Welcome to BIO 202 Human Anatomy and Physiology with Dr. Fernandez

Please check to make sure you are in the correct course sections:

- Lecture (14950) MW 9:30-10:45am LS 104
- Lab (14885) MW 8:00-9:20am LS 310

OR

- Lab (14859) MW 11:00-12:20pm LS 310

Endocrine System

Chapter 17

- Mechanisms of Cell Communication
- Endocrine vs Exocrine
- Neuro-endocrine Relationship
- Major Organs of the Endocrine System
- Hormones and their Actions
- Eicosanoids and Paracrine Signaling
- Endocrine Disorders

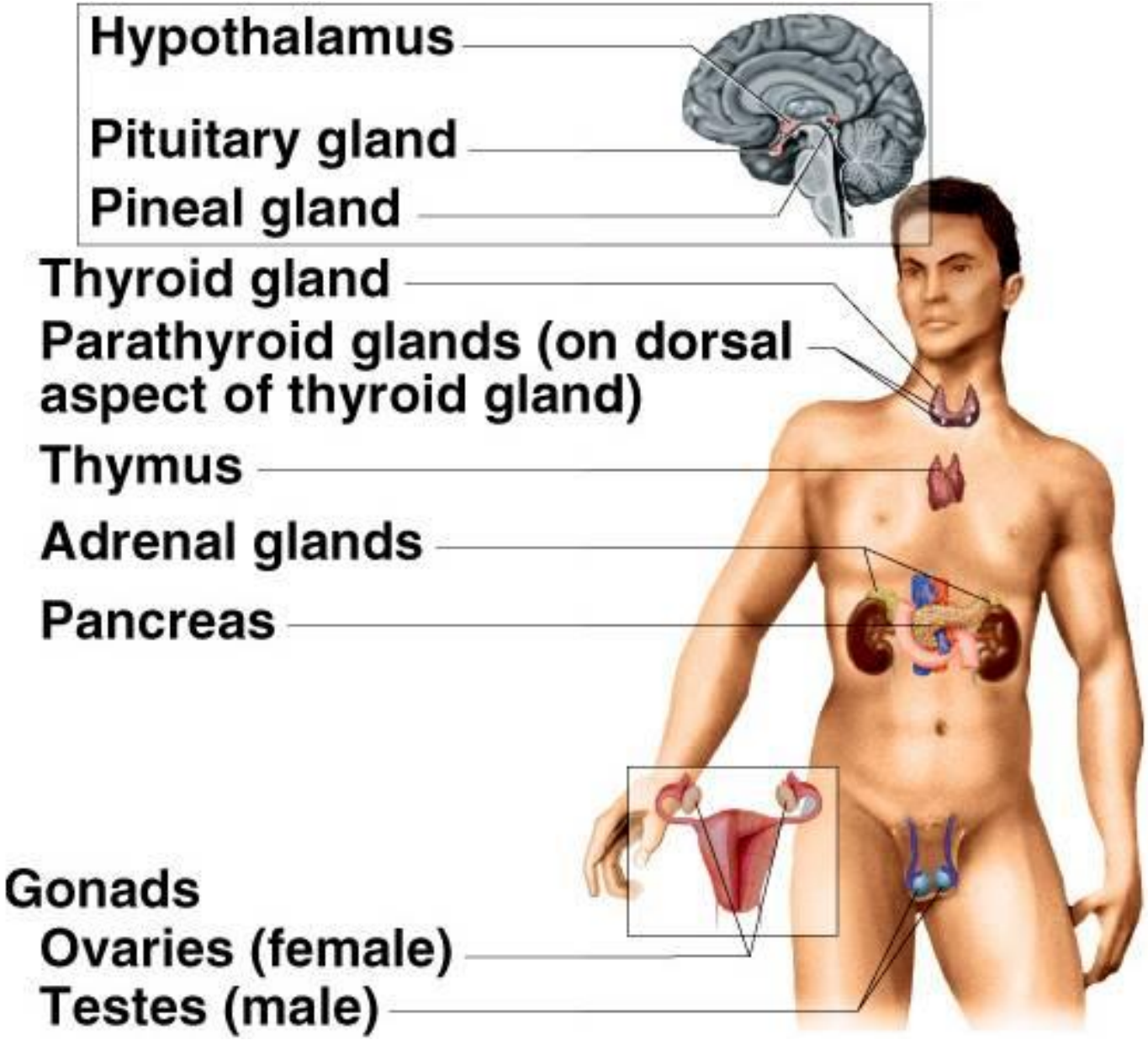
Overview of Cell Communication

- Communication among cells is necessary for coordinating important cell activities like growth maintenance and reproduction.
- Mechanisms of cell communication include:
  - gap junctions
    - pores in cell membranes that signaling chemicals can move through from cell to cell
  - neurotransmitters
    - released from neuron travels across a small gap to a 2nd cell
  - hormones
    - Classical definition of a hormone is a chemical messenger that travels in the bloodstream
  - paracrine hormones
    - chemical messengers secreted into tissue fluids that effect nearby cells

Endocrine System

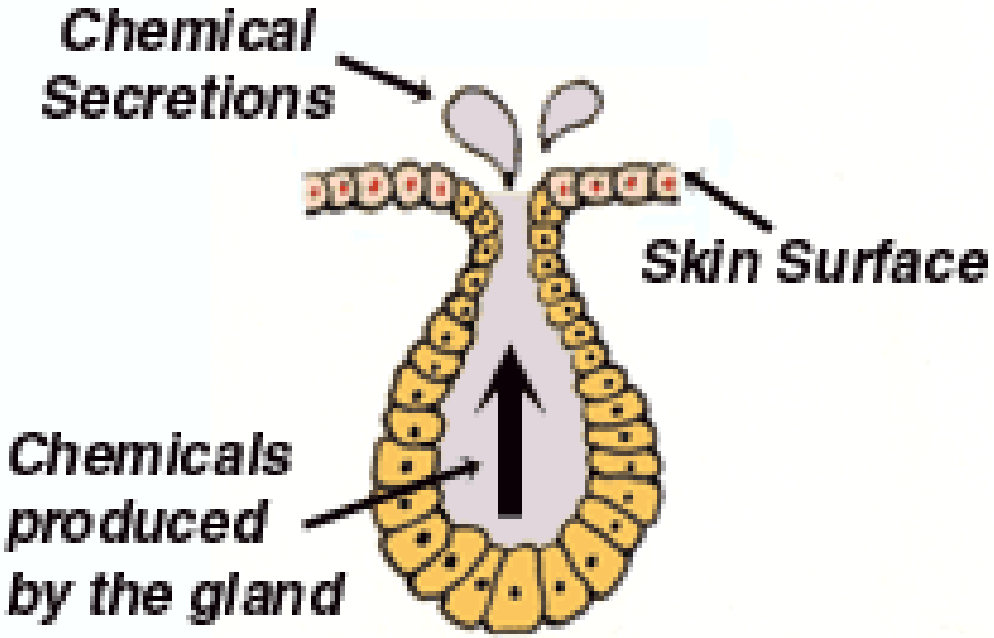
- Major endocrine organs include the:
  - pineal gland
  - pituitary gland
  - thyroid gland
  - parathyroid glands
  - thymus
  - adrenal glands
  - pancreas
- Endocrine System is composed of all of the major endocrine glands and hormone-secreting cells of other organs including the brain, heart, kidneys, organs of the digestive system, and reproductive organs.

Major Organs of the Endocrine System

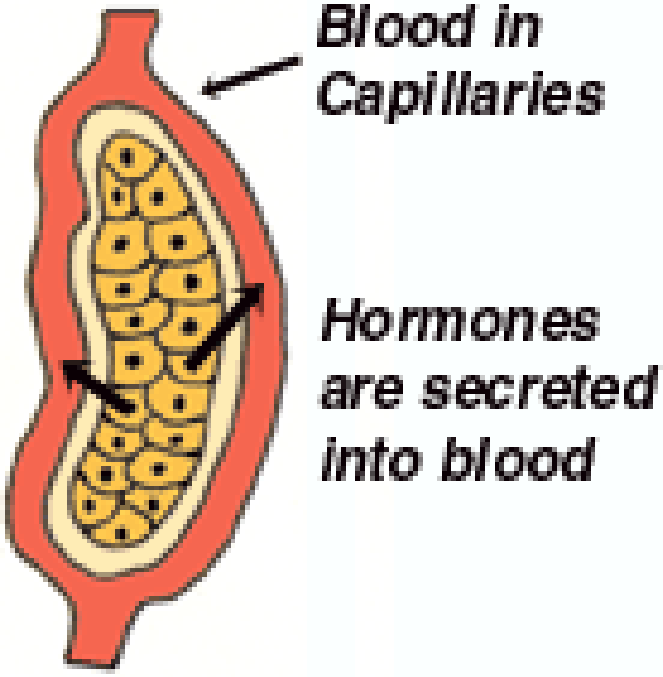


Differences between Exocrine Glands and Endocrine Glands

- Exocrine Glands
  - Exocrine glands have ducts that carry a secretion to a body surface or an organ cavity.
  - Exocrine glands produce extracellular effects.
  - Example: sweat glands release sweat onto the skin.
- Endocrine Glands
  - Endocrine glands do not have ducts.
  - Endocrine glands release hormones into intercellular space and can be absorbed into the blood.
  - Endocrine glands produce intracellular effects in target cells that will change the target cell’s metabolism.
  - Example: insulin is a hormone that causes cells to absorb glucose that is used as fuel for cell metabolism.



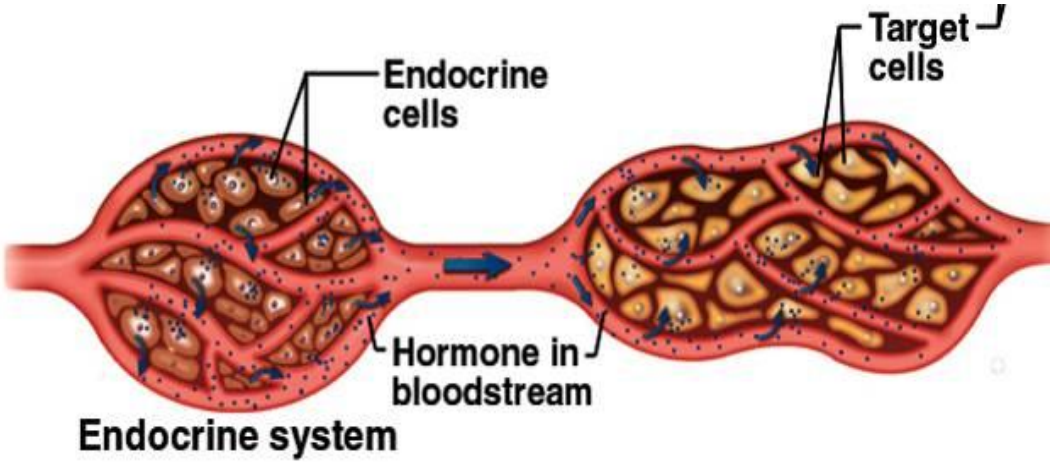
Exocrene Gland



Endocrine Gland

Components of the Endocrine System

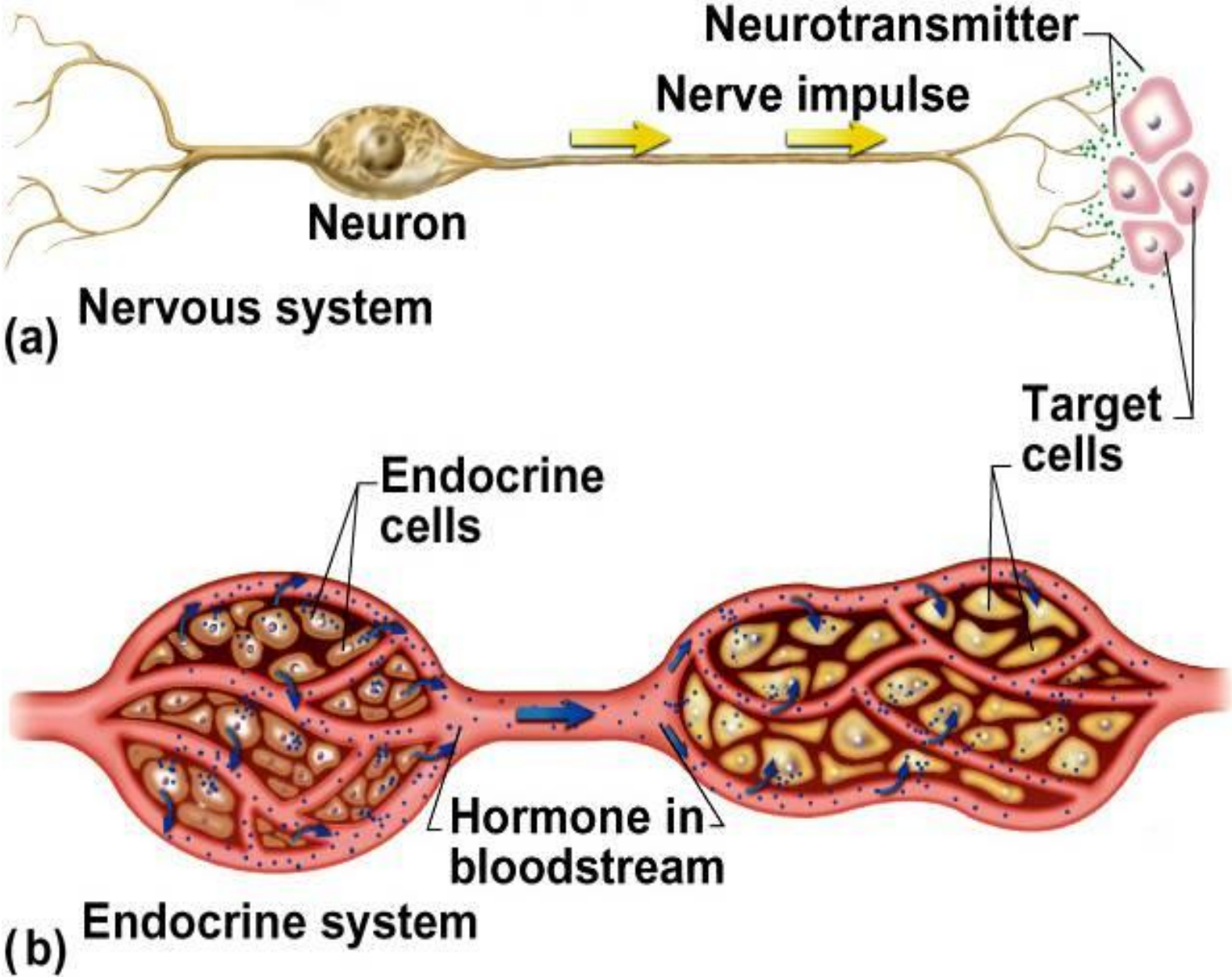
- Endocrine Glands secrete hormones into the interstitial space between cells.
- Hormones can be carried in the bloodstream as “chemical messengers” that produce a response in target cells of another tissue or organ.
- Target Cells respond to hormones by having a complementary receptor that matches a particular hormone.
- A hormone may stimulate or inhibit a target cell.



Similarities between the Nervous System and Endocrine System

- Several chemicals function as both hormones and neurotransmitters:
  - examples: norepinephrie, antidiuretic hormone (vasopressin)
- Both systems can have overlapping effects on the same target cells:
  - norepinephrine (from nervous system) and glucagon (from endocrine system) both cause glycogen hydrolysis in liver that elevates blood sugar levels.
- Systems regulate each other:
  - neurons can trigger hormone secretion
  - hormones can stimulate or inhibit neurons
- The term Neuroendocrine is used to describe overlapping functions of nervous and endocrine tissues.

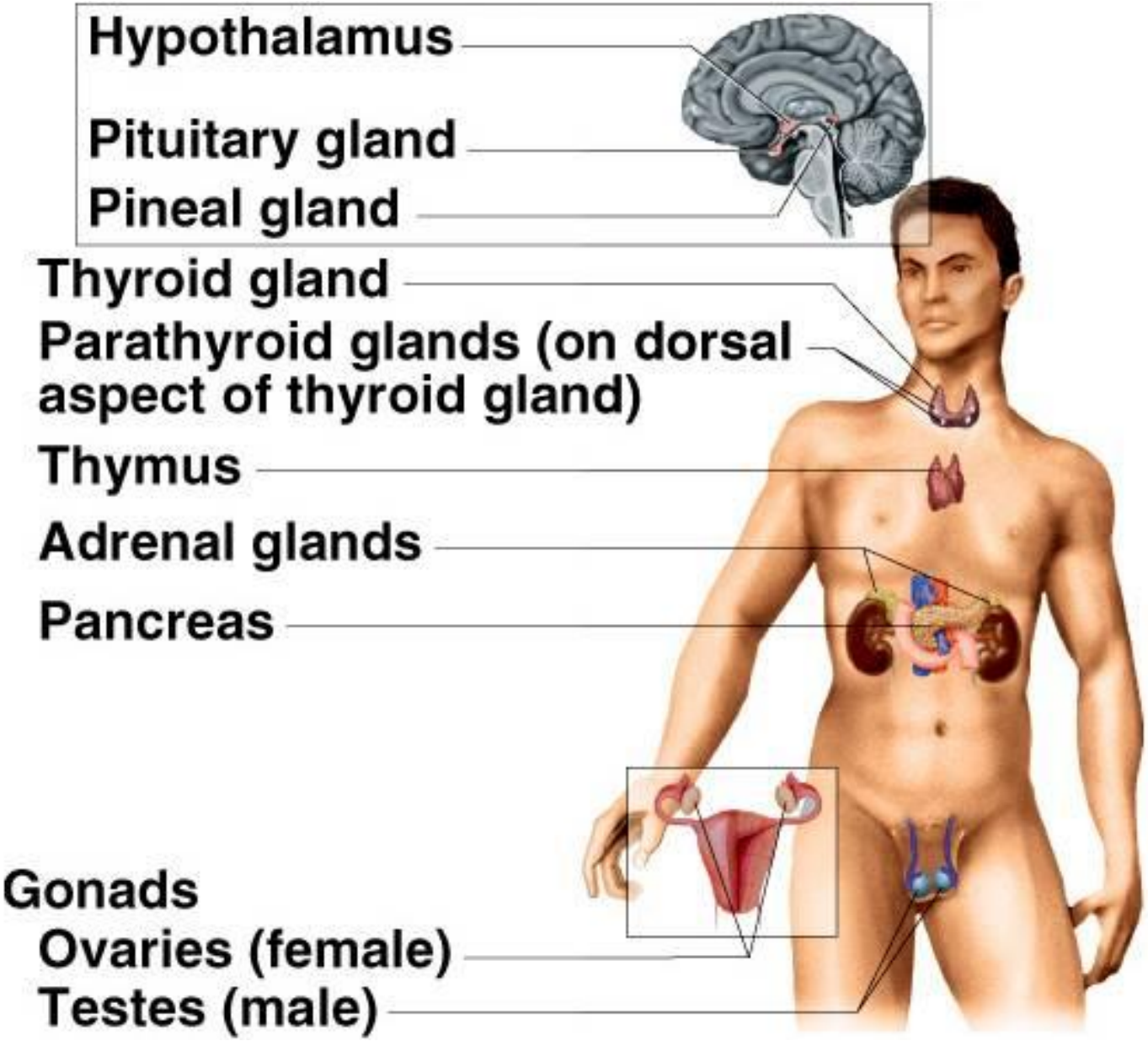
Communication is similar in the Nervous System and the Endocrine System



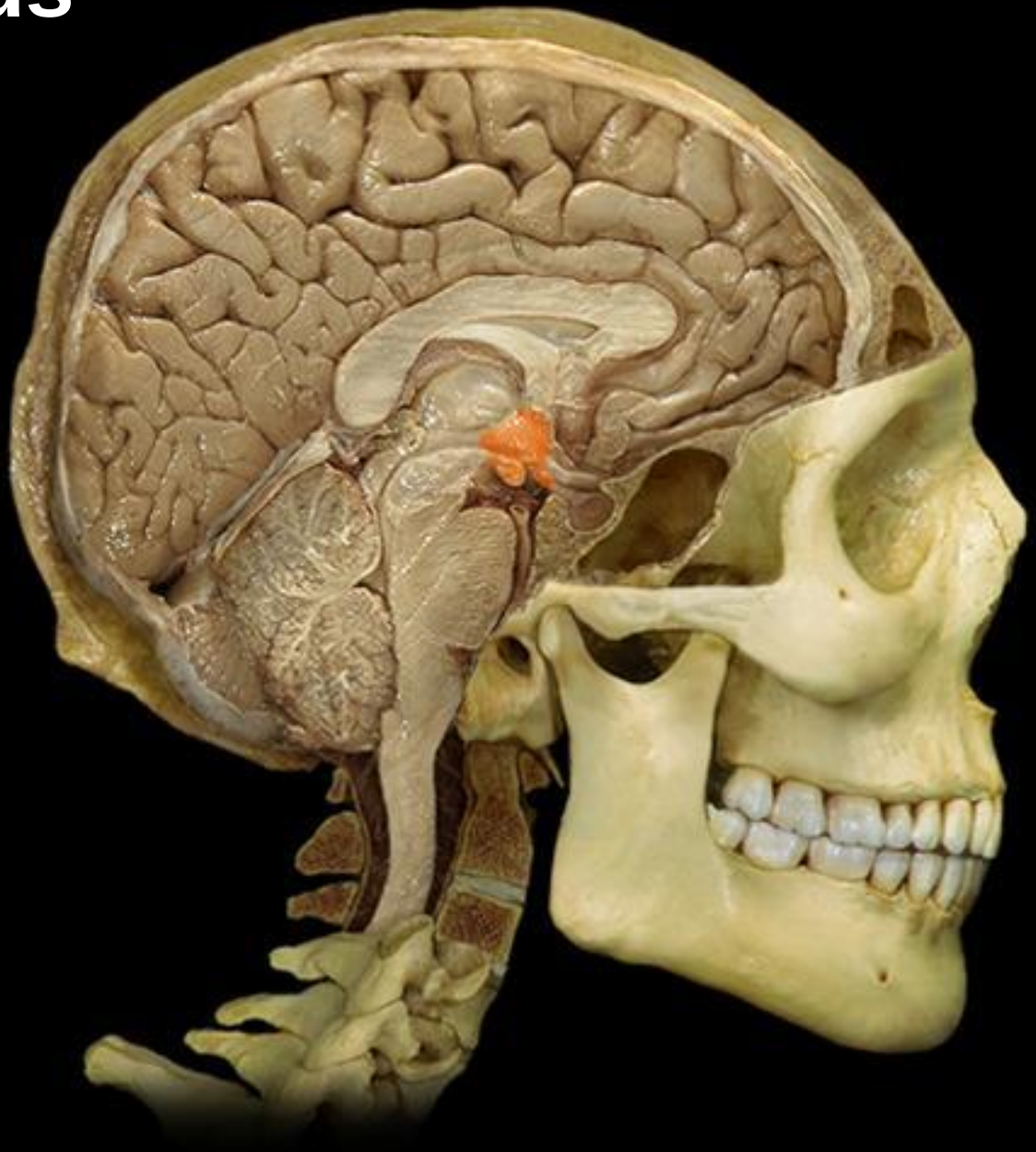
Differences between the Nervous System and Endocrine System

- Means of communication:
  - nervous system has both electrical and chemical methods
  - endocrine system has only chemical methods
- Speed and persistence of response:
  - nervous system reacts quickly (1 - 10 msec) and stops quickly
  - endocrine system reacts more slowly (hormone release in seconds or days) and effect may continue for weeks
- Adaptation to long-term stimuli:
  - nervous system adapts quickly and response declines quickly
  - endocrine system has more persistent responses
- Area of effect:
  - nervous system effects are very specific (one cell or organ)
  - endocrine system usually has more general, widespread effects on many organs

Major Organs of the Endocrine System



Hypothalamus

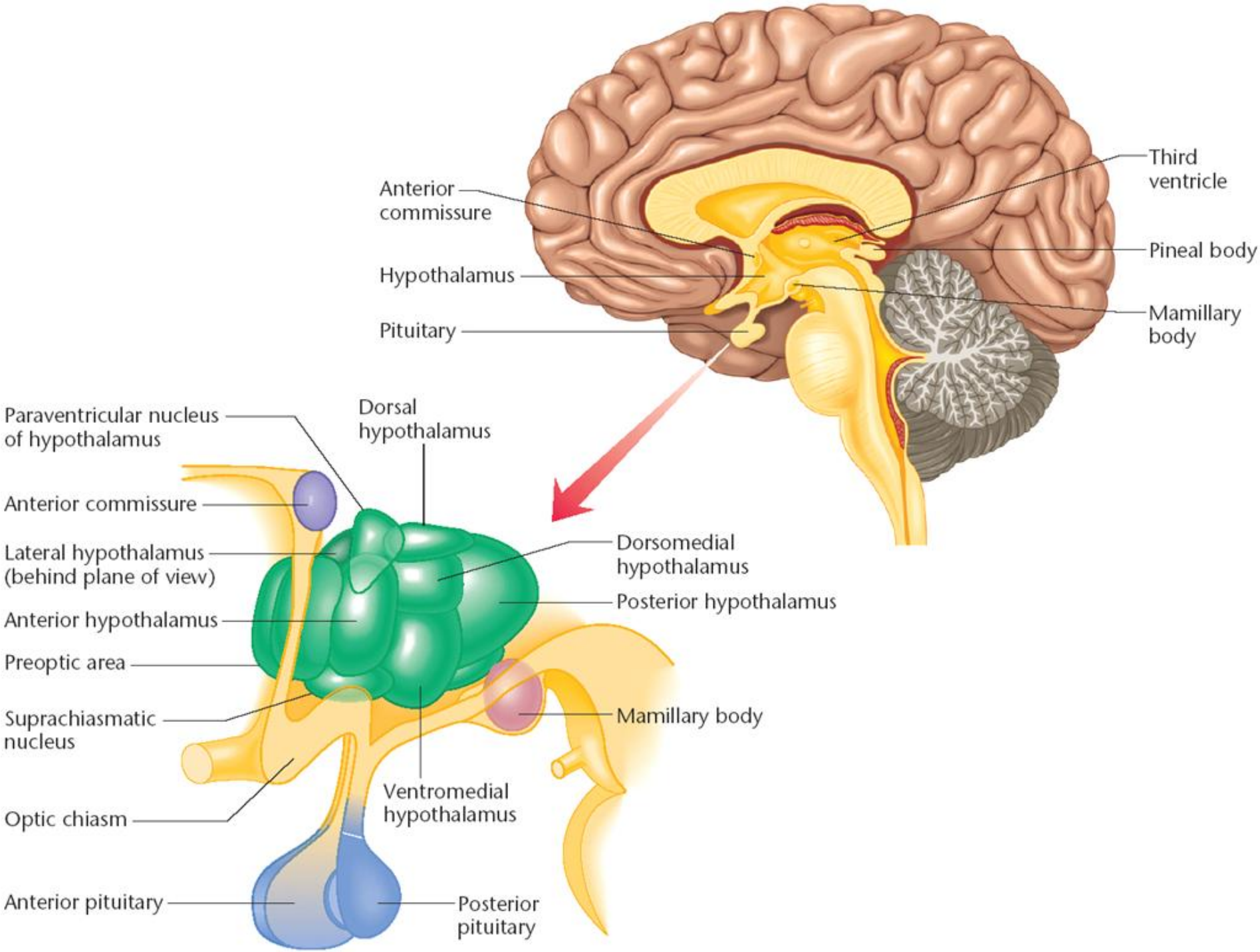


Hypothalamus

- Hypothalamus is a funnel-shaped structure composed of clusters of neurons in the floor and walls of third ventricle
  - these clusters of neurons in the brain are called “nuclei”
- The hypothalamus regulates many functions carried out by the pituitary gland including regulating:
  - body temperature, reproductive functions, growth of tissues, maintenance of tissues, stress management and other functions
- The hypothalamus regulates the pituitary gland through releasing hormones and release-inhibiting hormones (see next slide)

