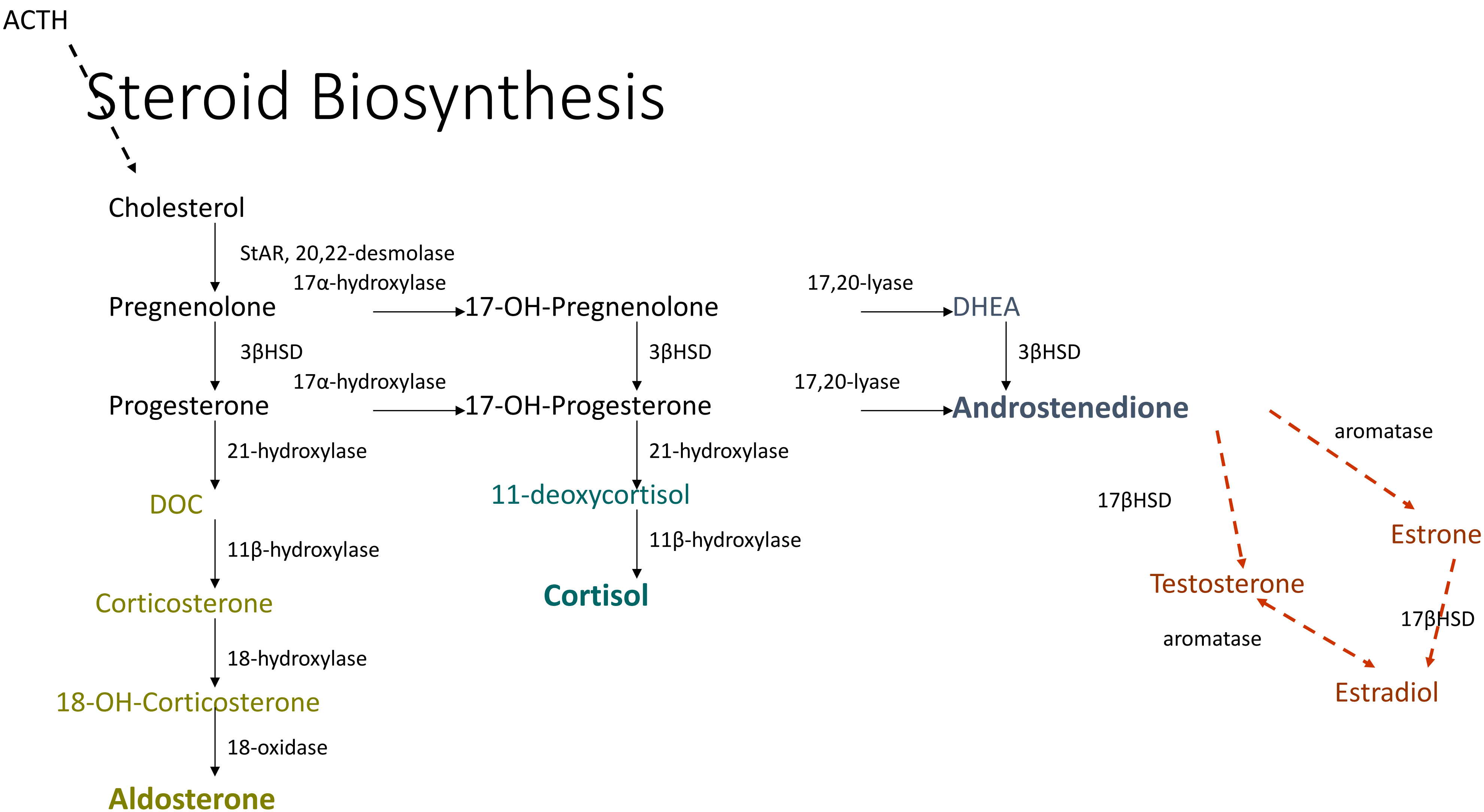
Adrenal glands



Glucocorticoids are chiefly produced in the zona fasciculata of the adrenal cortex
Cortisol (or hydrocortisone) is the most important human glucocorticoid.

Glucocorticoids are corticosteroids that bind to the glucocorticoid receptor

Steroid Biosynthesis



• GLUCOCORTICOIDS

(regulate metabolism & are critical in stress response)

– CORTISOL responsible for control and &metabolism of:

a. CHO (carbohydrates)

– increase glucose formed

– increase glucose released

CORTISOL

FATS-control of fat metabolism

• stimulates fatty acid mobilization from adipose tissue

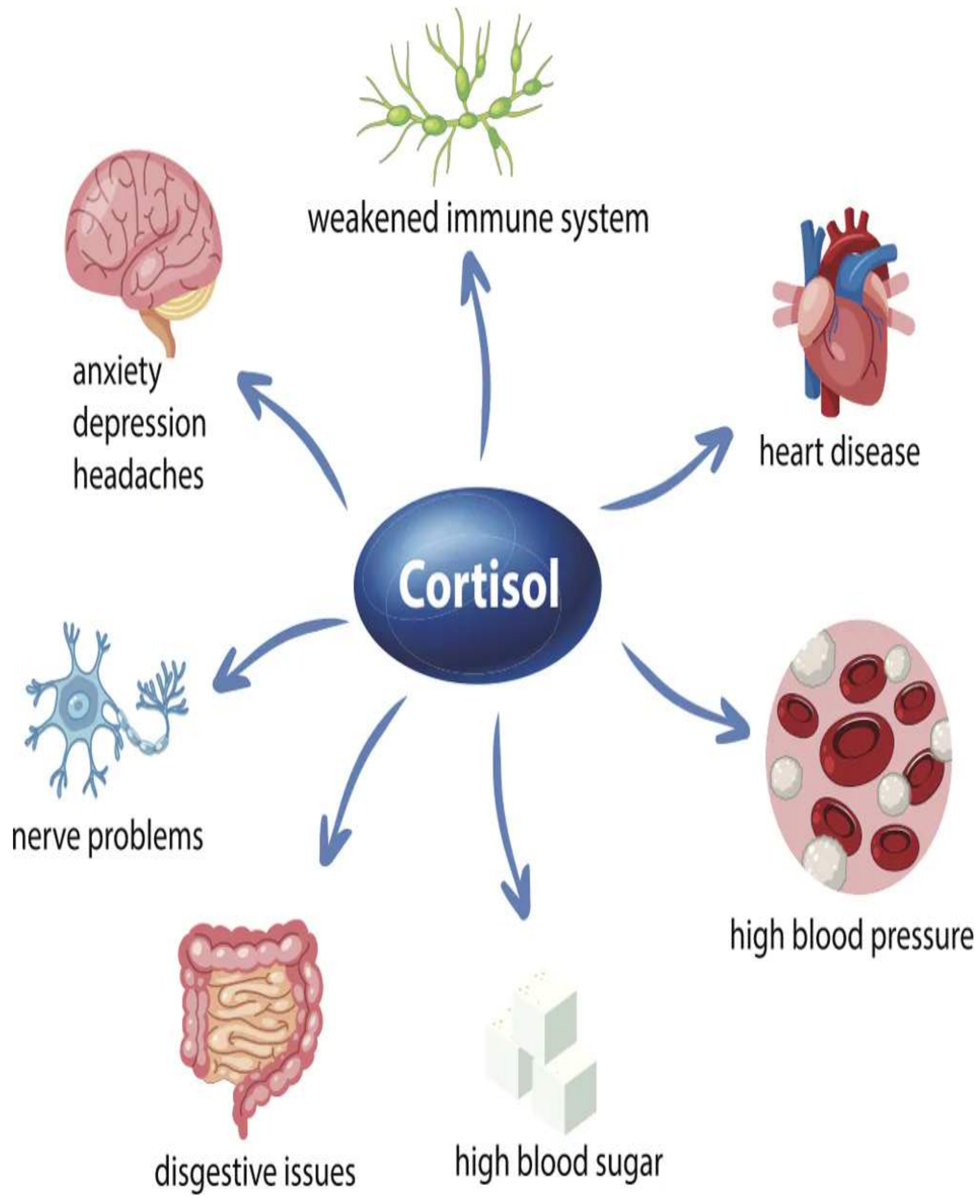
PROTEINS-control of protein metabolism

– stimulates protein synthesis in liver

– protein breakdown in tissues

– decrease inflammatory and allergic response

– decrease immune system therefore prone to infection



Glucocorticoid effects may be broadly classified into two major categories:
1/immunological
2/metabolic.

