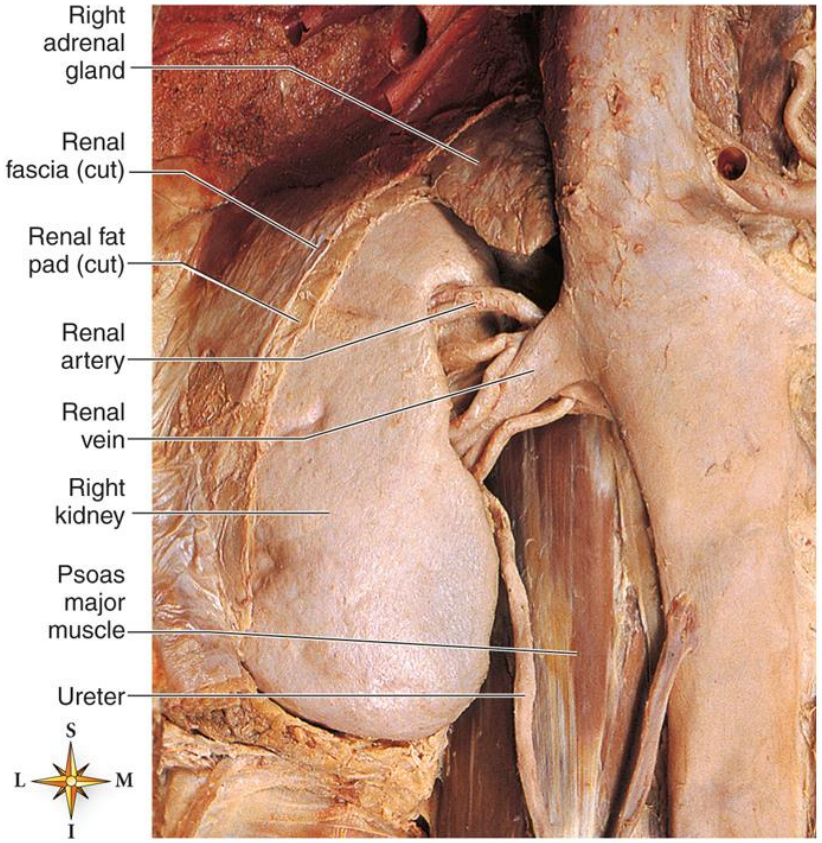
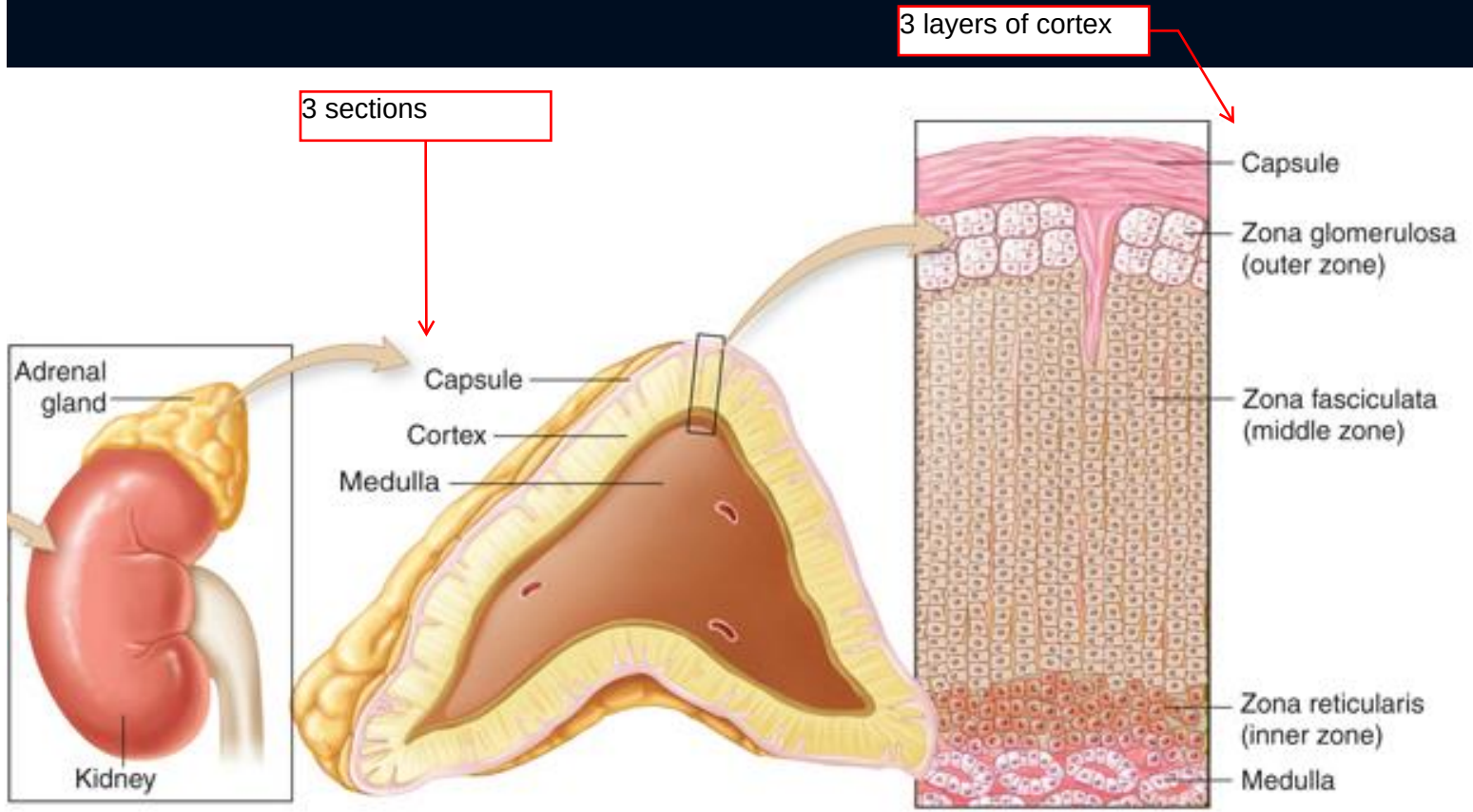
Endocrine Part 2

ADRENAL GLAND

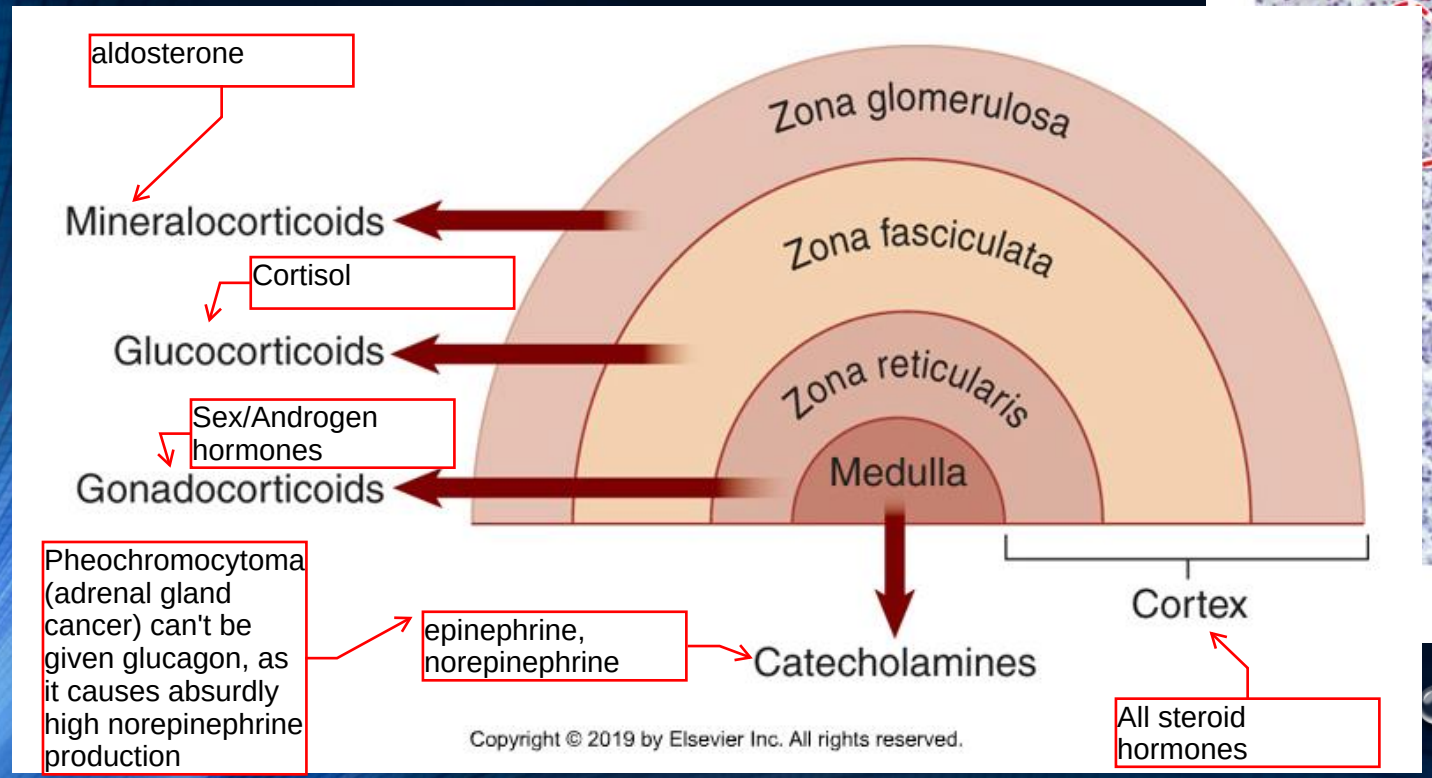
Adrenal Gland

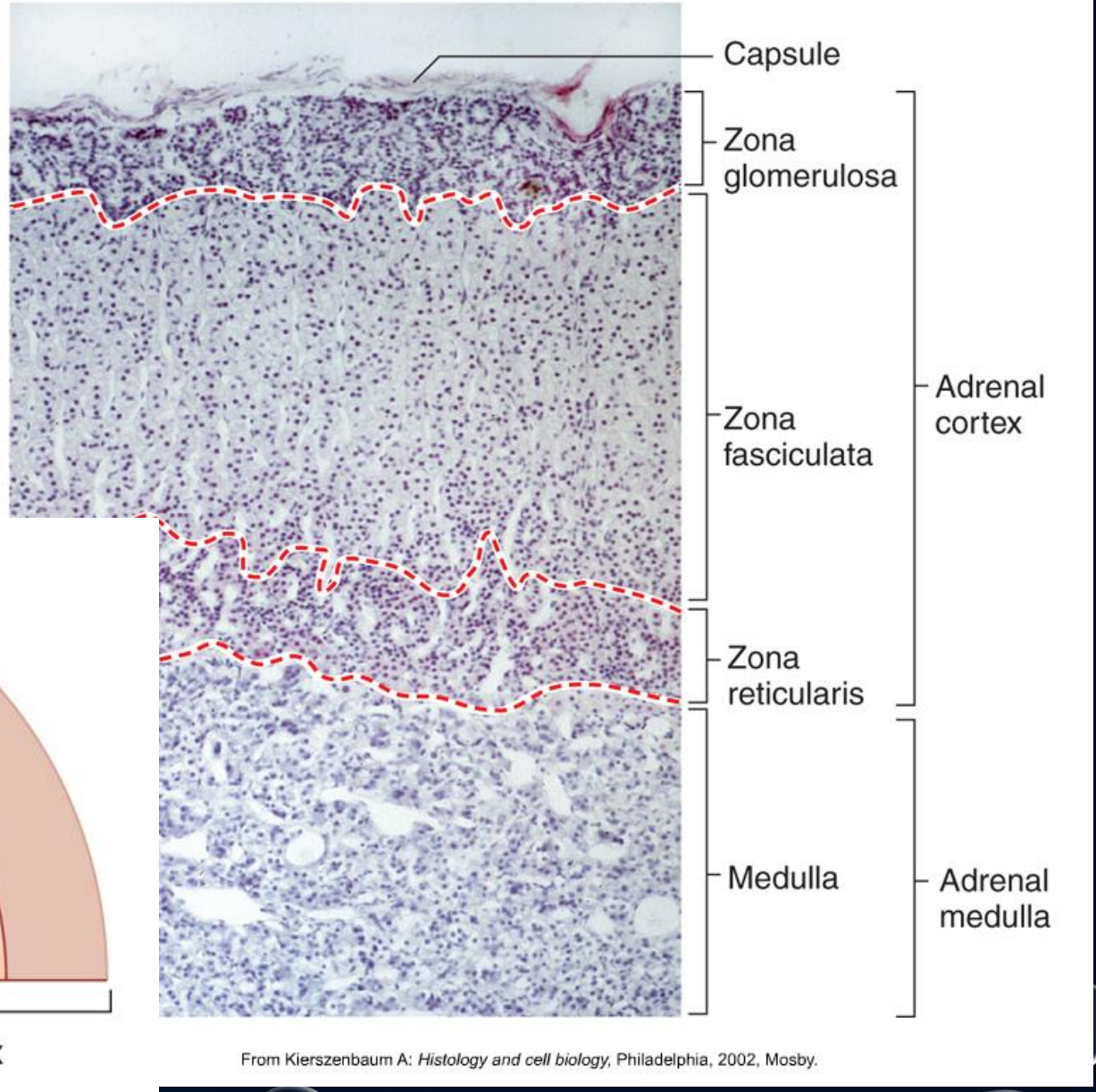


From Gosling J, Harris P, Whitmore I, Willan P: *Human anatomy,* ed 4, Philadelphia, 2002, Mosby.



Cross section of adrenal gland





From Kierszenbaum A: *Histology and cell biology*, Philadelphia, 2002, Mosby.

Mineralocorticoids (ie Aldosterone)

- What does it do?
  - Helps to regulate ECF volume by increasing reabsorption of Na+ and H2O in nephron
  - Regulates ECF K+ levels by increasing secretion of K+ in nephron
- When is it released?
  - When Angiotensin II levels increase in blood
  - When ECF K+ rises above its normal levels
  - When ACTH levels or ANP levels increase in Blood
- How does it work?
  - Epithelial Na+ channels allow Na+ to enter from lumen of nephron into cell
  - Epithelial K+ channels allow K+ to enter lumen from cell
  - Gradients maintained by Na+ / K+ pump
  - H20 follows the gradient

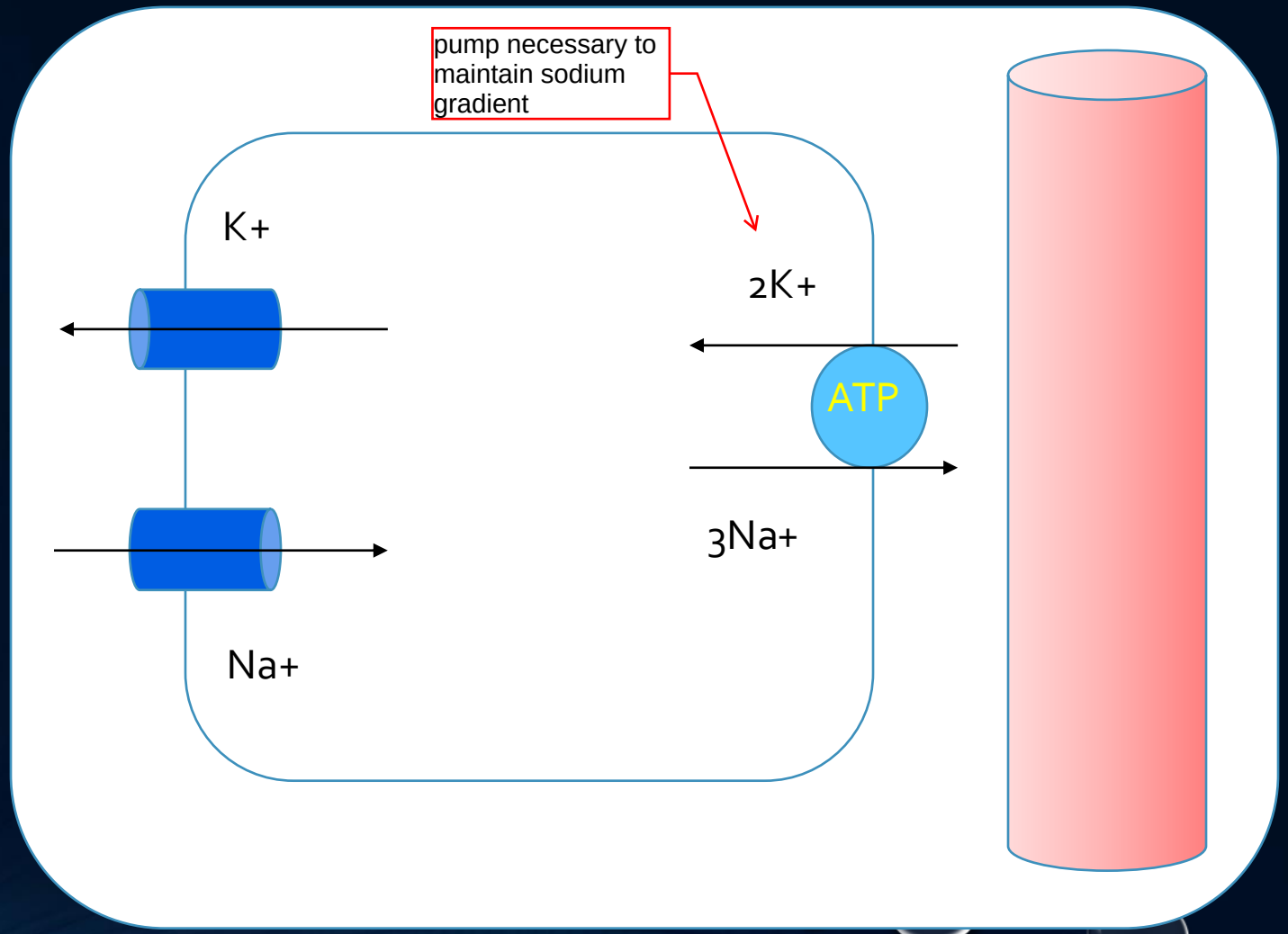
While ADH increases aquaporins, Aldosterone increases sodium channels, taking it and water out of urine.