Hypothalamus / Pituitary Axis

Hypothalamic Hormone	Effect on Anterior Pituitary
TRH: Thyrotropin-releasing H.	TSH secretion
CRH: Corticotropin-releasing H.	ACTH secretion
GnRH: Gonadotropin-releasing H.	FSH and LH secretion
GHRH: Growth hormone-releasing H.	GH secretion
Somatostatin	inhibits GH and TSH secretion
PIH: Prolactin-inhibiting H. (dopamine)	inhibits PRL secretion

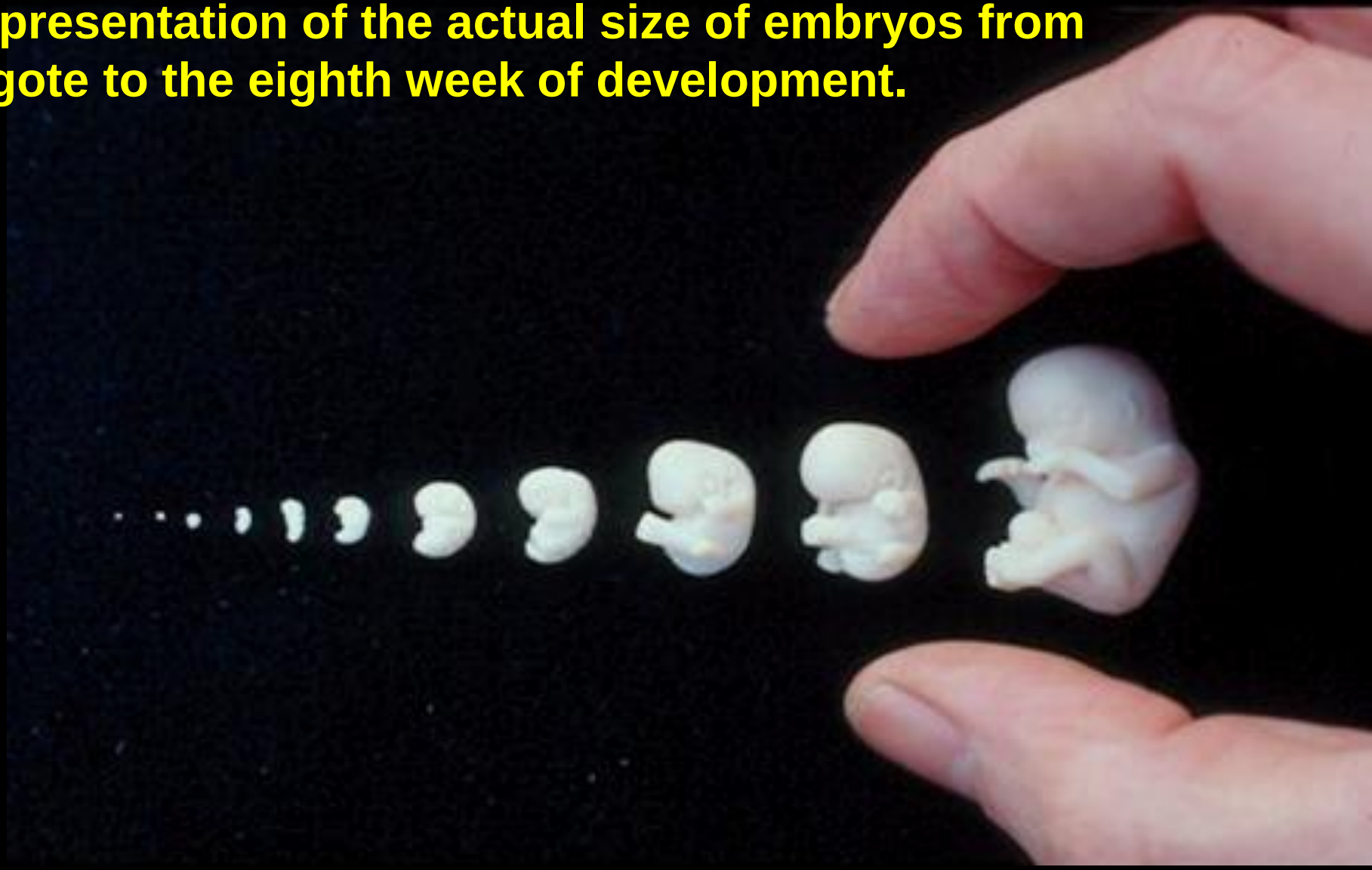

Anterior commissure
Hypothalamus
Pituitary
Third ventricle
Pineal body
Mamillary body
Paraventricular nucleus of hypothalamus
Dorsal hypothalamus
Anterior commissure
Lateral hypothalamus (behind plane of view)
Anterior hypothalamus
Preoptic area
Suprachiasmatic nucleus
Optic chiasm
Anterior pituitary
Dorsomedial hypothalamus
Posterior hypothalamus
Mamillary body
Ventromedial hypothalamus
Posterior pituitary

Pituitary Gland

Pituitary Gland (Hypophysis)

- The Pituitary is connected to the hypothalamus by a stalk called the **infundibulum.**
- The Pituitary is located in the ***sella turcica*** of the sphenoid bone of the skull.
- The Pituitary Gland is about 1.3 cm (about ½ inch) diameter
- 3 lobes of the Pituitary Gland:
  - **Anterior Lobe** (*pars distalis*, adenohypophysis) develops from oral ectoderm of the roof of the embryonic mouth (pharynx) forming Rathke's (hypophyseal) pouch.
  - **Posterior Lobe** (*pars nervosa*, neurohypophysis) develops from a neurohypophyseal bud of neural ectoderm from the floor of the diencephalon.
  - **Intermediate Lobe** (*pars intermedia*) tissue is induced from oral ectoderm that contacts neural ectoderm.

Representation of the actual size of embryos from zygote to the eighth week of development.



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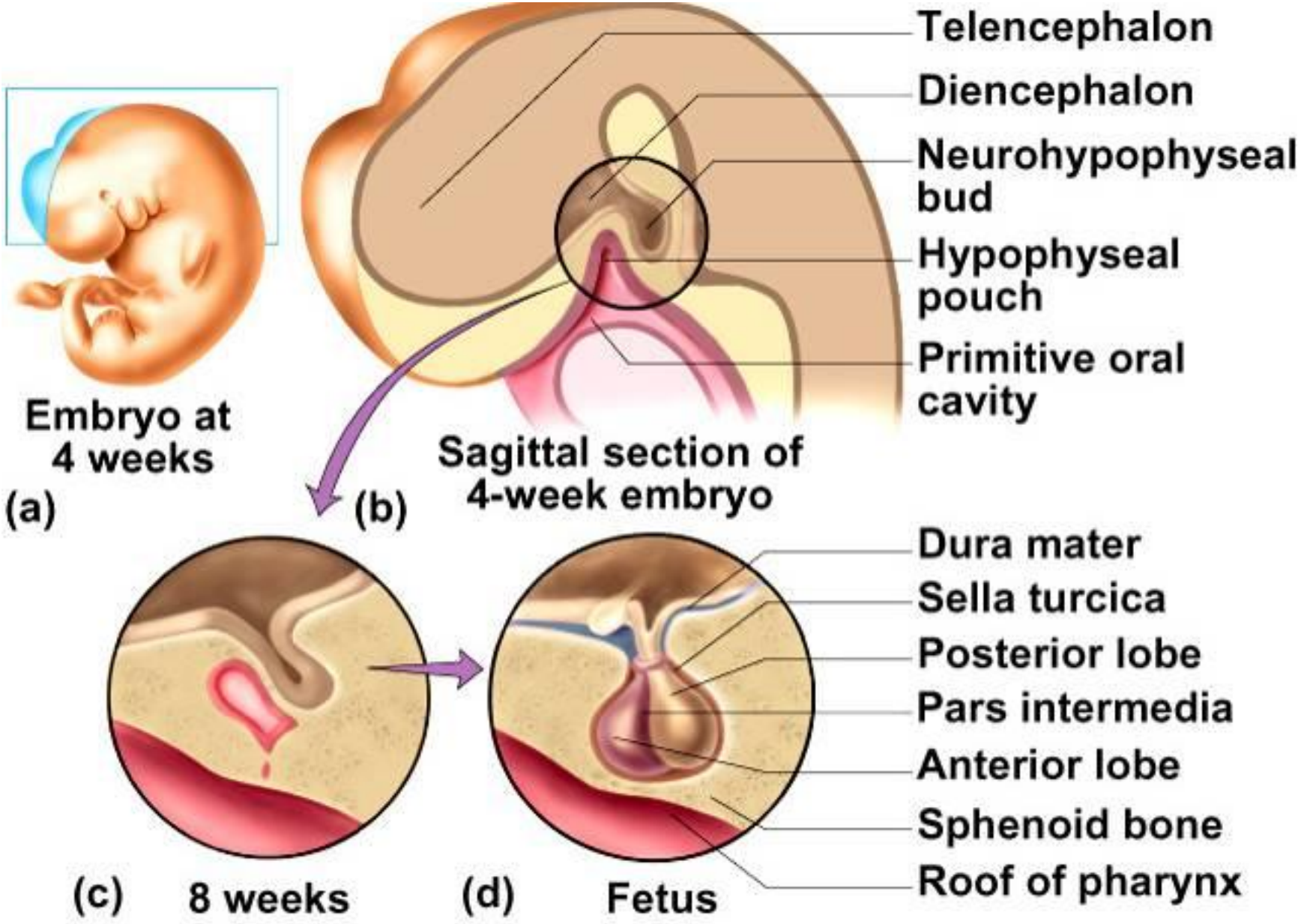
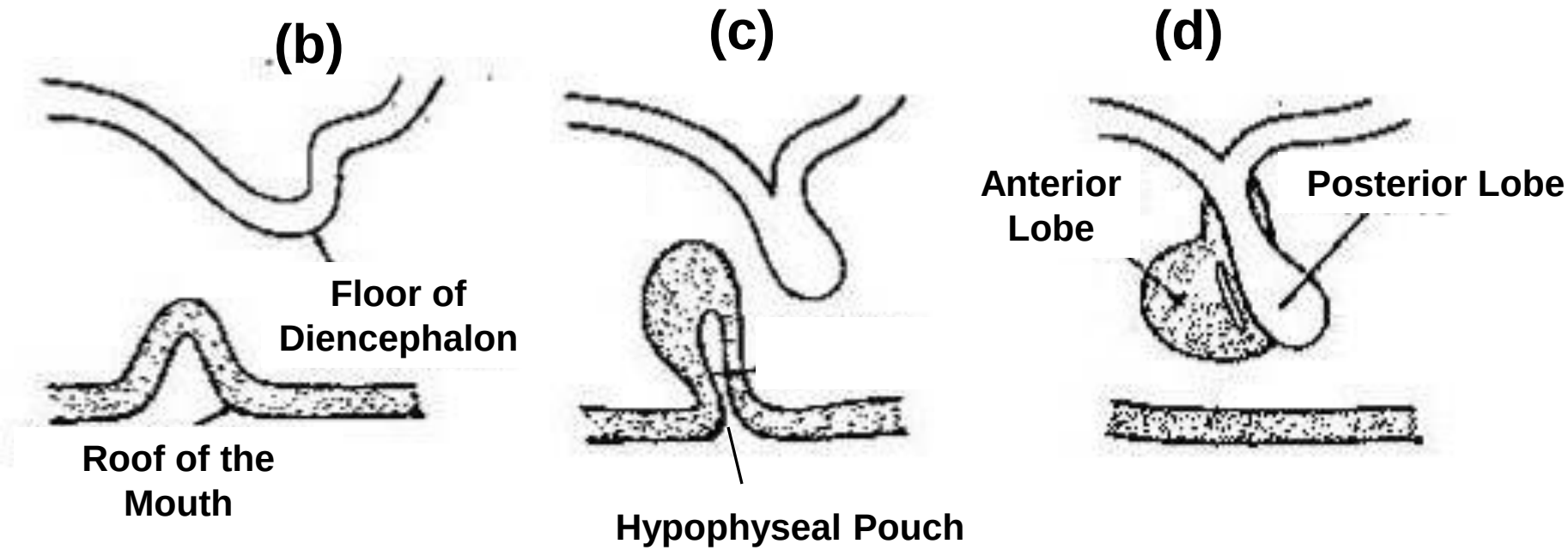
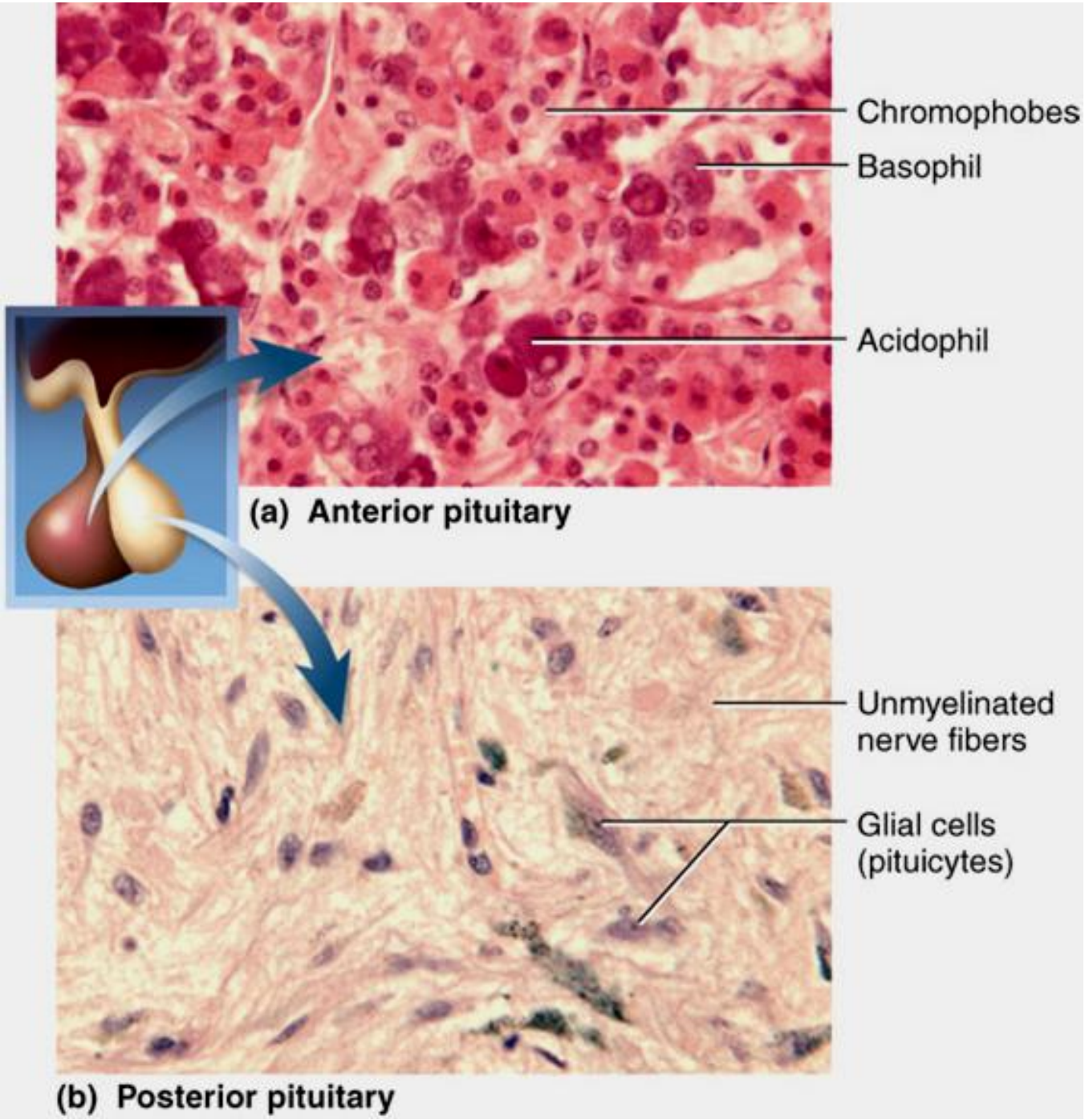
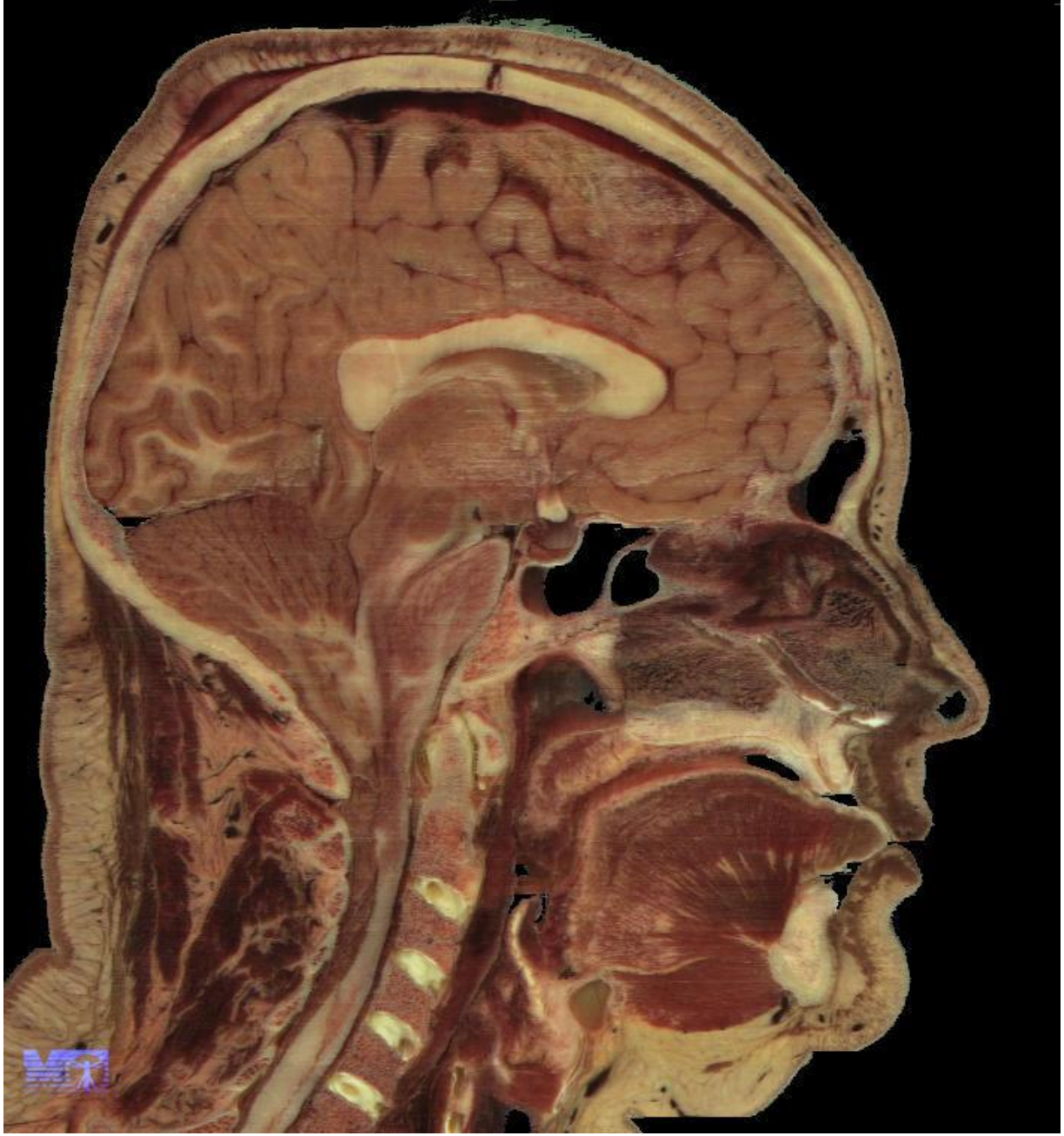
Embryonic Development of Pituitary



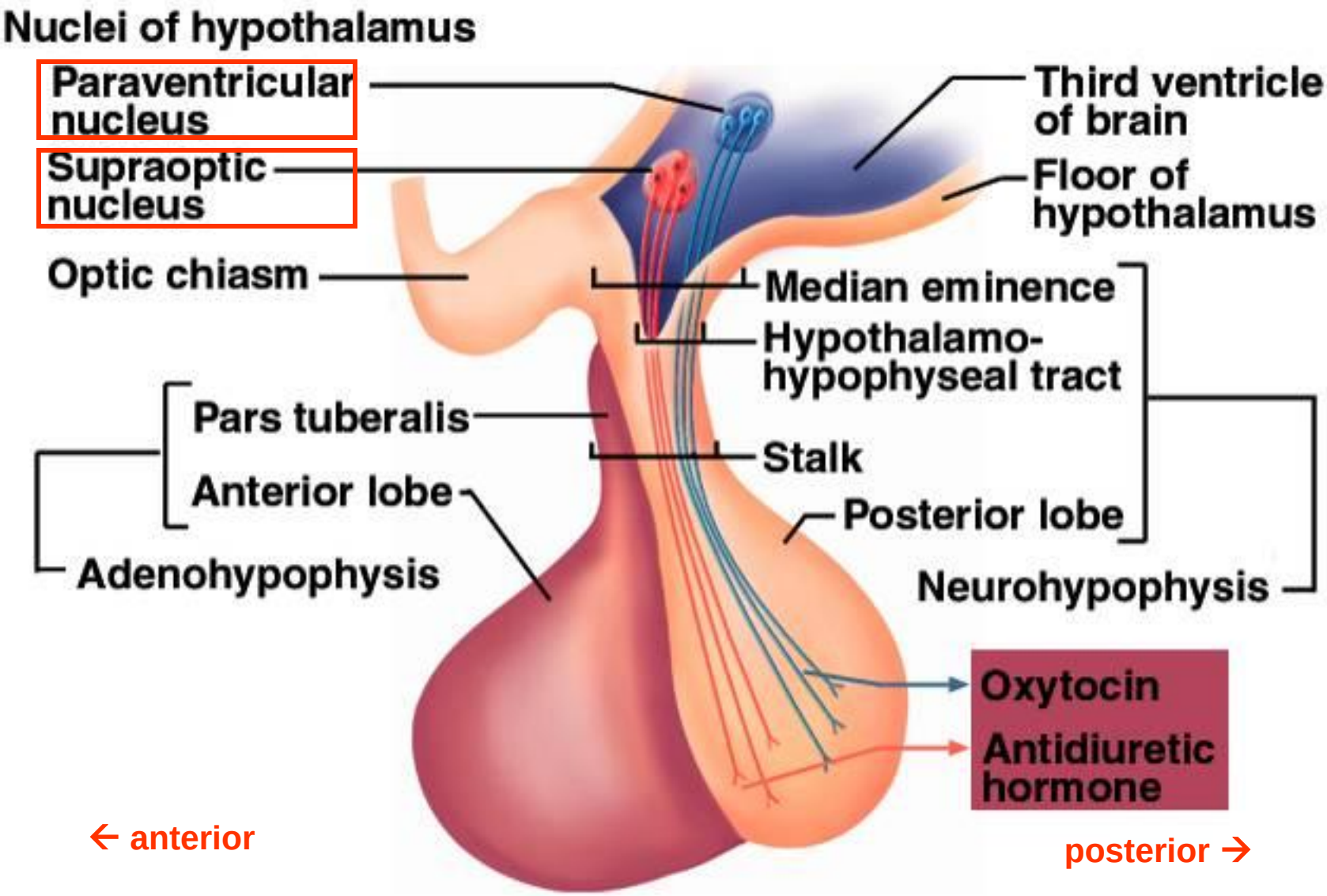

(b)
(c)
(d)
Floor of
Diencephalon
Roof of the
Mouth
Hypophyseal Pouch
Anterior
Lobe
Posterior Lobe


Chromophobes
Basophil
Acidophil
(a) Anterior pituitary
Unmyelinated nerve fibers
Glial cells (pituicytes)
(b) Posterior pituitary



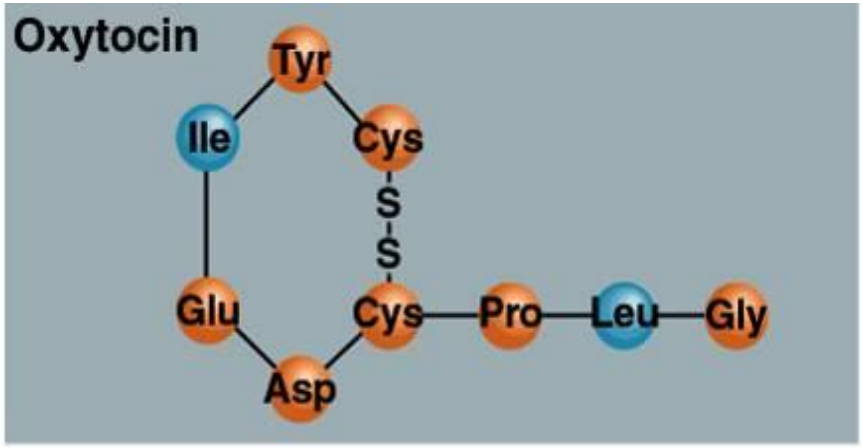
http://www.vivo.colostate.edu/hbooks/pathphys/endocrine/hypopit/anatomy.html

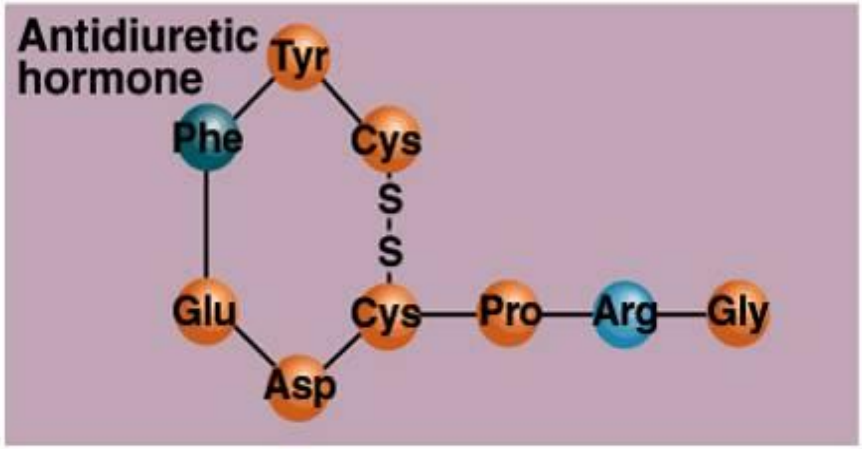
Pituitary Gland Anatomy and Hormones of the Posterior Lobe



Pituitary Hormones of the Posterior Lobe

- Posterior Lobe produces, stores and releases two hormones:
  - Oxytocin (OT)
  - Vasopressin (Antidiuretic Hormone – ADH)
- OT and Vasopressin are produced by neurons in the hypothalamus and are transported down axons to the posterior lobe
- OT is produced by the paraventricular nucleus
- Vasopressin is produced by the supraoptic nucleus
- Note similarity in molecular structure of the two hormones





Posterior Lobe Hormone Actions:

