

Patofyziologie poruch endokrinního systému – nadledviny, štítná žláza

Mezibuněčná komunikace

- Neurokrinní - neuroendokrinní
- Endokrinní (hormony)
- Parakrinní (cytokiny)
- Autokrinní (různé)

Hormones

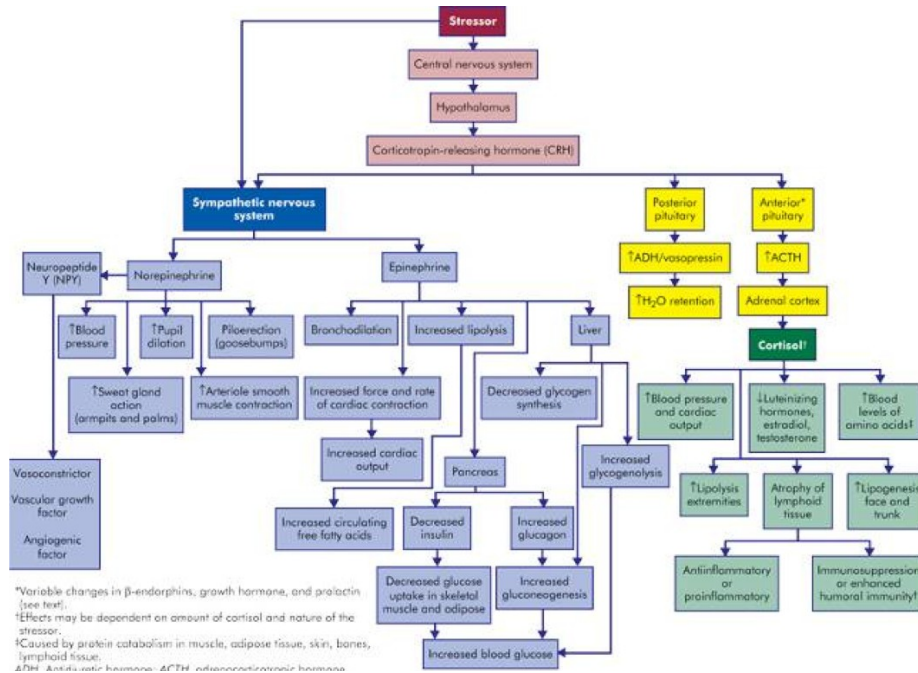
- Proteins / peptides
 - Preprohormone (ER, GA, secretion granules)
- Steroids
 - Cholesterol
- Amines
 - Tyrosine