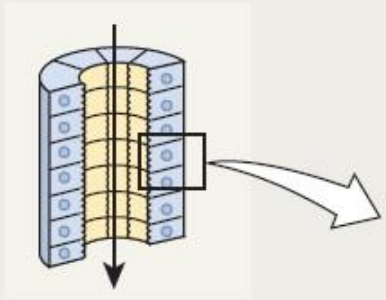
RAAS
Renin Angiotensin Aldosterone System also releases aldosterone. Renin enzyme secreted by justaglomerular cells in response to low BP. These cells are at teh kidney gloemerulus, with plenty of blood to check pressure via neghbouring baroreceptors.

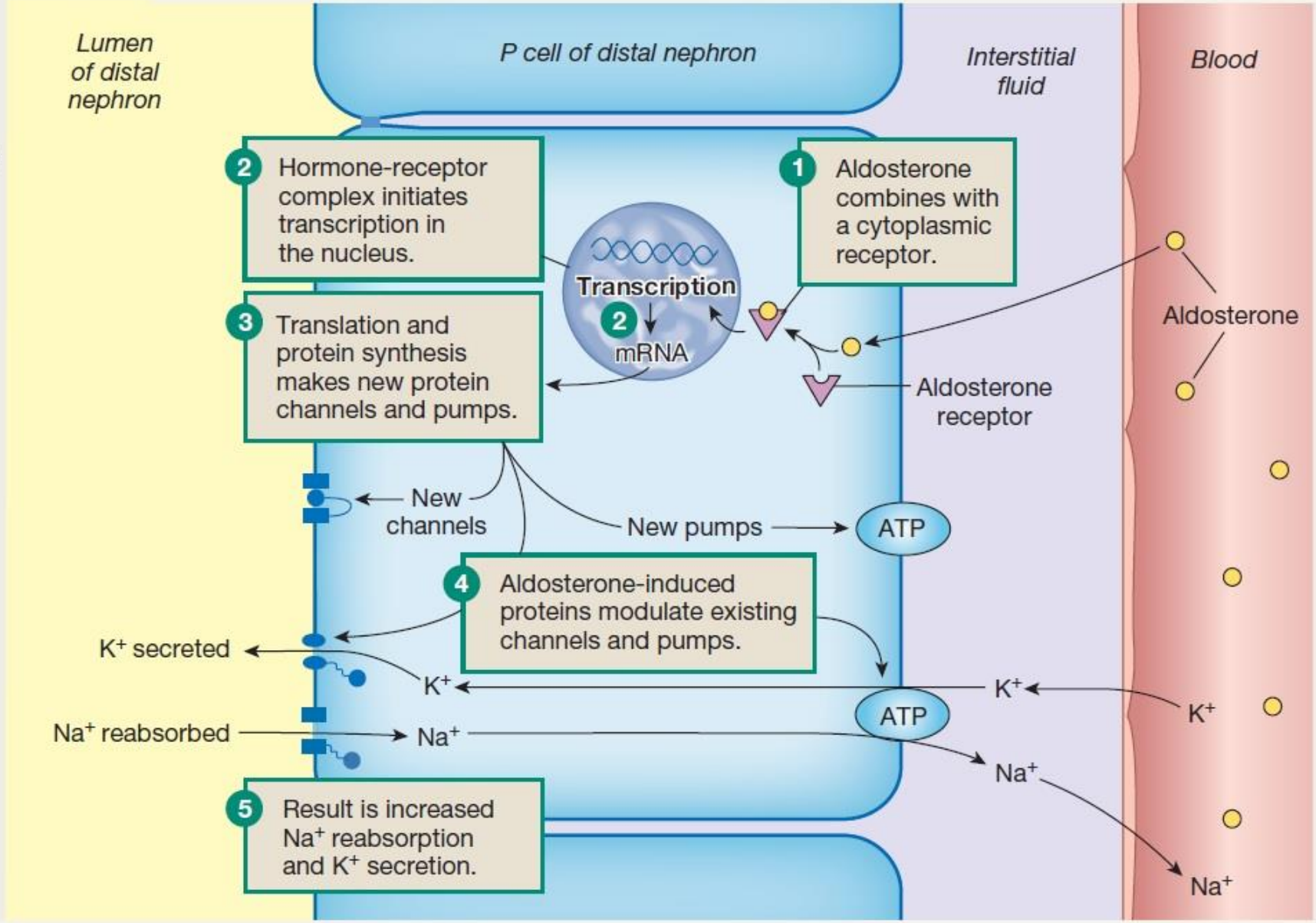
ACE inhibitors are common BP medications , as are Angiotensin receptor blocker. The former prevents angiotensin production, the latter prevents it from binding to receptors.

Renin converts Angioteninogen into angiotensin 1, circulating in the blood. In the lungs, angiotensin converting enzyme (ACE) converts it to angiotensin 2, which regulates BP via vasconstriction and aldosterone release

Effects of Aldosterone on Nephron Cells





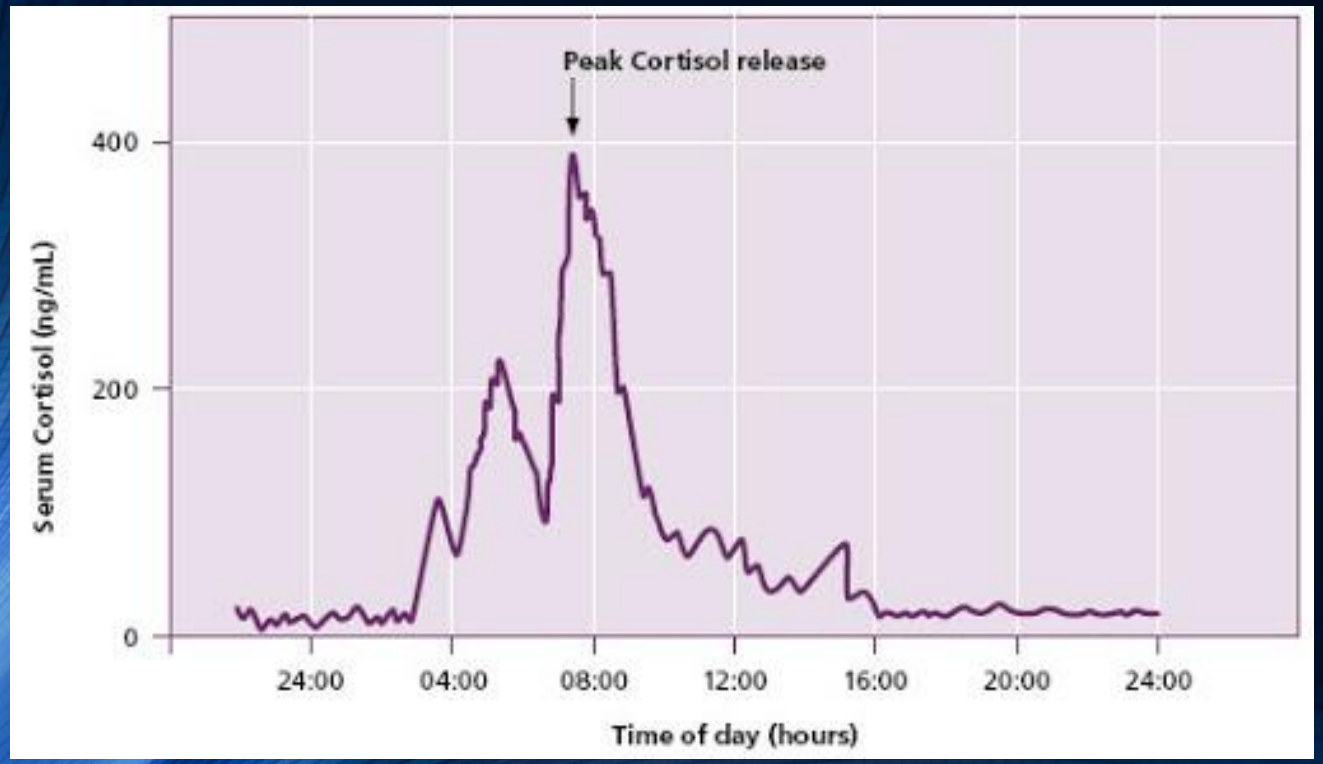

Lumen of distal nephron
P cell of distal nephron
Interstitial fluid
Blood
2 Hormone-receptor complex initiates transcription in the nucleus.
1 Aldosterone combines with a cytoplasmic receptor.
Transcription
2
mRNA
3 Translation and protein synthesis makes new protein channels and pumps.
Aldosterone
Aldosterone receptor
New channels
New pumps
ATP
4 Aldosterone-induced proteins modulate existing channels and pumps.
K+ secreted
K+
K+
K+
ATP
Na+ reabsorbed
Na+
Na+
Na+
5 Result is increased Na+ reabsorption and K+ secretion.

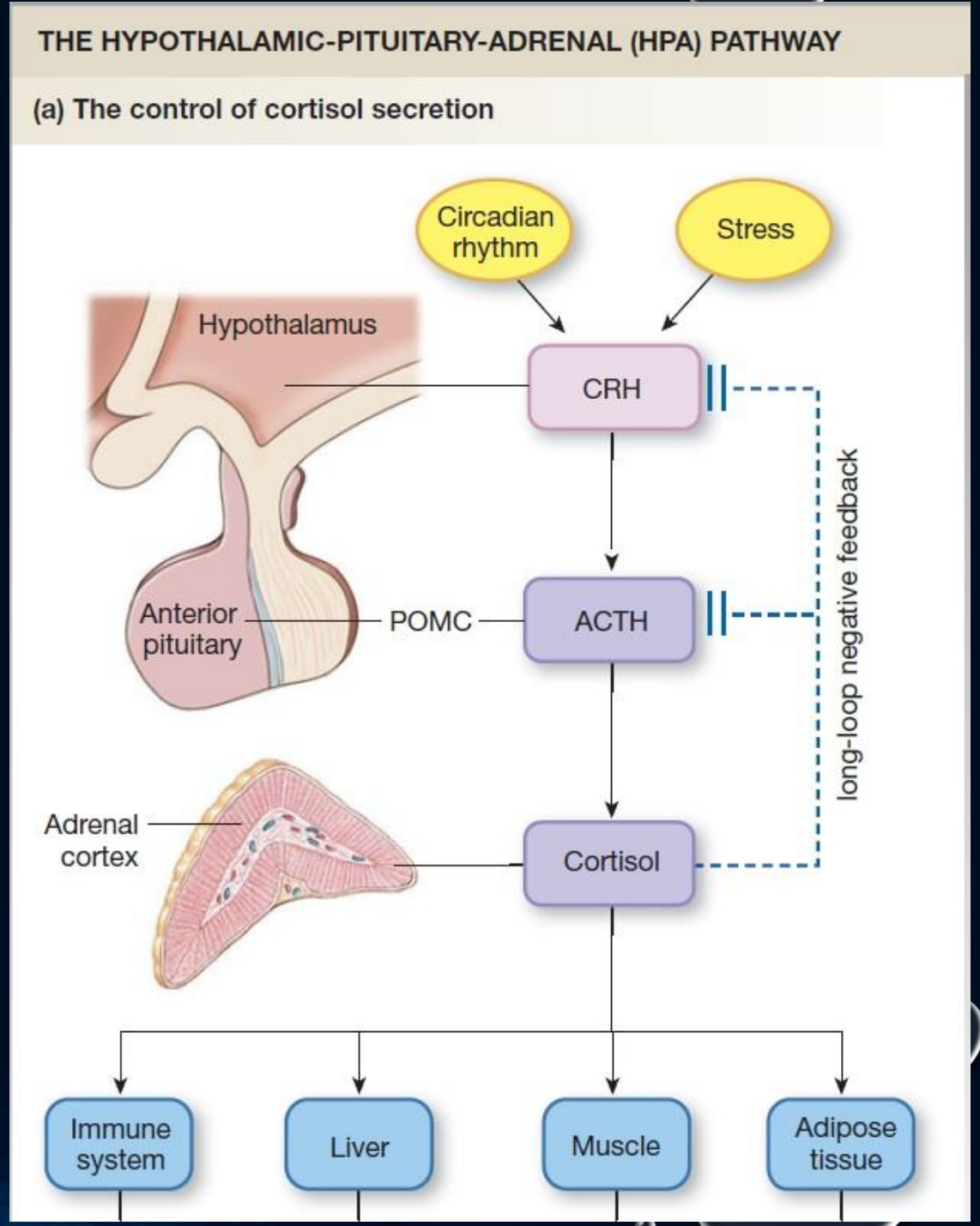
Glucocorticoids – Cortisol

- What does it do?
  - Increases blood glucose, AA and FA by altering metabolism of fats and proteins
  - Gluconeogenesis ← RELEVANT
  - Vasoconstriction (increases BP)
  - Anti-inflammatory
- When is it released?
  - As part of stress response
  - Regular release related to circadian rhythms and negative feedback mechanisms

Regulation Mechanisms

Short Loop Feedback
Long Loop Feedback
Circadian





Cushing's Disease / Syndrome

Disease – due to body producing too much cortisol, possibly due to a tumour

Syndrome – due to overuse of cortisol / an iatrogenic cause

Clinical Manifestations

Fat deposits – buffalo hump, moon face,

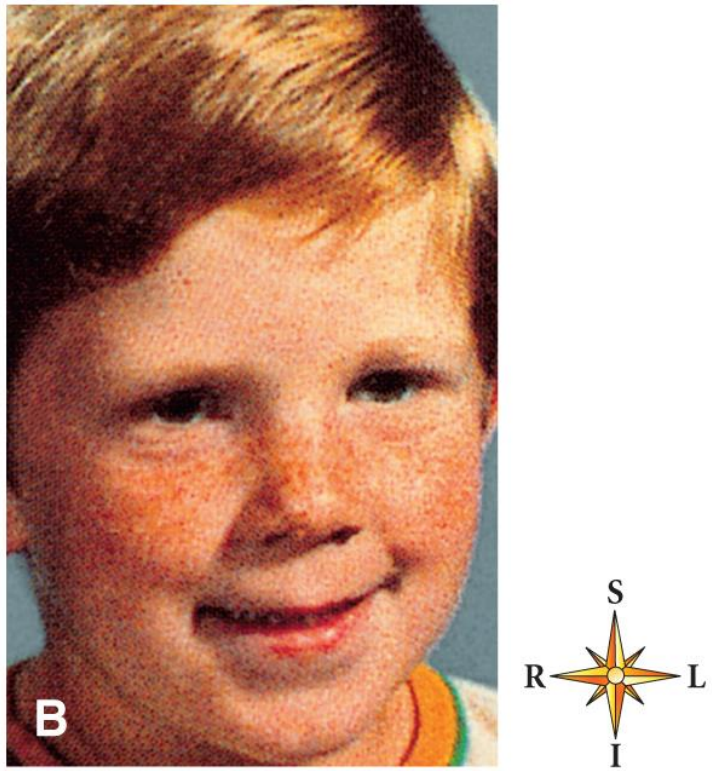
Steroid diabetes – cortisol increases blood glucose

Bone and muscle wasting

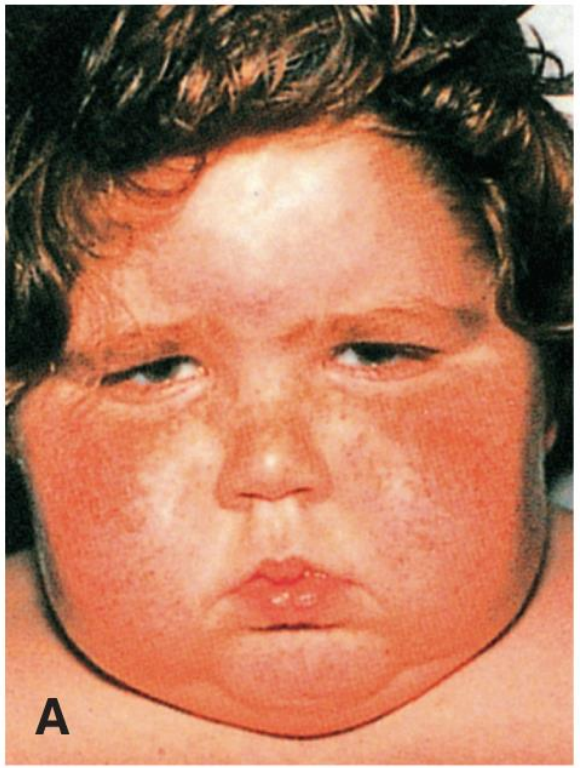
Increased water and Na+ retention – increased BP, EDEMA