- **Vasopressin (ADH)**
  - targets kidneys to ↑ water retention, reduce urine production
  - called vasopressin because it can cause vasoconstriction
  - also functions as a neurotransmitter in the brain
- **Oxytocin**
  - stimulates labor contractions during childbirth
  - stimulates flow of milk during lactation
  - promotes emotional bonding between lactating mother and infant
  - promotes feelings of sexual satisfaction and emotional bonding between partners
  - surge of oxytocin is released during sexual arousal and orgasm causing smooth muscle contractions in uterus and and propulsion of semen

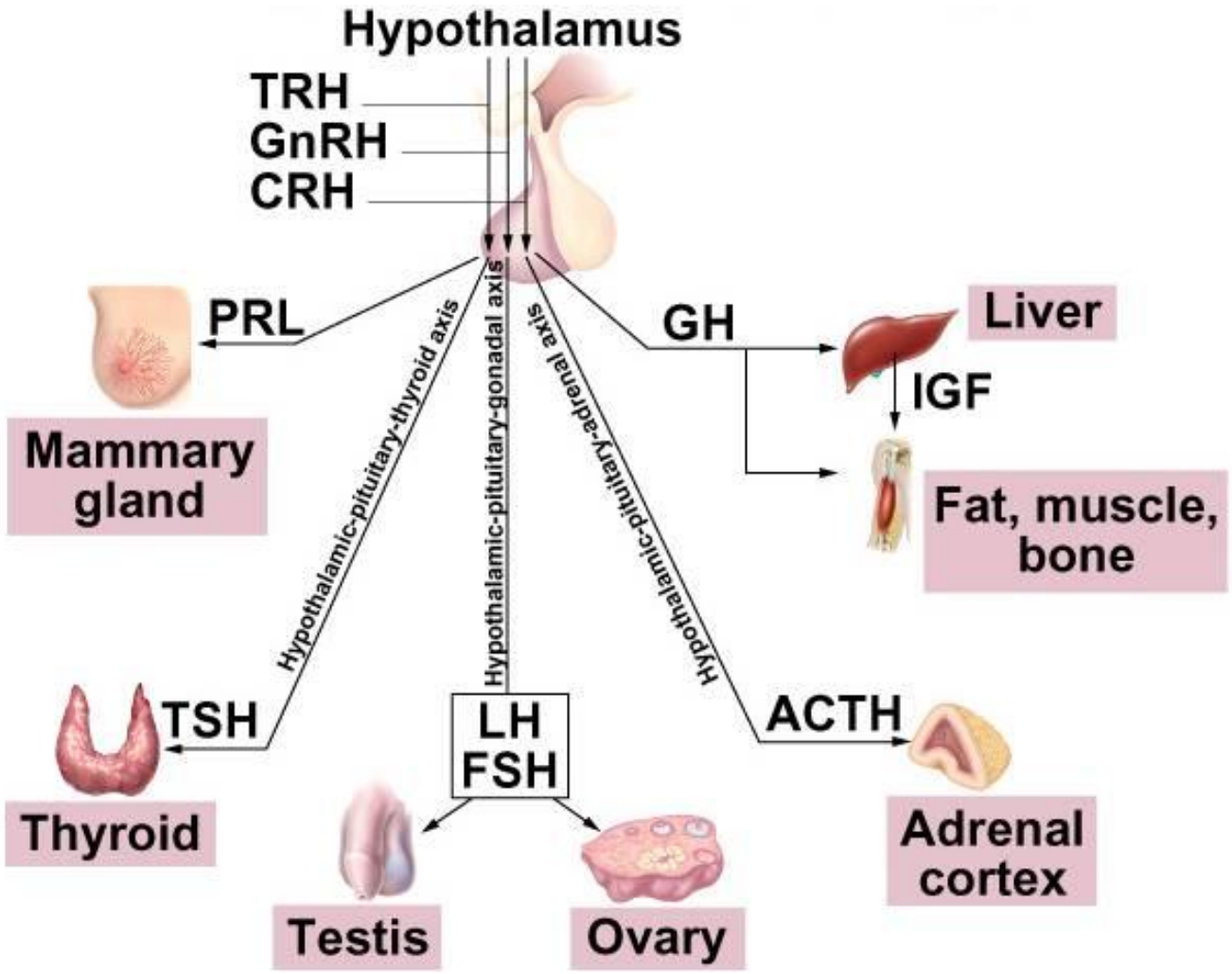
Pituitary Intermediate Lobe

- Melaonotroph cells of the intermediate lobe produce Melanocyte-Stimulating Hormone (MSH)
  - Intermediate Lobe is present in human fetuses but quickly degenerates into non-functional cysts in adults.
  - Human brain neurons produce a large prohormone, POMC (pro-opiomelanocortin), which is cleaved into several smaller products including MSH, ACTH, endorphins, b-lipotropic hormone and other neurohormones. MSH functions as a neurotransmitter in the human brain.
  - In other animals, MSH stimulates pigment cells to produce more melanin pigment which can darken skin, hair or feathers

6 Hormones of the Anterior Lobe

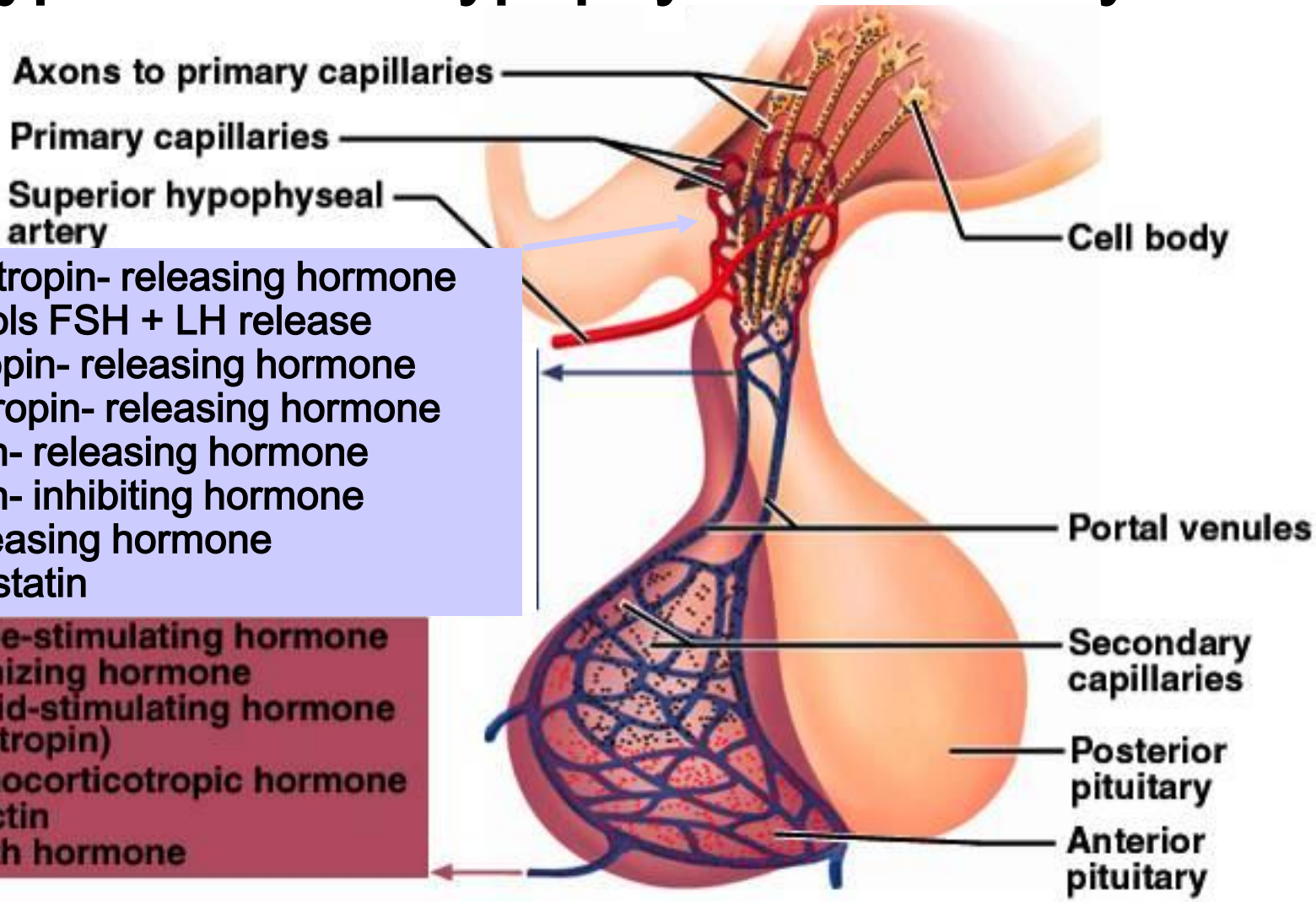
1. **FSH** (follicle stimulating hormone)
2. **LH** (luteinizing hormone)
3. **TSH** (thyroid stimulating hormone)
4. **ACTH** (adrenocorticotropic hormone)
5. **PRL** (prolactin)
6. **GH** (growth hormone)

6 Anterior Pituitary Hormones and their Target Organs



- Axis refers to the regulatory interactions between the hypothalamus, pituitary and other endocrine glands.

Hypothalamic-Hypophyseal Portal System



Gonadotropin- releasing hormone
controls FSH + LH release
Thyrotropin- releasing hormone
Corticotropin- releasing hormone
Prolactin- releasing hormone
Prolactin- inhibiting hormone
GH- releasing hormone
Somatostatin

Follicle-stimulating hormone
Luteinizing hormone
Thyroid-stimulating hormone (thyrotropin)
Adrenocorticotropic hormone
Prolactin
Growth hormone

- Releasing and inhibiting hormones secreted by the hypothalamus are absorbed by hypothalamic capillaries that drain into portal venules that connect to capillaries in the anterior pituitary

Actions of Anterior Lobe Hormones

- **FSH** (secreted by gonadotrope cells)
  - female: stimulates development of follicles in ovaries
  - male: stimulates production of sperm in testes
- **LH** (secreted by gonadotrope cells)
  - female: stimulates ovulation and maintains the corpus luteum to secrete progesterone and estrogen
  - male: stimulates interstitial cells of testes to secrete testosterone
- **TSH** (secreted by thyrotrope cells)
  - stimulates growth of thyroid gland and the secretion of thyroid hormone

Actions of Anterior Lobe Hormones continued:

- **ACTH** (secreted by corticotropes)
  - regulates response to chronic stress, stimulates adrenal cortex to secrete corticosteroids that regulate glucose, fat and protein metabolism
- **PRL** (secreted by lactotropes)
  - female: milk production by mammary glands
  - male: enhances secretion of testosterone by testes
- **GH** (secreted by somoatotropes)
  - see next 2 slides for functions of GH

Growth Hormone

- GH is also called somatotropin
- GH is secreted by somatotropes of the anterior pituitary
- GH promotes tissue growth through multiple mechanisms:
  - directly affects mitosis and cellular differentiation
  - stimulates **liver** to produce Insulin-like Growth Factors (IGF) that are also called somatomedins.
  - IGFs last 60x longer than than GH (20 hours vs 20 minutes)
- Functions of GH and IGF:
  - ↑ protein synthesis and ↓ protein catabolism
  - ↑ lipid metabolism which spares proteins and carbohydrates
  - Electrolyte balance: promotes Na^+, K^+, Cl^- retention and Ca^{+2} absorption

Growth Hormone and Aging

- During childhood and adolescence GH causes bone, cartilage and muscle growth
- GH in adults:
  - increases osteoblastic activity and appositional growth resulting in bone thickening and remodeling
- GH in old age:
  - blood concentration of GH normally decreases by age 75 to ¼ of that of adolescents
  - low GH in old age results in decrease protein synthesis that can cause wrinkling of skin and less muscle strength and muscle mass
- Levels of GH
  - are higher after high protein meals, after vigorous exercise, and during the first 2 hours of deep sleep
  - GH also increases after trauma

Growth Hormone Disorders

Hypersecretion of growth hormone during childhood can lead to gigantism.

Robert Pershing Wadlow (in 1938, at age 20 with actresses Maureen O'Sullivan, left, and Ann Morris) had grown to a record height of 8'11" by the time of his death at age 22.

Smithsonian August 2005 p. 76.

Robert Pershing Wadlow with his mother at his side in 1939.

In 2008, Leonid Stadnik was named the world's tallest man. Standing at 8 feet, 5 inches.
Here he walks near his home in the tiny village of Podolyantsi in central Ukraine.

Growth Hormone Disorders continued

- Hypersecretion of growth hormone in old age leads to **acromegaly**.
  - symptoms of acromegaly include thickening of hand, foot, jaw and brow bones and growth of soft tissues particularly in the nose and ears.

Age 9 Age 16 Age 33 Age 52

7 pounds at age 2

There are over 200 different types of dwarfism, all of which involve bone growth disorders (osteodysplasia) that result in short stature (adult height less than 4 ft. 10 in. tall).

Primordial Dwarfism is a group of disorders in which growth is proportional but severely delayed, beginning in the womb. This results in some of the smallest people in the world.

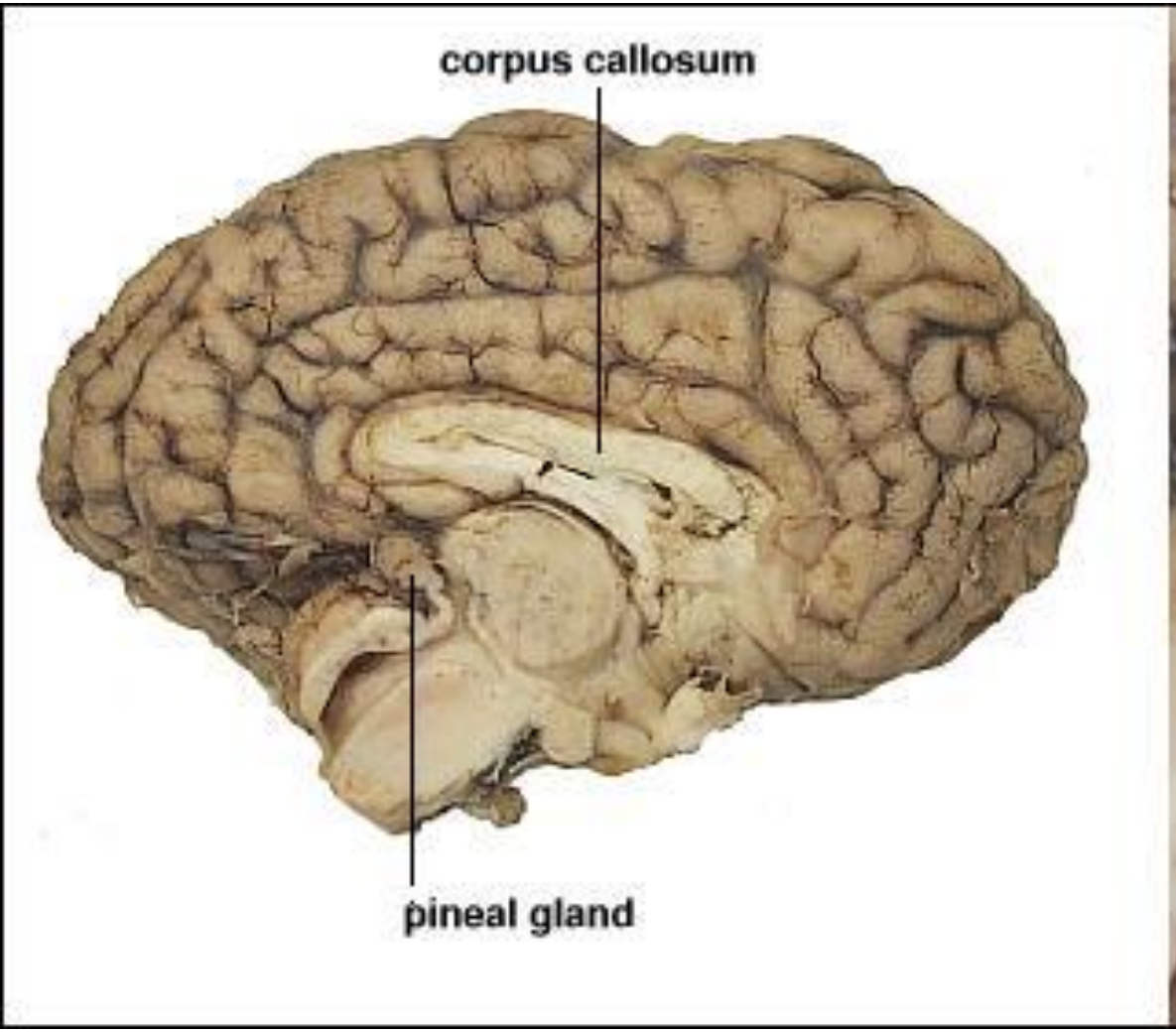
The individual pictured has Majewski osteodysplastic primordial dwarfism (MOPD) Type II. Only about 100 individuals worldwide have been identified as having MOPD type II. Both males and females of all ethnic backgrounds are affected. Some families have more than one child with MOPD Type II, which suggests that the disorder is inherited in an autosomal recessive manner.

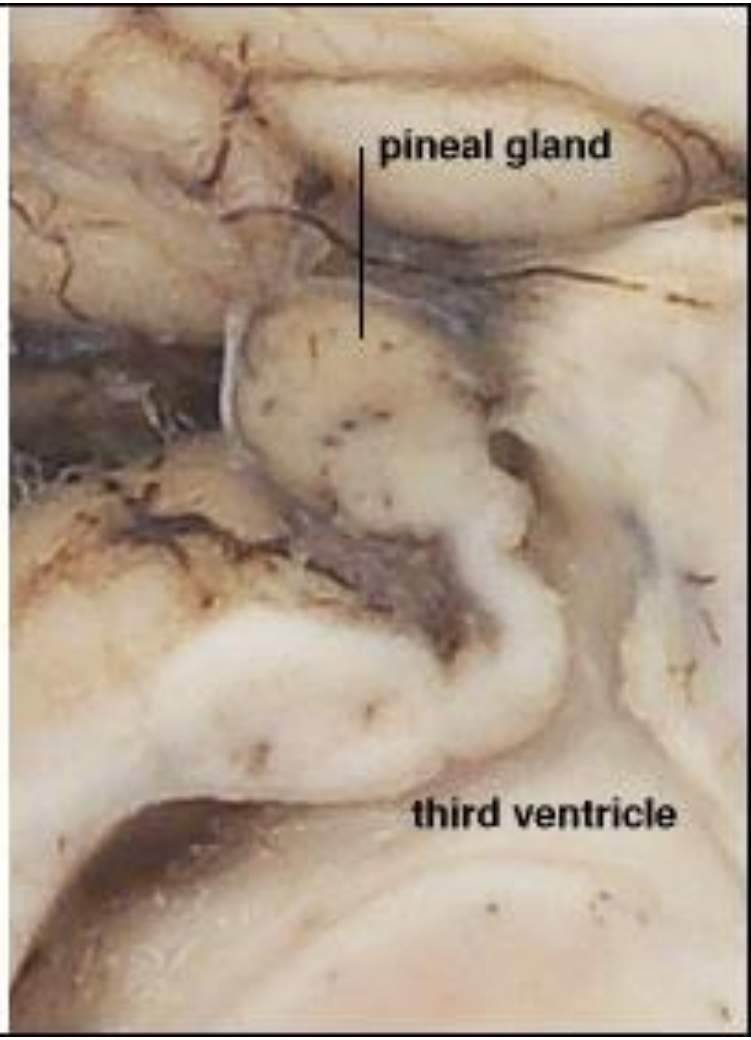
- Majewski osteodysplastic primordial dwarfism type II (MOPD II): natural history and clinical findings. Hall, Flora, Scott, Pauli, Tanaka, Am J. Med Genet A. 2004 Sep 15 ; 130A(1):55-72.

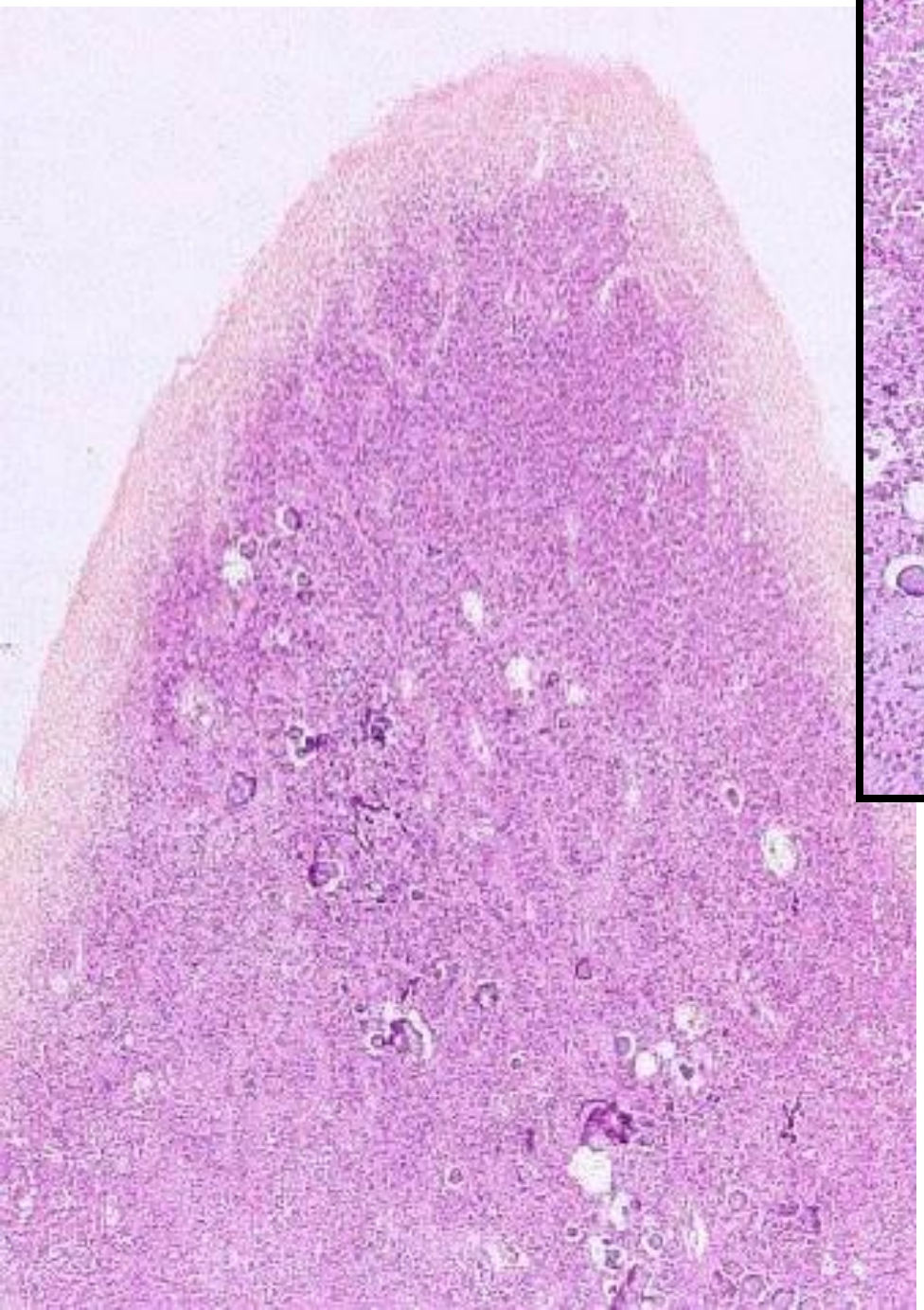
Pineal Gland (Epiphysis)

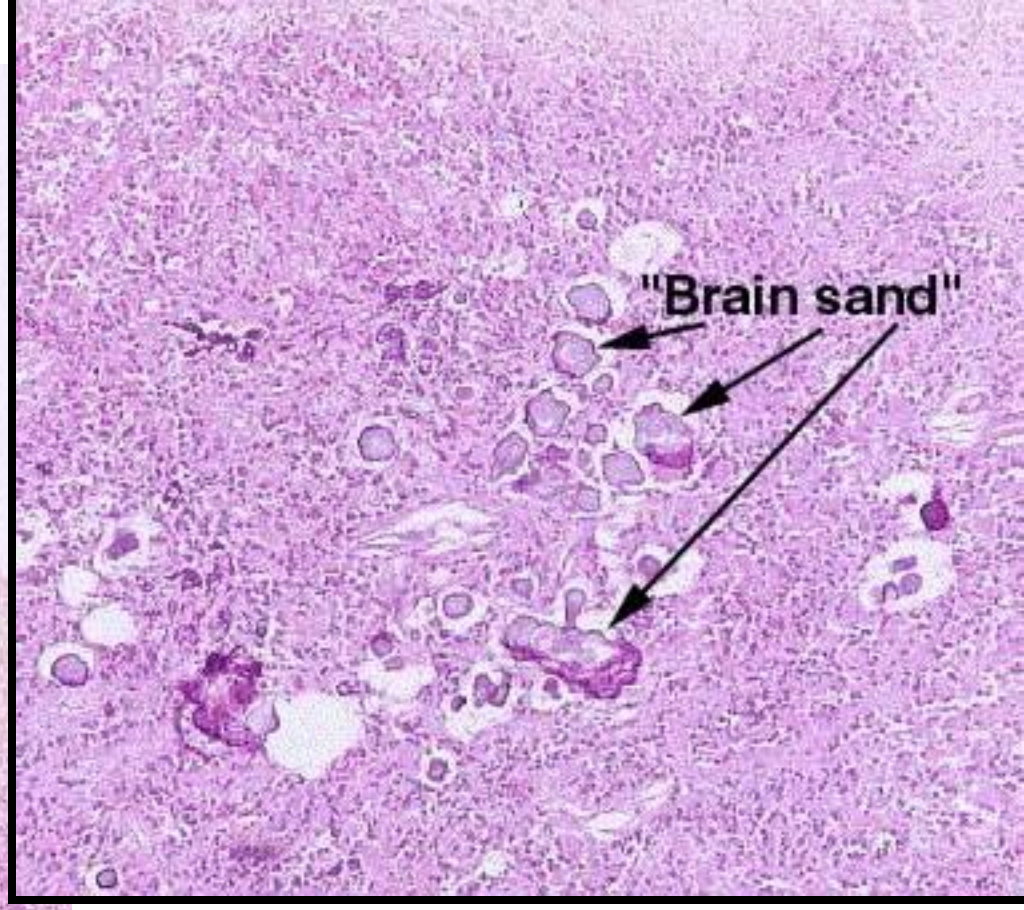
- Shaped like a PINE CONE
- The pineal gland secretes **melatonin** in darkness.
- The pineal is inhibited by light.
- Pinealocytes convert tryptophan into serotonin during the day (in bright light), then converts serotonin into melatonin at night (in darkness).
- Peak melatonin secretion in humans occurs at 1-5 years old.
- Melatonin inhibits puberty in humans. Levels drop 75% at puberty.
- Melatonin levels are correlated with human activity cycles (biorhythms).
- High melatonin levels are correlated with SAD and PMS with symptoms including:
  - depression
  - sleepiness, irritability
  - carbohydrate craving
- Melatonin levels may be manipulated by phototherapy and can reduce the affects of jet lag.
- In other animals, high levels of melatonin inhibit reproduction and inhibit melanogenesis which affects seasonal reproductive timing, and fur or feather color.