In addition, glucocorticoids play important roles in

1. **fetal development and body fluid homeostasis.**
2. **Immune**
3. **Metabolic**
4. **Developmental**
5. **Arousal and cognition**
6. **Body fluid homeostasis**

Cortisol and Immune

- up-regulate the expression of anti-inflammatory proteins.
- down-regulate the expression of proinflammatory proteins.

- Glucocorticoids are also shown to play a role in the development and homeostasis of T lymphocytes.
    - with either **increased or decreased sensitivity of T cell lineage to glucocorticoids.**

Metabolic

Involved in glucose metabolism.

In the fasted state, cortisol stimulates several processes that collectively serve to increase and maintain normal concentrations of glucose in blood.

Metabolic effects:

•Stimulation of gluconeogenesis, in particular, in the liver: This pathway results in the synthesis of glucose from non-hexose substrates, such as amino acids and glycerol from triglyceride breakdown.

•Mobilization of amino acids from extrahepatic tissues: These serve as substrates for gluconeogenesis.

•Inhibition of glucose uptake in muscle and adipose tissue: A mechanism to conserve glucose

•Stimulation of fat breakdown in adipose tissue: The fatty acids released by lipolysis are used for production of energy in tissues like muscle, and the released glycerol provide another substrate for gluconeogenesis.

•Increase in sodium retention and potassium excretion leads to hypernatremia and hypokalemia

•Increase in hemoglobin concentration, likely due to hindrance of the ingestion of red blood cell by macrophage or other phagocyte.

•Increased urinary uric acid

•Increased urinary calcium and hypocalcemia

•Alkalosis

•Leukocytosis

Excessive glucocorticoid levels resulting from administration as a drug or hyperadrenocorticism have effects on many systems.
Some examples include inhibition of bone formation, suppression of calcium absorption (both of which can lead to osteoporosis), delayed wound healing, muscle weakness, and increased risk of infection.
These observations suggest a multitude of less-dramatic physiologic roles for glucocorticoids.

Developmental

- Glucocorticoids have multiple effects on fetal development.
- An important example is their role in **promoting maturation of the lung and production of the surfactant necessary for extrauterine lung function.**

- In addition, glucocorticoids are necessary for **normal brain development, by initiating terminal maturation**, **remodeling axons and dendrites, and affecting cell survivaland may also play a role in hippocampal development**.

- Glucocorticoids **stimulate the maturation of the Na^+/K^+/ATPase, nutrient transporters, and digestion enzymes, promoting the development of a functioning gastro-intestinal system.**

- Glucocorticoids also support the development of the **neonate's renal system by increasing glomerular filtra**tion.

Body fluid homeostasis

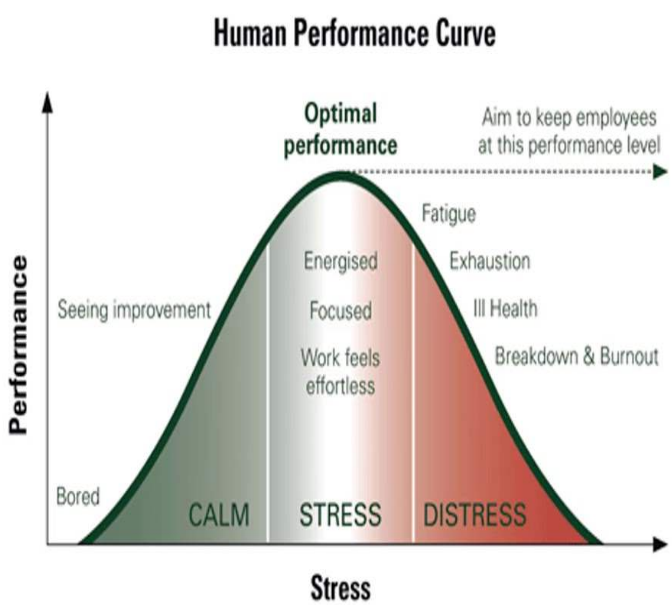
- Glucocorticoids could act centrally, as well as peripherally, to assist in the normalization of extracellular fluid volume by regulating body's action to atrial natriuretic peptide (ANP).

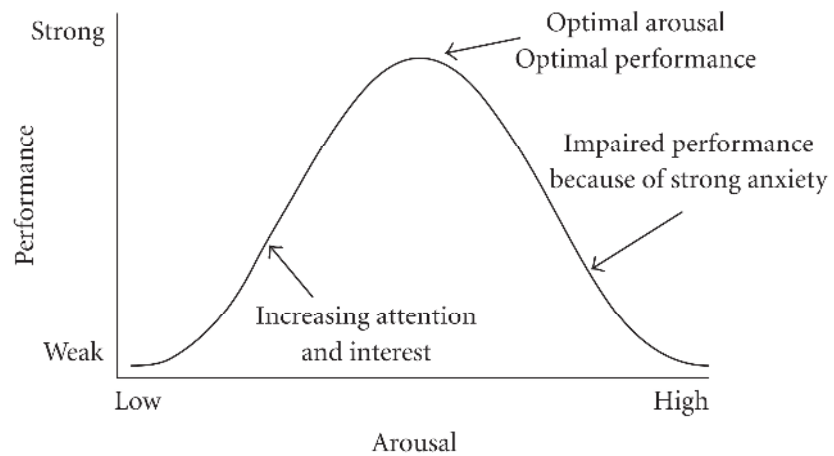
- Centrally, glucocorticoids could inhibit dehydration induced water intake
- Peripherally , glucocorticoids could induce a potent diuresis.