Inability to manage infections

Cushing's syndrome



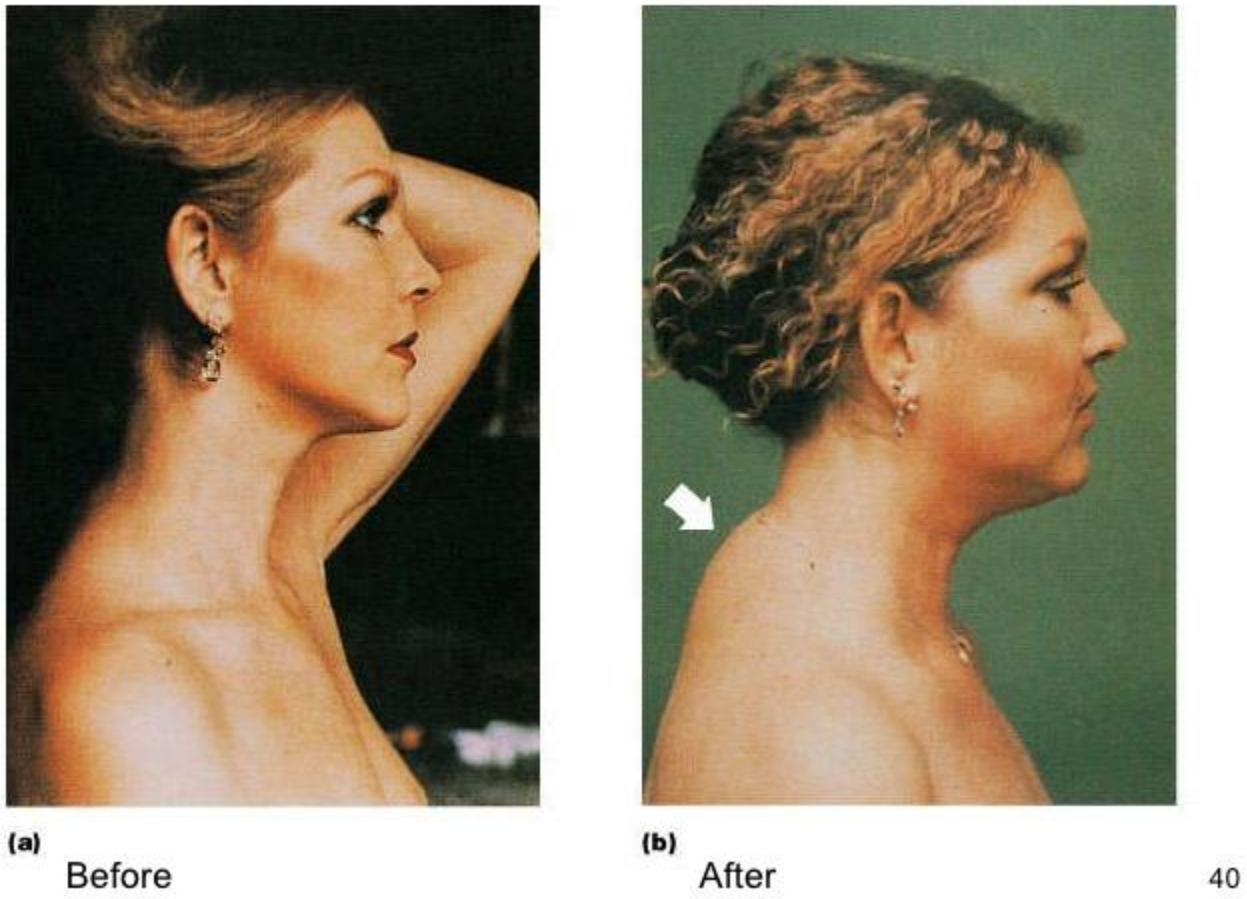
Courtesy Gower Medical Publishers.



Courtesy Gower Medical Publishers.

Cushing's syndrome

Before and after onset of Cushing's disease



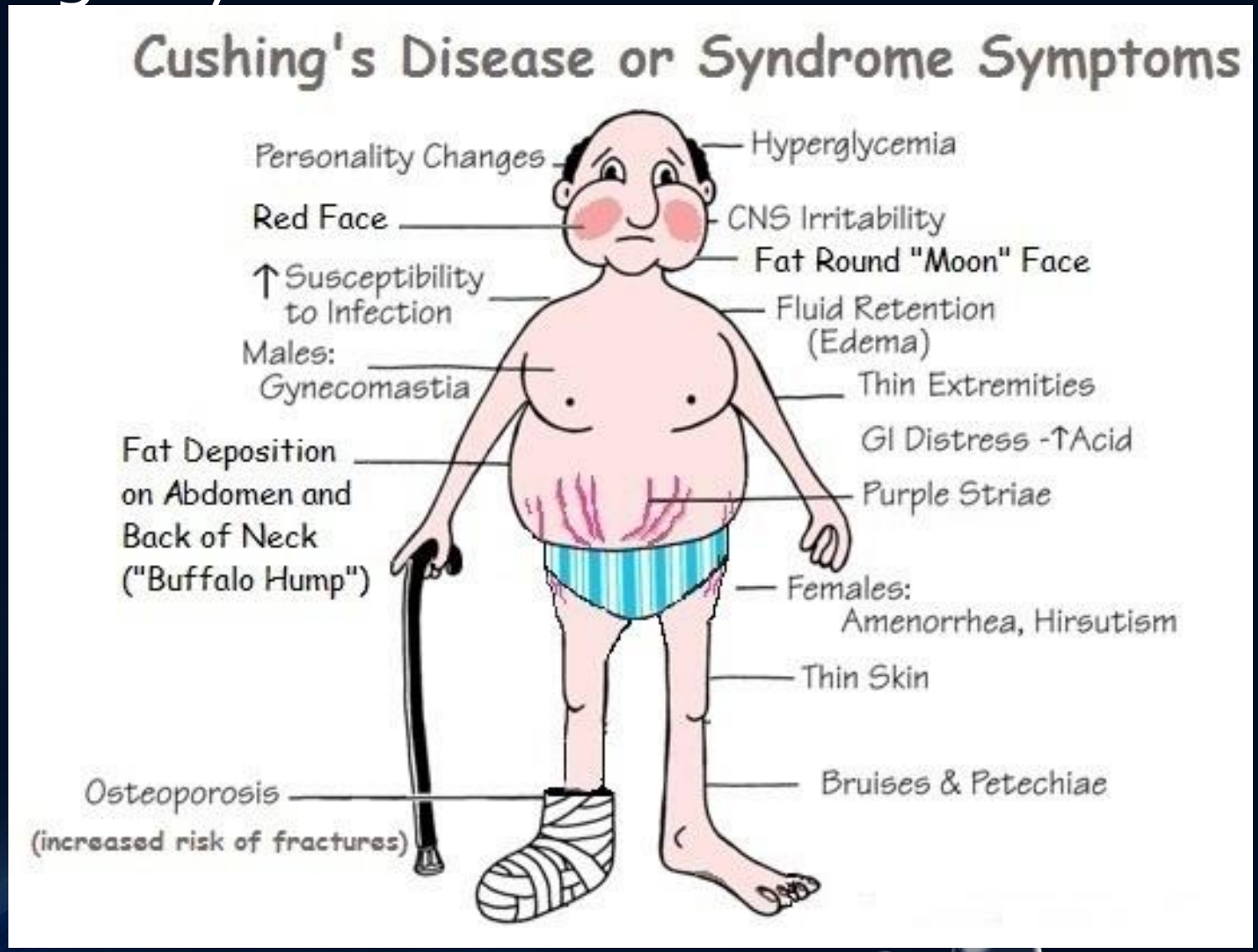
(a) Before

(b) After

40

https://www.google.ca/url?sa=i&source=images&cd=&cad=rja&uact=8&ved=2ahUKEwje5dTc903fAhVEnuAKHUm1ByUQjRx6BAgBEAU&url=http%3A%2F%2Fbulk.medicalcertificate.me%2Fcjc-1295%2F02190-moon-face-steroids.html&psig=AOvVawogA7X00ShwMaTMk418KHWB&ust=1544279088928398

Cushing's syndrome



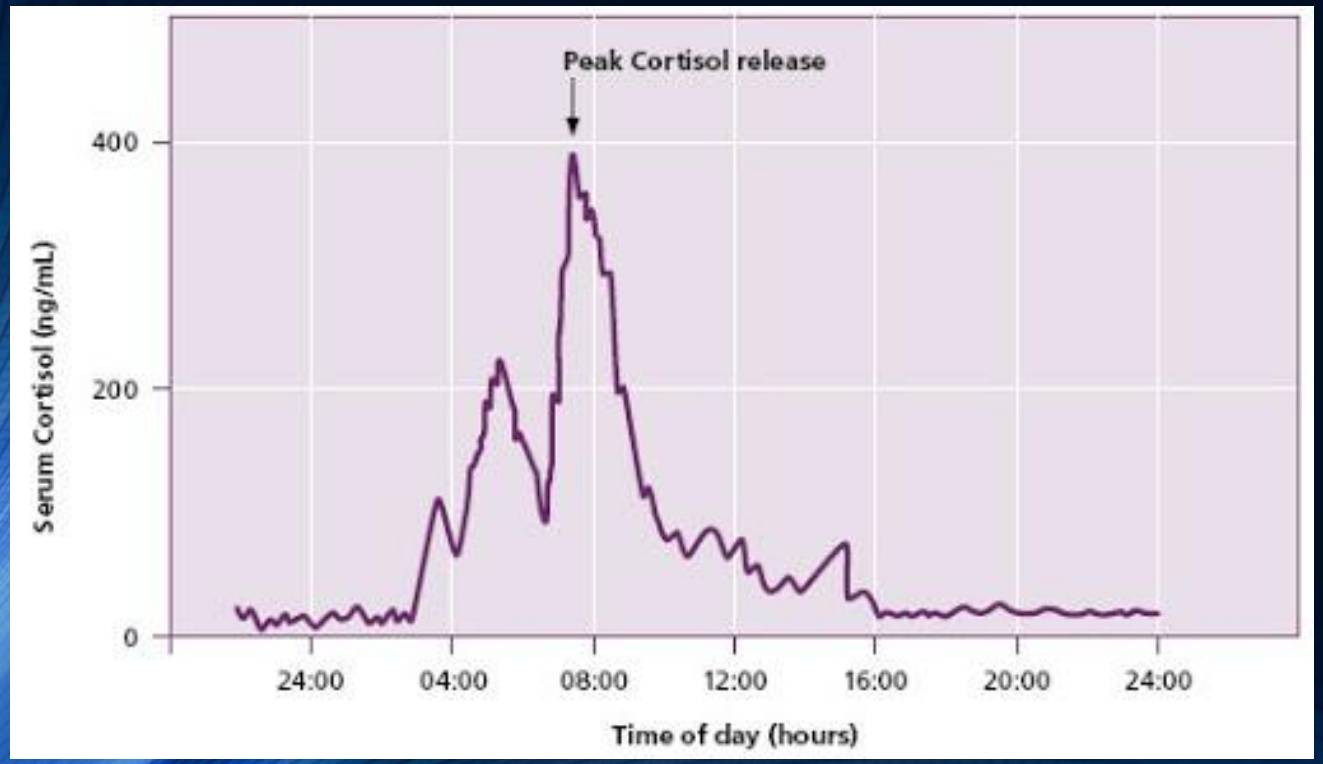
https://www.google.ca/url?sa=i&source=images&cd=&cad=rja&uact=8&ved=2ahUKEwjZqdX-903fAhXhTN8KHfVKAJIQjRx6BAgBEAU&url=https%3A%2F%2Fwww.quora.com%2FWhat-is-Cushing-syndrome&psig=AOvVaw0gA7X00ShwMaTMk418KHWB&ust=1544279088928398

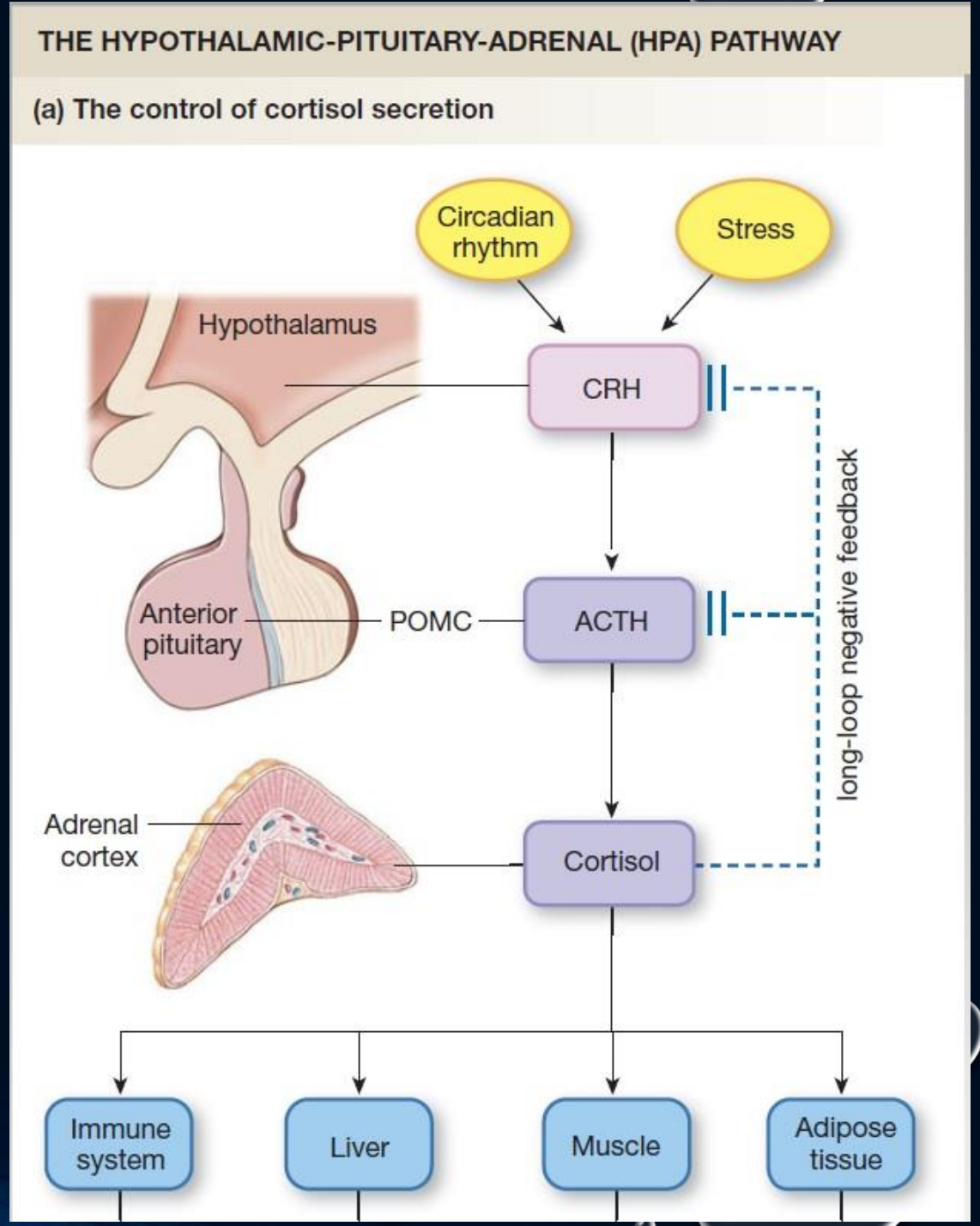
Hyposecretion of Adrenal Cortex – Addison's Disease

- Affects cortisol and aldosterone production
- Loss of Na+ & H20 – dehydration and hypotension (lack of aldosterone)
- Increased ECF K+ (lack of aldosterone)
- Decreased blood glucose (lack of cortisol)
- Bronzing of the skin
  - ACTH causes increased production of melanin
    - Decreased cortisol leads to increase ACTH
    - ACTH derived from pro opio melanocortin (POMC)
    - Alpha Melanocyte Stimulating Hormone (alpha MSH) derived from POMC
    - Alpha MSH increases melanin production and expression!