Pineal Gland (Epiphysis)



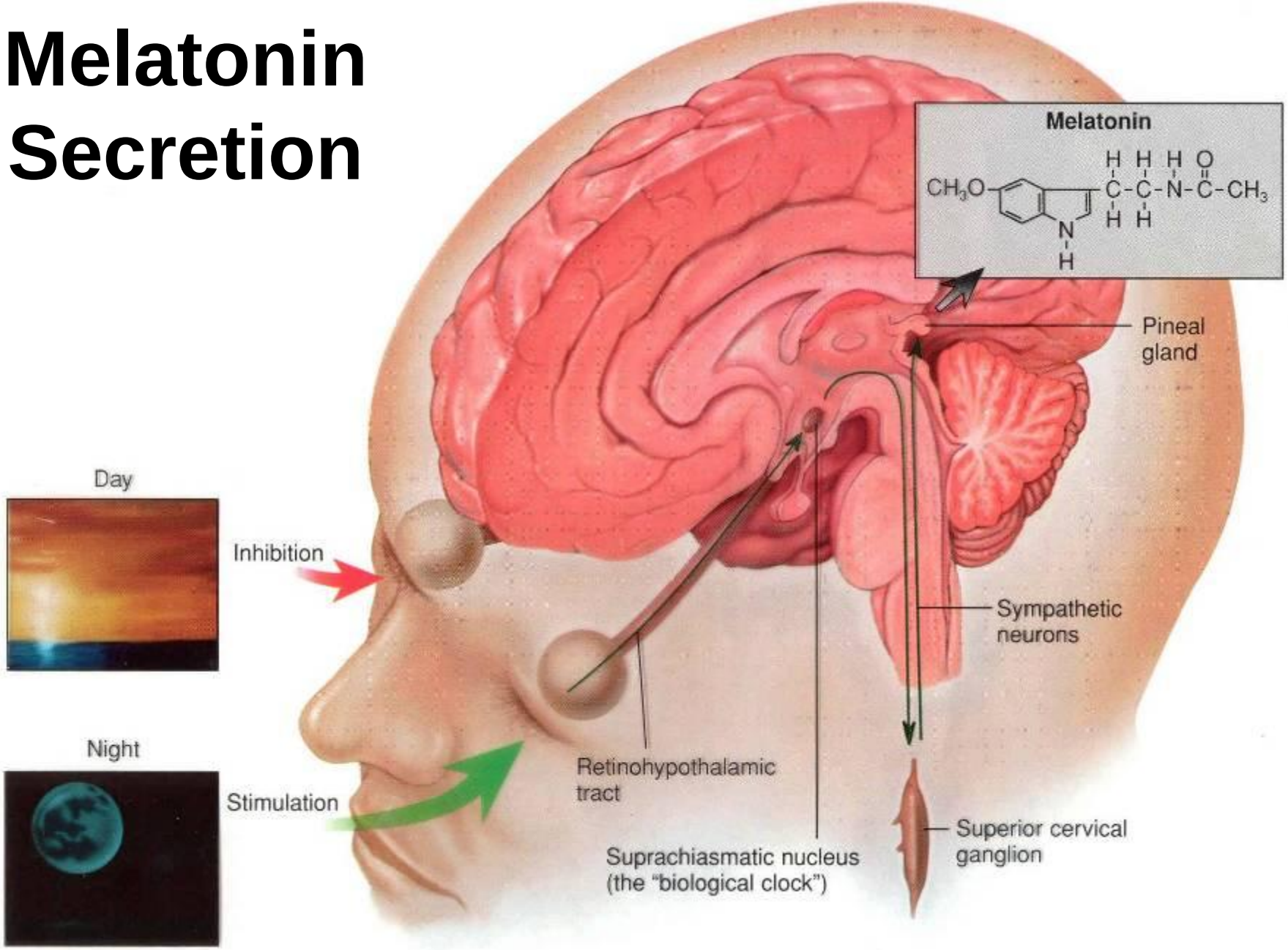






Pineal Gland Histology

Melatonin Secretion



snowshoe hare

snowy owl

Winter: Long nights, pinealocytes uninhibited, high levels of melatonin inhibit pigment cells and gonads.

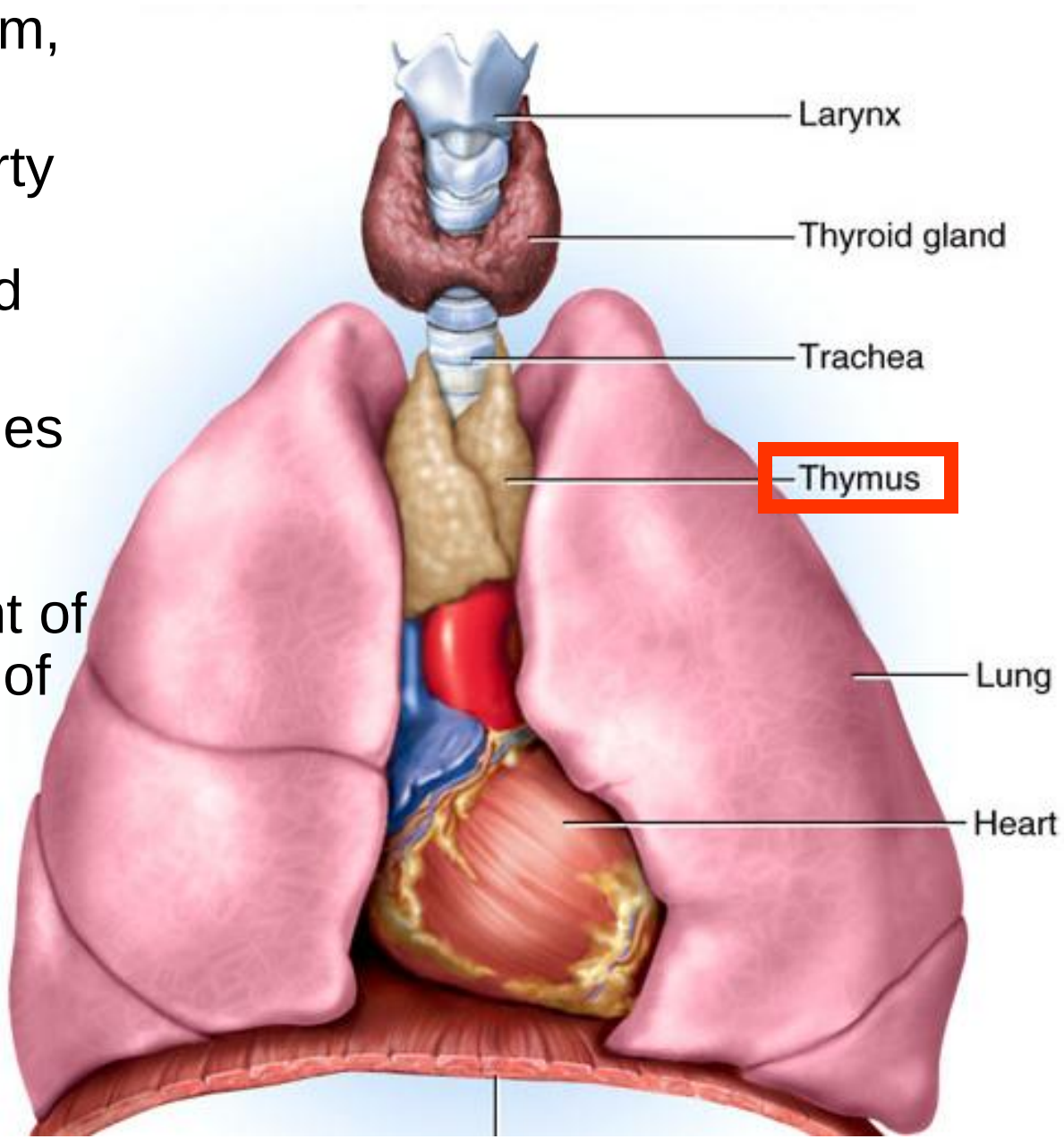
snowshoe hare

snowy owl

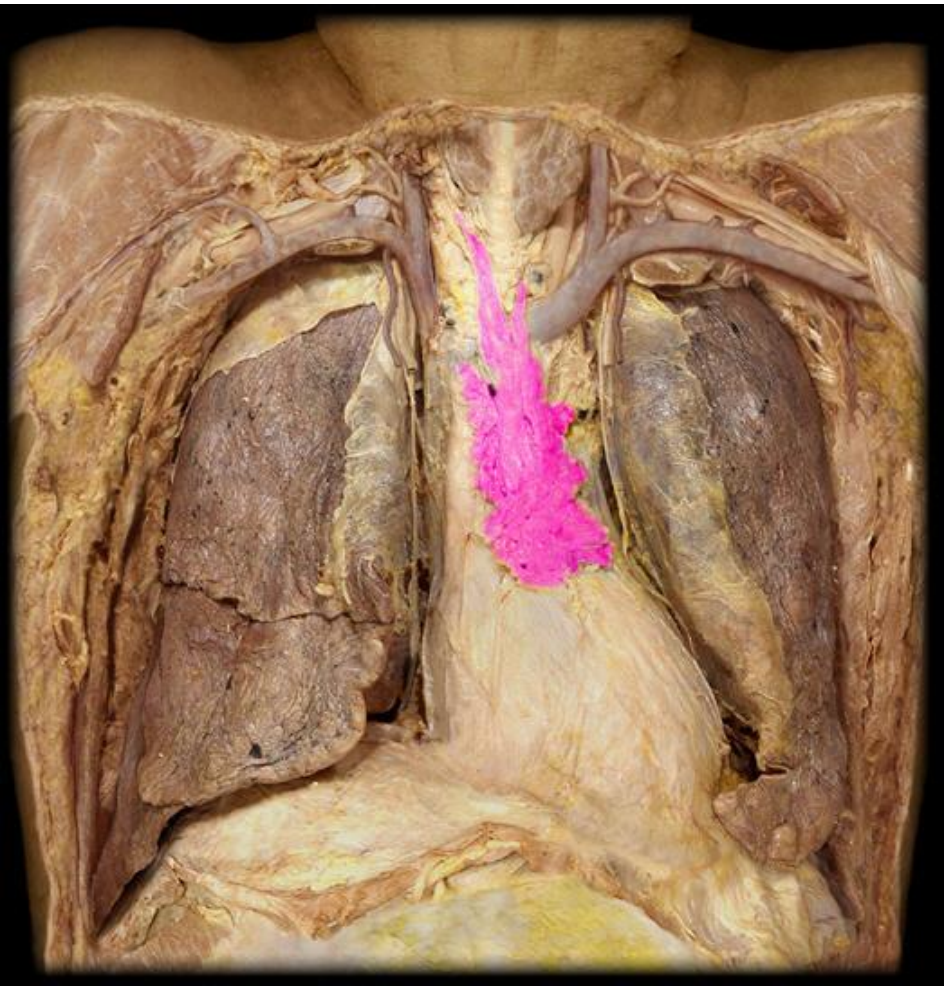
Summer: Long days, pinealocytes inhibited, low levels of melatonin, uninhibited pigment cells and gonads.

Thymus

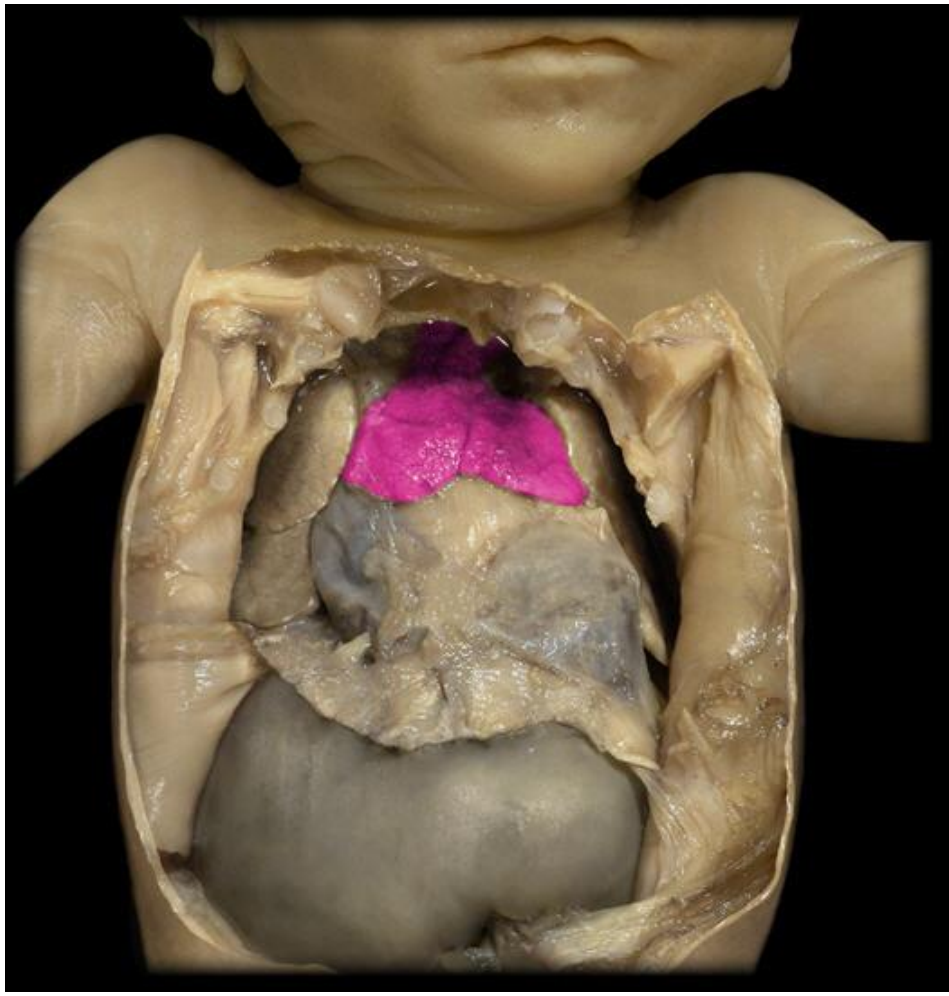
- Location: mediastinum, superior to heart
- Involution after puberty (converts to fibrous connective tissue and adipose)
- Secretes the hormones **Thymosin** and **Thymopoietin** that regulate development of T-lymphocytes (type of white blood cell)



Thymus Gland



adult thymus



infant thymus

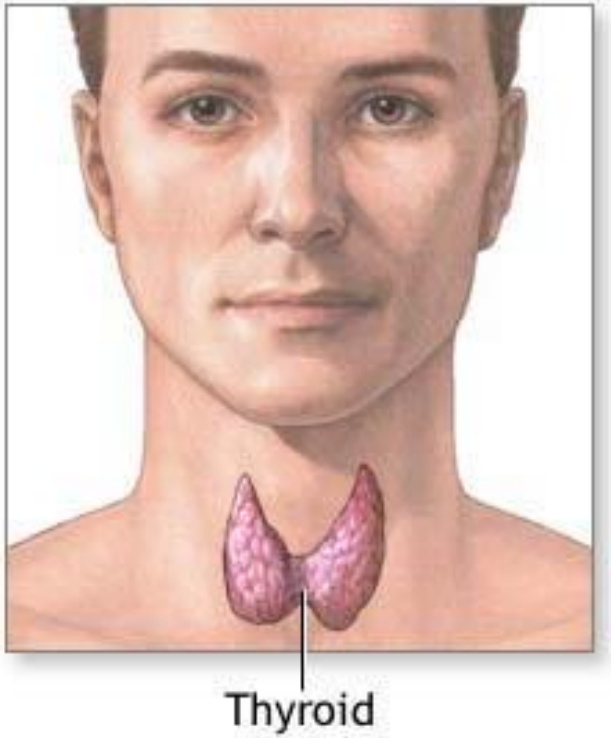
Athymic Nude Mice play an important role in immunology research and cancer research.

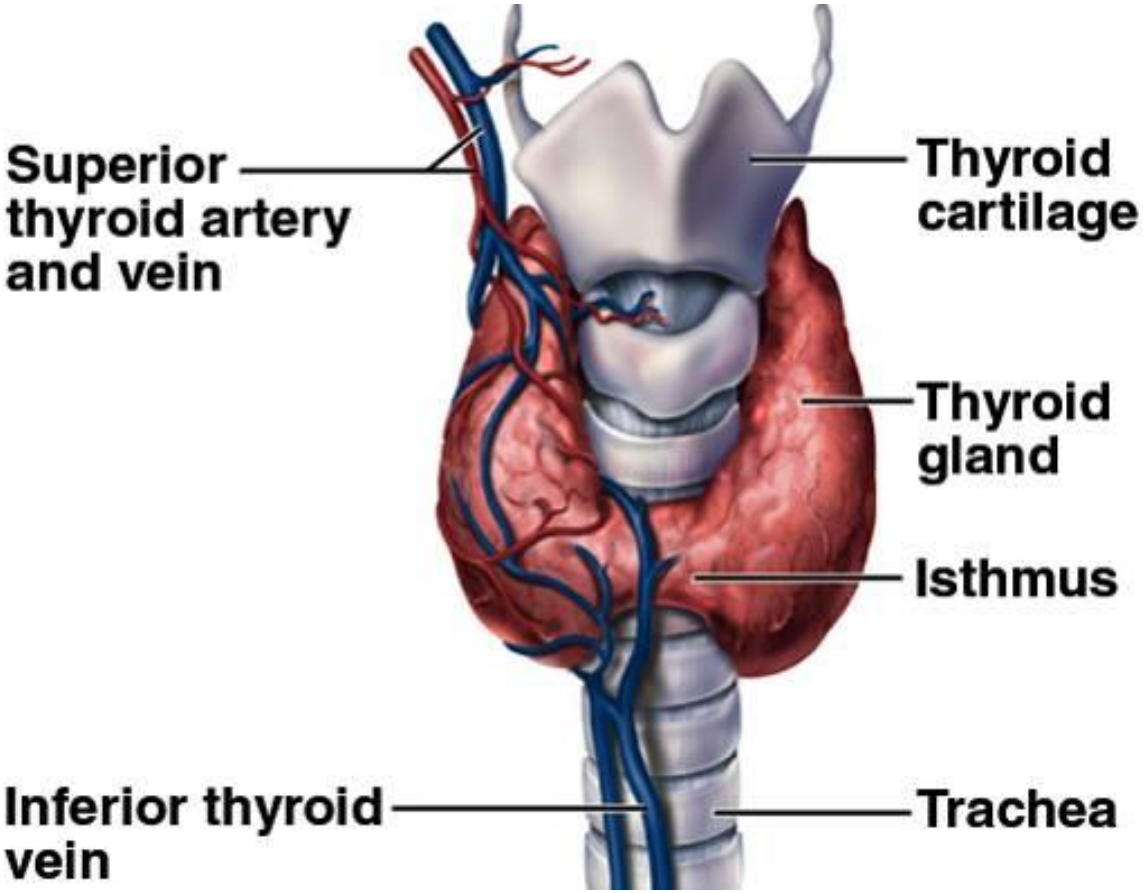
These mouse colonies must be maintained in absolutely sterile conditions.

Severe Combined Immunodeficiency Disease

- Hereditary lack of T and B lymphocytes
- Extreme vulnerability to opportunistic infection

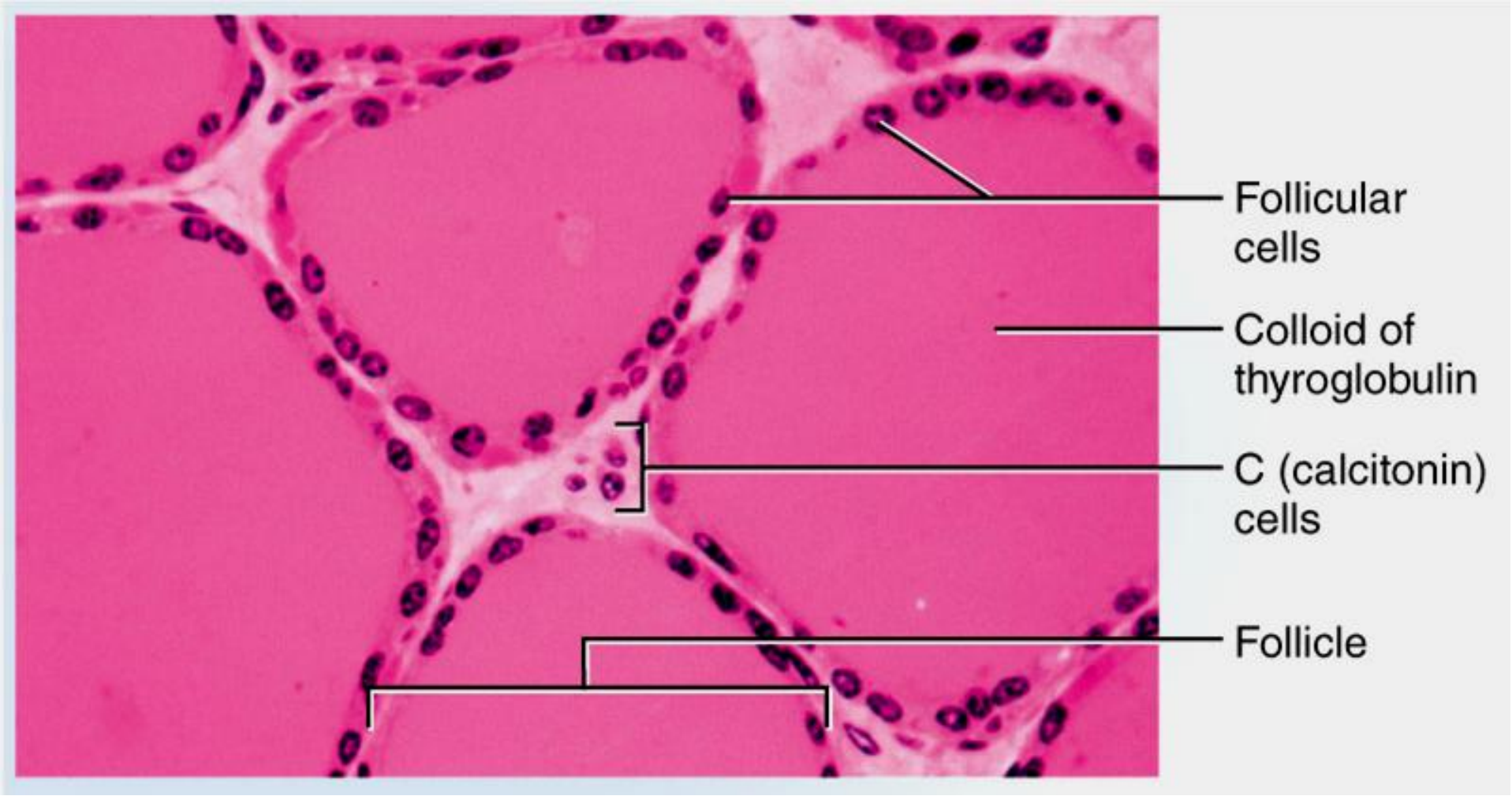
Thyroid Gland Anatomy





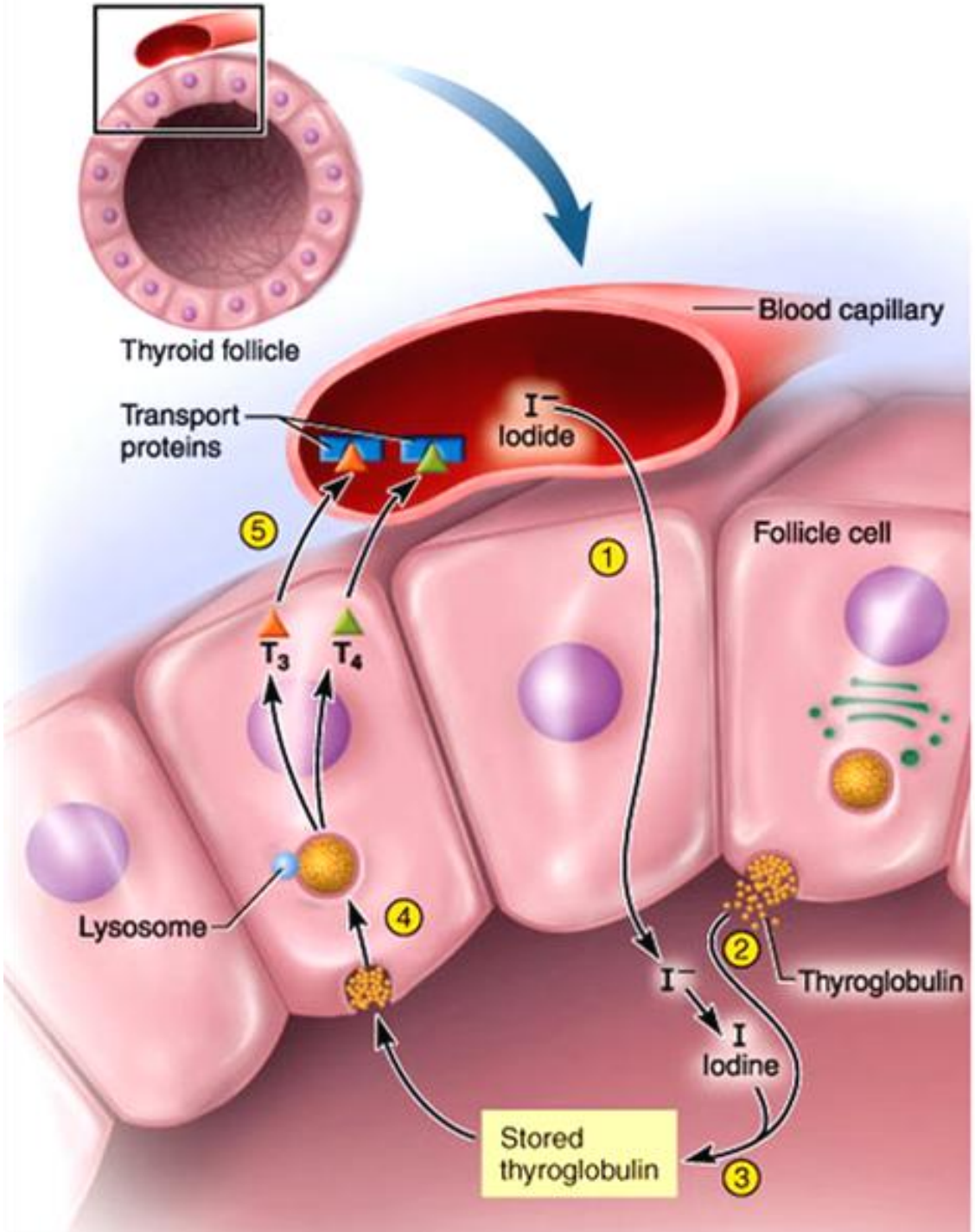
- Thyroid gland is located on the anterior and lateral sides of trachea.
- 2 large lobes of thyroid tissue are connected by an isthmus of thyroid tissue.
- Thyroid gland is highly vascular and receives a large volume of blood flow.