Arousal and cognition

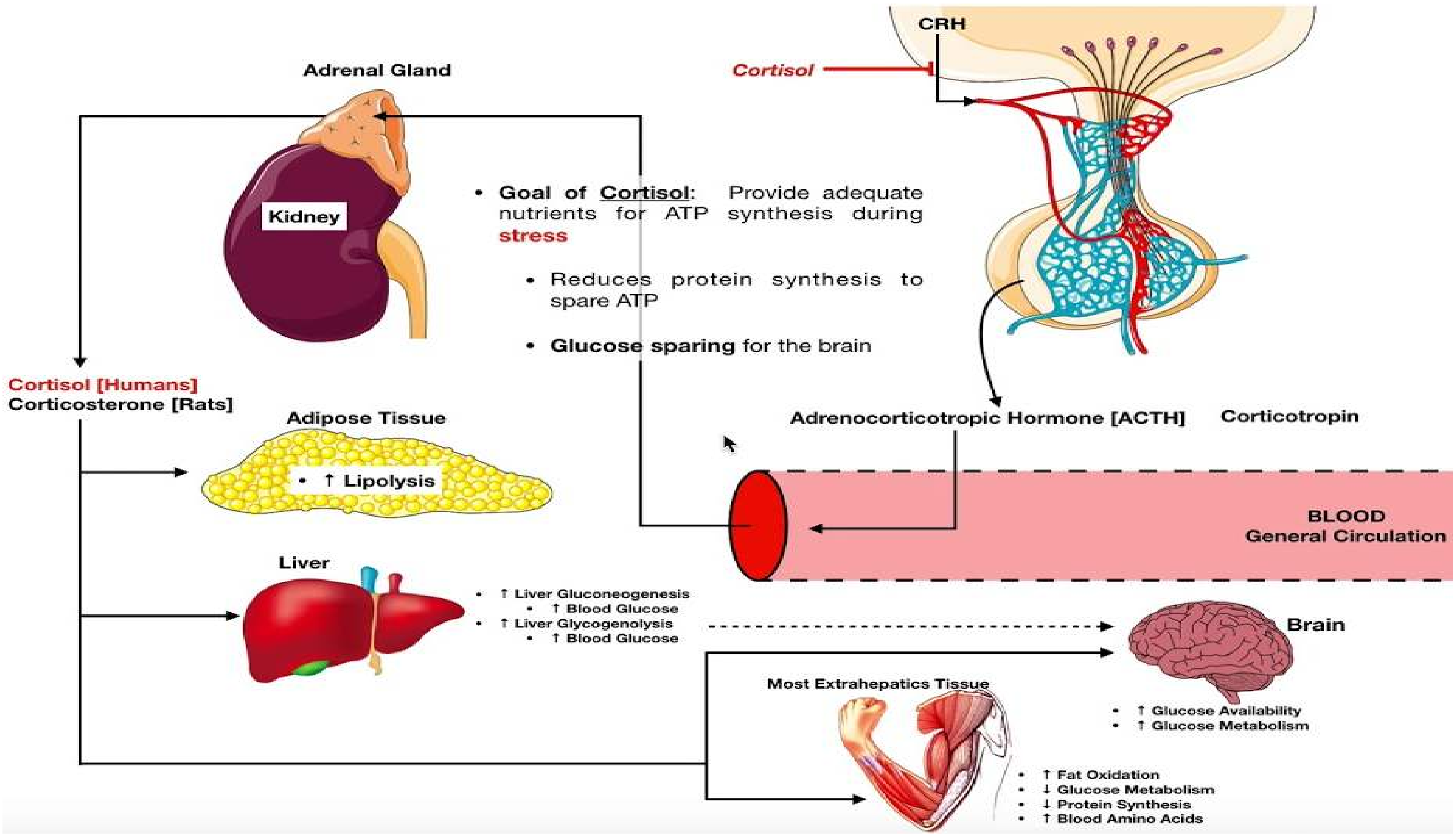
- A graphical representation of the Yerkes-Dodson curve
- Glucocorticoids act on the hippocampus, amygdala, and frontal lobes. Along with adrenaline, these enhance the formation of flashbulb memories of events associated with strong emotions, both positive and negative.
- Glucocorticoids have also been shown to have a significant impact on vigilance (attention deficit disorder) and cognition (memory).

Figure 1: The Yerkes-Dodson Human Performance and Stress Curve





The **Yerkes-Dodson law**," performance increases with physiological or mental arousal (stress) but only up to a point. When the level of stress becomes too high, performance decreases. There's more: The shape of the **curve** varies based on the complexity and familiarity of the task



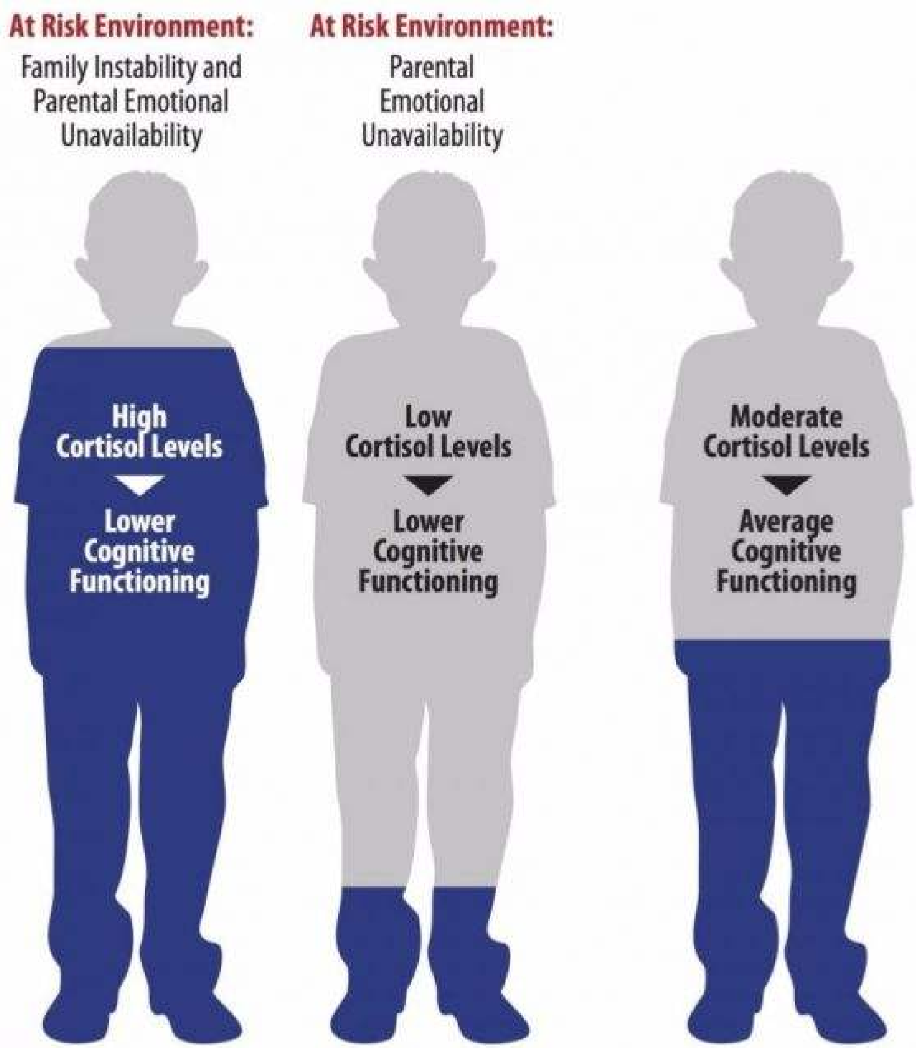
CRH
Cortisol
Adrenal Gland
Kidney
• Goal of Cortisol: Provide adequate nutrients for ATP synthesis during stress
• Reduces protein synthesis to spare ATP
• Glucose sparing for the brain
Cortisol [Humans]
Corticosterone [Rats]
Adipose Tissue
• ↑ Lipolysis
Adrenocorticotropic Hormone [ACTH]
Corticotropin
BLOOD
General Circulation
Liver
• ↑ Liver Gluconeogenesis
• ↑ Blood Glucose
• ↑ Liver Glycogenolysis
• ↑ Blood Glucose
Brain
• ↑ Glucose Availability
• ↑ Glucose Metabolism
Most Extrahepatics Tissue
• ↑ Fat Oxidation
• ↓ Glucose Metabolism
• ↓ Protein Synthesis
• ↑ Blood Amino Acids