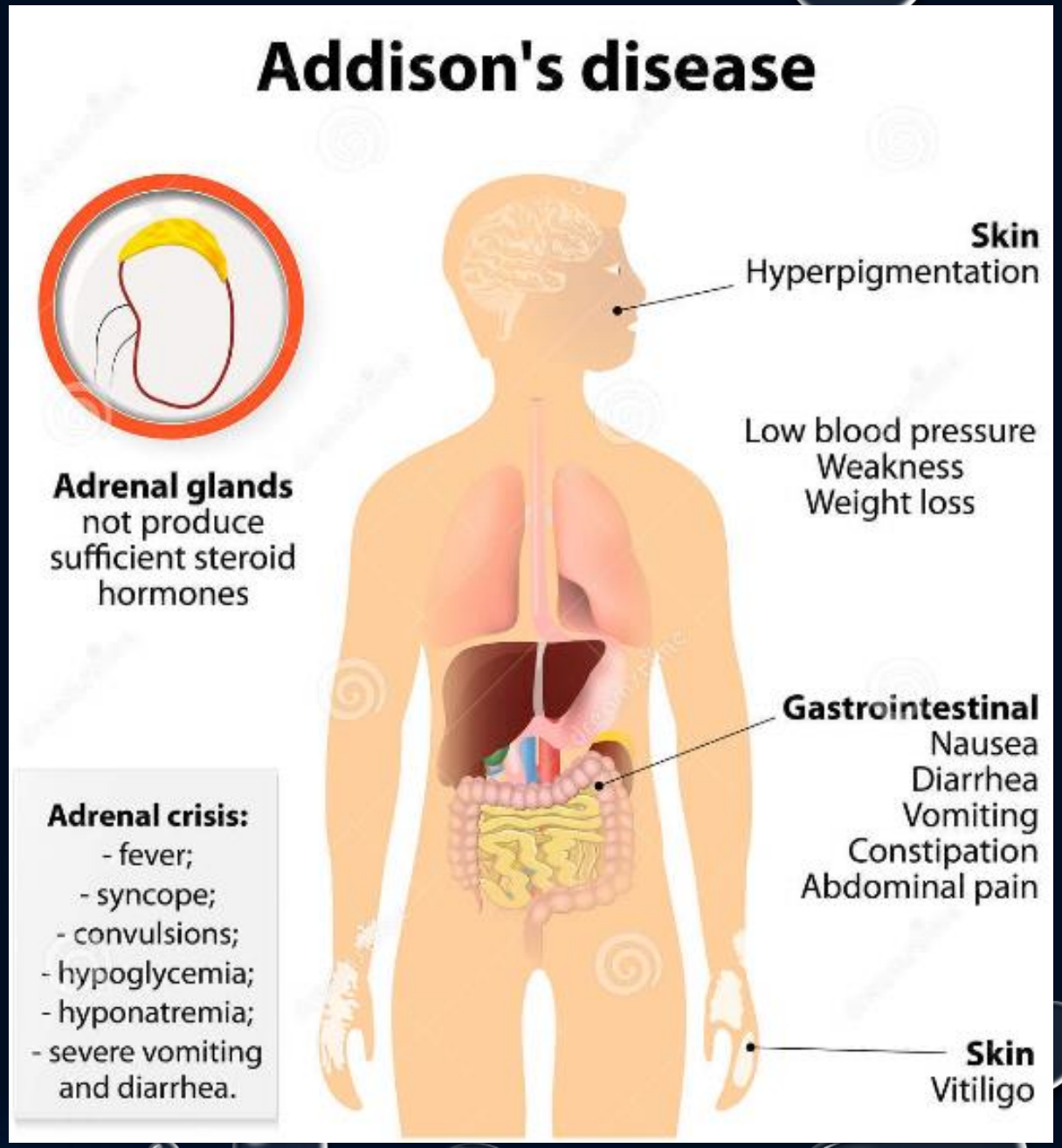
Regulation Mechanisms

Short Loop Feedback
Long Loop Feedback





Addison’s disease



https://healedbybacon.files.wordpress.com/2015/11/addisons.png?w=607&h=661

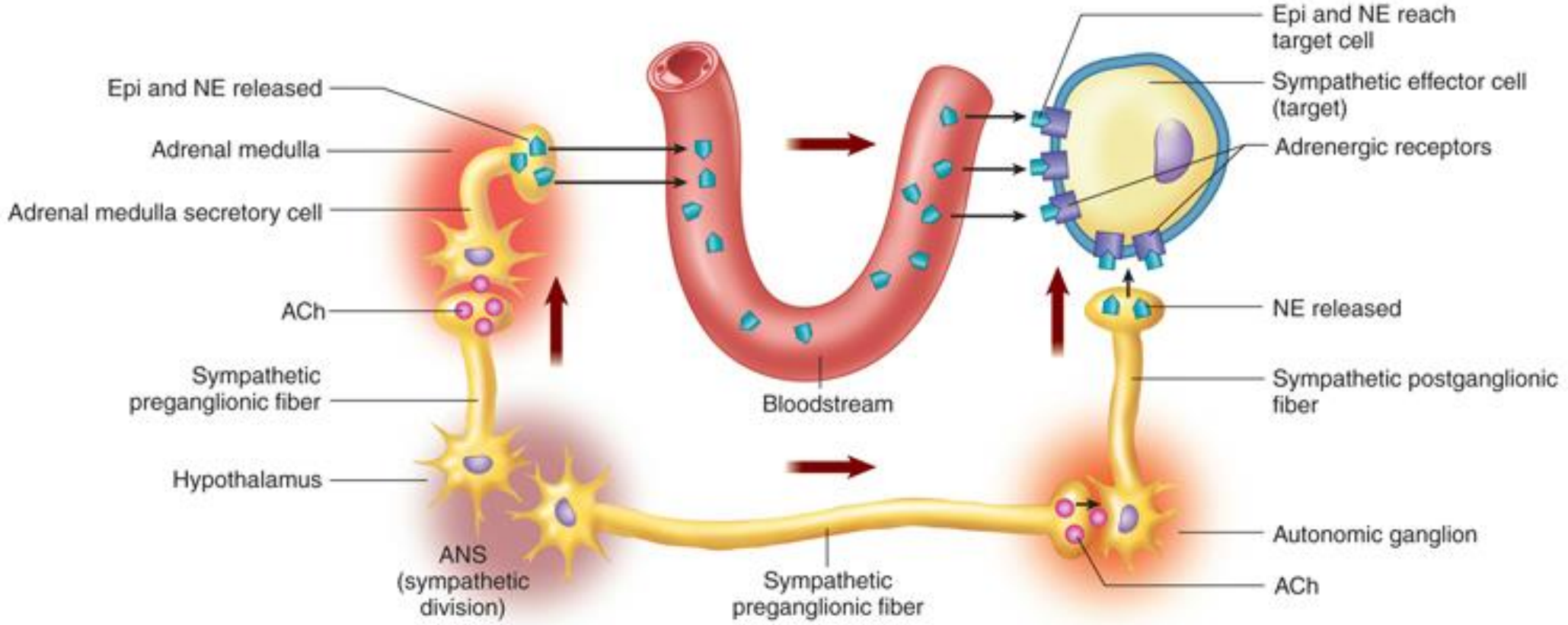
Adrenal Medulla

- Modified post-ganglionic sympathetic neurons called medullary chromaffin cells that are surrounded by lots of blood vessels
- Chromaffin cells produce NE (20%) and E (80%) – catecholamines
- Promotes fight / flight responses – same as activation of SNS
- Effects
  - Increase Heart rate & blood pressure
  - Pupils dilate
  - GI tract becomes less active
  - Skeletal muscles become more active
  - Increase Respiratory rate
  - Increase blood glucose
  - Increase CNS alertness
  - Increase sweating

General Adaptation Syndrome

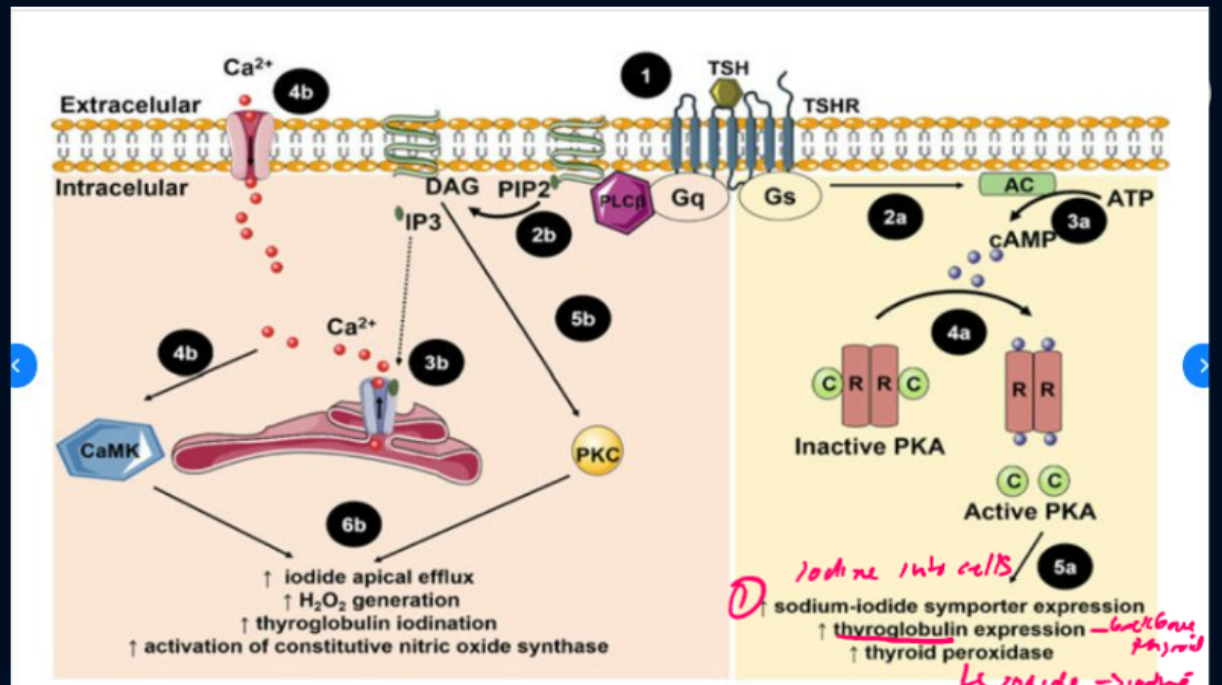
- Stressor – real or perceived threat to well-being
- Three stage process
  - Alarm – stress increases activity of parts of the hypothalamus
    - Increased secretion of cortisol, increased activation of sympathetic nervous system (fight or flight response)
  - Resistance – maintenance of alarm stage, forming a new set point for homeostasis
    - Body attempts to compensate
    - If stressor is managed, homeostasis returns to normal set points
    - If stressor is not managed, alarm stage will continue – will eventually be counter-productive
  - Exhaustion – body's resources have been depleted
    - Increased risk of becoming sick

Stress response – GAS



RELEVANT

- TSH binds to TSH-R on basolateral aspect of thyroid follicular cell
- TSH-R – G-protein coupled receptor, activates adenylyl cylcase and cAMP. Increases protein kinase A (PKA)
- PKA has number of effects

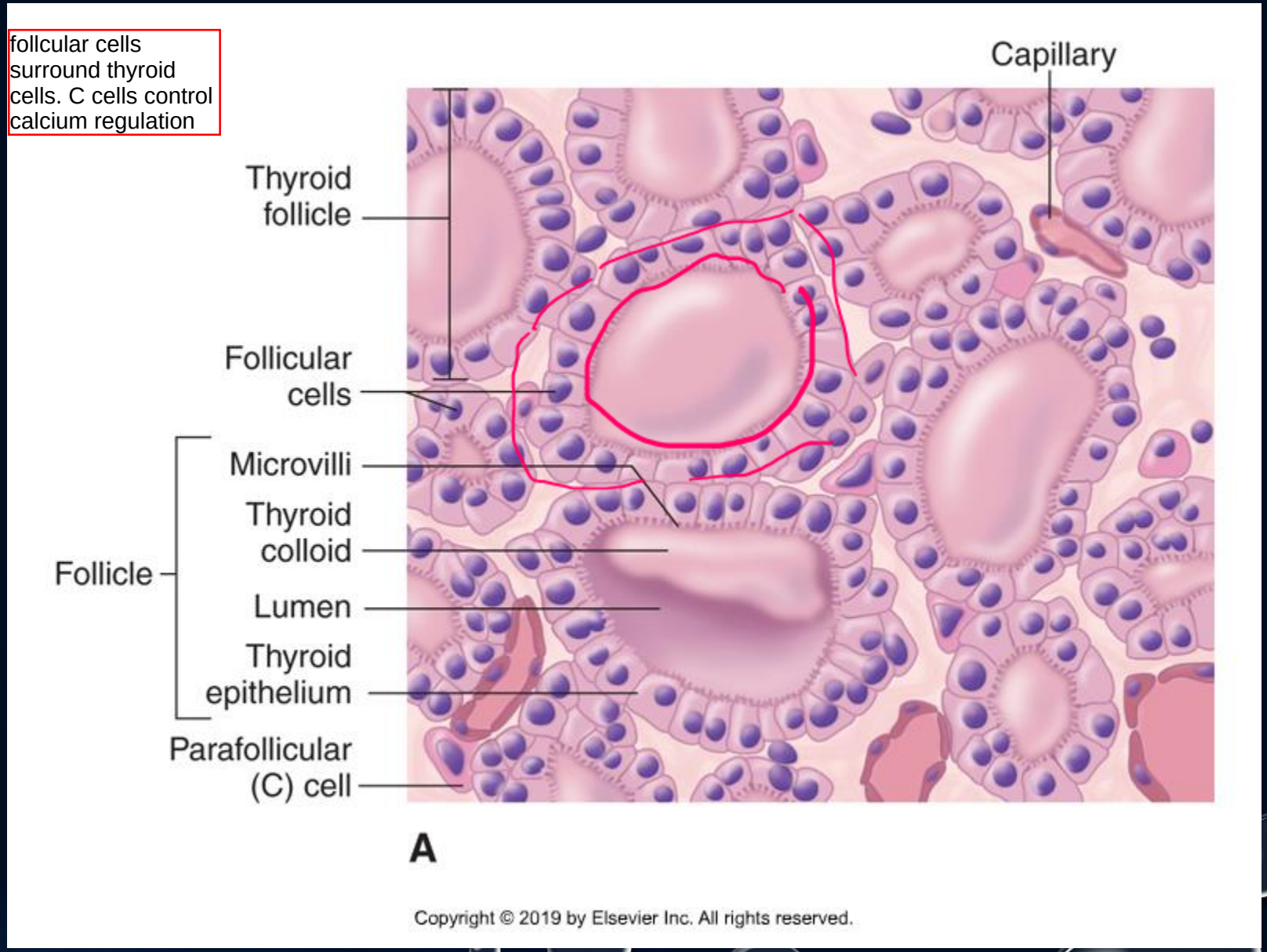


2 Signaling pathways activated by thyroid stimulating hormone (TSH) in thyroid follicular cells. (1) TSH binds to the thyroid stimulating hormone receptor (THSR), activating two Gα protein subtypes: Gs and Gq. These proteins activate two different regulatory pathways: cAMP and phospholipase-C (PLC) pathways, respectively. cAMP pathway: (2a) Gs activates adenylate cyclase (AC); (3a) AC converts adenosine triphosphate (ATP) to cAMP; (4a) cAMP binds to the regulatory subunits (R) of protein kinase A (PKA), releasing and activating the catalytic subunits (C) of this protein (5a) Activated PKA activates transcription of genes involved in the thyroid hormone production: sodium-iodide symporter, thyroglobulin and thyroid peroxidase. PLC pathway: (2b) Gq activation stimulates PLC that hydrolyzes phosphatidylinositol 4,5-bisphosphate (PIP2) into diacylglycerol (DAG) and inositol 1,4,5-triphosphate (IP3); (3b) IP3 binds to its endoplasmic reticulum receptors releasing the Ca 2+ stored in this organelle; (4b) Increased intracellular Ca 2+ is followed by an increase of Ca 2+ from the extracellular medium and calmodulin-dependent protein kinases (CaMK) activation; (5b) DAG activates the protein kinase C (PKC); (6b) PLC pathway, through CaMK and PKC activation, regulate the iodide apical efflux, H 2 O 2 generation, thyroglobulin iodination and constitutive activation of nitric oxide synthase. Notes Dotted arrows depict particles movement

B: From Jacob S: *Atlas of human anatomy*, Edinburgh, 2002, Churchill Livingstone.