Thyroid Gland Histology



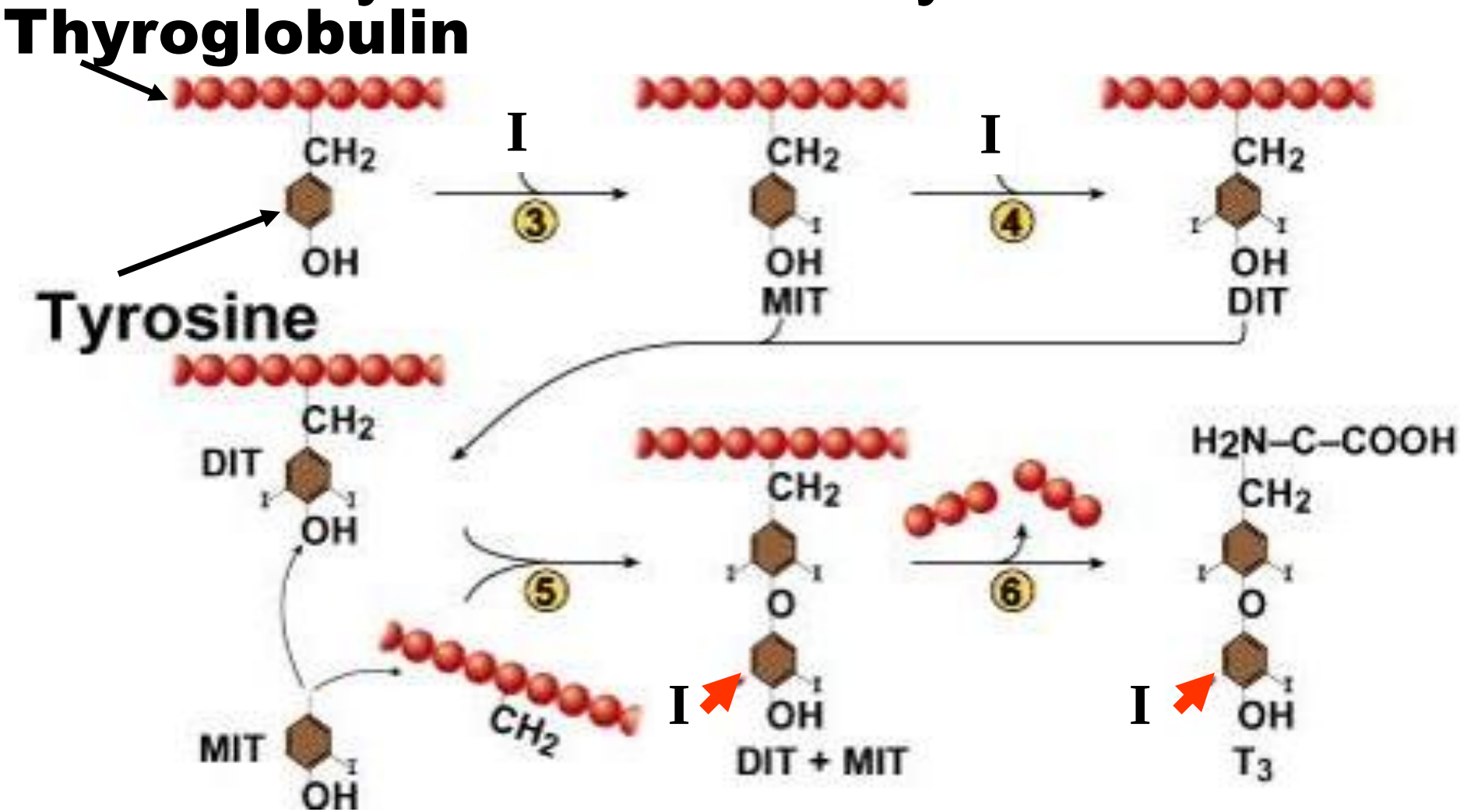
Cells of the Thyroid Gland

- Thyroid Follicles
  - Spheres of simple cuboidal cells (follicular cells) filled with a colloid of 2 thyroid hormones, T_3 and T_4 bound to thyroglobulin
  - T_3 = triiodothyronine T_4 = tetraiodothyronine
  - T_3 contains 3 iodine atoms, T_4 contains 4 iodine atoms
  - Follicles produce 90% T_4 and 10% T_3
  - T_3 is more potent than T_4
  - In circulation and in cells, T_4 is broken down into T_3
  - Thyroid hormone functions:
    - ↑ metabolic rate, O_2 consumption and heat production
    - ↑ heart rate and respiratory rate
    - stimulates appetite and breakdown of carbohydrates, lipids and proteins
- C-cells (calcitonin cells or parafollicular cells)
  - cells are located in between the follicles.
  - cells produce the hormone calcitonin that ↓ blood Ca^{+2} and promotes Ca^{+2} deposition in bone, especially in children.



1. Iodide absorption and oxidation
2. Thyroglobulin synthesis and secretion
3. Iodine added to tyrosines of thyroglobulin
4. Thyroglobulin uptake and hydrolysis
5. Release of T_3 and T_4 into the blood

Thyroid Hormone Synthesis



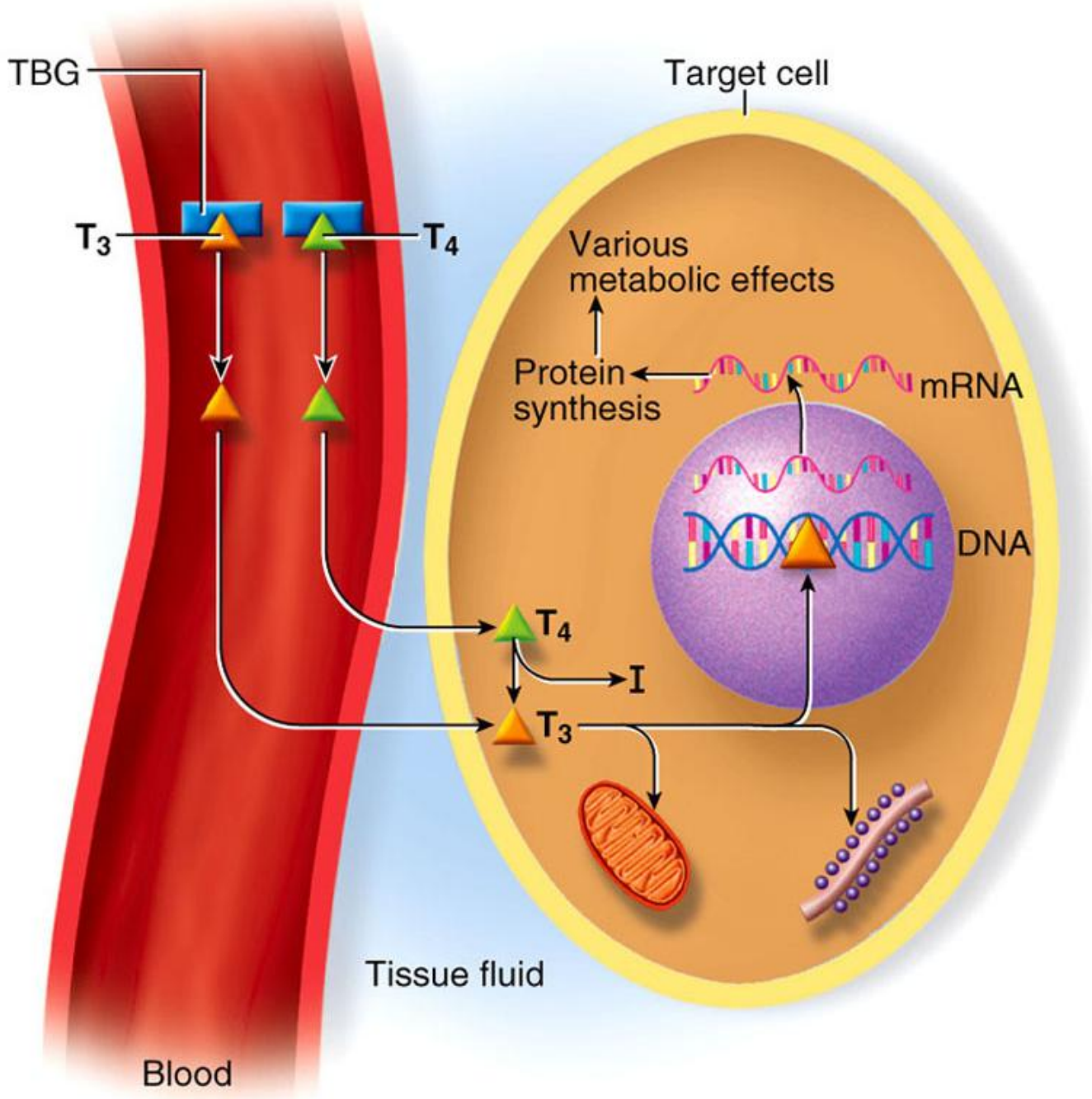
(**3**) Iodine added to a tyrosine forms monoiodothyronine (MIT). (**4**) Iodine added to MIT forms diiodothyronine (DIT). (**5**) DIT + MIT = T_3.

(**6**) Lysosome enzymes cleave T_3 from the thyroglobulin. Arrows indicate where adding another iodine would form T_4.

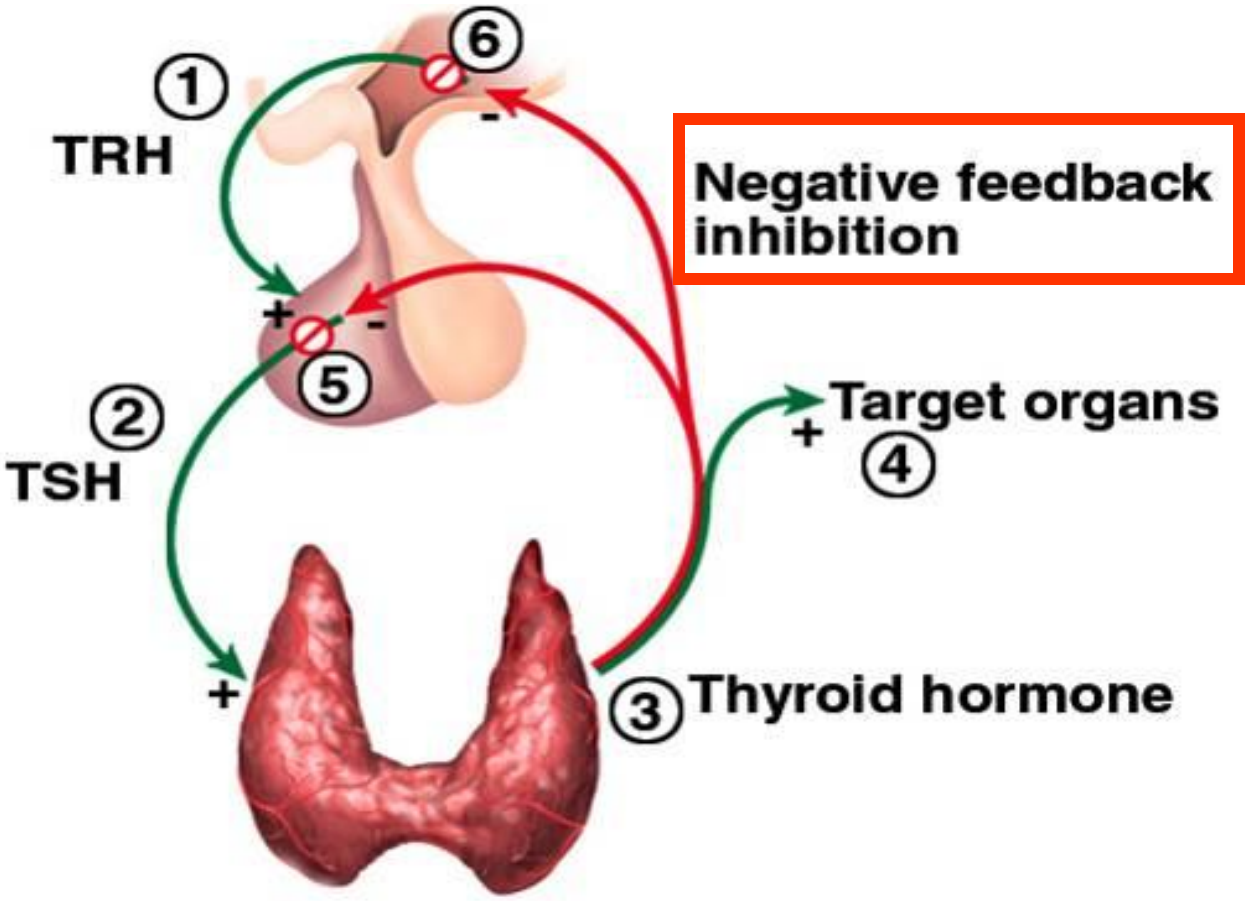
Thyroid Hormone Effects

- T_3 and T_4 dissociate from thyroxine-binding globulin (TBG), leave bloodstream and enter target cell. T_4 is converted into T_3.
- T_3 can
  - bind to receptors on mitochondria that ↑ rate of aerobic respiration
  - activate ribosomes that ↑ protein synthesis
  - enter the nucleus and activate genes and ↑ protein synthesis
- Example: one protein that can be produced is Na^+-K^+ ATPase and the activity of this protein generates heat

Thyroid Hormone Transport and Effects



Thyroid Hormone Control



High thyroid hormone levels inhibit release of tropic hormones (TRH, TSH).

Thyroid Gland Disorders

- Congenital hypothyroidism (↓ TH)
  - infant suffers abnormal bone development, thickened facial features, low body temperature, lethargy, brain damage. Can be treated with synthroid.
- Myxedema (adult hypothyroidism, ↓ TH)
  - low metabolic rate, sluggishness, sleepiness, weight gain, puffy face, constipation, dry skin and hair, cold sensitivity, ↑ blood pressure and tissue swelling
- Graves Disease (a type of hyperthyroidism)
  - antibodies mimic TSH, ↑ TH secretion, exophthalmos
- Endemic Goiter (goiter = enlarged thyroid gland)
  - dietary iodine deficiency, low TH, low - feedback, ↑ TSH

Congenital Hypothyroidism

Congenital hypothyroidism results from chronically low levels of TH.

Infants suffer abnormal bone development, thickened facial features, low body temperature, lethargy, brain damage. Can be treated with synthroid.

Myxedema

In this patient with advanced pretibial myxedema, these striking skin changes are due to accumulations of mucopolysaccharides ("myxedema"). These changes are reversible with thyroid hormone.

Myxedema (adult hypothyroidism) chronically low TH results in low metabolic rate, sluggishness, sleepiness, weight gain, puffy face, constipation, dry skin and hair, cold sensitivity, increased blood pressure and tissue swelling.

Exophthalmos – a symptom of Graves' Disease

Figure 11.26 **A symptom of hyperthyroidism.** Hyperthyroidism is characterized by an increased metabolic rate, weight loss, muscular weakness, and nervousness. The eyes may also protrude (exophthalmos) due to edema in the orbits.

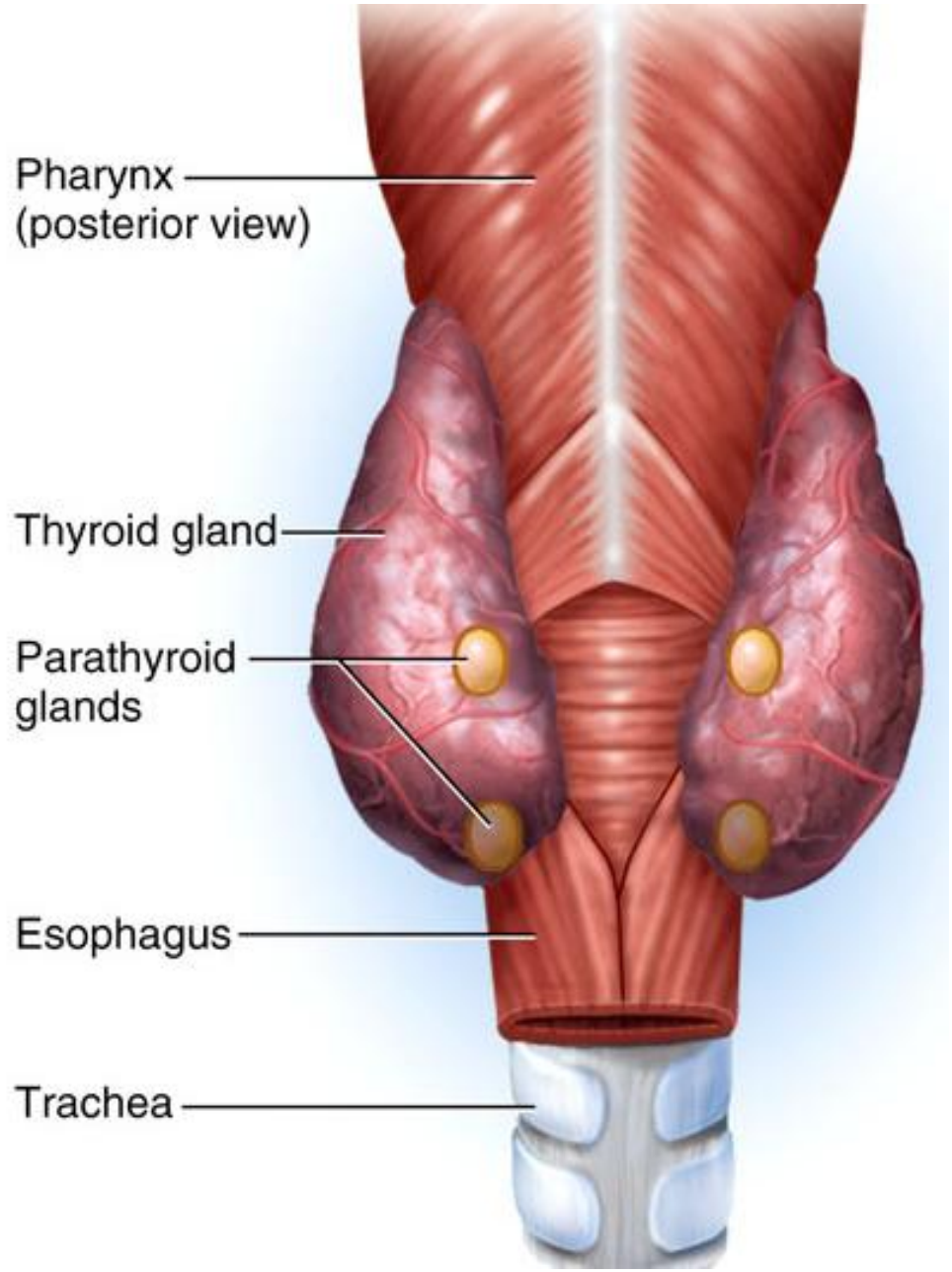
Graves Disease (a type of hyperthyroidism) results from production of antibodies that mimic TSH resulting in increased TH secretion.

Endemic Goiter

Endemic Goiter (goiter = enlarged thyroid gland) due to dietary iodine deficiency results in low TH synthesis and reduced feedback resulting in increased TSH and thyroid growth.

Parathyroid Glands

- Multiple lobes of tissue on the posterior surface of the thyroid gland. There may also be other ectopic sites.
- Produces Parathyroid Hormone (PTH or parathormone)
  - PTH increases blood Ca^{+2} levels and synthesis of calcitriol (Vitamin D) resulting in:
    - ↑ absorption of Ca^{+2}
    - ↓ urinary Ca^{+2} excretion
    - ↑ urinary PO^{-4} excretion
    - ↑ bone erosion

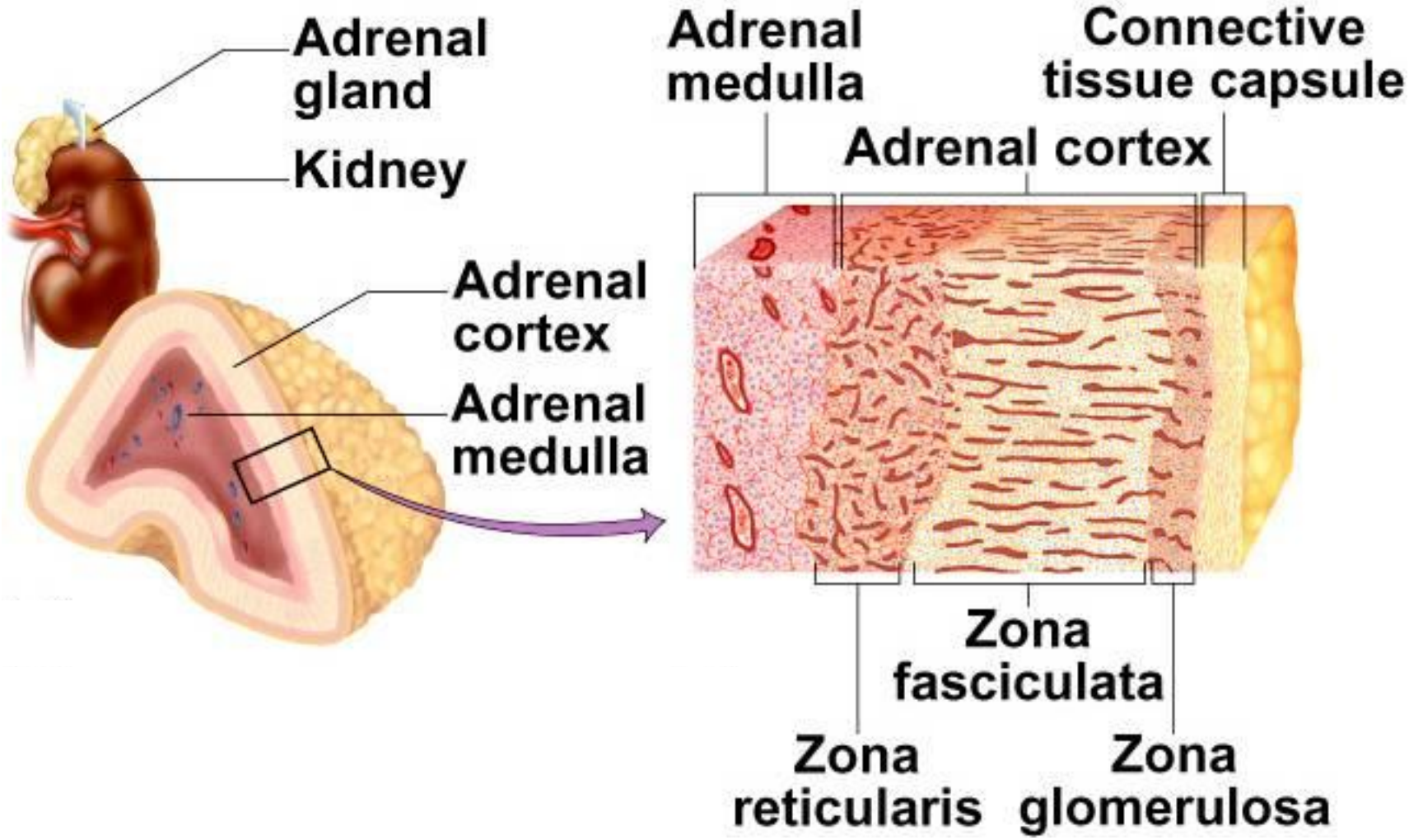


Parathyroid Disorders

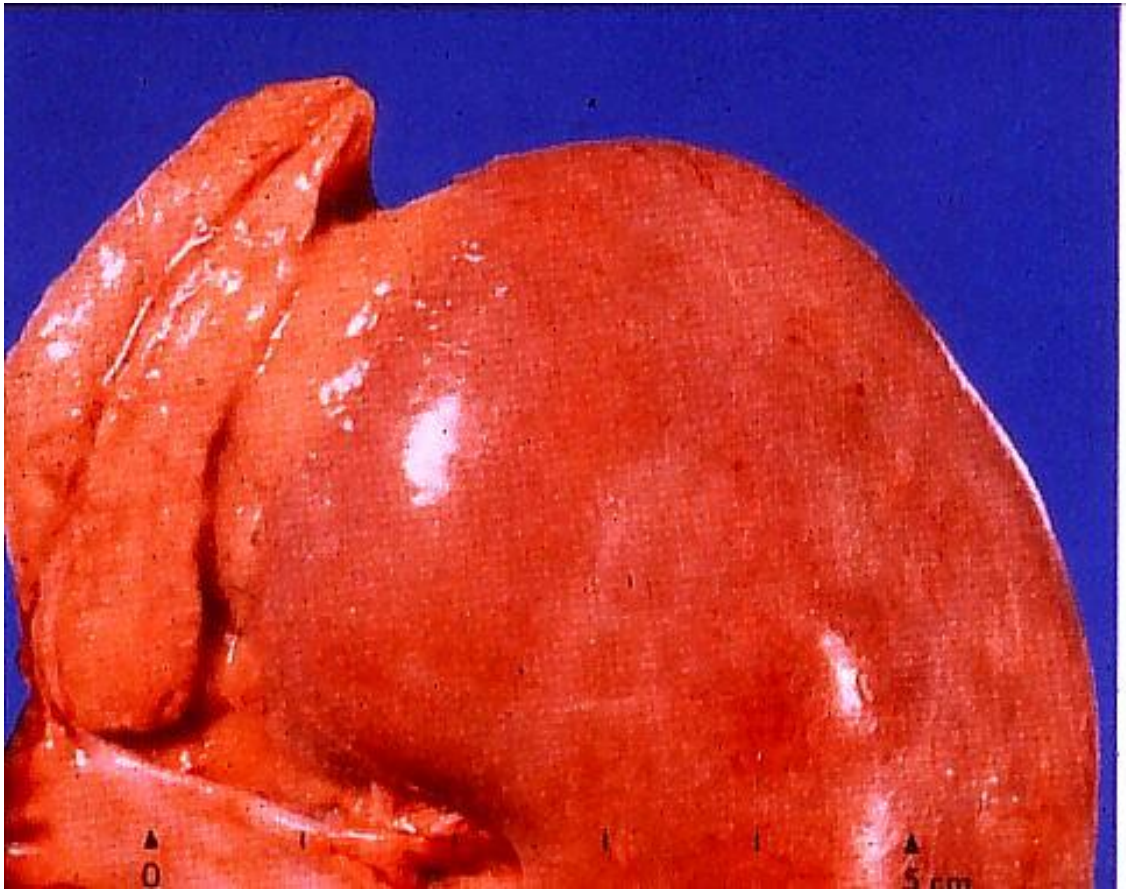
- Hypoparathyroid
  - usually results from surgical excision during thyroid surgery
  - can result in fatal tetany in 3-4 days from low Ca^{+2}
- Hyperparathyroid
  - Excess PTH secretion can result from a tumor
  - causes soft, fragile and deformed bones, extremely high blood Ca^{+2}, and renal calculi (kidney stones).