Endocrine regulation

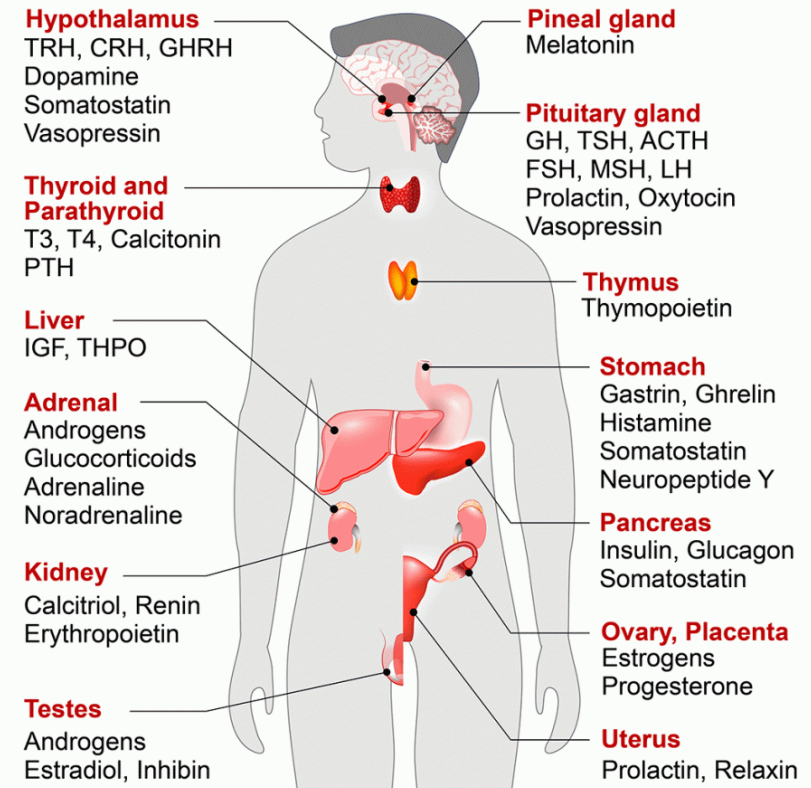
- Negative feedback
- Positive feedback

- Production (endocrine gland)
- Transport (binding proteins in plasma)
- Target tissue (receptors on cells)

Endokrinní systém

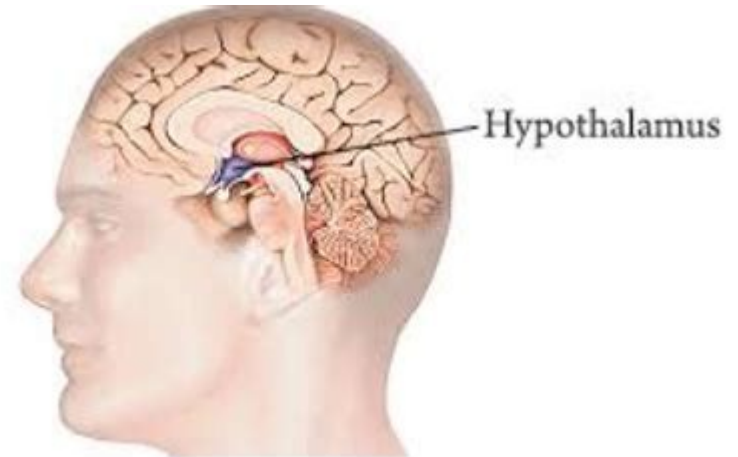


HORMONES



Hypothalamus

- Neural regulation of the autonomic nervous system - adrenal medulla
- Production of ADH and oxytocin
- Regulation of the pituitary



Hypothalamus

- Liberins
 - CRH (ACTH), TRH (TSH), GHRH (GH), GnRH (LH, FSH), Salsolinol (PRL)
- Statins
 - Somatostatin (GH), Dopamine (PRL)

Endokrinní hypotalamus

Uvolňovací faktory pro

Růstový hormon
(GHRH)
Štítnou žlázu (TRH)
Kortikotropin (CRH)
Pohlavní hormony
(FSH RH, LH RH)