Thyroid Gland Tissue Level

follcular cells surround thyroid cells. C cells control calcium regulation



RELEVANT. ALSO KNOW HOW TSH works from what i pasted 2 slides ago

iodine required to make thyroid hormones, so intake increased. Thyroglobulin made more as backbone. Thyrod perxidase also increased to combine the iodine and thyroglobulin. C

TSH increases sodium iodine transporters

Tyrosine are the units making up a thyroglobulin

T3 T4 Synthesis

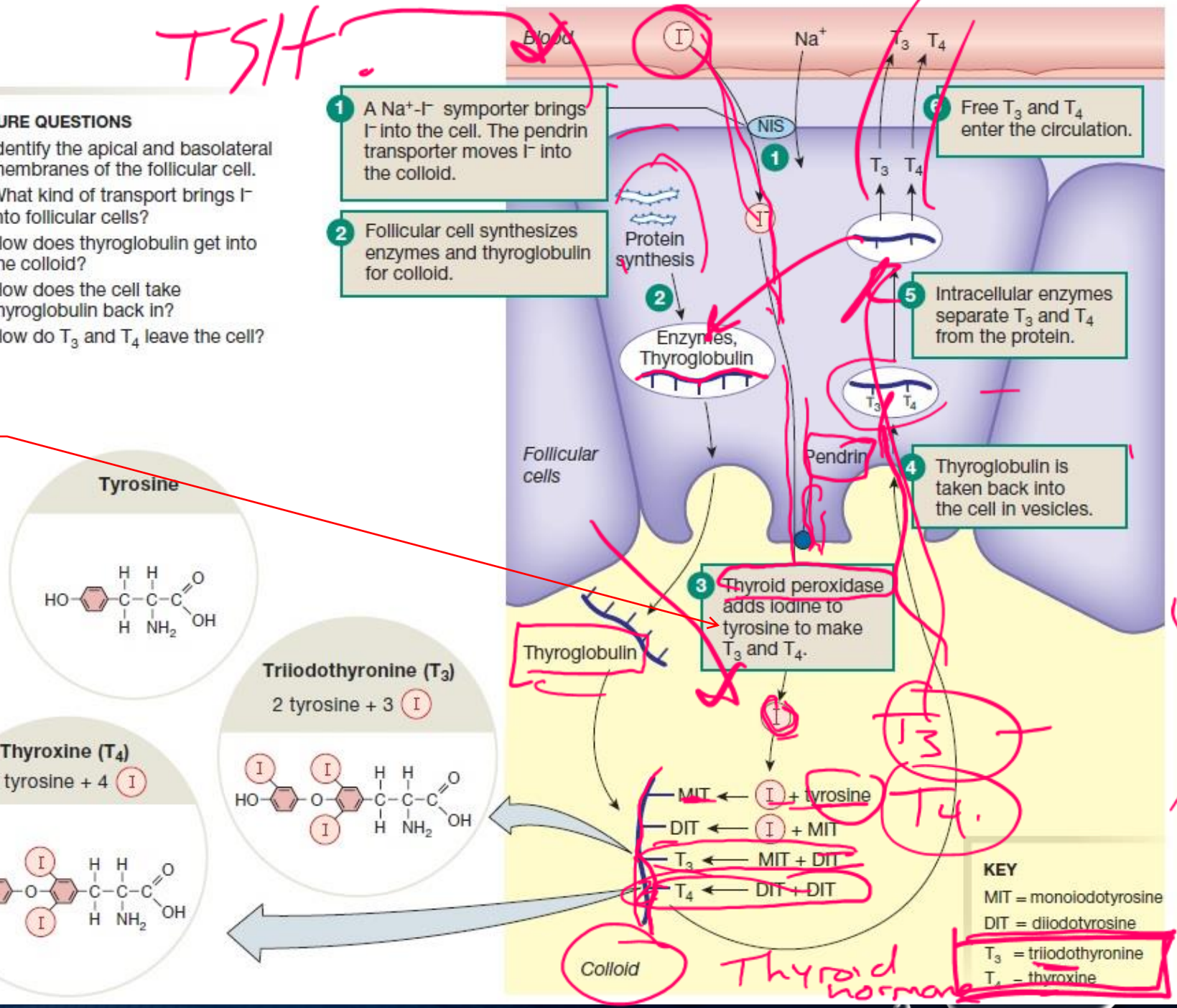
follicular cells assemble components, colloid cells combine components into thyroid hormones

Thyroid hormones move back out of follicular cells into blood stream

TSH

FIGURE QUESTIONS

1. Identify the apical and basolateral membranes of the follicular cell.
2. What kind of transport brings I^- into follicular cells?
3. How does thyroglobulin get into the colloid?
4. How does the cell take thyroglobulin back in?
5. How do T_3 and T_4 leave the cell?



T4 is more abundant, acts as storage molecules. T3 is more active.

Transportation and Activation of T3 & T4

- Thyroxine binding globulin carries T3 and **T4** in blood – specific binding
- Serum Albumen Carries T3 and T4 – Low affinity but high capacity

- At tissue, T4 is converted to T3 (more biologically active than t4) by deiodinase
- Starvation response – reduction in deiodinase activity except in brain, heart, skeletal muscle and thyroid. Why?

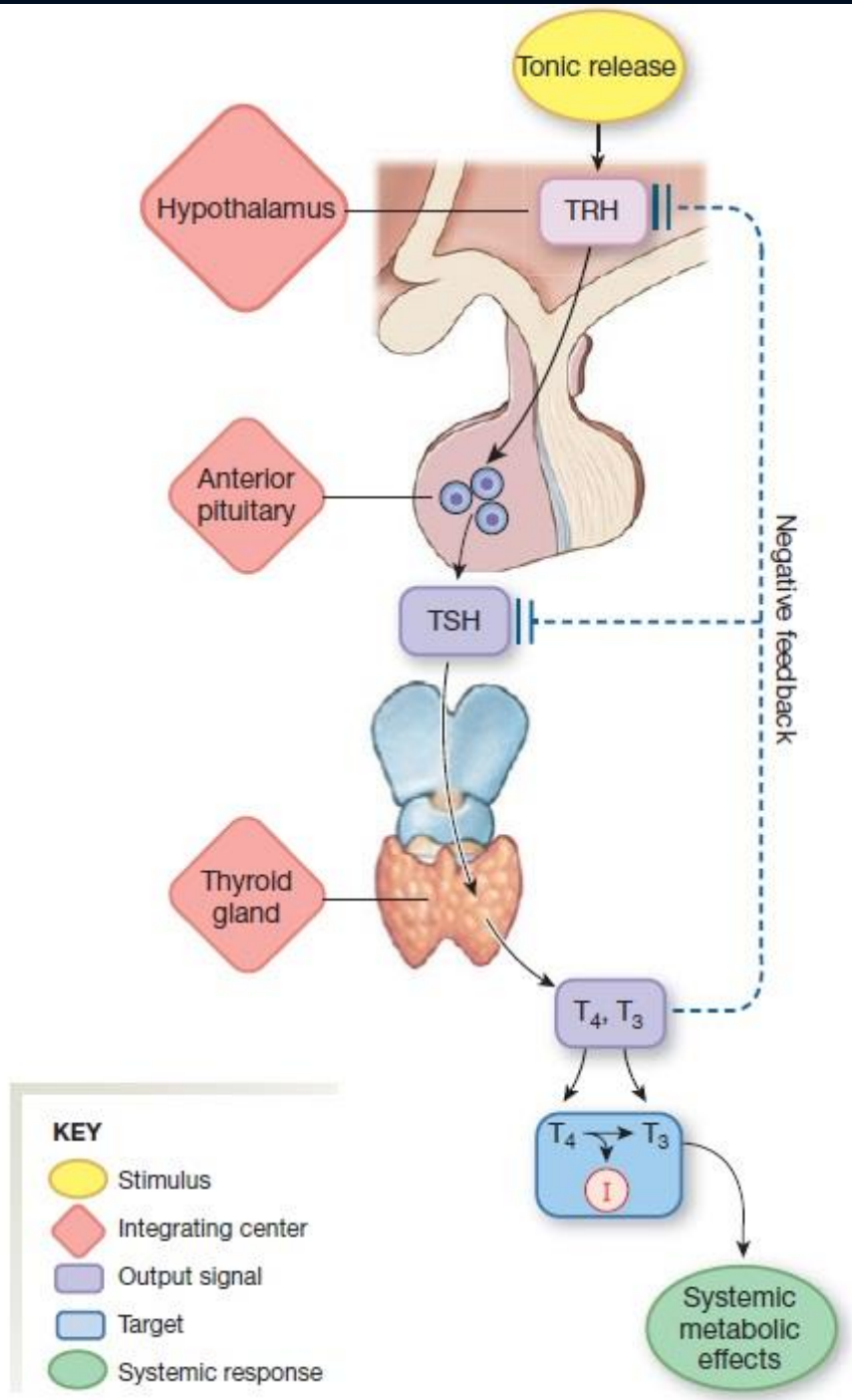
Thyroid hormones control metabolism. Too much speeds everything up (high bp, high temp), too little slows things down (bradychardia, hypothermic)

Effects of T3 & T4

- Increase basal metabolic rate (BMR; consumption of O2 and energy to meet minimum requirements to survive)
- Increases protein synthesis and protein degradation
- Increases rate of glycogenolysis and gluconeogenesis
- Increases lipolysis
- Increases HR, FoC and cardiac output

- In neonate, essential for normal neurologic development (particularly myelin, axon development and neurotransmitters

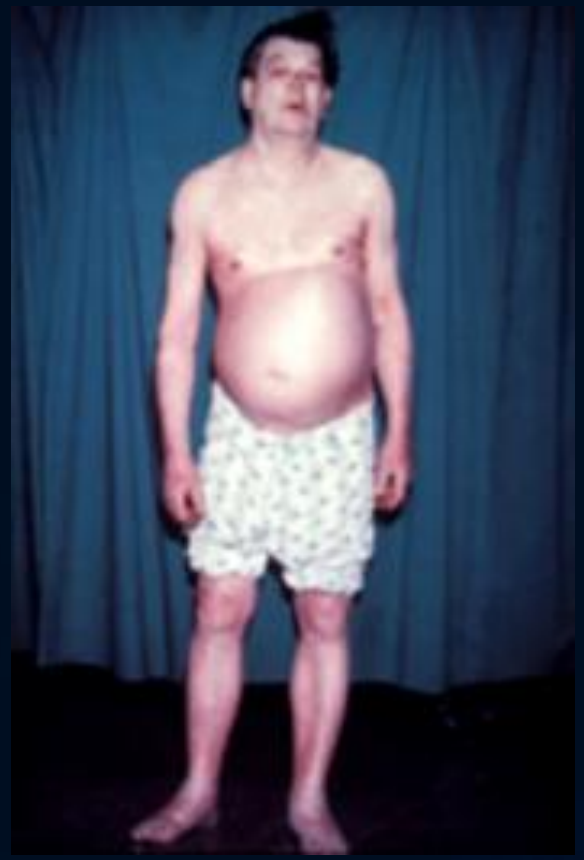
Regulation of Secretion of T3 & T4



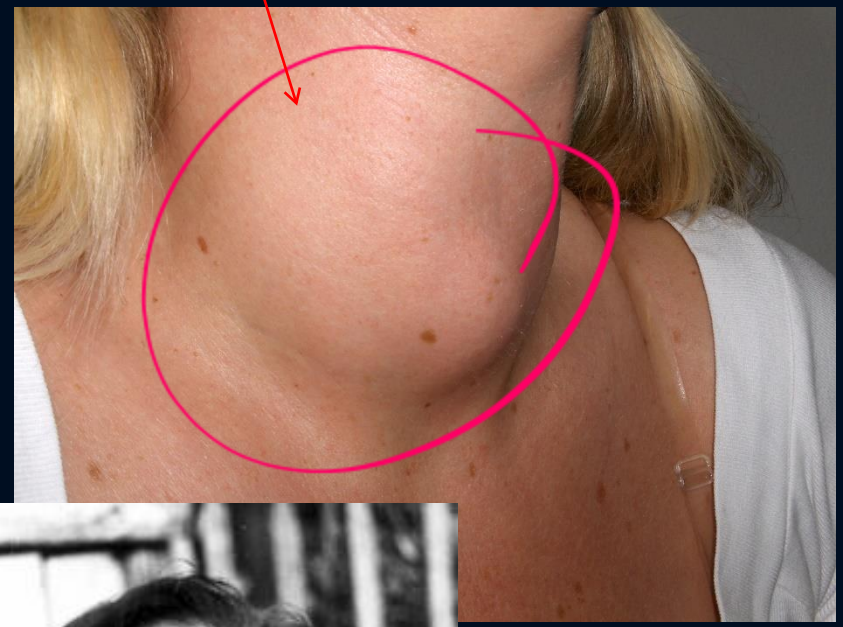
Thyroid Hormones	
Cell of origin	Thyroid follicle cells
Chemical nature	Iodinated amine
Biosynthesis	From iodine and tyrosine. Formed and stored on thyroglobulin in follicle colloid.
Transport in the circulation	Bound to thyroxine-binding globulin and albumins
Half-life	6-7 days for thyroxine (T_4); about 1 day for triiodothyronine (T_3)
Factors affecting release	Tonic release
Control pathway	TRH (hypothalamus) → TSH (anterior pituitary) → T_3 + T_4 (thyroid) → T_4 deiodinates in tissues to form more T_3
Target cells or tissues	Most cells of the body
Target receptor	Nuclear receptor
Whole body or tissue reaction	↑ Oxygen consumption (thermogenesis). Protein catabolism in adults but anabolism in children. Normal development of nervous system
Action at cellular level	Increases activity of metabolic enzymes and Na^+-K^+-ATPase
Action at molecular level	Production of new enzymes
Feedback regulation	T_3 has negative feedback on anterior pituitary and hypothalamus.

Hypothyroidism

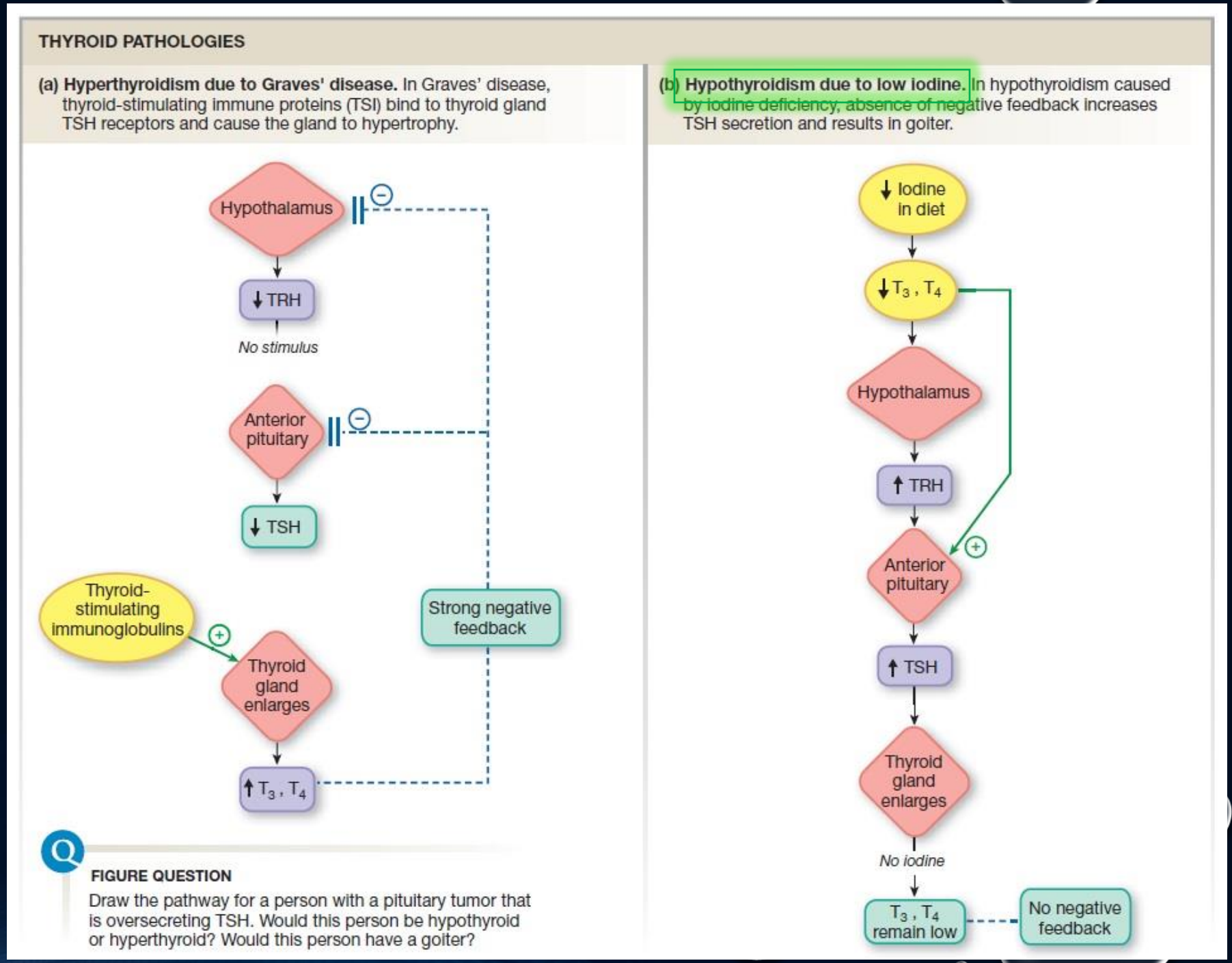
- Causes
  - lack of Iodine (primary hypothyroidism)
  - lack of response to TSH
- S&S
  - Weight gain
  - Cold intolerance
  - Slow HR, low cardiac output
  - Fatigue
  - Cool extremities
  - Dry skin
  - Flat, lack of energy
  - constipation
- Treatment – exogenous T4 (levothyroxine)