Adrenal (Suprarenal) Glands

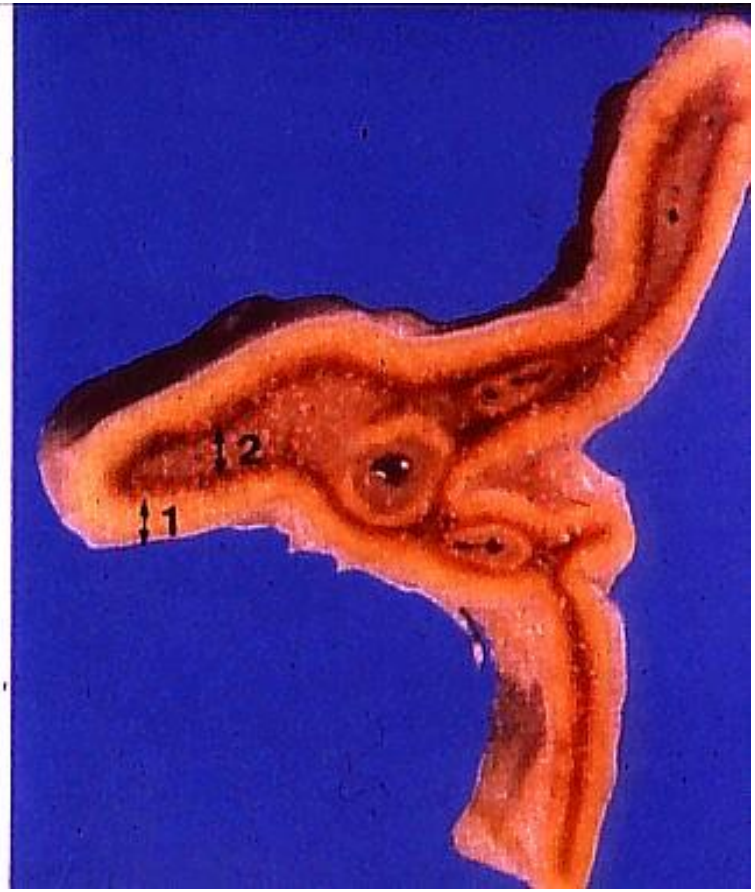
Adrenal Gland



Adrenal Gland



Adrenal Gland *in situ* on kidney



Cross Section

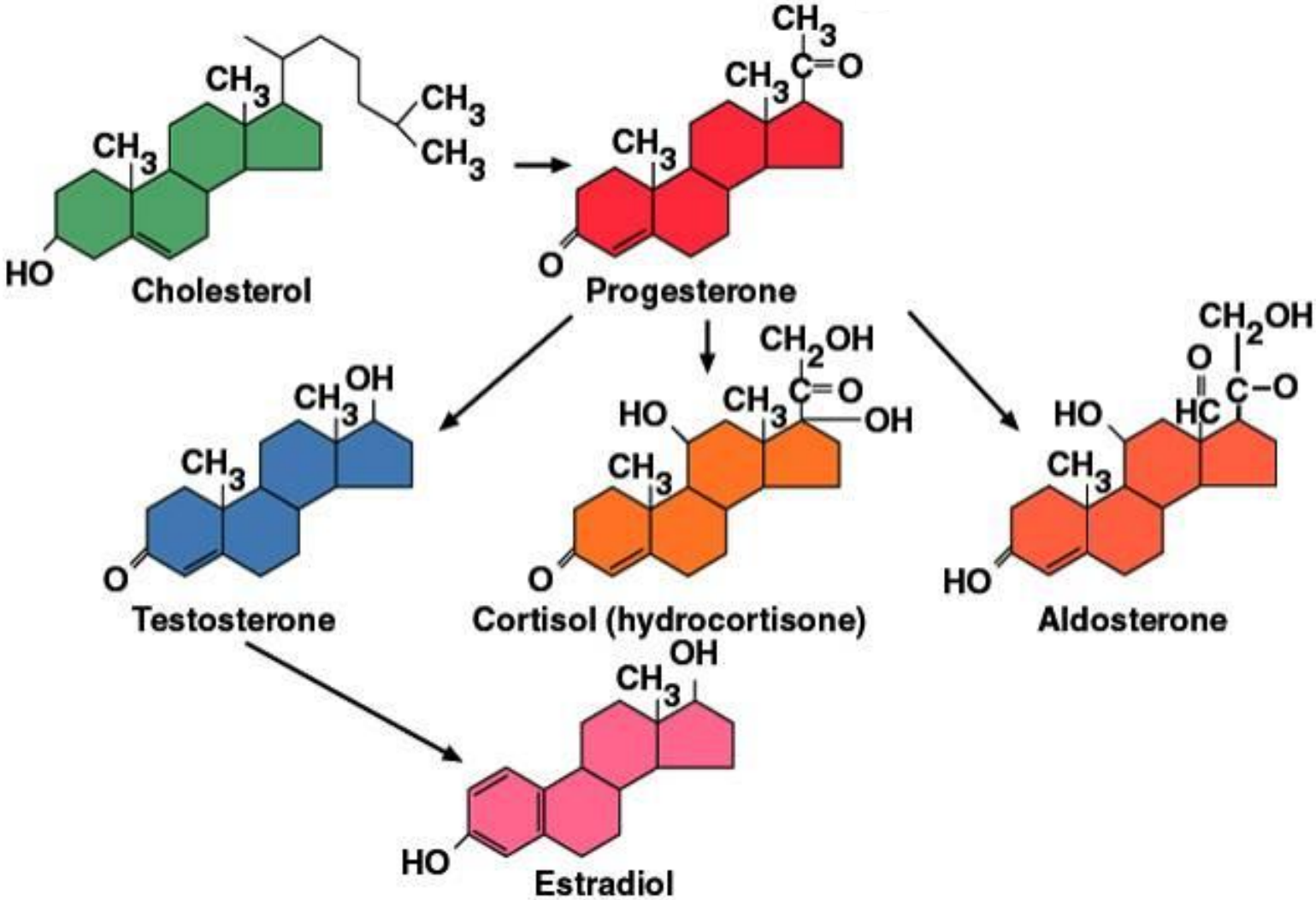
Adrenal Medulla

- Postganglionic sympathetic neurons innervated by sympathetic preganglionic fibers.
  - consists of modified neurons called chromaffin cells
  - stimulation causes release of adrenaline into bloodstream
- Responds to ACUTE stress (fight or flight)
- Hormonal effect is relatively long lasting (minutes) compared to nervous system (fractions of a second).
  - increases BP and heart rate
  - increases blood flow to skeletal muscle
  - increases pulmonary air flow
  - stimulates gluconeogenesis and glycogenolysis
  - decreases digestion and urine formation

Adrenal Cortex

- Response to CHRONIC stress (long duration – weeks or more)
- Three Layers - (outer) zona glomerulosa, (middle) zona fasciculata, (inner) zona reticularis
- All three layers produce Corticosteroids from cholesterol
  - Zona Glomerulosa produces the mineralocorticoid **aldosterone**
    - controls electrolyte balance by conserving Na^+
  - Zona Fasciculata produces the glucocorticoids **cortisol, corticosterone** and **cortisone**
    - cortisol stimulates fat and protein catabolism, gluconeogenesis (from amino acids and fatty acids) and release of fatty acids and glucose into blood
    - anti-inflammatory effect suppresses the immune system
  - Zona Reticularis produces the sex steroids **testosterone** and **estrogen**
    - important source of estrogen in women after after menopause

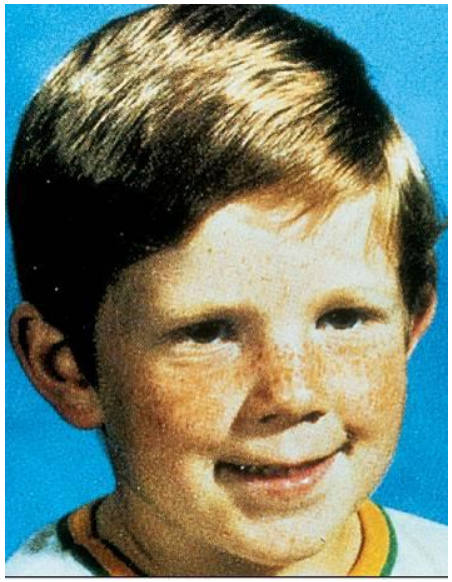
Steroid Hormone Synthesis



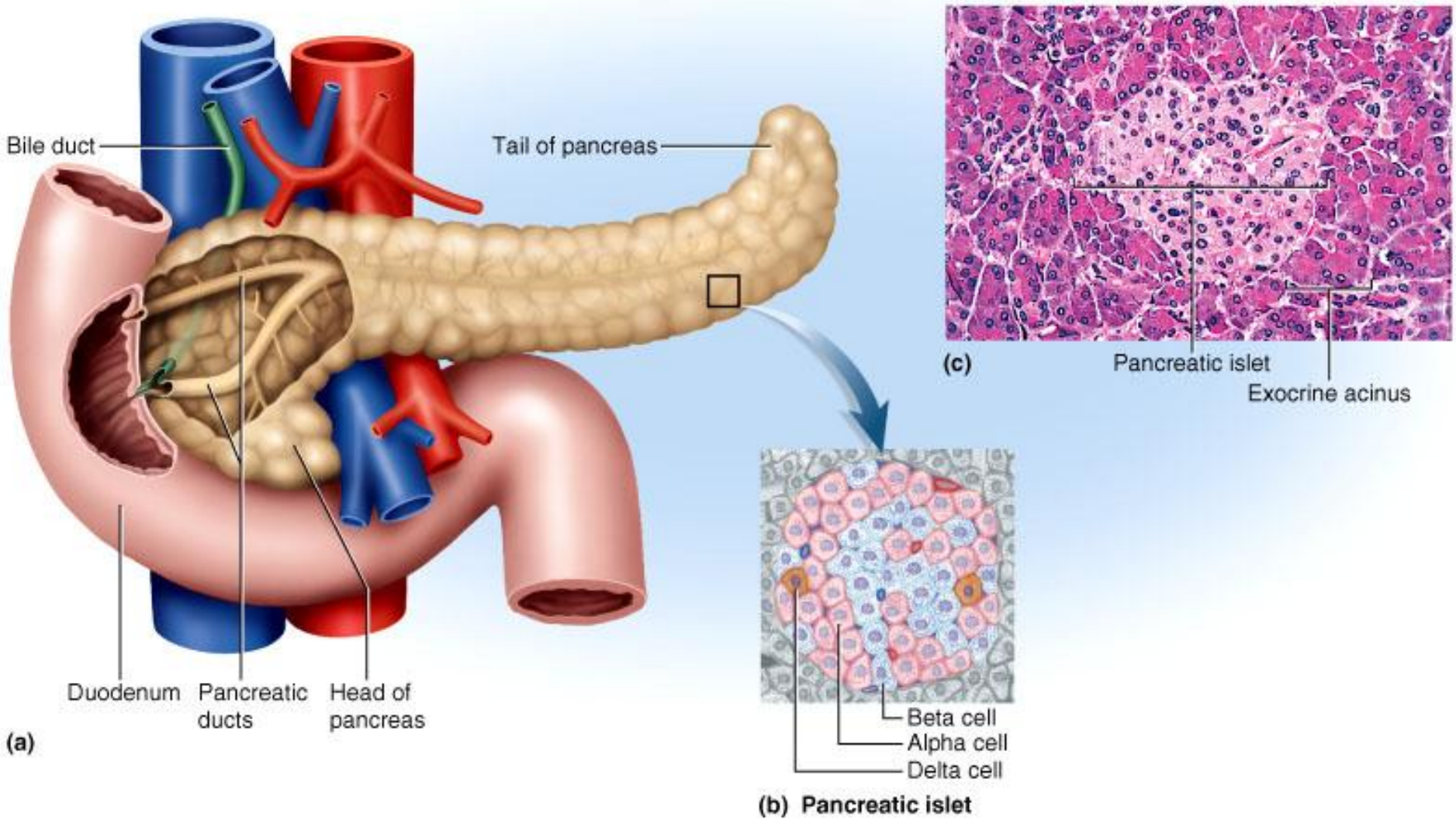
All steroid hormones are synthesized from cholesterol – the various hormones differ in functional groups attached to a 4-ringed steroid backbone

Adrenal Cortex Disorders

- **Cushing's Syndrome** is excessive secretion of cortisol
  - can be caused by pituitary hypersecretion of ACTH, ACTH-secreting tumor, over activity of adrenal cortex
  - causes hyperglycemia, hypertension, weakness, edema
  - muscle and bone loss occurs with protein catabolism
  - buffalo hump and moon face caused by abnormal fat deposition between shoulders and in face
- **Adrenogenital Syndrome** (AGS)
  - adrenal androgen hypersecretion causes enlargement of external sexual organs in children and early onset of puberty
  - can cause masculinizing effects on females (deeper voice, beard growth, male-like genitalia)



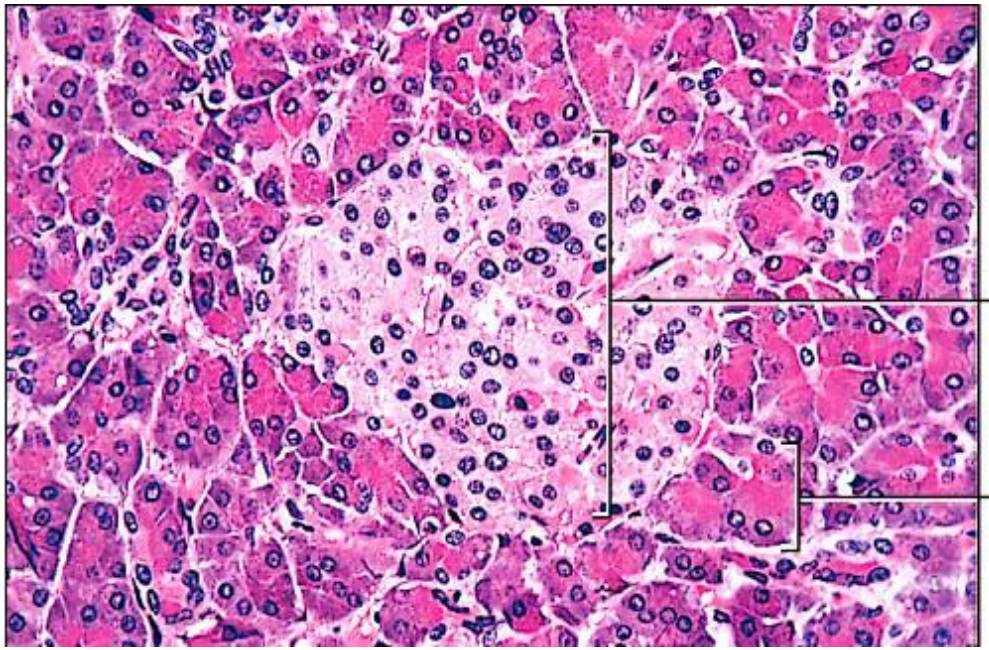
Pancreas



Pancreas location is retroperitoneal and inferior and dorsal to stomach

Products of the Pancreas

- 98% of pancreas is EXOCRINE – produces digestive enzymes and bicarbonate from acinar tissue.
- 2% of pancreas is ENDOCRINE – produces at least 5 hormones – best understood are insulin, glucagon and somatostatin.
- Endocrine tissue is in 1-2 million pancreatic islets of Langerhans.



Pancreatic Hormones

- Insulin (from β cells)
  - insulin is secreted when blood sugar levels are high as in after a meal
  - insulin receptors are on most cells of the body
  - insulin stimulates cells to take up glucose and amino acids
  - insulin antagonizes glucagon
- Glucagon (from α cells)
  - glucagon is secreted when blood glucose levels are low as it is between meals
  - glucagon stimulates glycogenolysis (breakdown of glycogen), fat catabolism (release of free fatty acids) and promotes absorption of amino acids for gluconeogenesis (production of glucose from amino acids)
- Somatostatin (from delta δ cells)
  - secreted with rise in blood glucose and amino acids after a meal
  - paracrine secretion modulates secretion of α and β cells
- Hyperglycemic hormones raise blood glucose: glucagon, epinephrine, norepinephrine, cortisol and corticosterone
- Hypoglycemic hormone, insulin, lowers blood glucose

Diabetes Mellitus

- Diabetes Mellitus is a disease resulting from the hyposecretion or inaction of insulin.

- Extremely high blood glucose levels can exceed the kidney tubule transport maximum of glucose reabsorption and cause osmotic diuresis: glucose remains in urine, osmolarity increases and draws water into urine.

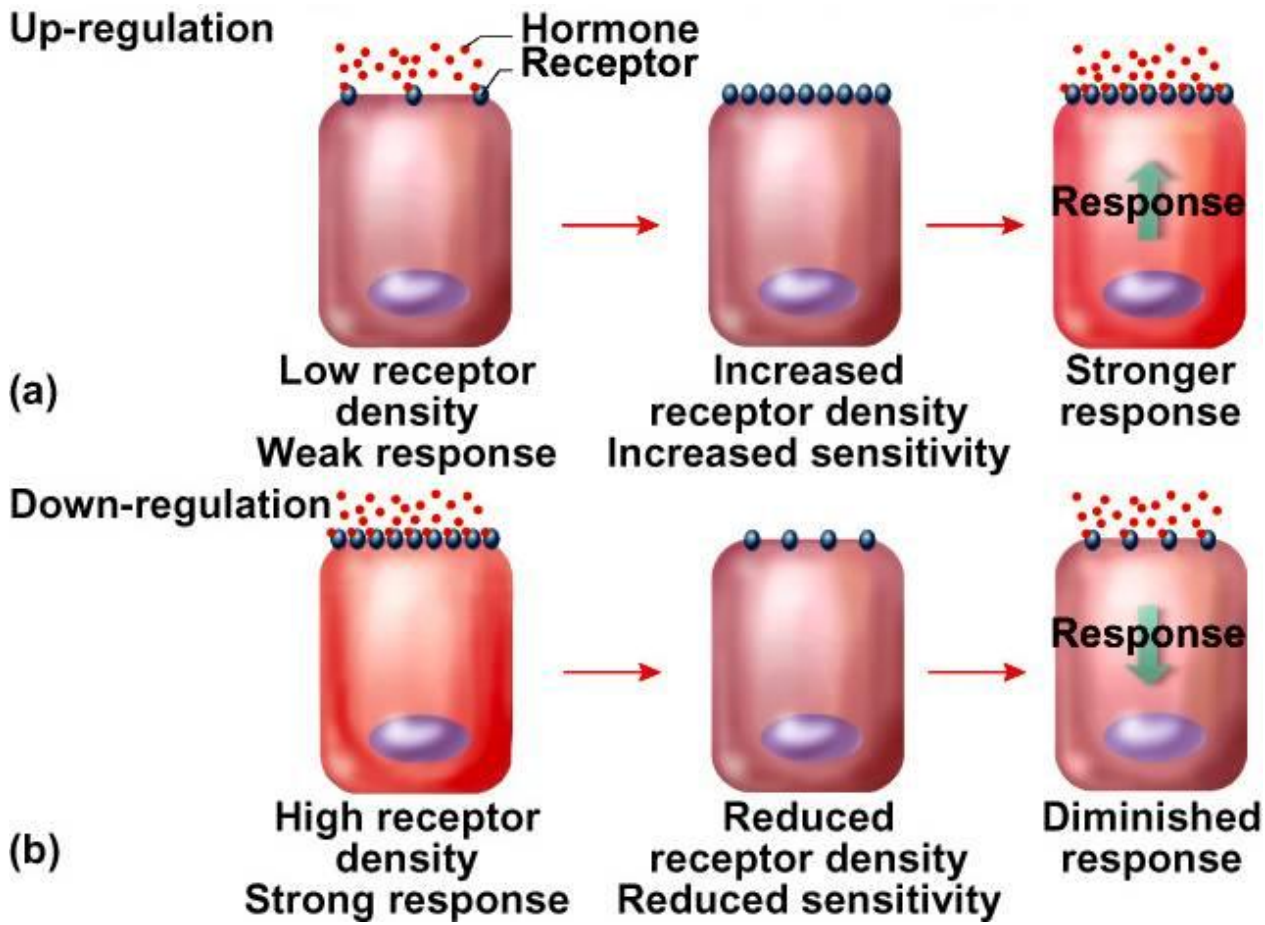
Diabetes Mellitus

- Signs and symptoms of Diabetes Mellitus
  - polyuria, polydipsia, polyphagia
  - hyperglycemia, glycosuria, ketonuria
  - blood glucose levels up to 100 mg/dL are considered normal. (mg/dL = milligrams per deciliter)
  - Diabetes is typically diagnosed when fasting blood glucose levels are 126 mg/dL or higher.
  - Glucose is a major source of energy for most cells of the body. Some cells (for example, brain and red blood cells), are almost totally dependent on blood glucose as a source of energy. The brain requires that glucose concentrations in the blood remain within a certain range in order to function normally. Concentrations of less than 30 mg/dL or greater than 300 mg/dL can produce confusion or unconsciousness.
  - Ketones are a metabolic breakdown product of fatty acid metabolism. Some cells will use fatty acids for fuel if glucose is not available and produce ketones as waste.

Types of Diabetes Mellitus

- Type I (insulin dependent diabetes mellitus = IDDM)
  - 10% of diabetes mellitus cases
  - Caused by autoimmune destruction of β cells
  - Usually diagnosed at about age 12
  - Treated with diet, exercise, monitoring of blood glucose and periodic injections of insulin (new delivery methods include pumps and inhalers).
- Type II (non-insulin dependent diabetes mellitus = NIDDM)
  - 90% of diabetes mellitus cases
  - Patients develop insulin resistance which is a failure of target cells to respond to insulin due to receptor downregulation (see next slide).
  - 3 major risk factors are heredity, age (40+) and obesity
  - Treated with programs for weight loss through diet and exercise.
  - Some patients are helped by oral medications (like glucophage) that decrease intestinal absorption of glucose, decrease hepatic glucose production and improve target cell sensitivity to insulin.

Receptor Regulation on Target Cells



- Down-regulation: Long-term exposure to high levels of a hormone can result in target cells reducing the number of receptors to the hormone as in Type II Diabetes.
- Up-regulation results from chronically low levels of hormone.

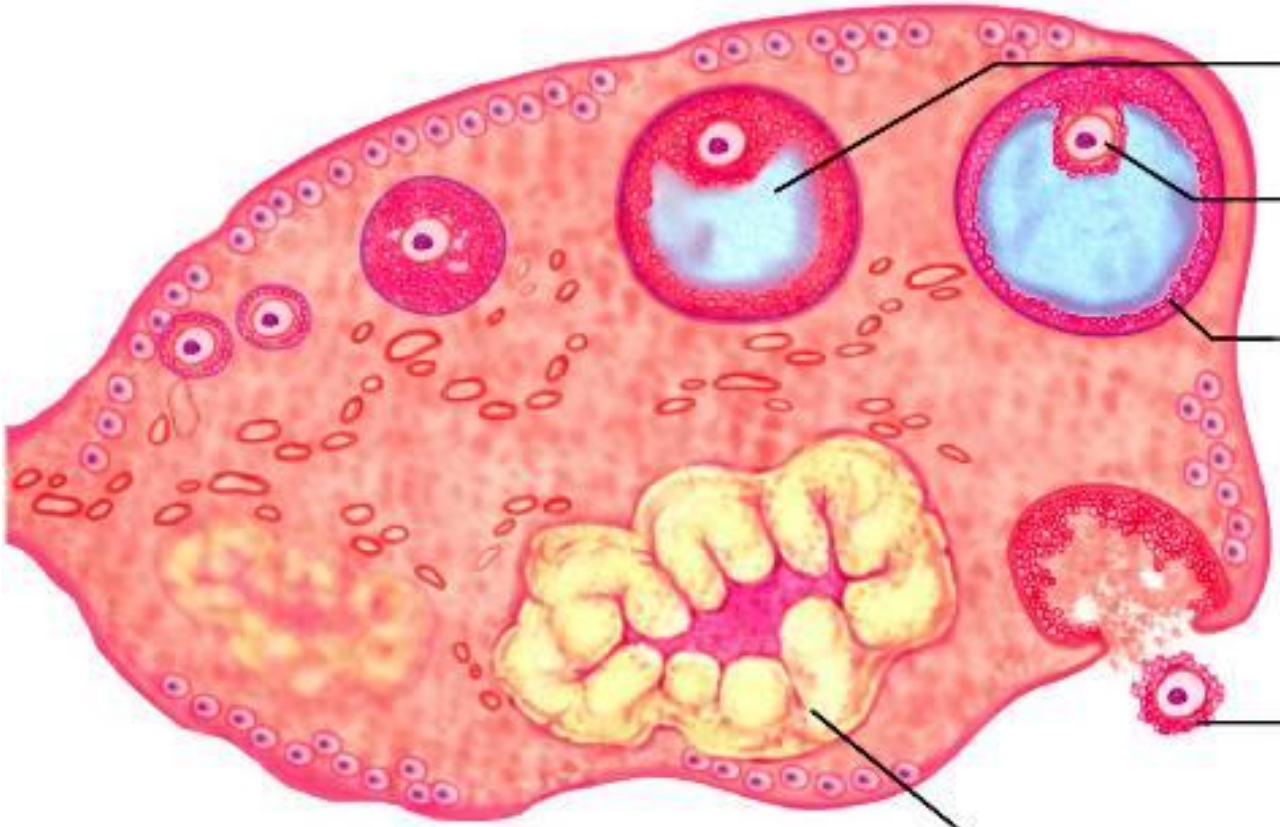
Pathology of Diabetes

- Acute pathology: cells cannot absorb glucose, so instead they rely on fat and proteins resulting in weight loss and weakness.
  - fat catabolism ↑ FFA's and ketones in blood
  - ketonuria promotes osmotic diuresis, loss of Na^+, K^+
  - ketoacidosis occurs as ketones ↓ blood pH
- Chronic pathology:
  - chronic hyperglycemia leads to neuropathy and cardiovascular damage:
    - retina and kidney damage (common in type I), atherosclerosis leading to heart failure (common in type II), and gangrene

Hyperinsulinism

- From excess insulin injection or pancreatic islet tumor
- Causes hypoglycemia, weakness and hunger
  - triggers secretion of epinephrine, GH and glucagon
  - side effects: anxiety, sweating and ↑ HR
- Insulin shock
  - uncorrected hyperinsulinism causes disorientation, convulsions or unconsciousness because the brain requires a constant supply of glucose.