Blokující faktory pro

Prolaktin (PIF)
Růstový hormon

Pro přední lalok
hypofýzy

Hormony

Vasopresin (ADH)
Oxytocin

Pro zadní lalok
hypofýzy



Hypothalamus - poruchy

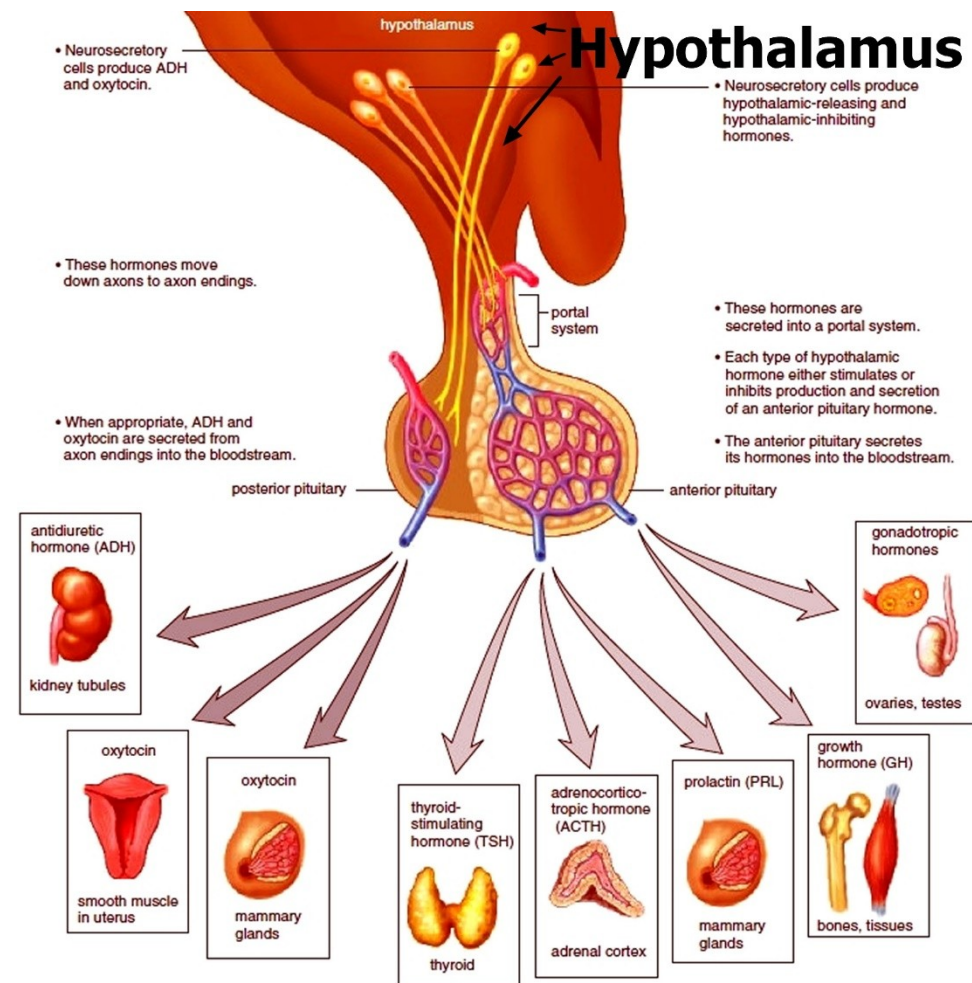
Příčiny: ↑ tu, ↓ trauma, kongenitální změny, poruchy prokrvení, autoimunita

Hypersekrece: jednotlivé hormony – typické příznaky

Hyposekrece:

hypotalamický panhypopituitarismus = snížení sekrece všech hormonů hypofýzy kromě prolaktinu

- porucha sexuálního vyžívání, spermatogeneze a menstruačního cyklu (FSH, LH)
- snížená odpověď na zátěž (stres) (CRH)
- hypotyreóza (TRH)
- poruchy růstu (GHRH)