ACTH

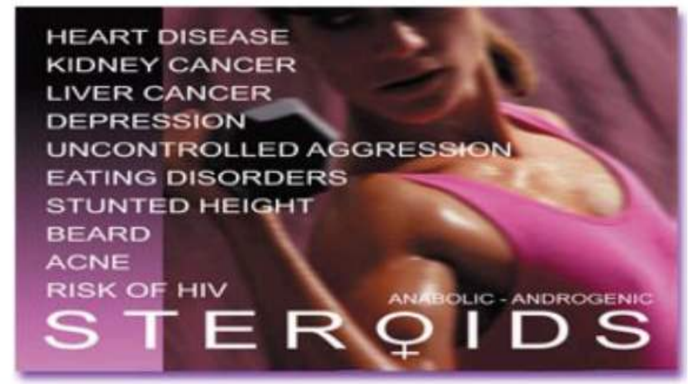
cortisol

↓ – levels cause stimulation of ACTH

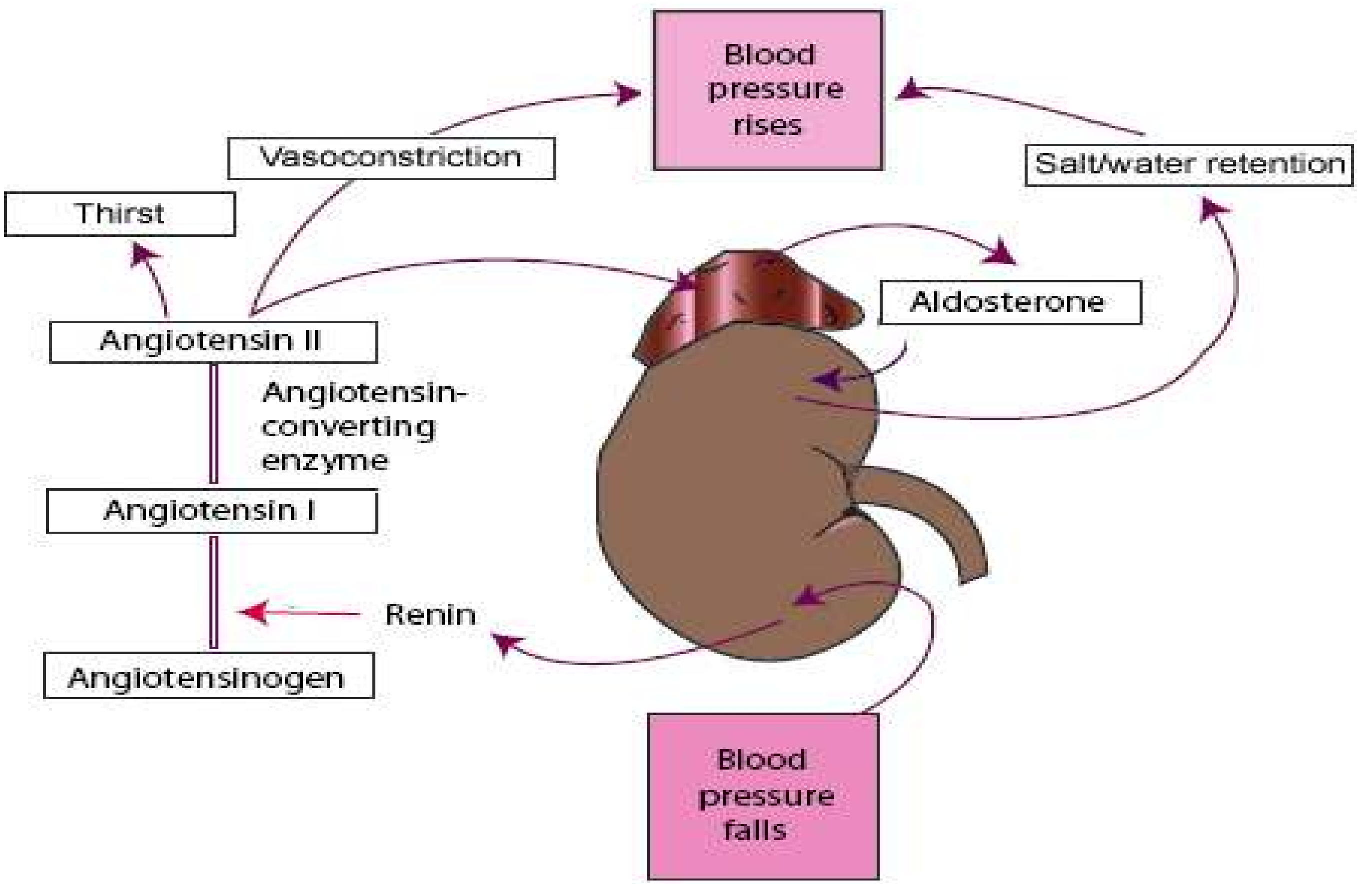
↑ – levels cause dec. release of ACTH



Too many steroids



Adrenal physiology :Renin-angiotensin system



<u>Mineralocorticoids</u> (F & E balance)
– Aldosterone (renin from kidneys controls adrenal
cortex production of aldosterone)

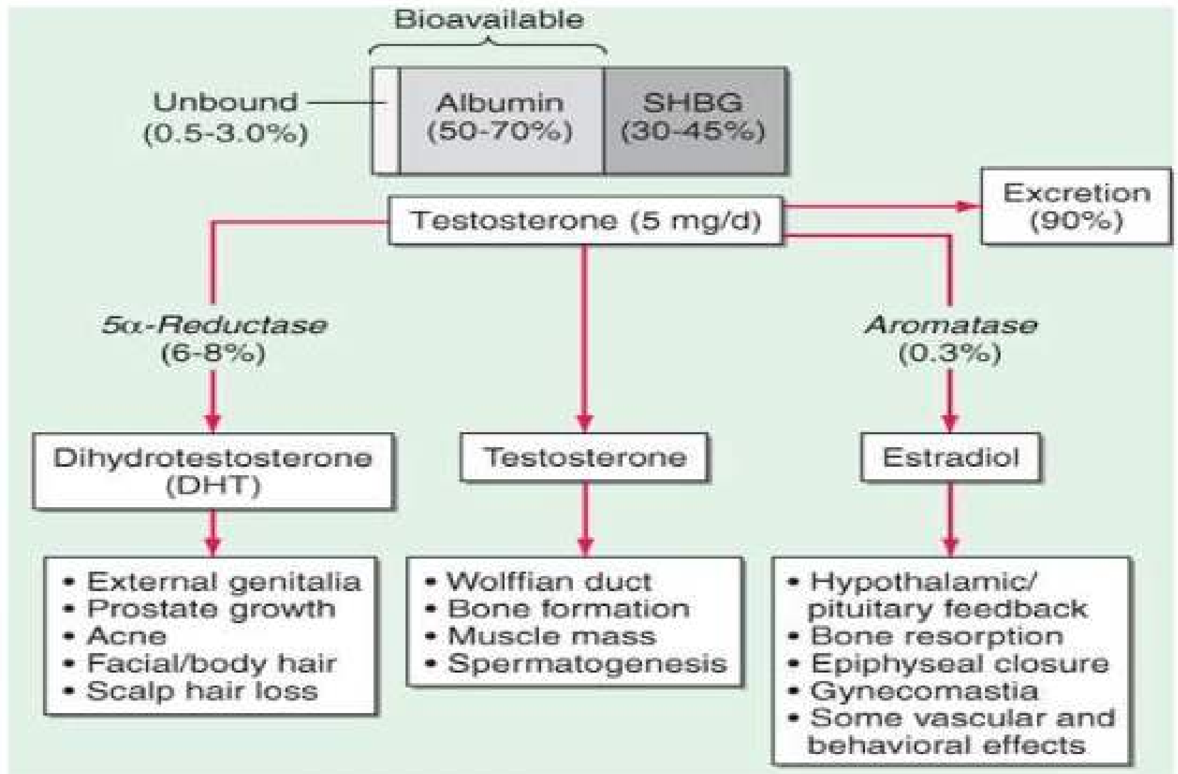
- Na retention
- Water retention
- K excretion