Gonadal Hormones: the Ovary

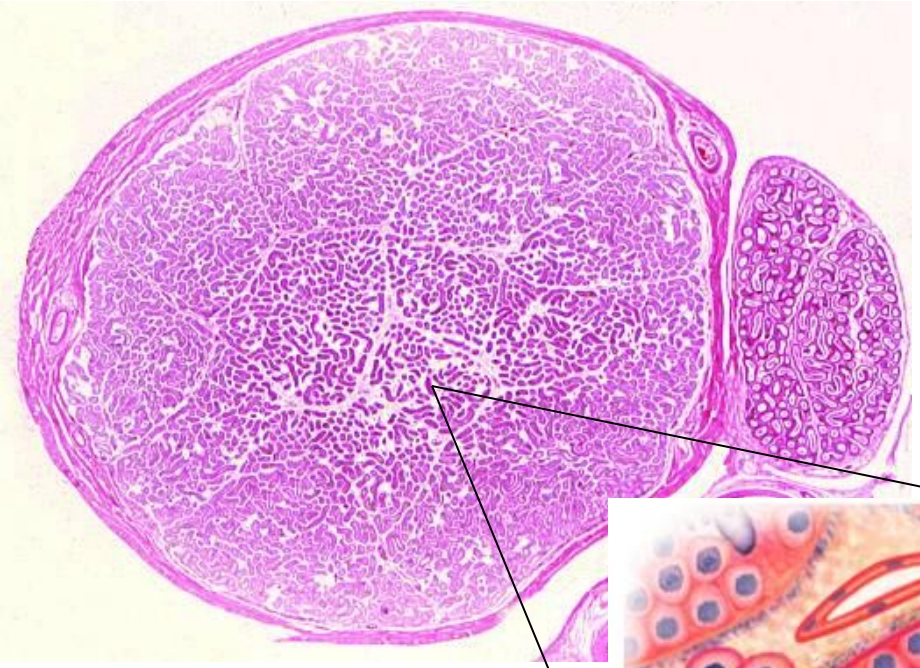


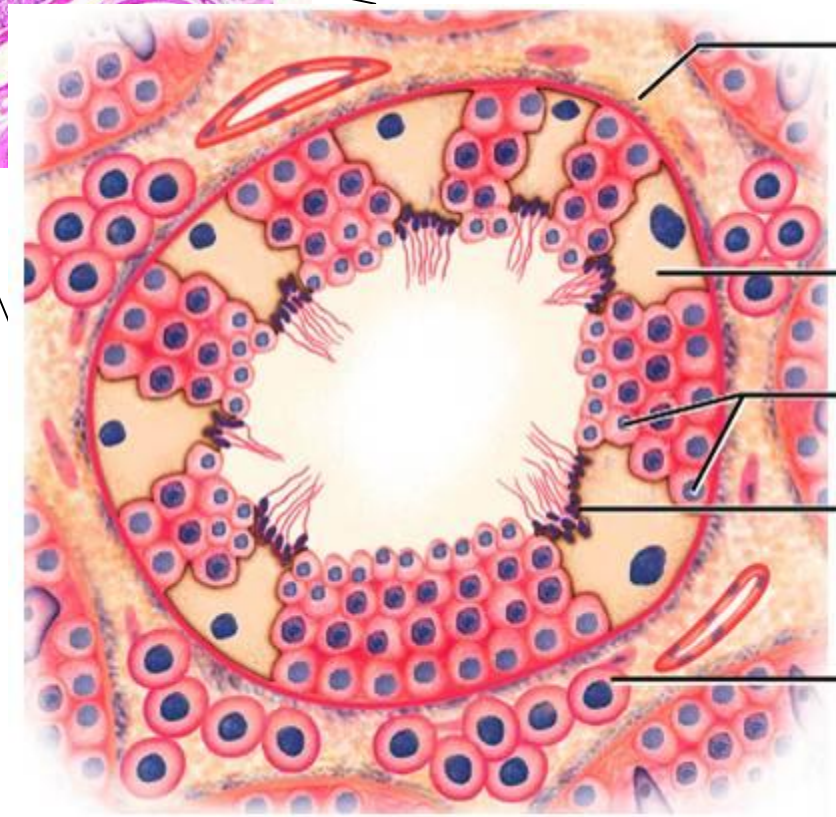
Follicle = egg surrounded by granulosa cells

Ovary

- Granulosa cells in wall of ovarian follicle
  - stimulated by follicle-stimulating hormone (FSH)
  - produce **estrogen** during the menstrual cycle
- Corpus Luteum: follicle after ovulation
  - stimulated by luteinizing hormone (LH)
  - produces **estrogen** and **progesterone** for 12 days if no fertilization or 8-12 weeks with pregnancy
- Functions of estrogen and progesterone
  - development of female reproductive system and physique including bone growth
  - regulates menstrual cycle, sustains pregnancy
  - prepares mammary glands for lactation

Gonadal Hormones: the Testis





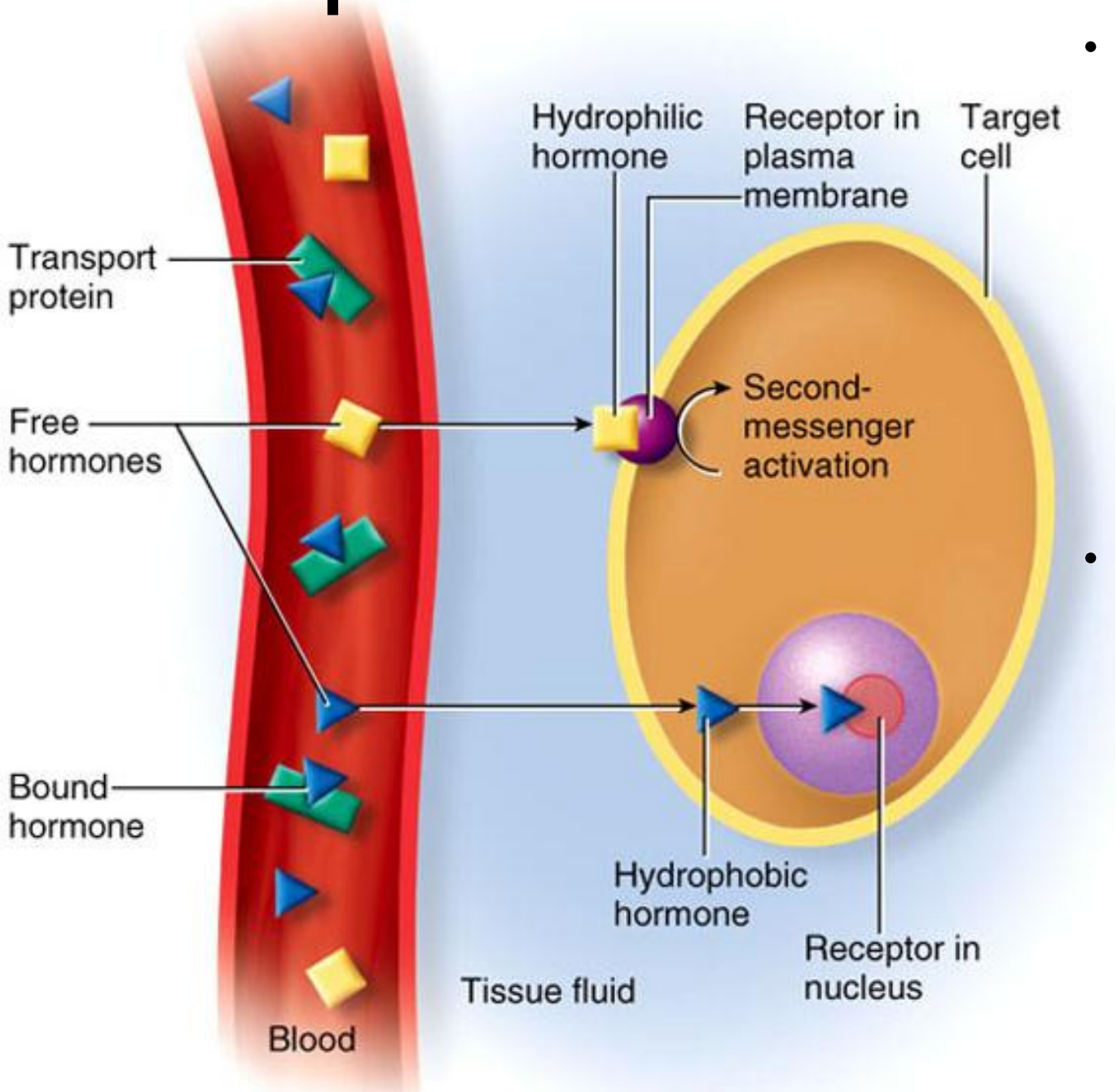
Testes

- Interstitial Cells (Leydig cells)
  - between seminiferous tubules
  - Stimulated by LH and FSH
  - produce **testosterone** (and small amounts of estrogen)
  - testosterone causes development of male reproductive system and physique
  - sustains sperm production and sex drive
- Sustentacular Cells (Sertoli cells)
  - secrete **inhibin** which regulates sperm production rate.

Chemical Classification of Hormones

- Steroid Hormones are all derived from cholesterol
  - aldosterone, cortisol, cortisone, corticosterone, progesterone, testosterone, estrogen, calcitrol
- Oligopeptides are chains of 3-10 amino acids
  - angiotensin II, vasopressin (ADH), GnRH, Oxytocin, TRH
- Polypeptides are chains of 14-199 amino acids
  - ACTH, atrial naturitic peptide, calcitonin, CRH, glucagon, growth hormone, GHRH, insulin, PTH, PRL, somatostatin
- Glycoproteins are two amino acid chains with a carbohydrate
  - FSH, LH, TSH, HCG, inhibin
- Monoamines or Biogenic Amines are all made from the amino acid tyrosine except melatonin which is made from tryptophan
  - dopamine, epinephrine, norepinephrine, serotonin, melatonin, T_3, T_4

Transport and Action of Hormones



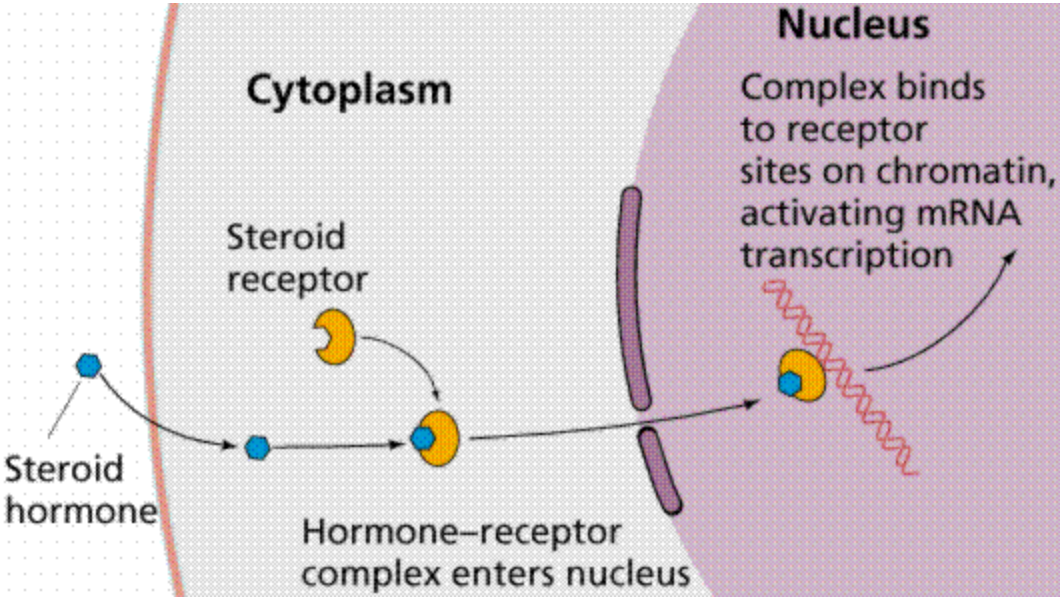
- Hydrophobic hormones (steroids and thyroid hormone) are carried in the blood on carrier proteins to increase their solubility. Free hormone can penetrate plasma membrane and enter the nucleus.
- Hydrophilic hormones (monoamines and peptides, glycoproteins) are soluble in plasma, but can not pass through membranes so they must bind to cell-surface receptors.

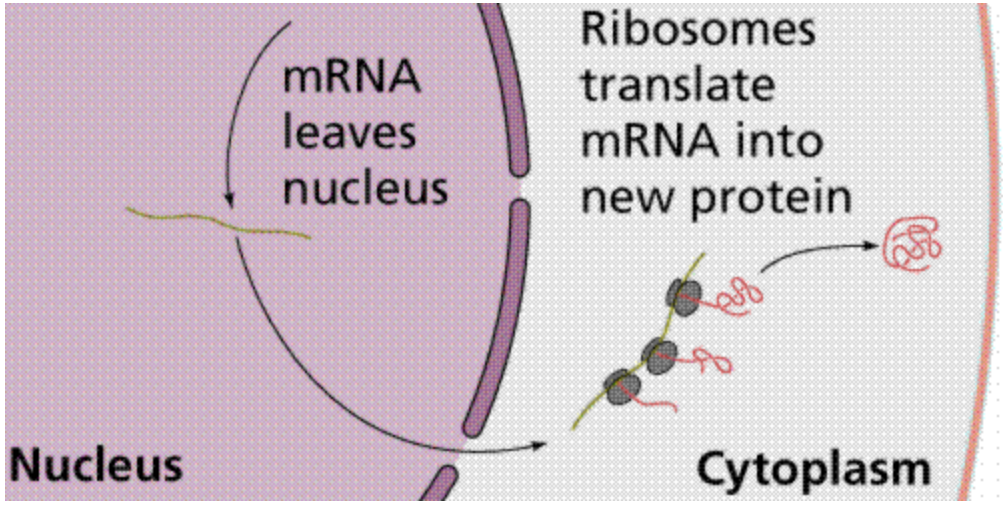
Steroid Hormones are derived from cholesterol and diffuse easily through the plasma membranes of cells.

Once in the cell, the hormone binds to a receptor forming a hormone-receptor complex.

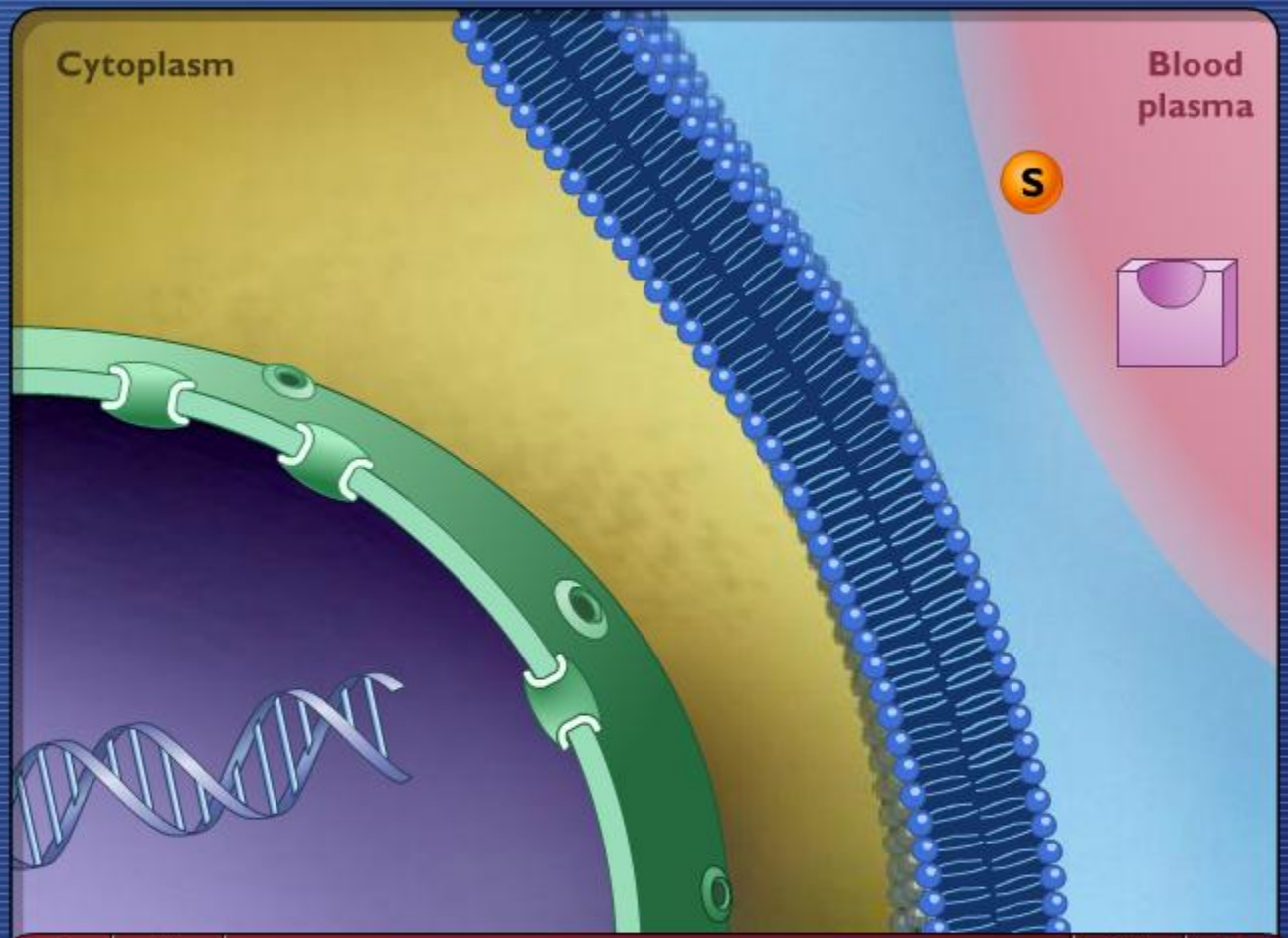
The complex can bind to DNA in the nucleus and either activate or inhibit the genes.

Activation of genes leads to protein synthesis.





Mechanism of Steroid Hormone Action



Play Pause Audio Text

Steroid hormones are not water-soluble. They travel in the blood attached to protein carriers.

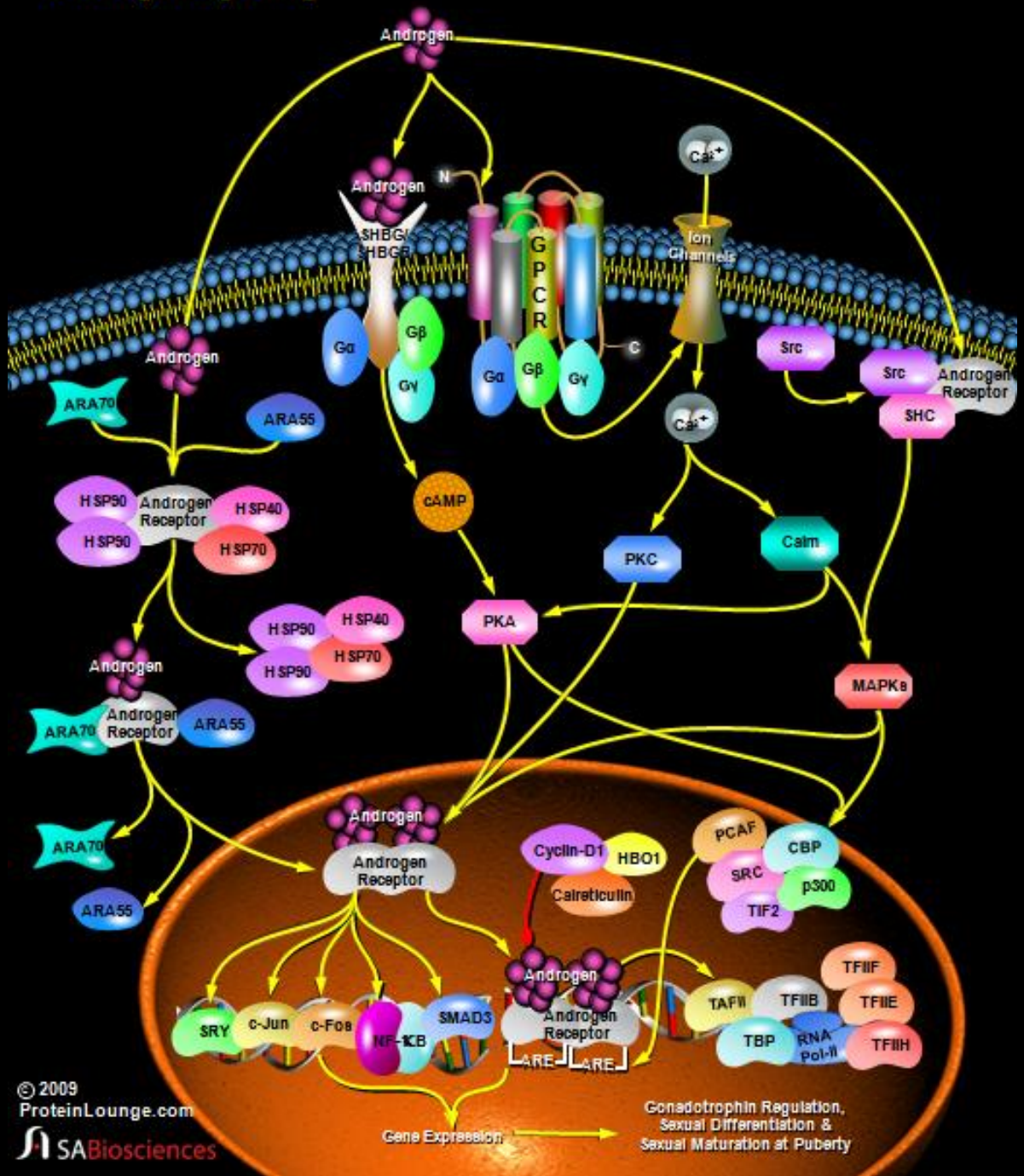
Mechanism of Steroid Hormone Action Animation

http://highered.mcgraw-hill.com/sites/0072437316/student_view0/chapter47/animations.html#

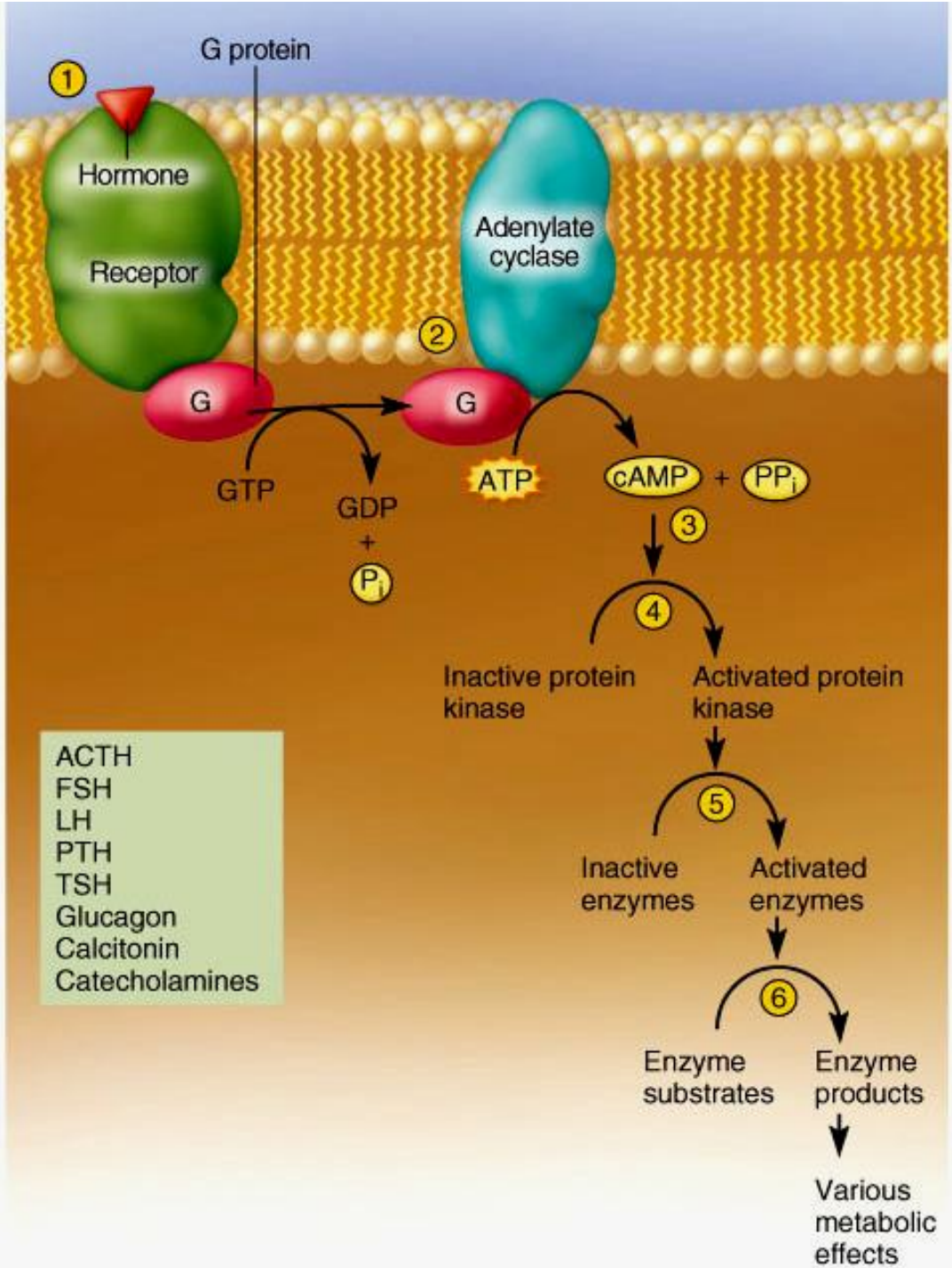
Other Endocrine System Animations

http://nhscience.lonestar.edu/biol/ap1int.htm#endocrine

Androgen Signaling

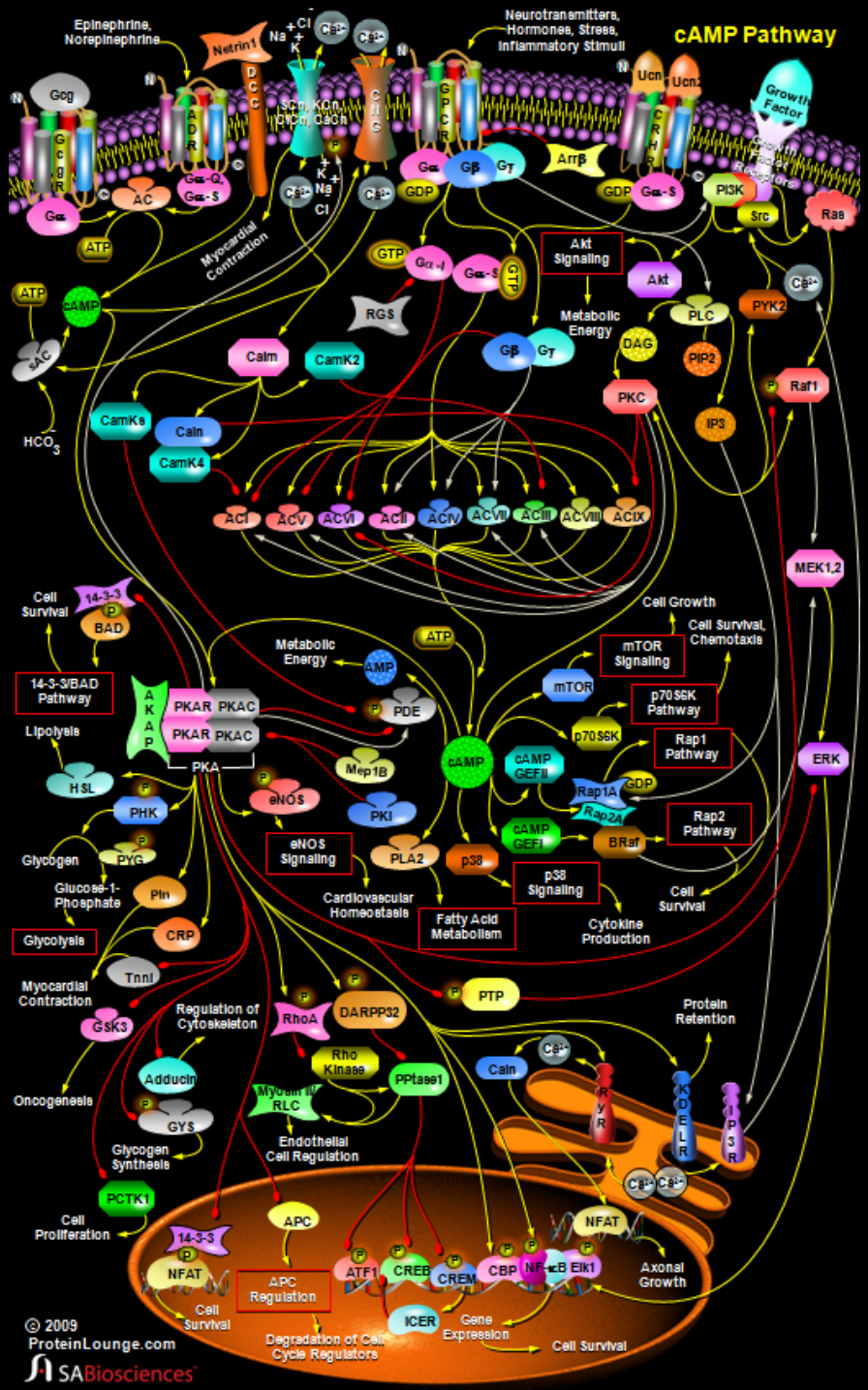


Hydrophilic Hormones using the cAMP Second Messenger



1. Hormone–receptor binding activates a G protein.
2. G protein activates adenylate cyclase.
3. Adenylate cyclase produces cAMP.
4. cAMP activates protein kinases.
5. Protein kinases phosphorylate enzymes. This activates some enzymes and deactivates others.
6. Activated enzymes catalyze metabolic reactions with a wide range of possible effects on the cell.