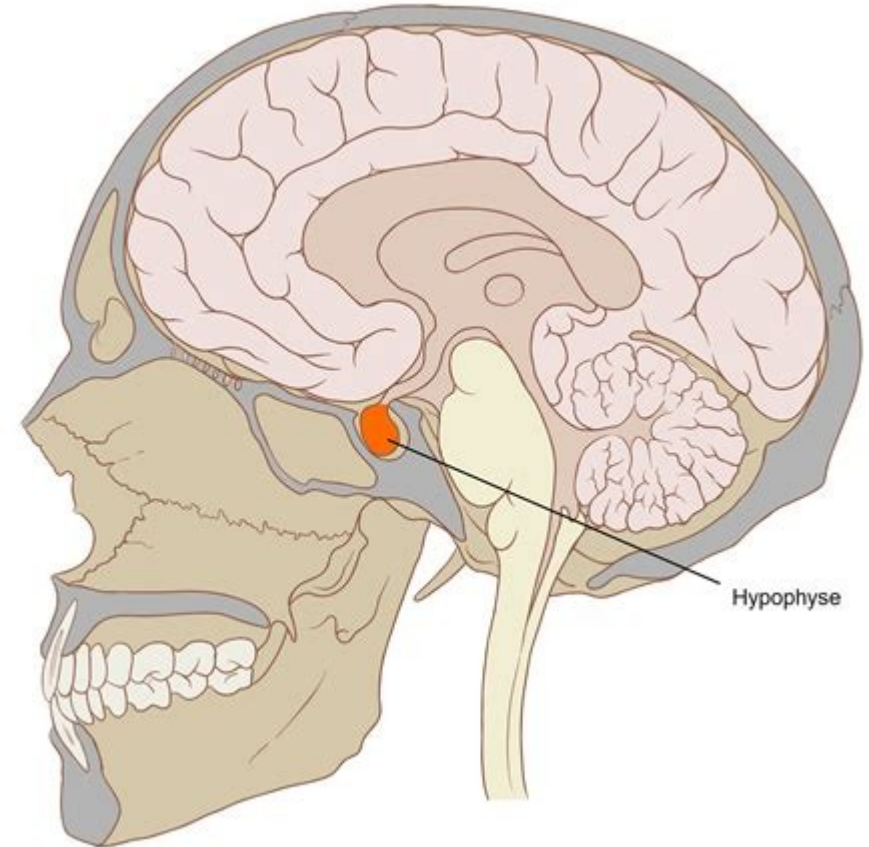


Hypothalamus

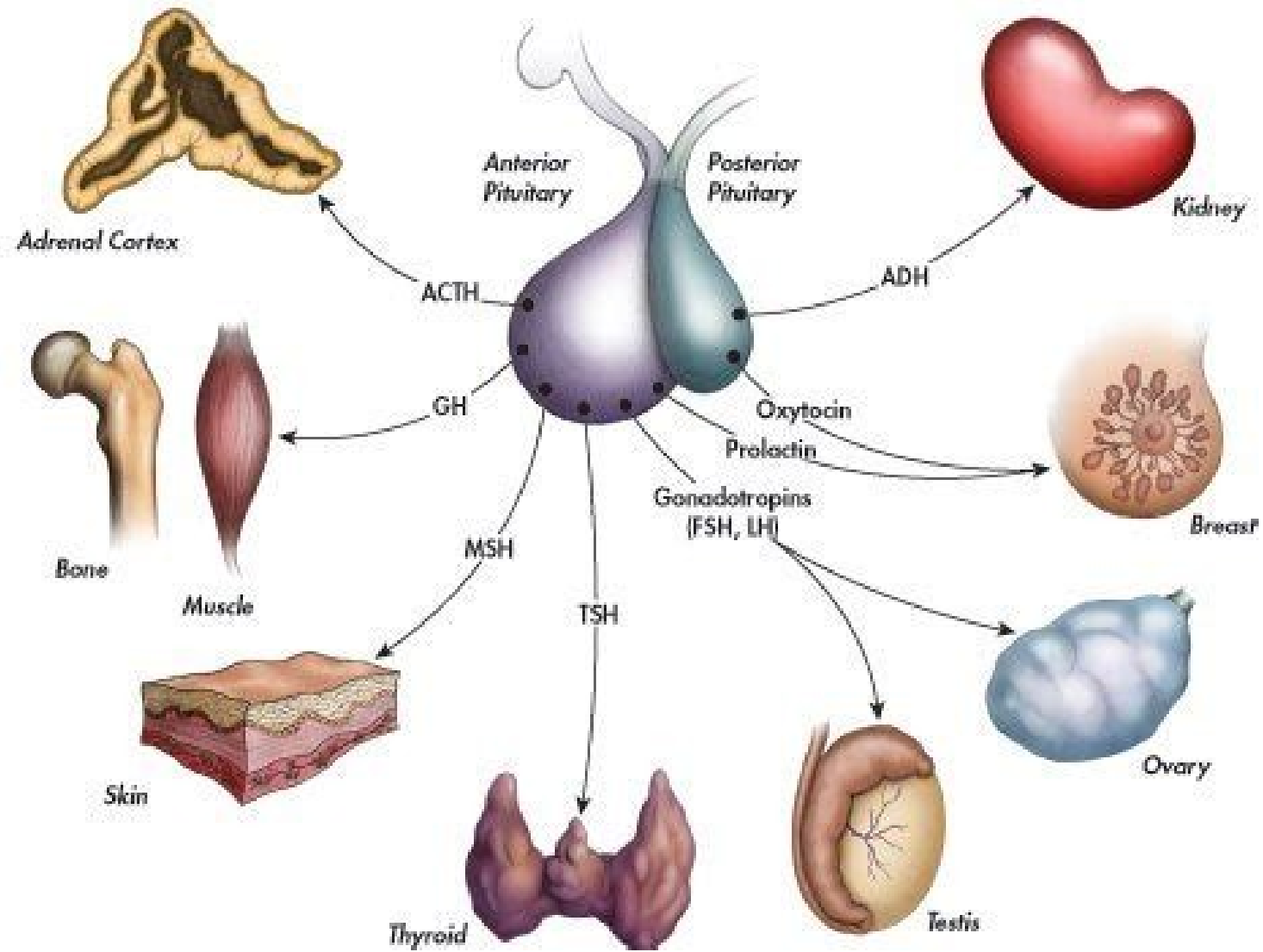
- Hypothalamic - pituitary axis
- Control of the production and release of pituitary hormones
- Pulsatile secretion
- Specific membrane receptors
- Second messenger
- Autoregulation