goiter



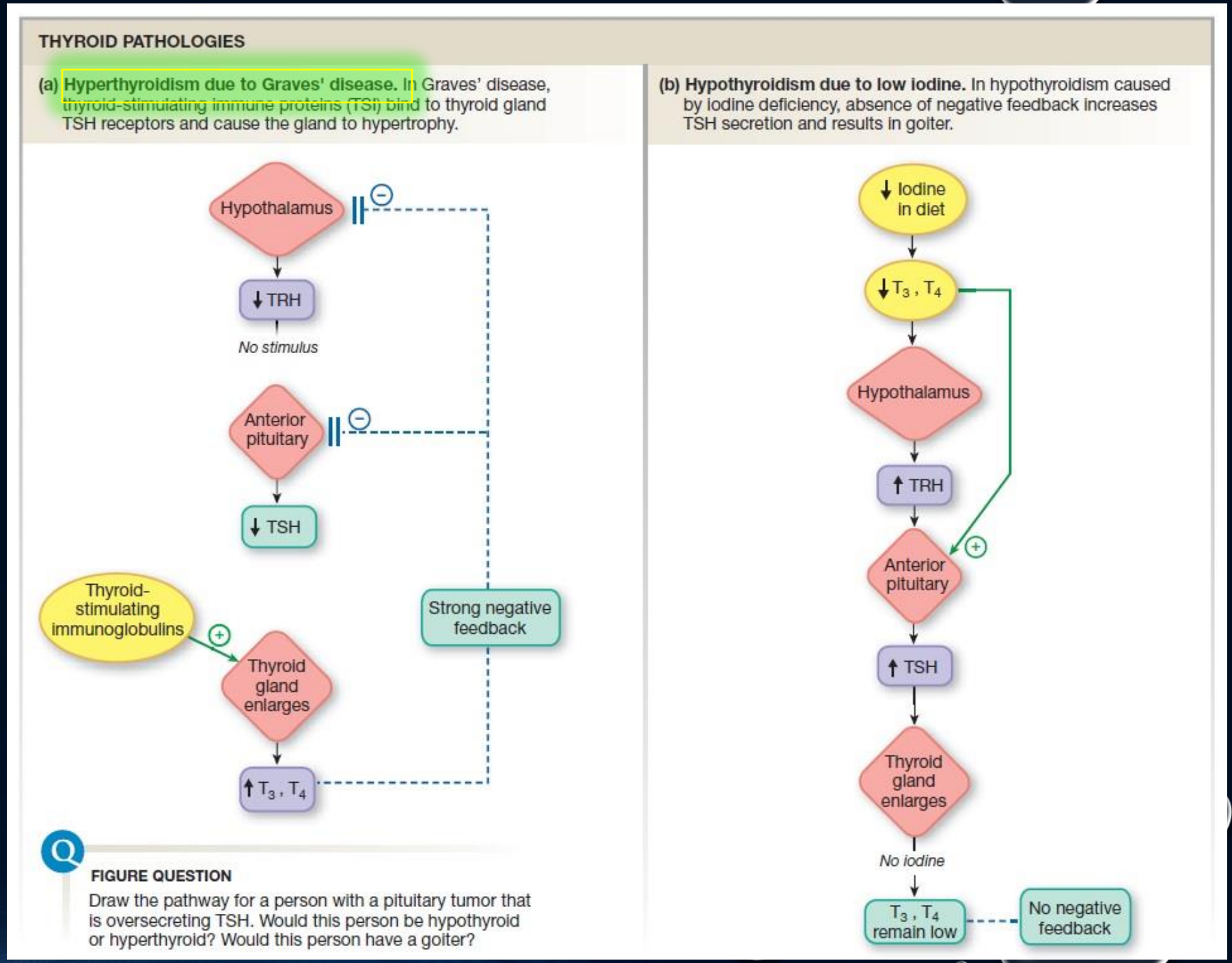
Hypothyroidism – Feedback



Hyperthyroidism

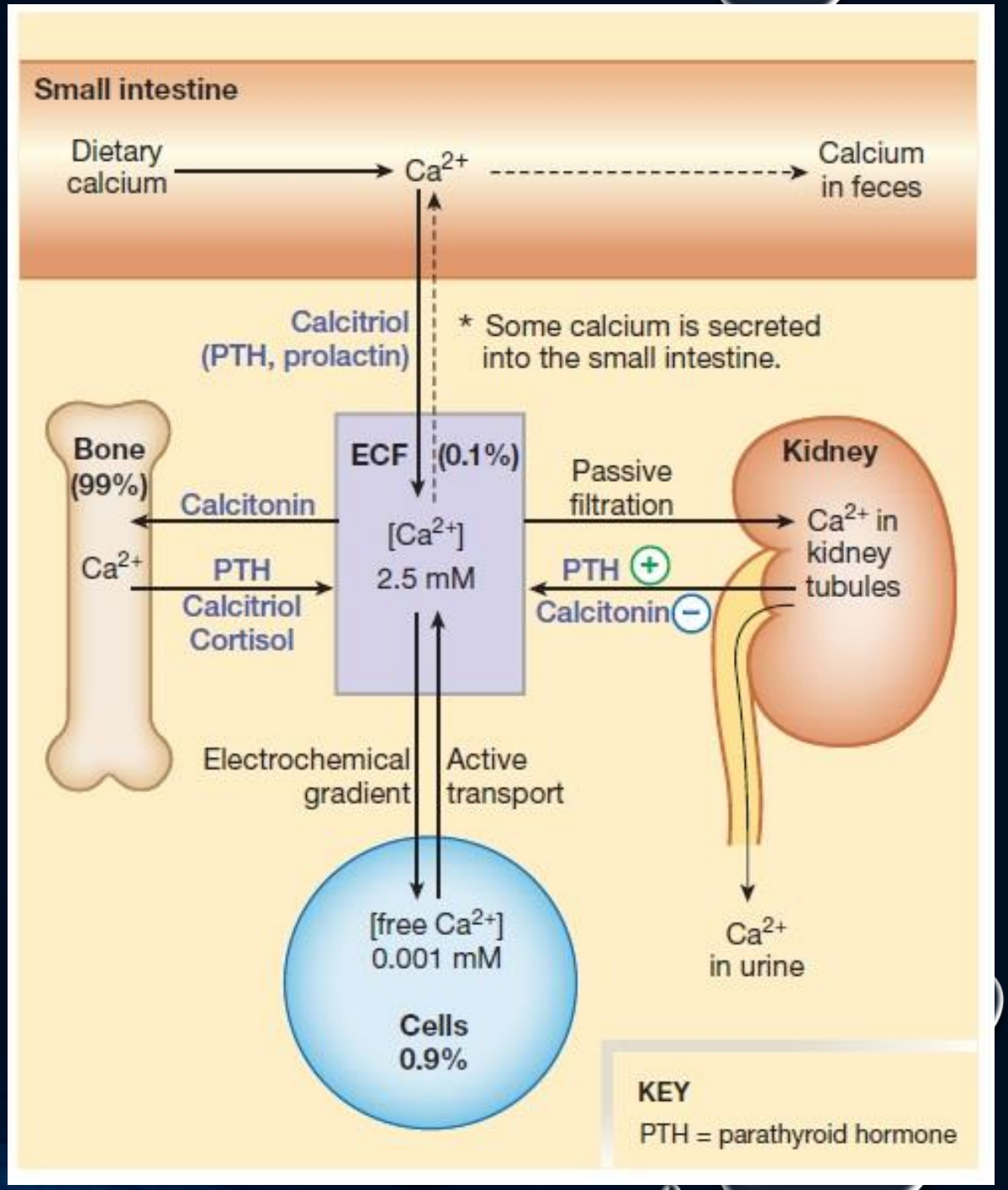
- Causes
  - Graves disease (autoimmune stim of TSH receptor)
  - Thyroid tumour
- S&S
  - Weight loss, high blood sugar
  - heat intolerance
  - Fast HR, High cardiac output
  - "Spun" / irritable
  - Cool extremities
  - thin skin (little subcutaneous fat)
  - Exopthalmos
  - Hypermotility of GI tract
- Treatment – depends on the cause; antithyroids, beta blockers, radioactive iodine

Hypothyroidism – Feedback

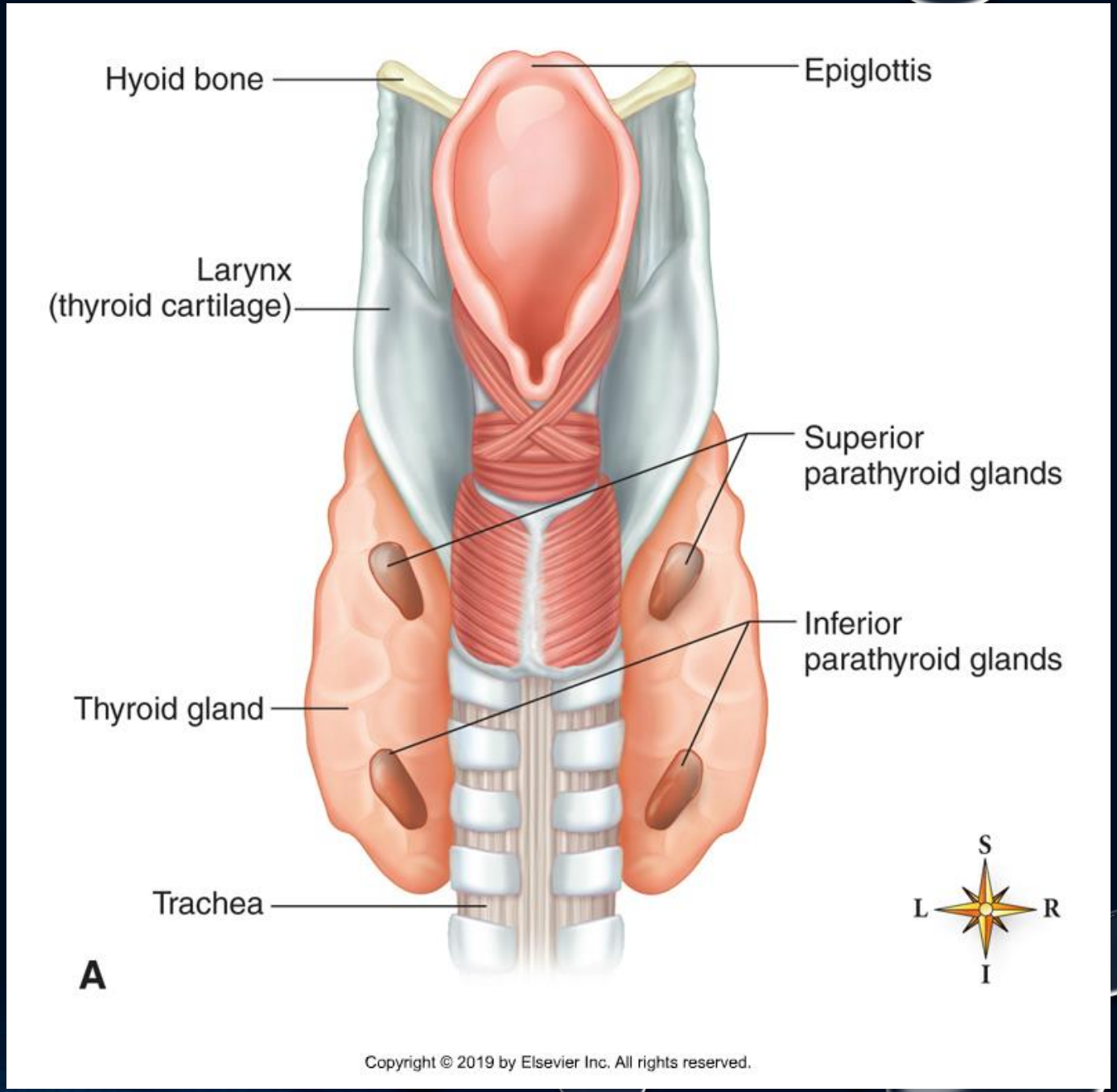


Calcium Regulation

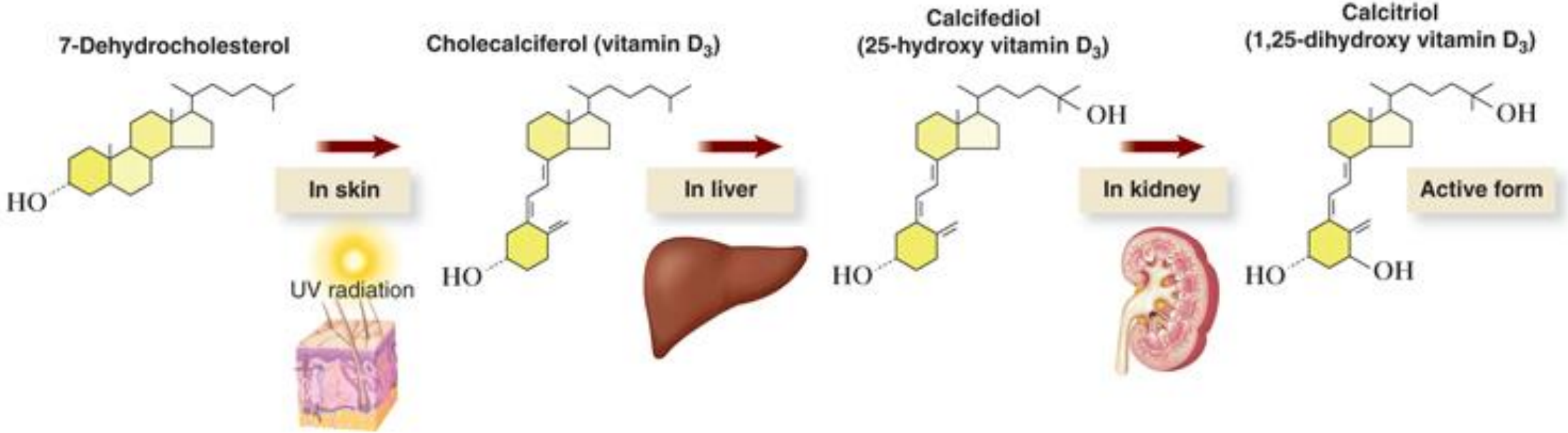
- Parathyroid hormone
  - Raise ECF Ca+2 by increasing Bone resorption, Ca+2 absorption & Ca+2 reabsorption
- Vitamin D
  - Active form increases Ca+2 absorption, raising ECF Ca+2
- Calcitonin
  - Decreases ECF Ca+2 by increasing bone matrix deposition