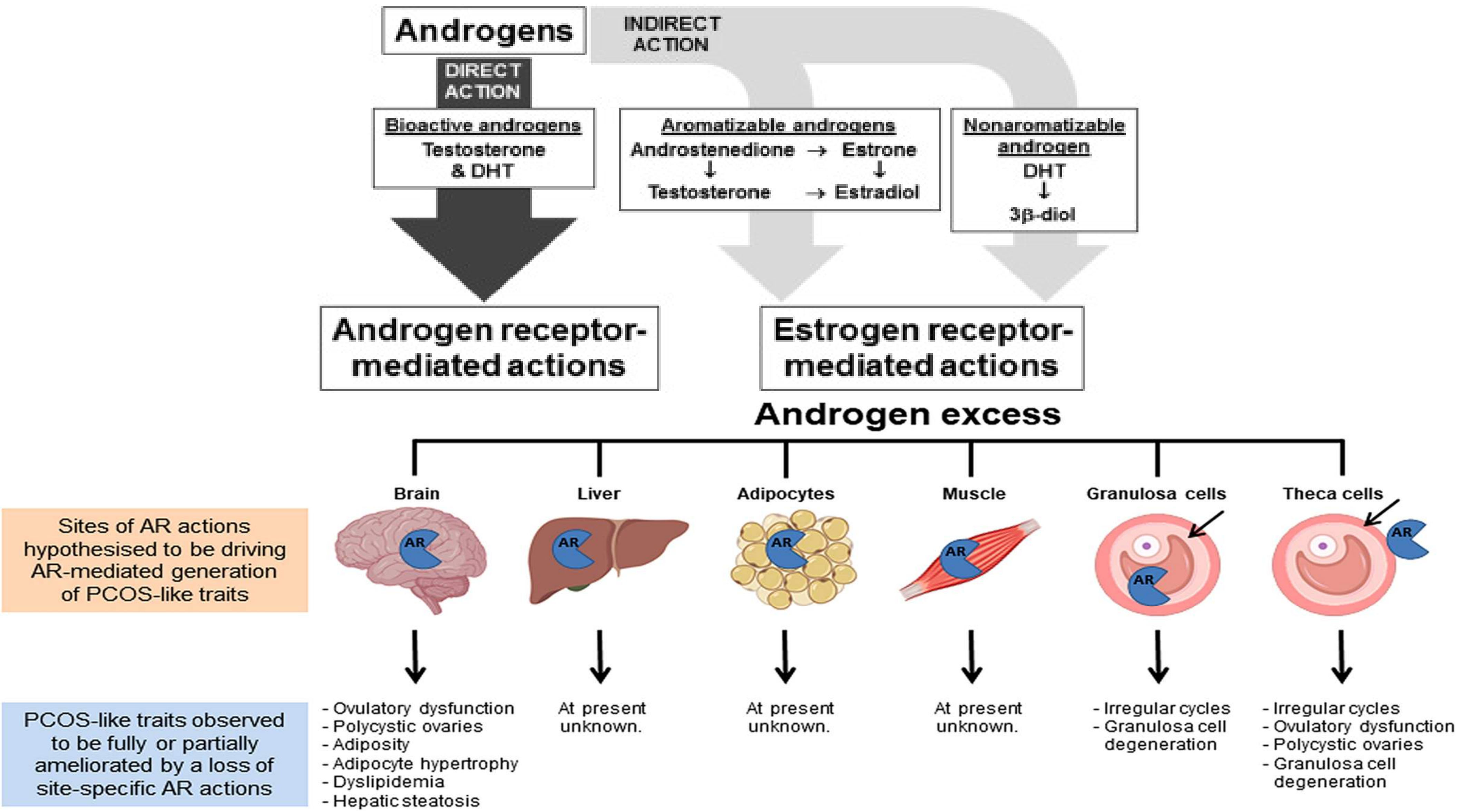
ANDROGENS = SEX HORMONES

- – hormones which male characteristics
- • release of testosterone INCREASED
- Clear more in women than men