note: caffeine inhibits breakdown of cAMP


cAMP Pathway
Epinephrine, Norepinephrine
Neurotransmitters, Hormones, Stress, Inflammatory Stimuli
Netrin1
Gcg
Gcg R
Gα
AC
Gα-Q, Gα-S
ATP
cAMP
sAC
HCO3
Myocardial Contraction
Na+ K+ Cl-
Ca2+
Kcn, Kvcn, dscn
CNG
GPCR
Gα
Gβ
Gγ
GDP
GTP
Gα-i
Gα-s
GTP
Arrβ
Ucn1
Ucn2
CRF1
Growth Factor
Receptor Tyrosine Kinase
PI3K
Src
Ras
Akt Signaling
Akt
Metabolic Energy
PLC
DAG
PIP2
PKC
IP3
PYK2
Raf1
RGS
Calm
CamK2
CamKs
Caln
CamK4
ACI
ACV
ACVI
ACII
ACIV
ACVII
ACIII
ACVIII
ACIX
MEK1,2
ERK
Cell Survival
14-3-3
BAD
14-3-3/BAD Pathway
Lipolysis
HSL
PHK
PYG
Glycogen
Glucose-1-Phosphate
Pln
CRP
Glycolysis
Tnnl
Myocardial Contraction
GSK3
Oncogenesis
Adducin
GYS
Glycogen Synthesis
PCTK1
Cell Proliferation
AKAP
PKAR
PKAC
PKA
Metabolic Energy
AMP
PDE
Mep1B
eNOS
PKI
eNOS Signaling
PLA2
Cardiovascular Homeostasis
Fatty Acid Metabolism
p38
p38 Signaling
Cytokine Production
Cell Survival
Cell Growth
Cell Survival, Chemotaxis
mTOR Signaling
mTOR
p70S6K Pathway
p70S6K
Rap1 Pathway
cAMP GEFII
Rap1A
Rap2A
GDP
cAMP GEFI
BRaf
Rap2 Pathway
RhoA
DARPP32
Rho Kinase
PPtase1
Regulation of Cytoskeleton
Myosin II RLC
Endothelial Cell Regulation
PTP
Protein Retention
Caln
RyR
KDELR
IP3R
APC
APC Regulation
Degradation of Cell Cycle Regulators
14-3-3
NFAT
Cell Survival
ATF1
CREB
CREM
CBP
NF-κB
Elk1
ICER
Gene Expression
Cell Survival
Axonal Growth
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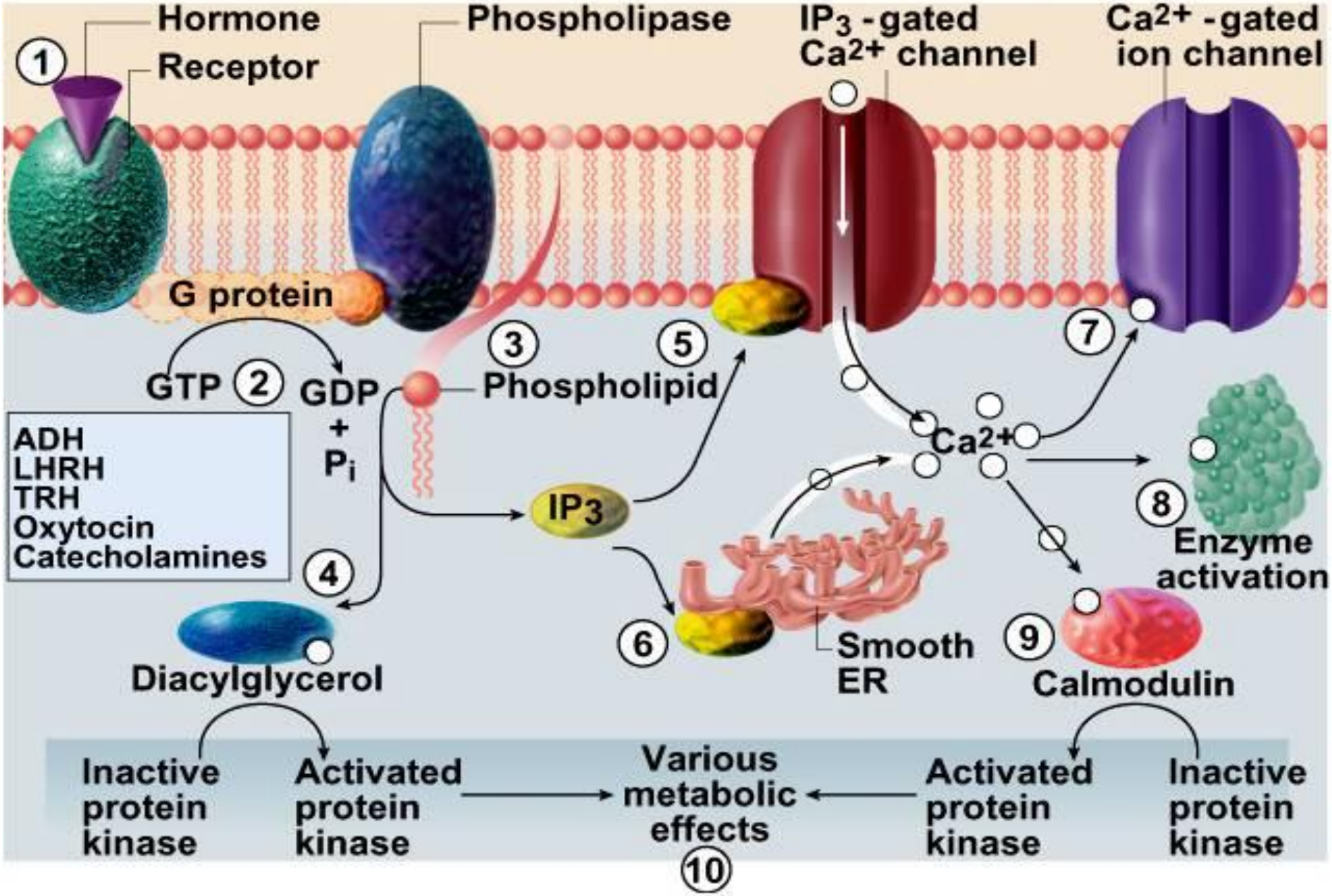
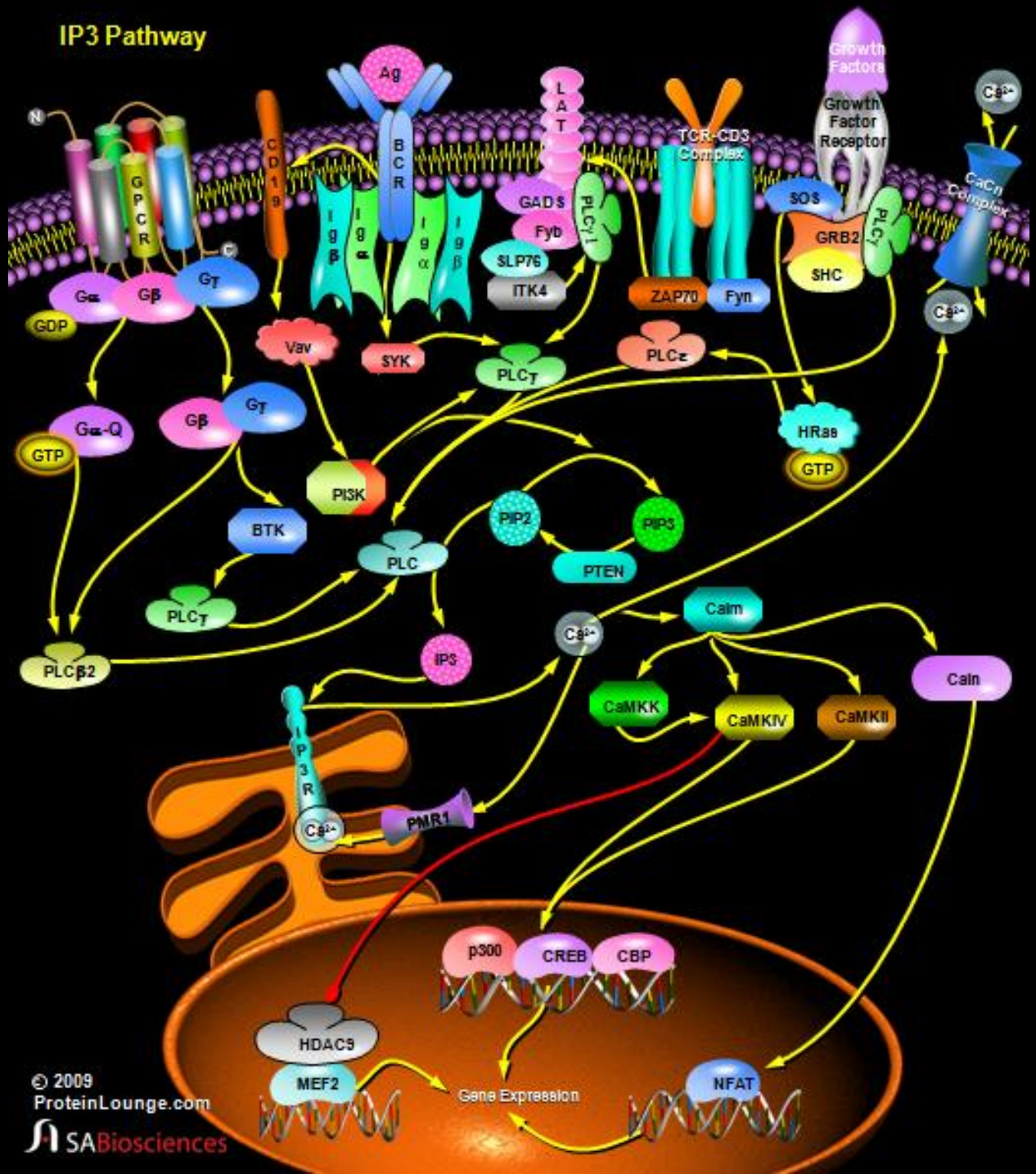


Hydrophilic hormones may also work through a phospholipase-mediated second messenger system.


IP3 Pathway
Ag
BCR
Igβ
Igα
Igα
Igβ
CD19
LAT
GADS
Fyb
SLP76
ITK4
PLCγ1
TCR-CD3 Complex
ZAP70
Fyn
Growth Factors
Growth Factor Receptor
SOS
GRB2
SHC
PLCγ1
CaCn Complex
Ca2+
GPCR
N
C
Gα
Gβ
Gγ
GDP
Vav
SYK
PLCγ
PLCε
HRas
GTP
Gα-Q
GTP
Gβ
Gγ
PI3K
BTK
PIP2
PIP3
PTEN
PLC
PLCγ
PLCβ2
IP3
Ca2+
Calm
Caln
CaMKK
CaMKIV
CaMKII
IP3R
Ca2+
PMR1
p300
CREB
CBP
HDAC5
MEF2
Gene Expression
NFAT
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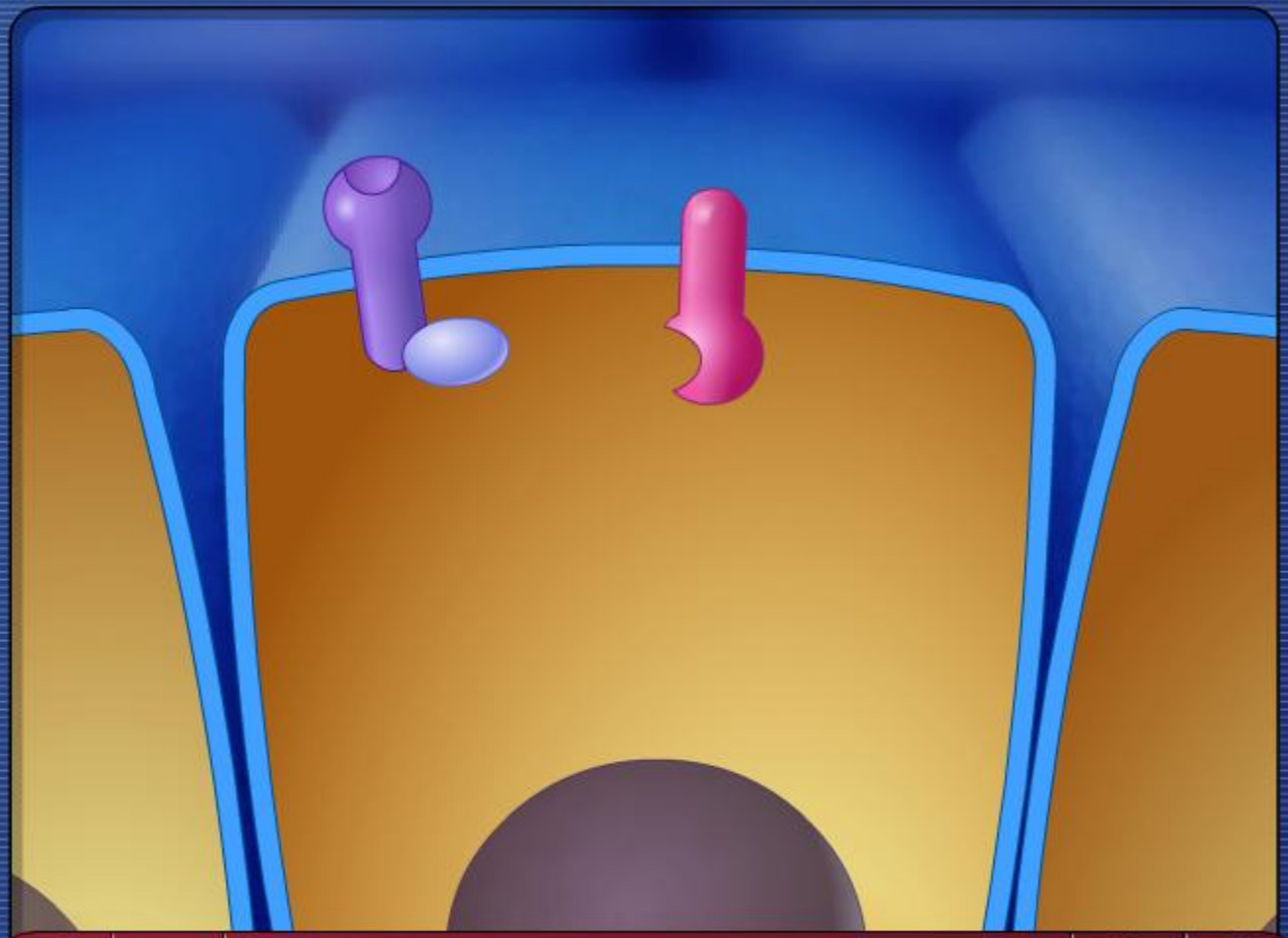
Second Messengers
The cAMP & Ca^{++} Pathways



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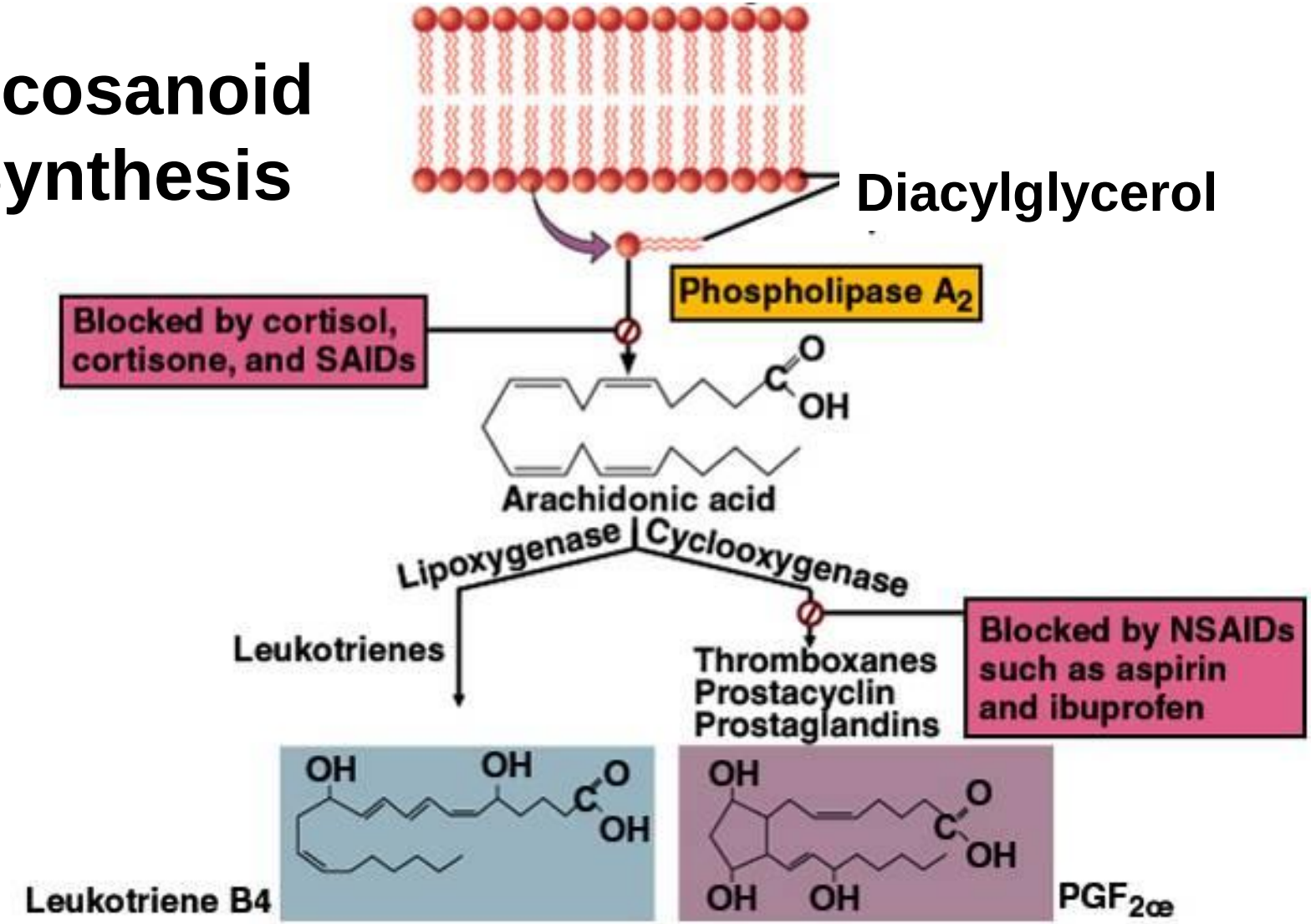
When a signal molecule such as epinephrine binds to a cell surface receptor protein, it activates a G protein on the inside of the cell.

Eicosanoids

- Diacylglycerol → Arachidonic Acid → Eicosanoids
- Diacylglycerol is converted into Arachidonic Acid by a phospholipase enzyme and this process can be inhibited by steroidal anti-inflamitants like cortisol and corticosterone
- Arachidonic acid is converted into various eicosanoids by 2 enzymes:
  - **lipoxygenase** converts arachidonic acid into **leukotrienes** that mediate allergic and inflammatory reactions.
  - **cyclooxygenase** converts arachidonic acid into prostacyclins, thromboxanes and prostaglandins and can be inhibited by NSAIDs:
    - **prostacyclins**: produced by blood vessel walls, inhibits blood clotting and vasoconstriction
    - **thromboxanes**: produced by blood platelets after injury, they override prostacyclin and stimulate vasoconstriction and clotting
    - **prostaglandins**: diverse group including:
      - PGE's: relaxes smooth muscle in bladder, intestines, bronchioles, uterus and stimulates contraction of blood vessels
      - PGF's: opposite effects

Eicosanoid Synthesis

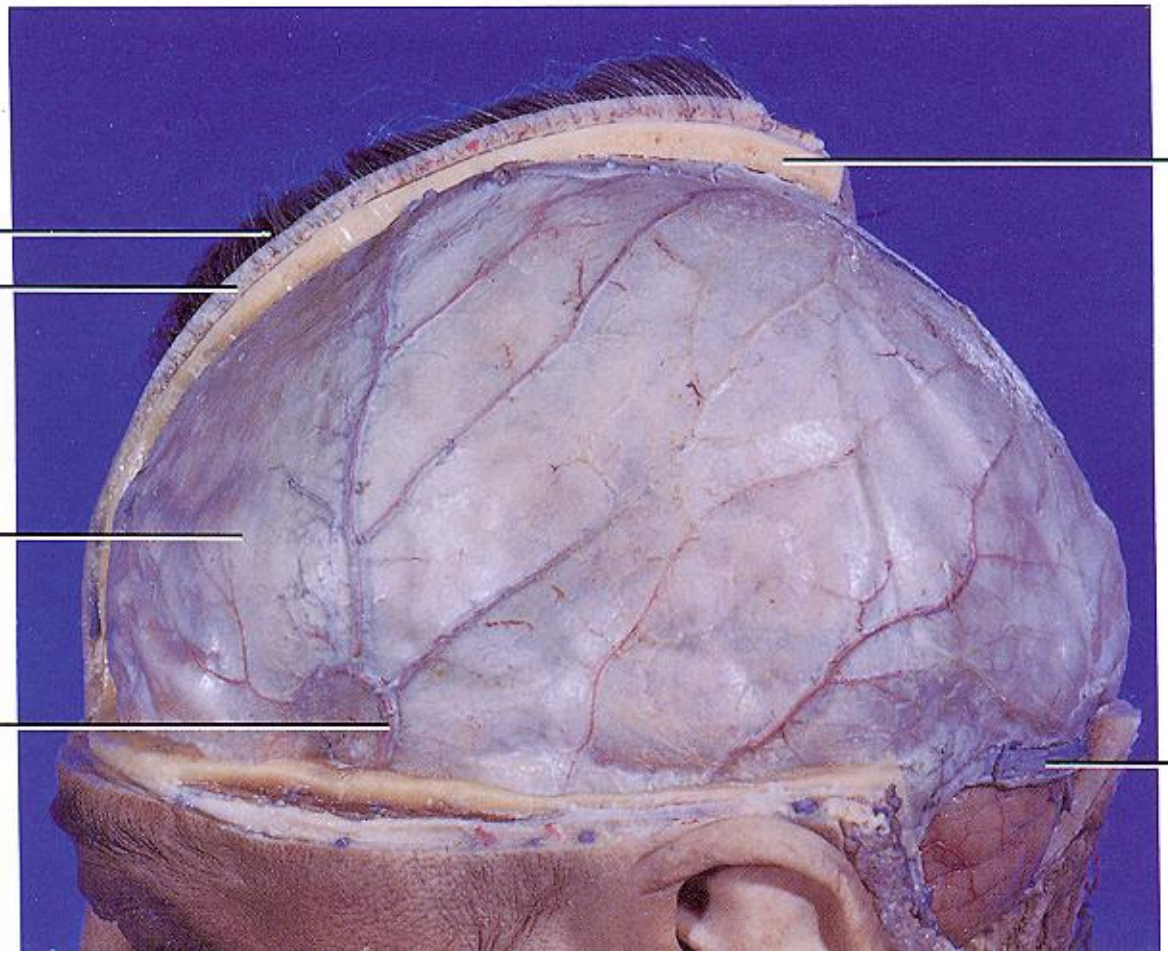


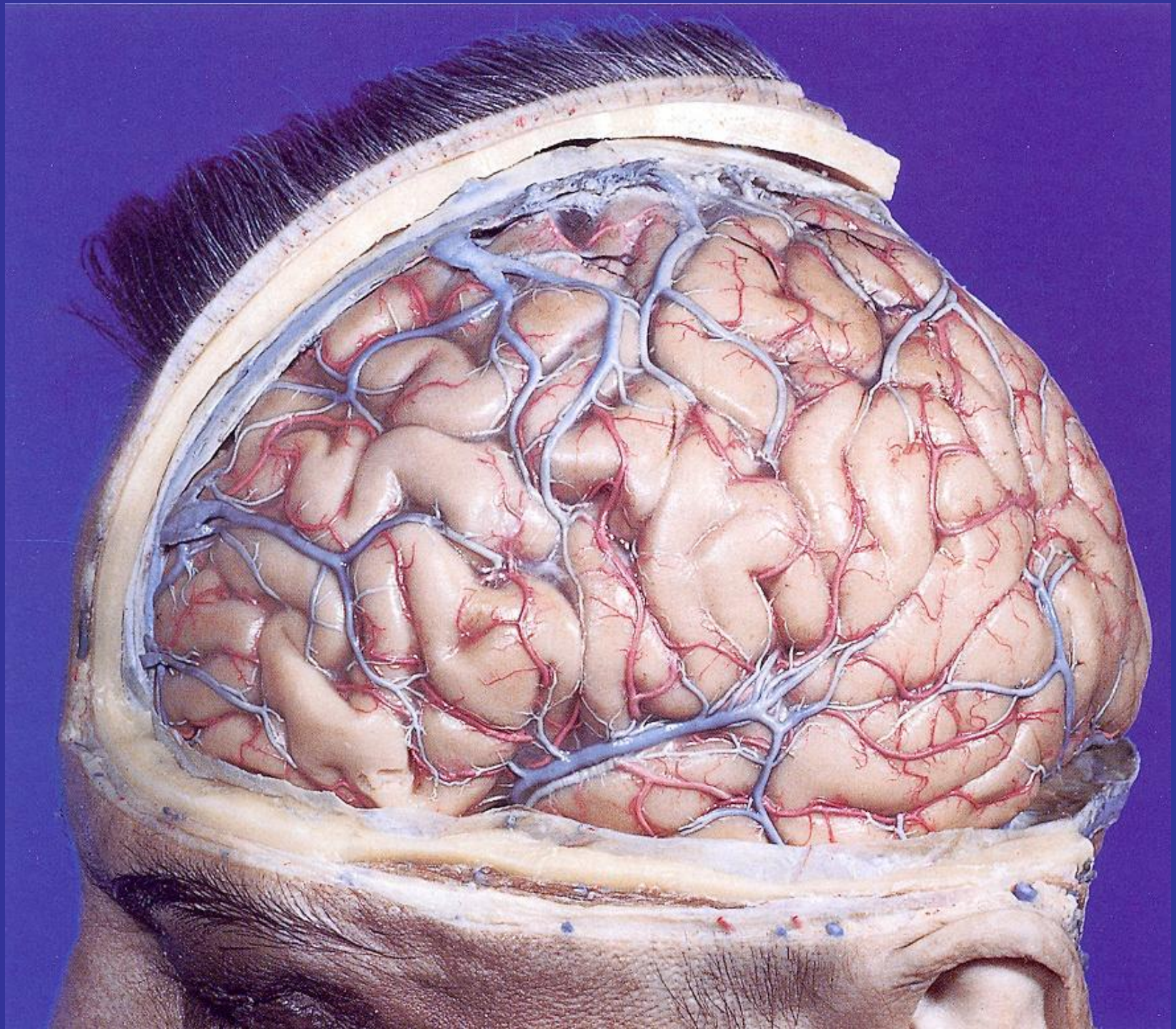
NSAIDs = non-steroidal anti-inflammatory drugs (aspirin, ibuprofen, naproxen, indomethacin) are also called COX inhibitors since they inhibit **c**yclo**ox**ygenase

SAIDs = steroidal anti-inflammatory drugs like cortisol, cortisone.

Eicosanoids and Headaches

- The vascular theory of headaches states that the constriction of peripheral arteries and the dilation of cerebral blood vessels lead to a headache. The vasoconstiction leads to a loss of cerebral oxygen in the blood, therefore, the compensatory mechanism is vasodilation. The dilation and constriction of vessels is sensed as pain.


Parietal bone
Hair
Dermis
Dura mater
Middle meningeal artery
Transverse sinus



Endocrine Functions of Other Organs

- Heart produces atrial natriuretic peptide regulates blood pressure
- Liver
  - source of IGF that works with GH
  - secretes about 15% of erythropoietin
  - secretes angiotensinogen (a prohormone involved in blood pressure regulation)
- Kidneys produce 85% of erythropoietin which stimulates bone marrow to produce RBC's
- Stomach and Small Intestines produce 10 enteric hormones that coordinate digestive motility and secretion
- Placenta secretes estrogen, progesterone and other hormones that regulate pregnancy, stimulate development of fetus and mammary glands