Parathyroid Glands

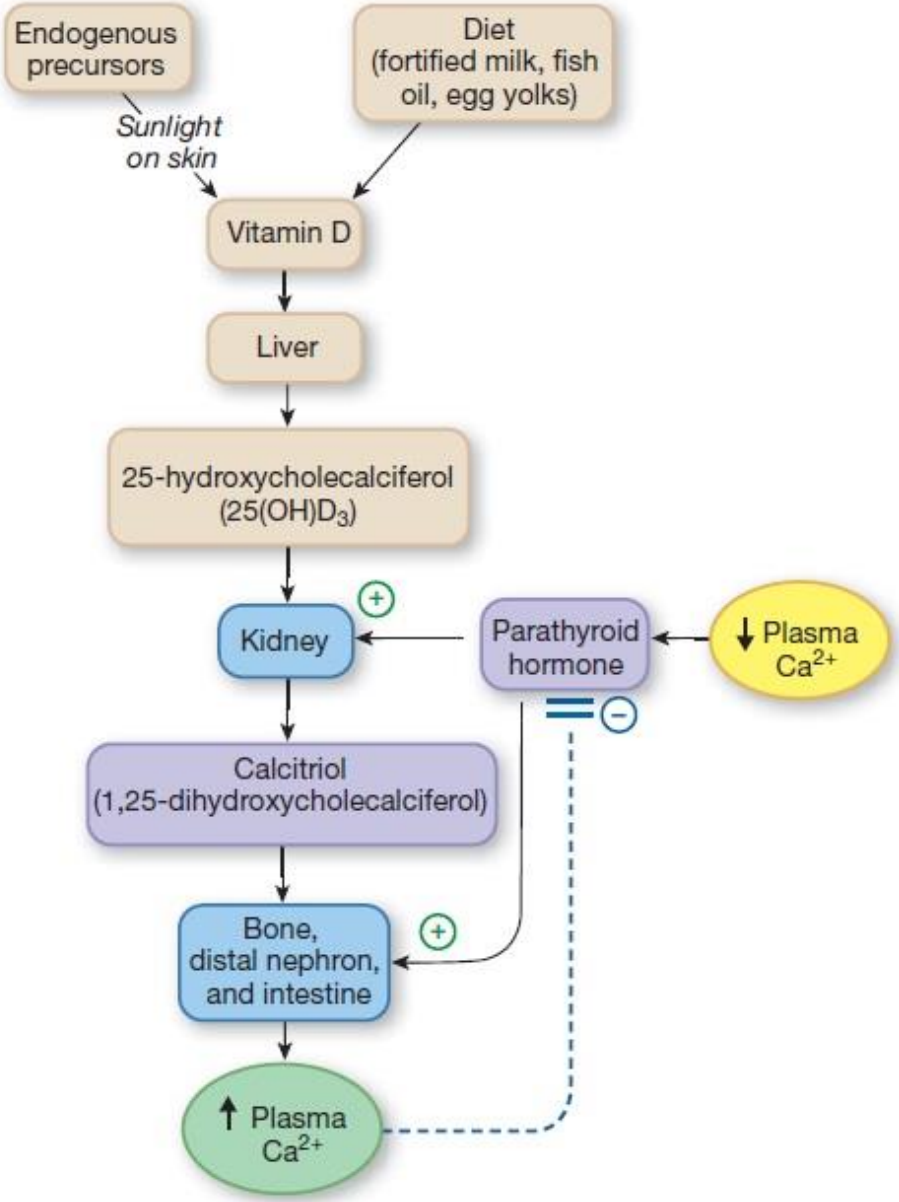


Vitamin D Metabolism



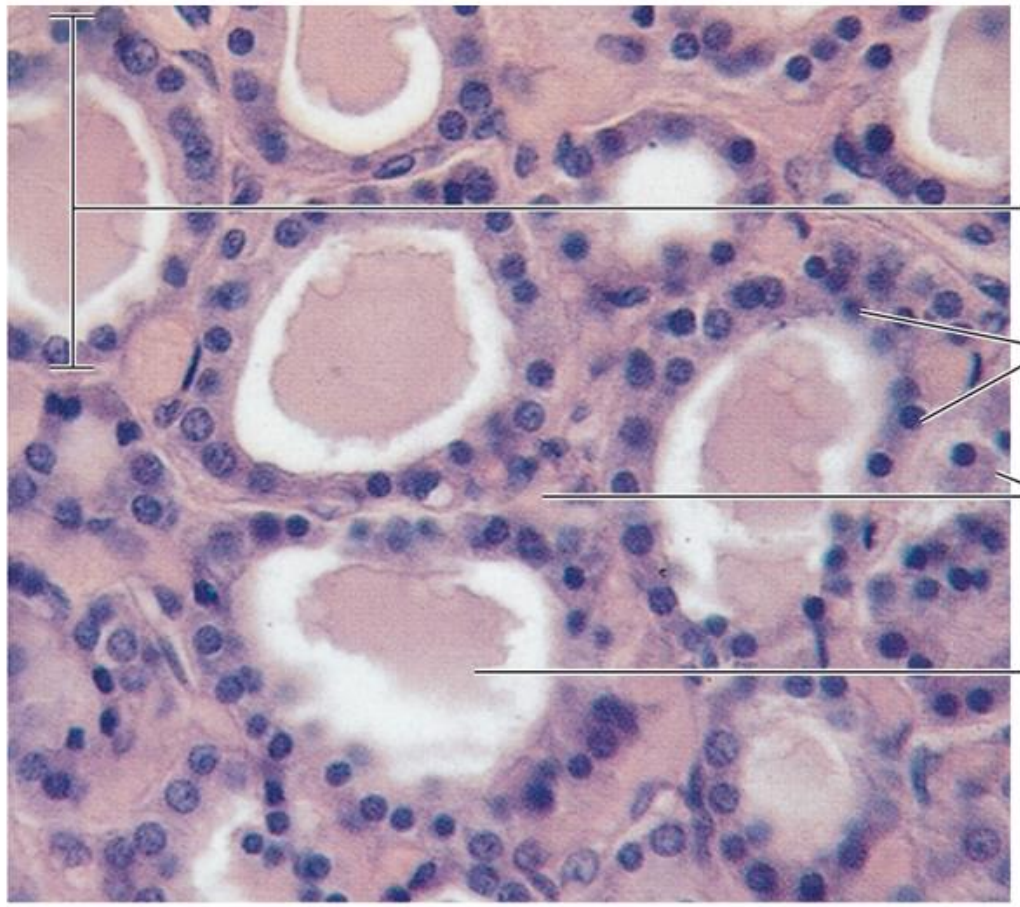
ENDOCRINE CONTROL OF CALCIUM BALANCE

PTH works with calcitriol to promote bone resorption, intestinal Ca^{2+} absorption, and distal nephron Ca^{2+} reabsorption, all of which tend to elevate plasma Ca^{2+} concentrations.



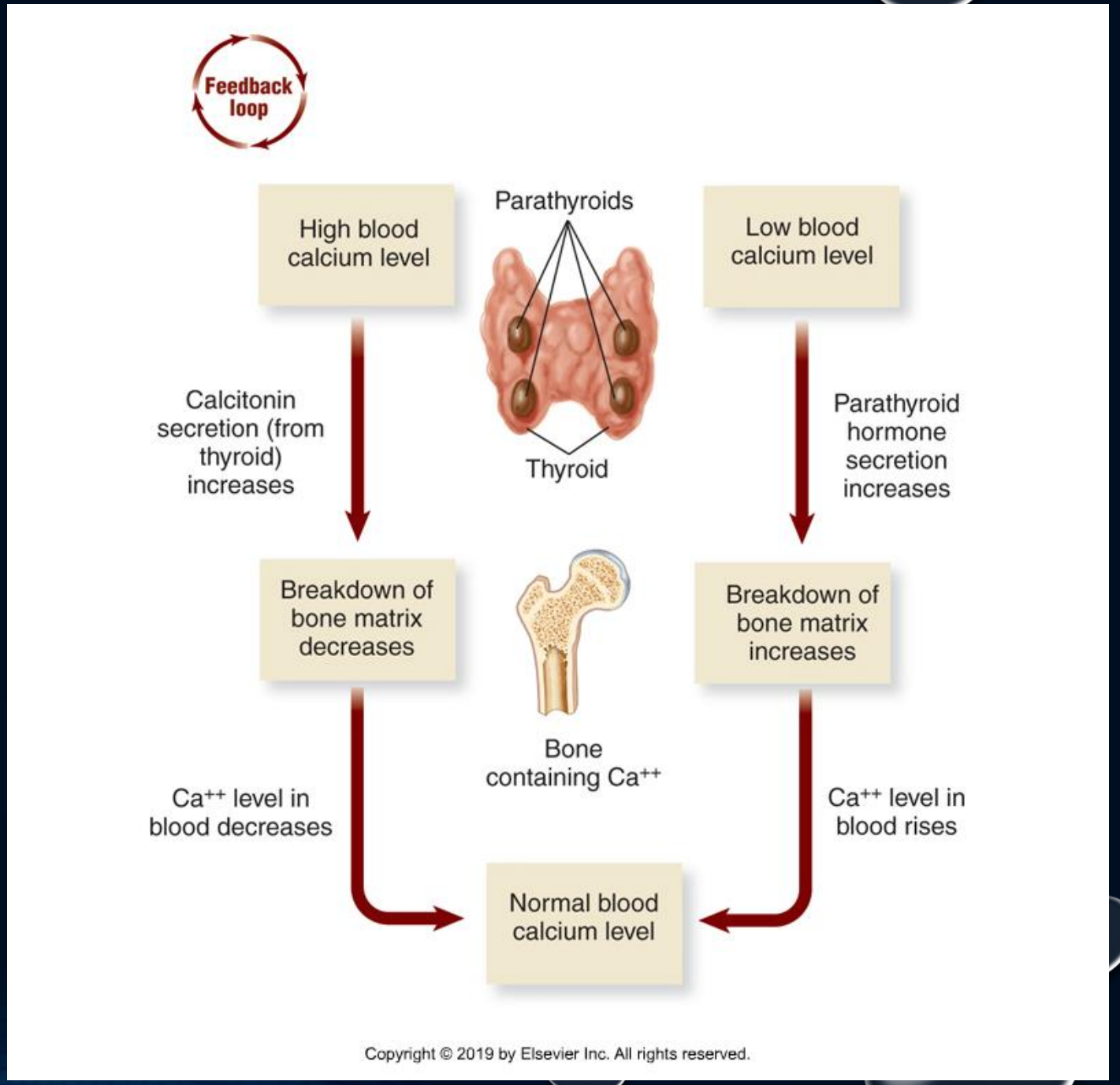
VITAMIN D_3 (CALCITRIOL, 1,25-DIHYDROXYCHOLECALCIFEROL)	
Origin	Complex biosynthesis; see below
Chemical nature	Steroid
Biosynthesis	Vitamin D formed by sunlight on precursor molecules or ingested in food; converted in two steps (liver and kidney) to $1,25(OH)_2D_3$
Transport in the circulation	Bound to plasma protein
Stimulus for synthesis	↓ Ca^{2+}. Indirectly via PTH. Prolactin also stimulates synthesis.
Target cells or tissues	Intestine, bone, and kidney
Target receptor	Nuclear
Whole body or tissue reaction	↑ Plasma Ca^{2+}
Action at molecular level	Stimulates production of calbindin, a Ca^{2+}-binding protein, and of CaSR in parathyroid gland. Associated with intestinal transport by unknown mechanism
Feedback regulation	↑ Plasma Ca^{2+} shuts off PTH secretion