Details will be discussed in male reproduction

ANDROGEN METABOLISM AND ACTIONS

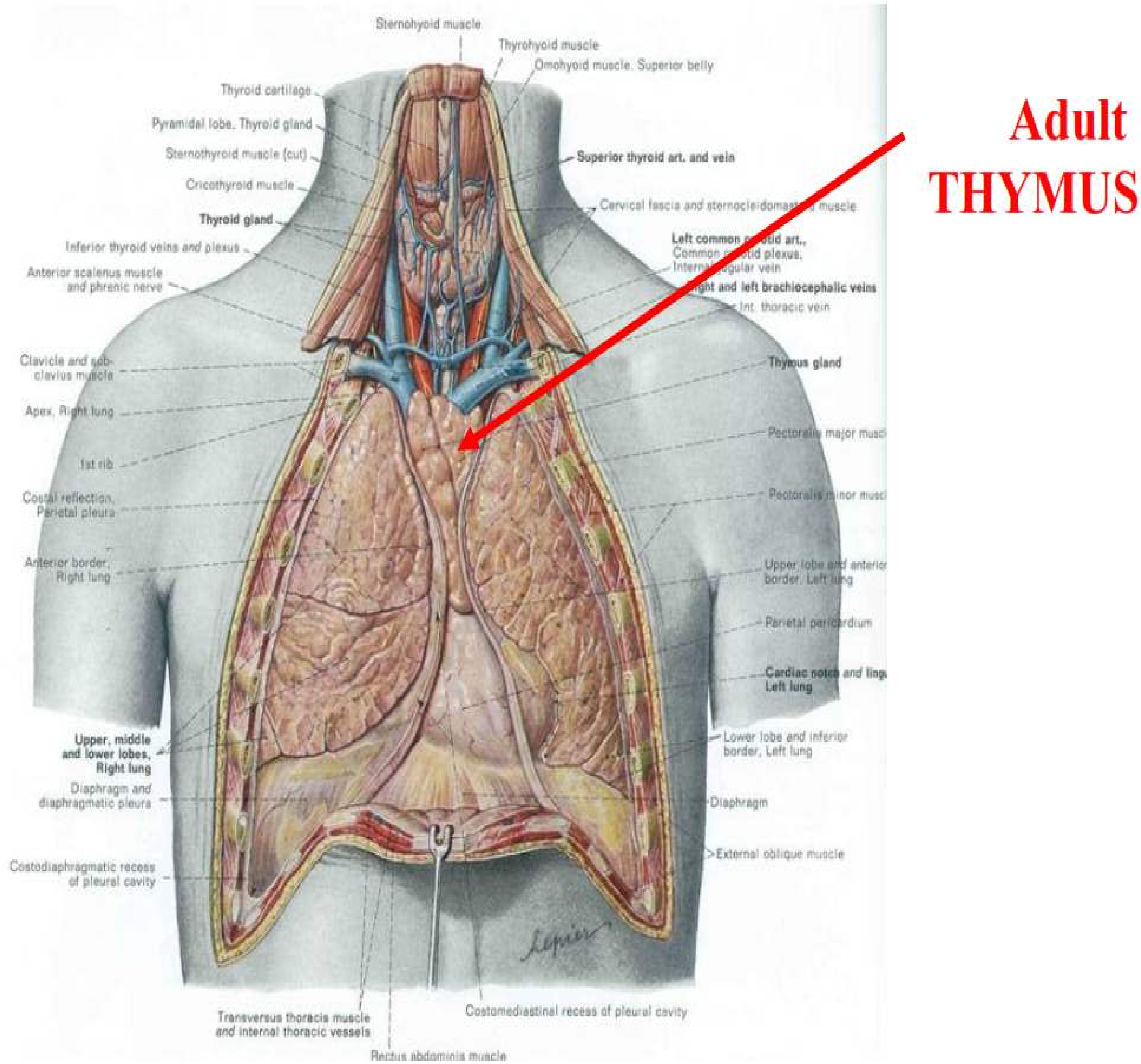


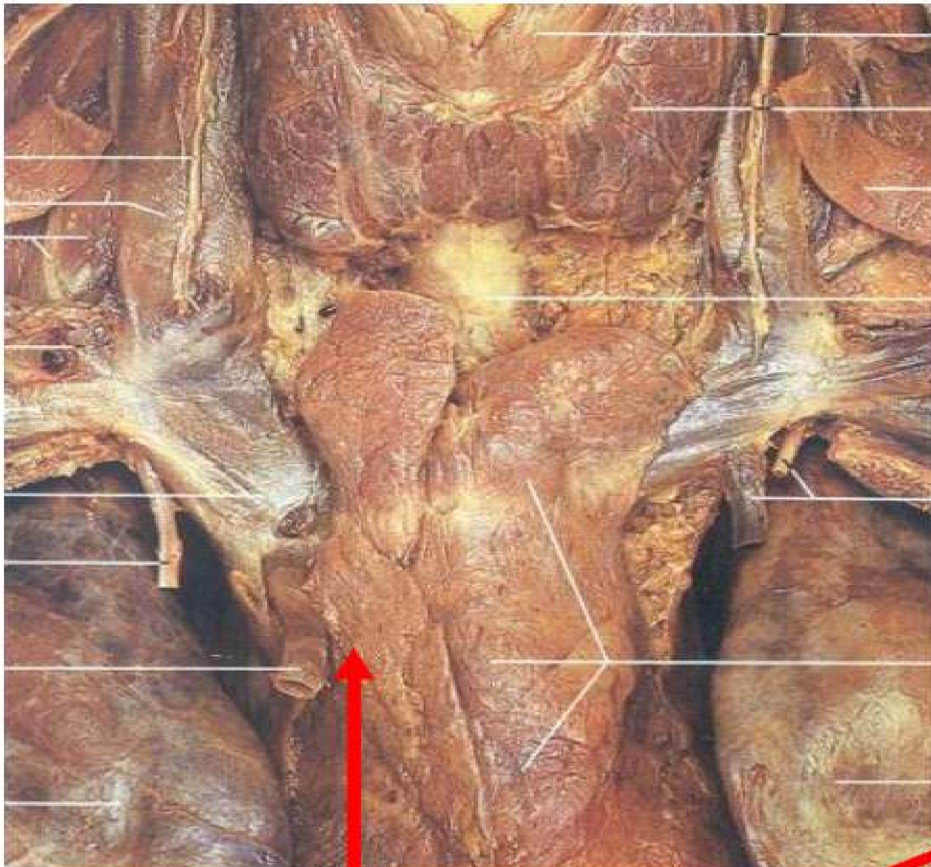


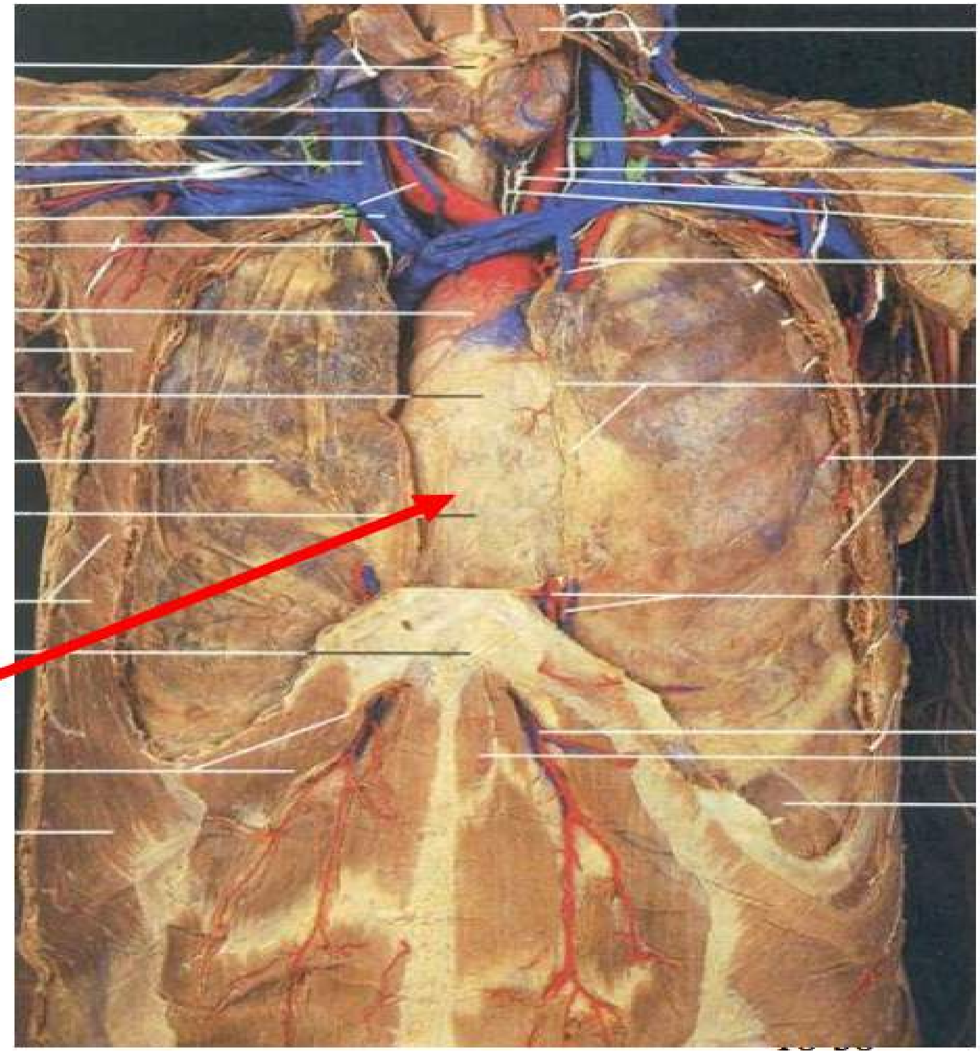
Androgens
DIRECT ACTION
INDIRECT ACTION
Bioactive androgens
Testosterone & DHT
Aromatizable androgens
Androstenedione → Estrone
Testosterone → Estradiol
Nonaromatizable androgen
DHT
3β-diol
Androgen receptor-mediated actions
Estrogen receptor-mediated actions
Androgen excess
Brain
Liver
Adipocytes
Muscle
Granulosa cells
Theca cells
AR
Sites of AR actions hypothesised to be driving AR-mediated generation of PCOS-like traits
PCOS-like traits observed to be fully or partially ameliorated by a loss of site-specific AR actions
- Ovulatory dysfunction
- Polycystic ovaries
- Adiposity
- Adipocyte hypertrophy
- Dyslipidemia
- Hepatic steatosis
At present unknown.
At present unknown.
At present unknown.
- Irregular cycles
- Granulosa cell degeneration
- Irregular cycles
- Ovulatory dysfunction
- Polycystic ovaries
- Granulosa cell degeneration

THYMUS GLAND

- Located in the upper thorax region.
- • Large in infants and children, it decreases in size throughout adult hood.
- • By old age, it is composed mostly of fibrous connective tissue and fat.
- • Thymus produces a hormone called **thymosin.**
- • During childhood, it acts as an incubator for the maturation of a special group of whiteblood cells(T lymphocytes or T cells)**.**
- • T cells are play a great role in immune response.







Adult THYMUS

- Many body organs not normally considered endocrine organs contain isolated cell clusters that secrete hormones.