Calcitonin

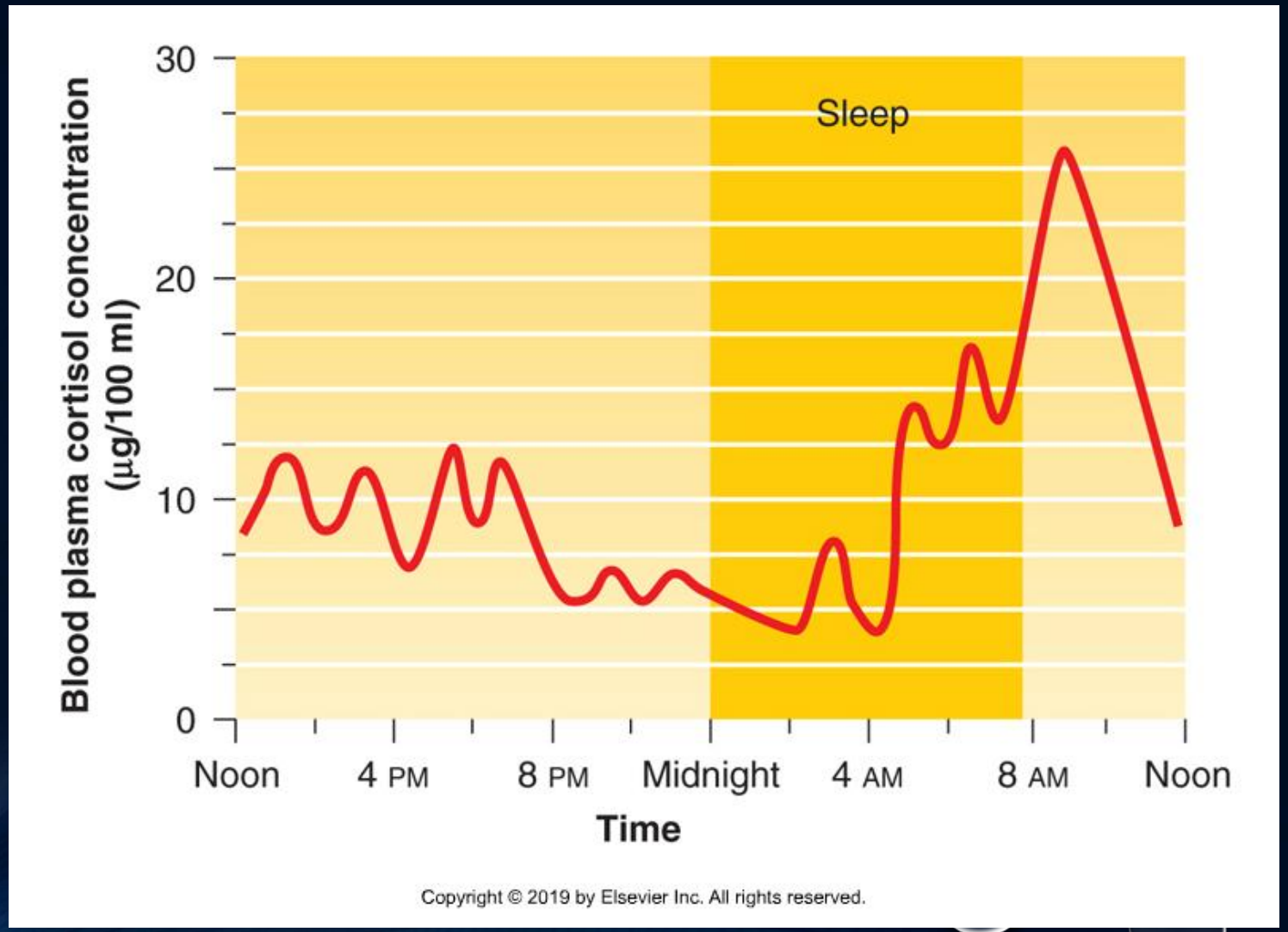


B

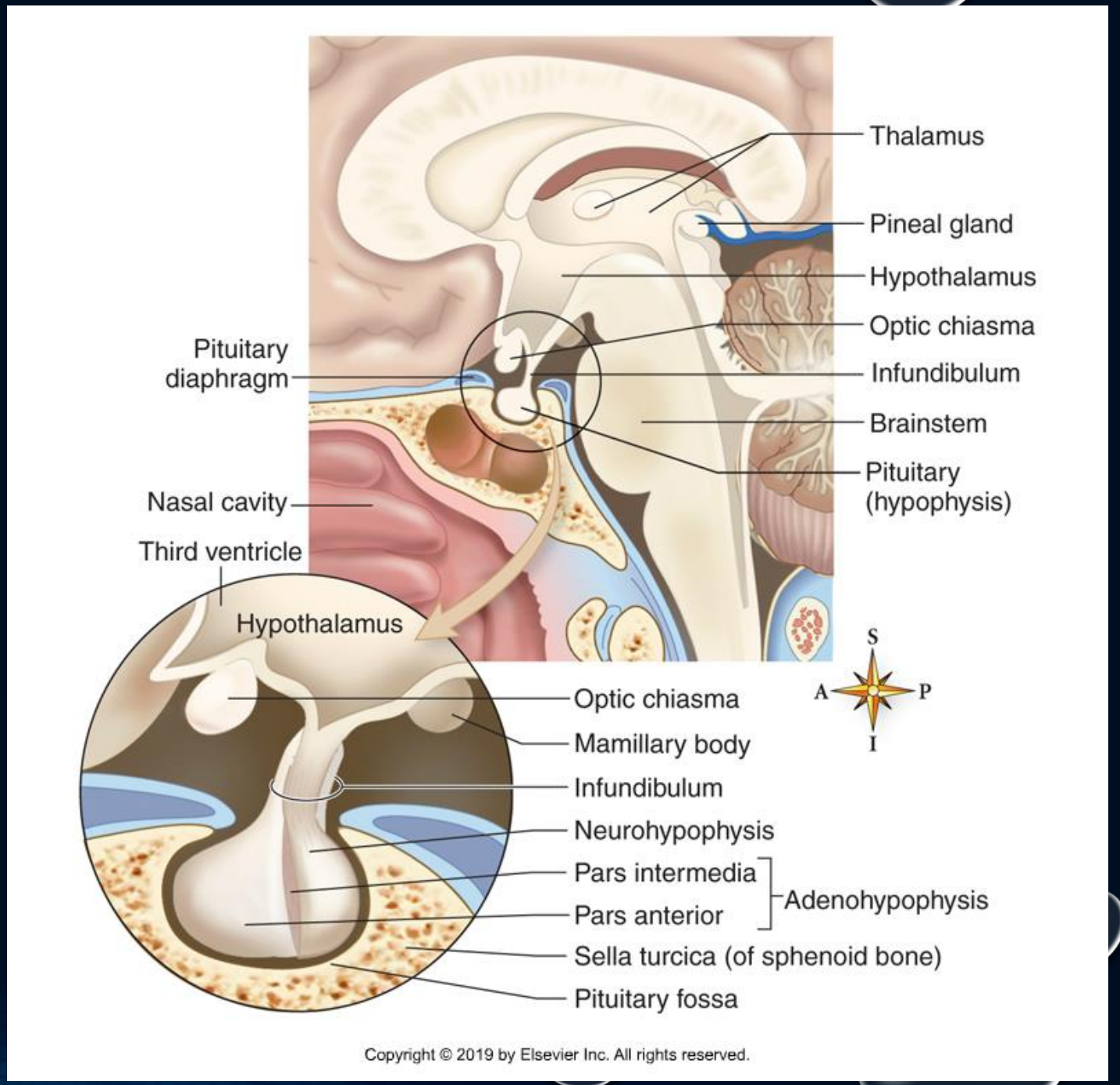
Calcitonin – role in Ca+2 regulation



Circadian Rhythms



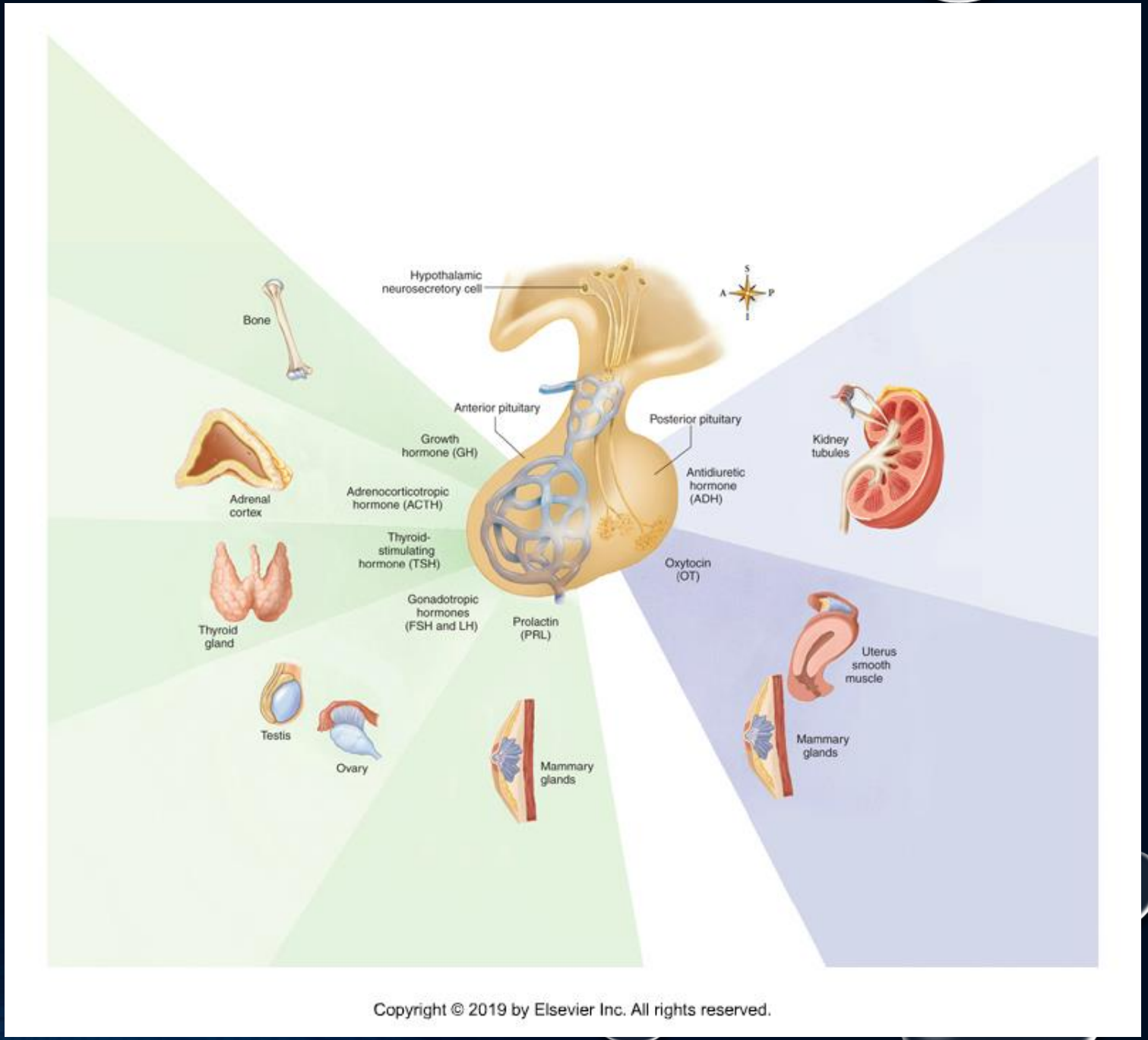
Pineal gland

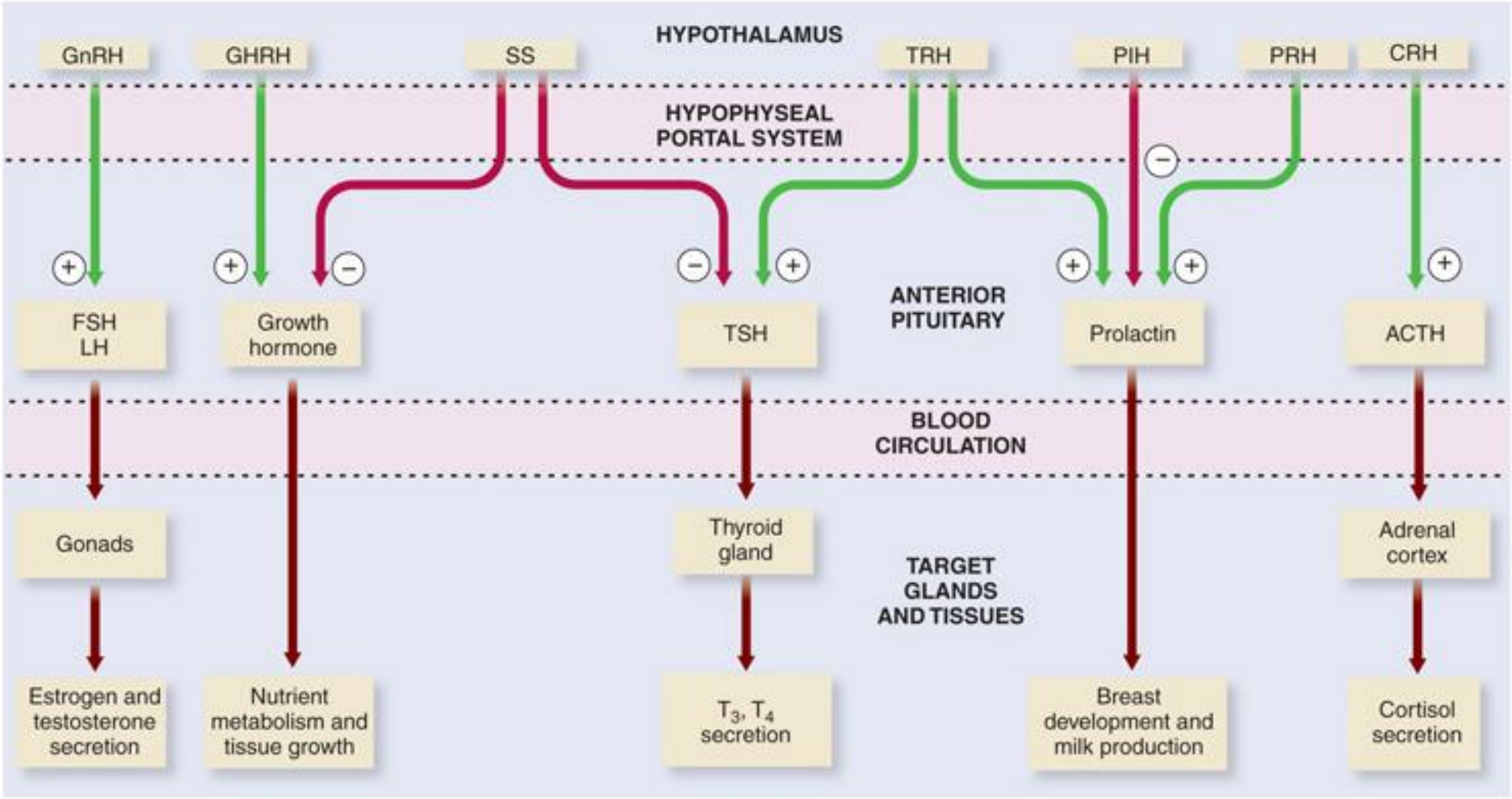


Circadian Rhythms

- Circadian regulation of many variables
  - Temperature, blood glucose, cortisol, growth hormone, sleep cycles
- Suprachiasmatic nucleus as primary pacemaker, entrained by light dark cycles
- Light / dark information relayed to SCN through retinohypothalamic neurons
- SCN sends messages through adrenergic neurons to pineal gland which secretes melatonin
- Melatonin binds to MT1 and Mt2 receptors to inhibit firing of SCN neurons
  - Darkness – melatonin increases
  - Light – melatonin decreases

Adenohypophysis vs neurohypophysis

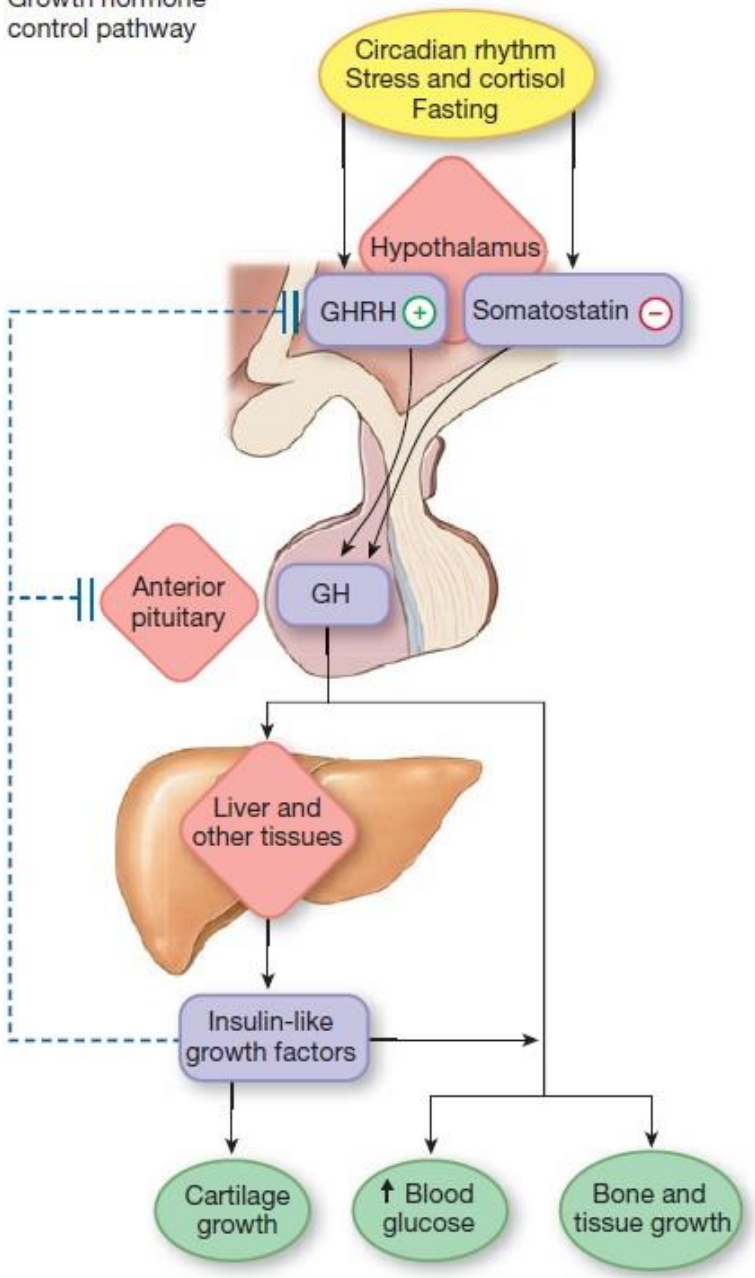




Growth Hormone (GH) Regulation

GROWTH HORMONE

Growth hormone control pathway



GROWTH HORMONE (hGH)	
Origin	Anterior pituitary
Chemical nature	191-amino acid peptide; several closely related forms
Biosynthesis	Typical peptide
Transport in the circulation	Half is dissolved in plasma, half is bound to a binding protein whose structure is identical to that of the GH receptor
Half-life	18 minutes
Factors affecting release	Circadian rhythm of tonic secretion; influenced by circulating nutrients, stress, and other hormones in a complex fashion
Control pathway	GHRH, somatostatin (hypothalamus) → growth hormone (anterior pituitary)
Target cells or tissues	Trophic on liver for insulin-like growth factor production; also acts directly on many cells
Target receptor	Membrane receptor with tyrosine kinase activity
Whole body or tissue reaction (with IGFs)	Bone and cartilage growth; soft tissue growth; ↑ plasma glucose
Action at cellular level	Receptor linked to kinases that phosphorylate proteins to initiate transcription

Growth Hormone (somatotropin)

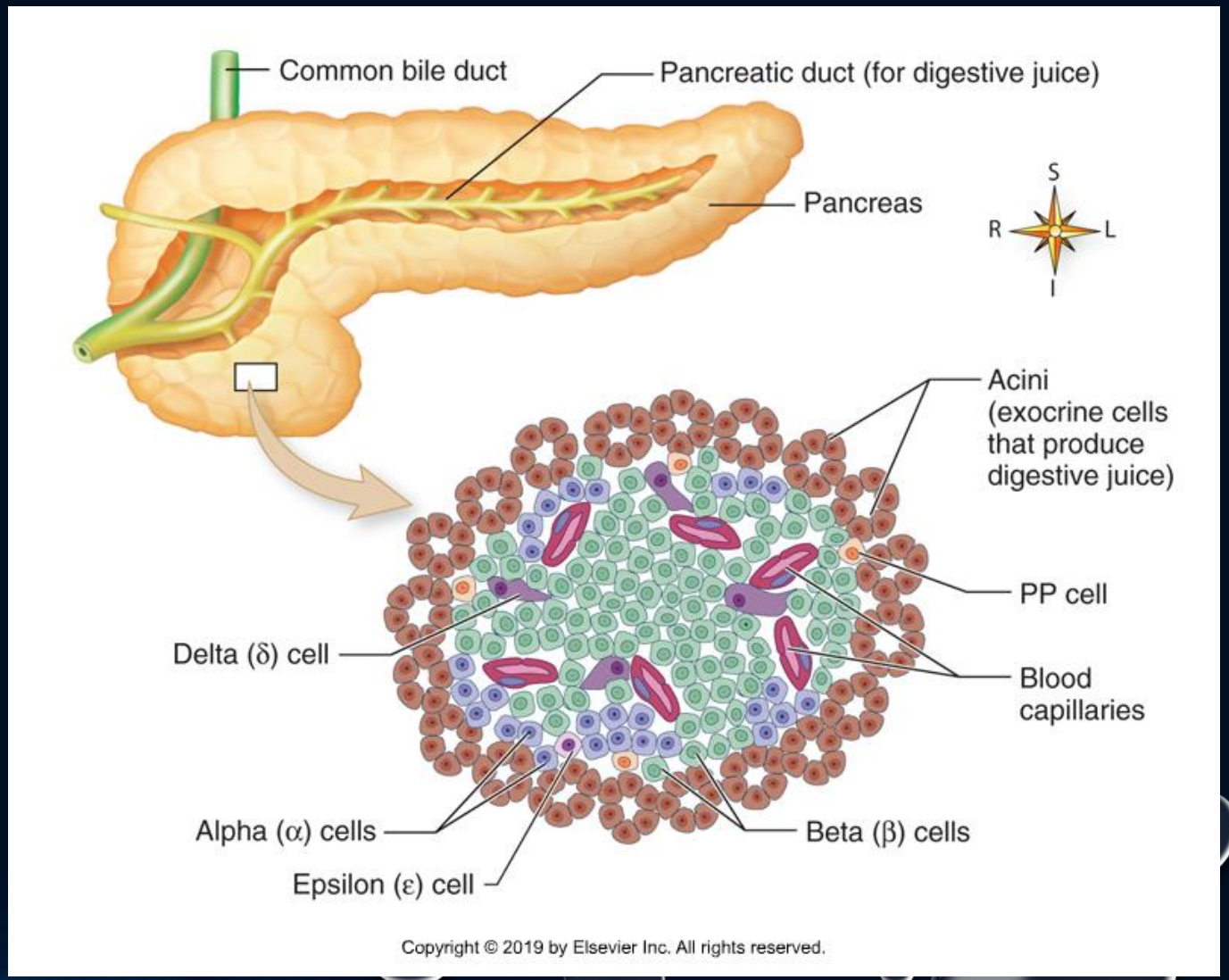
- GH Release is influenced by Growth hormone releasing hormone (somatocrinin / somatorelin) and growth hormone inhibiting hormone (somatostatin)
- Major effects of GH
  - Stimulates liver to secrete Insulin-like growth factor (IGF-1)
  - Increased Ca+2 retention and formation of bone matrix
  - Increased muscle mass, increased protein synthesis
  - Gluconeogenesis, decreases glucose uptake by liver
- Use in sports?

Pancreatic hormones

- Alpha cells – glucagon
- Beta cells – insulin
- Delta cells – somatostatin – paracrine influence on other islet cells
- Epsilon cells – ghrelin (increases appetite
- PP Cells – pancreatic polypeptide
- Acini cells – exocrine pancreas functions

VS islet of langerhans cells - endocrne cells

Pancreatitis; digestive enzyme ducts blocked, eats pancreas itself



Regulation of Blood Glucose

- Insulin – hormone of the fed state
  - Signals to release – high blood glucose, PNS
  - Actions
    - increase expression of glucose 4 transport protein
    - Increase cellular uptake and storage of lipids, aA and glucose as TGs, proteins and glycogen
- Glucagon – hormone of the fasted state
  - SIGNALS to release – low blood glucose, SNS
  - Actions
    - Increased Glycogenolysis
    - Increased gluconeogenesis
    - Increased secretion of glucose into blood