- Examples include
  - the heart (atrial natriuretic peptide);
  - gastrointestinal tract organs (gastrin, secretin, and others);
  - the placenta (hormones of pregnancy—estrogen, progesterone, and others);
  - the kidneys (erythropoietin and renin);
  - the thymus; skin (cholecalciferol);
  - adipose tissue (leptin and resistin).
  - Bones

Hormonal tables
https://en.wikipedia.org/wiki/List_of_human_hormones

Name	Abbreviation	Tissue	Cells/Amino acid	Receptor	Target Tissue	Effect
Adrenaline, also known as epinephrine	EPI	adrenal gland	Adrenal medulla / Tyrosine	adrenergic receptor	nearly all tissues	blood pressure, glycogenolysis, lipolysis, etc.
Melatonin	MT	pineal gland	Pinealocyte / Tryptophan	melatonin receptor	CNS and peripheral tissue	circadian rhythm
Noradrenaline, also known as norepinephrine	NE	adrenal gland	Adrenal medulla / Tyrosine	noradrenergic receptor	nearly all tissues	blood pressure, glycogenolysis, lipolysis, etc.
Triiodothyronine	T_3	peripheral tissue of thyroid gland	Thyroid follicular cell / Tyrosine	thyroid hormone receptor	nearly every cell in the body	increased metabolism
Thyroxine	T_4	thyroid gland	Thyroid follicular cell / Tyrosine	thyroid hormone receptor	same as above	similar effect as T_3 but much weaker; converted to T3 in target cells
Dopamine	DA	**substantia nigra** (mainly)	Phenylalanine / Tyrosine	D1 and D2	system-wide	regulation of cellular cAMP levels, prolactin antagonist

Eicosanoid for more information about this class of paracrine signalling chemicals and hormones.

Name	Abbreviation	Tissue	Cells	Receptor	Target Tissue	Effect
Prostaglandins	PG	seminal vesicle		prostaglandin receptor		vasodilation
Leukotrienes	LT	Blood	white blood cells	G protein-coupled receptors		increase vascular permeability
Prostacyclin	PGI_2	endothelium		prostacyclin receptor		vasodilation, platelet activation inhibtor
Thromboxane	TXA_2	Blood	platelets	thromboxane receptor		vasoconstriction, Platelet Aggregation

Peptide

Vasoactive intestinal peptide	VIP	gut, pancreas, and suprachiasmatic nuclei of the hypothalamus			stimulates contractility in the heart, causes vasodilation, increases glycogenolysis, lowers arterial blood pressure and relaxes the smooth muscle of trachea, stomach and gall bladder
Uroguanylin	UGN	renal tissues			regulates electrolyte and water transport in renal epithelia.
Thyrotropin-releasing hormone	TRH	hypothalamus	Parvocellular neurosecretory neurons	anterior pituitary	Release thyroid-stimulating hormone (primarily) Stimulate prolactin release
Thyroid-stimulating hormone (or thyrotropin)	TSH	anterior pituitary	thyrotropes	thyroid gland	secrete thyroxine (T_4) and triiodothyronine (T_3)
Thrombopoietin	TPO	liver, kidney, striated muscle	Myocytes	megakaryocytes	produce platelets[6]
Somatostatin (or growth hormone–inhibiting hormone or growth hormone release–inhibiting hormone or somatotropin release–inhibiting factor or somatotropin release–inhibiting hormone)	GHIH or GHRIH or SRIF or SRIH	hypothalamus, islets of Langerhans, gastrointestinal system	delta cells in islets Neuroendocrince cells of the Periventricular nucleus in hypothalamus		Inhibit release of GH and TRH from anterior pituitary Suppress release of gastrin, cholecystokinin (CCK), secretin, motilin, vasoactive intestinal peptide (VIP), gastric inhibitory polypeptide (GIP), enteroglucagon in gastrointestinal system Lowers rate of gastric emptyingReduces smooth muscle contractions and blood flow within the intestine[4] Inhibit release of insulin from beta cells[5] Inhibit release of glucagon from alpha cells[5] Suppress the exocrine secretory action of pancreas.
Secretin	SCT	duodenum	S cell		Secretion of bicarbonate from liver, pancreas and duodenal Brunner's glandsEnhances effects of cholecystokinin Stops production of gastric juice
Renin		Kidney	Juxtaglomerular cells		Activates the renin–angiotensin system by producing angiotensin I of angiotensinogen
Relaxin	RLN	Corpus luteum, Uterus, placenta, and Mammary gland	Decidual cells		Unclear in humans
Prolactin-releasing hormone	PRLH	hypothalamus			Release prolactin from anterior pituitary

Prolactin	PRL	anterior pituitary, uterus	lactotrophs of anterior pituitary Decidual cells of uterus	milk production in mammary glands sexual gratification after sexual acts
Pituitary adenylate cyclase-activating peptide	PACAP	multiple		Stimulates enterochromaffin-like cells
Parathyroid hormone	PTH	parathyroid gland	parathyroid chief cell	•increase blood Ca^{2+}:indirectly stimulate osteoclasts •Ca^{2+} reabsorption in kidney •activate vitamin D (Slightly) decrease blood phosphate: •(decreased reuptake in kidney but increased uptake from bones •activate vitamin D)
Pancreatic polypeptide		Pancreas	PP cells	Self-regulation of pancreatic secretions (endocrine and exocrine). It also affects hepatic glycogen levels and gastrointestinal secretions.
Oxytocin	OXT	posterior pituitary	Magnocellular neurosecretory cells	release breast milkStimulates contraction of cervix and vagina. Involved in orgasm, trust between people,[2] and circadian homeostasis (body temperature, activity level, wakefulness).[3]
Osteocalcin	OCN	Skeleton	Osteoblasts	Favors muscle function, memory formation, testosterone synthesis and energy expenditure[1]
Orexin		hypothalamus		wakefulness and increased energy expenditure, increased appetite
Motilin	MLN	Small intestine		stimulates gastric activity
Melanocyte stimulating hormone	MSH or α-MSH	anterior pituitary/pars intermedia	Melanotroph	melanogenesis by melanocytes in skin and hair
Luteinizing hormone	LH	anterior pituitary	gonadotropes	In female: ovulationIn male: stimulates Leydig cell production of testosterone
Lipotropin	LPH	anterior pituitary	Corticotropes	lipolysis and steroidogenesis, stimulates melanocytes to produce melanin
Leptin	LEP	adipose tissue		decrease of appetite and increase of metabolism.
Insulin-like growth factor (or somatomedin)	IGF	liver	Hepatocytes	insulin-like effectsregulate cell growth and development

Insulin	INS	pancreas	beta cells	Intake of glucose, glycogenesis and glycolysis in liver and muscle from bloodintake of lipids and synthesis of triglycerides in adipocytes Other anabolic effects
Inhibin		testes, ovary, fetus	Sertoli cells of testes granulosa cells of ovary trophoblasts in fetus	Inhibit production of FSH
Human placental lactogen	HPL	placenta		increase production of insulin and IGF-1increase insulin resistance and carbohydrate intolerance

Human chorionic gonadotropin	hCG	placenta	syncytiotrophoblast cells	promote maintenance of corpus luteum during beginning of pregnancyInhibit immune response, towards the human embryo.
Hepcidin	HAMP	liver		inhibits iron export from cells
Guanylin	GN	gut		regulates electrolyte and water transport in intestinal epithelia.
Growth hormone-releasing hormone	GHRH	hypothalamus		Release GH from anterior pituitary
Growth hormone	GH or hGH	anterior pituitary	somatotropes	stimulates growth and cell reproductionRelease Insulin-like growth factor 1 from liver
Gonadotropin-releasing hormone	GnRH	hypothalamus		Release of FSH and LH from anterior pituitary.
Glucagon-like peptide-1	GLP1	ileum	L cells	Stimulates the adenylyl cyclase pathway, resulting in increased synthesis and release of insulin
Glucagon	GCG	pancreas	alpha cells	glycogenolysis and gluconeogenesis in liverincreases blood glucose level
Ghrelin		stomach	P/D1 cell	Stimulate appetite,secretion of growth hormone from anterior pituitary gland
Gastrin	GAS	stomach, duodenum	G cell	Secretion of gastric acid by parietal cells
Gastric inhibitory polypeptide	GIP	mucosa of the duodenum and the jejunum	K cell	Induces insulin secretion

Galanin	GAL	central nervous system and gastrointestinal tract			modulation and inhibition of action potentials in neurons
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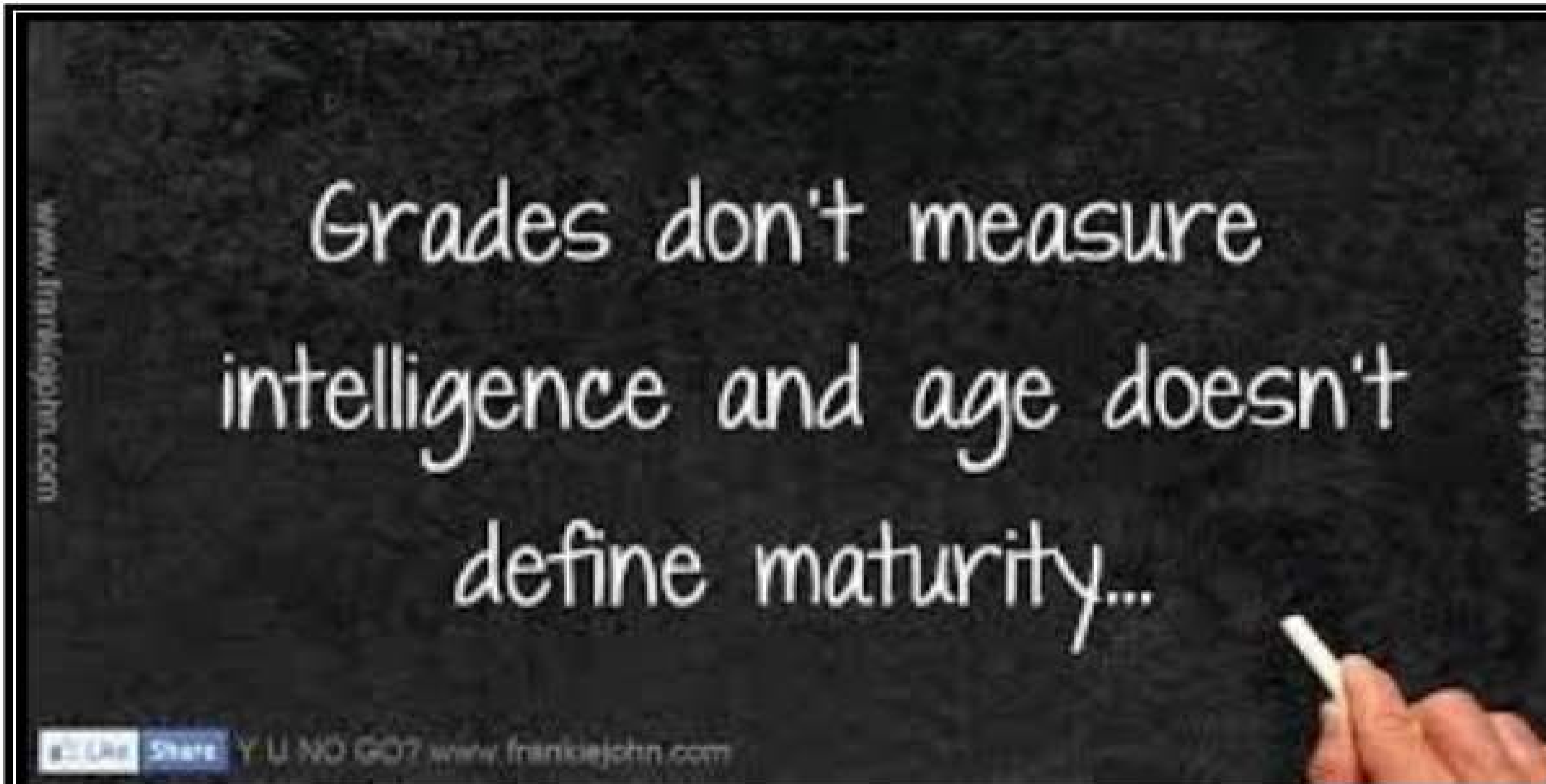
Uroguanylin	UGN	renal tissues			regulates electrolyte and water transport in renal epithelia.

Steroid

Chemical class	Name	Abbreviation	Tissue	Cells	Target Tissue	Effect
androgen	Testosterone		testes, ovary	Leydig cells		libido, Anabolic: growth of muscle mass and strength, increased bone density, growth and strength,Virilizing: maturation of sex organs, formation of scrotum, deepening of voice, growth of beard and axillary hair.
androgen	Dehydroepiandrosterone	DHEA	testes, ovary, kidney	Zona fasciculata and Zona reticularis cells of kidney theca cells of ovary Leydig cells of testes		Virilization, anabolic
androgen	Androstenedione		adrenal glands, gonads			Substrate for estrogen
androgen	Dihydrotestosterone	DHT	multiple			5-DHT or DHT is a male reproductive hormone that targets the prostate gland, bulbourethral gland, seminal vesicles, penis and scrotum and promotes growth/mitosis/cell maturation and differentiation. Testosterone is converted to 5-DHT by 5alpha-reductase, usually with in the target tissues of 5-DHT because of the need for high concentrations of 5-dht to produce the physiological effects.
mineralocorticoid	Aldosterone		adrenal cortex (zona glomerulosa)			Increase blood volume by reabsorption of sodium in kidneys (primarily)Potassium and H^+ secretion in kidney.

estrogen	Estradiol	E_2	females: ovary, males testes	females: granulosa cells, males: Sertoli cell		**Females**:Structural: •promote formation of female secondary sex characteristics •stimulate endometrial growth •increase uterine growth •maintenance of blood vessels and skin •reduce bone resorption •increase hepatic production of binding proteins Coagulation: •increase circulating level of factors 2, 7, 9, 10, antithrombin III, plasminogen •increase platelet adhesiveness Fluid balance: •salt (sodium) and water retention •increase growth hormone •increase cortisol, SHBG Gastrointestinal tract: •reduce bowel motility •increase cholesterol in bile Lung function: •promote lung function by supporting alveoli.[7] **Males**: Prevent apoptosis of germ cells[8]

estrogen	Estrone		ovary	granulosa cells, Adipocytes	
estrogen	Estriol	E_3	placenta	syncytiotrophoblast	
glucocorticoid	Cortisol		adrenal cortex (zona fasciculata and zona reticularis cells)		Stimulation of gluconeogenesisInhibition of glucose uptake in muscle and adipose tissue Mobilization of amino acids from extrahepatic tissues Stimulation of fat breakdown in adipose tissue anti-inflammatory and immunosuppressive
progestogen	Progesterone		ovary, adrenal glands, placenta (when pregnant)	Granulosa cells theca cells of ovary	•Support pregnancy:[9]Convert endometrium to secretory stage •Make cervical mucus permeable to sperm •Inhibit immune response, e.g. towards the human embryo. •Decrease uterine smooth muscle contractility[9] •Inhibit lactation •Inhibit onset of labor •Support fetal production of adrenal mineralo- and glucosteroids Other: •Raise epidermal growth factor-1 levels •Increase core temperature during ovulation[10] •Reduce spasm and relax smooth muscle (widen bronchi and regulate mucus) •Antiinflammatory. Regulate immune response •Reduce gall-bladder activity[11] •Normalize blood clotting and vascular tone, zinc and copper levels, cell oxygen levels, and use of fat stores for energy •Assist in thyroid function and bone growth by osteoblasts •Resilience in bone, teeth, gums, joint, tendon, ligament and skin healing by regulating collagen •Nerve function and healing by regulating myelin •Prevent endometrial cancer by regulating effects of estrogen
secosteroid	Calcitriol (1,25-dihydroxyvitamin D_3)		skin/proximal tubule of kidneys		Active form of vitamin D_3Increase absorption of calcium and phosphate from gastrointestinal tract and kidneys inhibit release of PTH
secosteroid	Calcidiol (25-hydroxyvitamin D_3)		skin/proximal tubule of kidneys		Inactive form of vitamin D_3



Monday, March 14, 2016