Pituitary

- Anterior pituitary
 - Adenohypophysis
 - ACTH, TSH, FSH, LH, PRL, GH, MSH
 - Endocrine regulation
- Posterior pituitary
 - Neurohypophysis
 - ADH, Oxytocin
 - Neural regulation of hormone release



Hypofýza



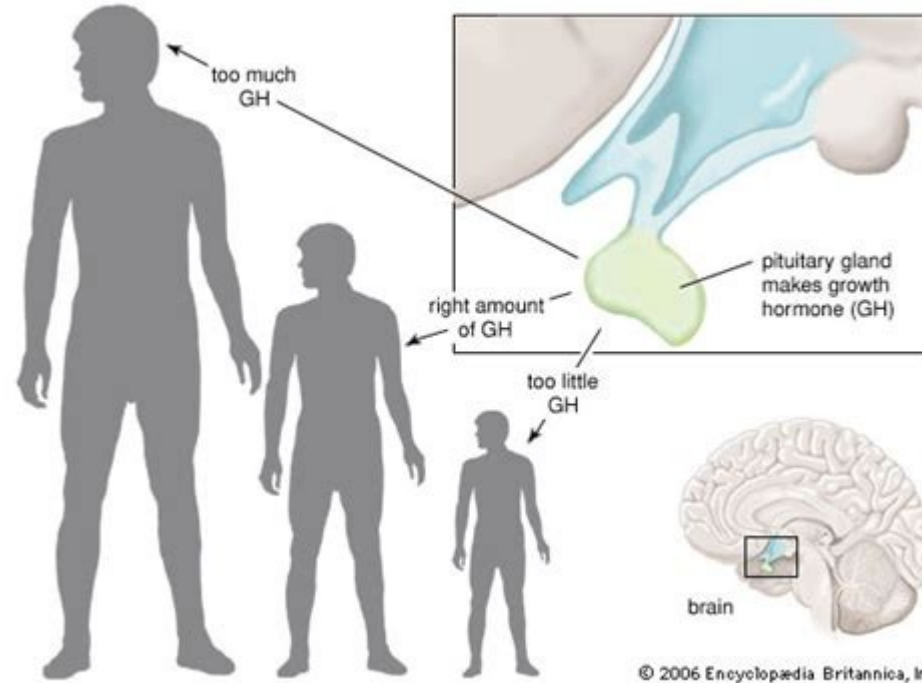
Hypopituitarism

- General
- Selective

- Infections, infarctions, cysts, tumors, injuries, iatrogenic, Sheehan syndrome
- Fertility, Growth ...
- Therapy - supplementation

Poruchy rústového hormonu

- GH overproduction
 - Gigantism
 - Before puberty
 - Acromegaly
 - After puberty



Poruchy růstového hormonu - akromegalie



Age 9



Age 16



Age 33



Age 52



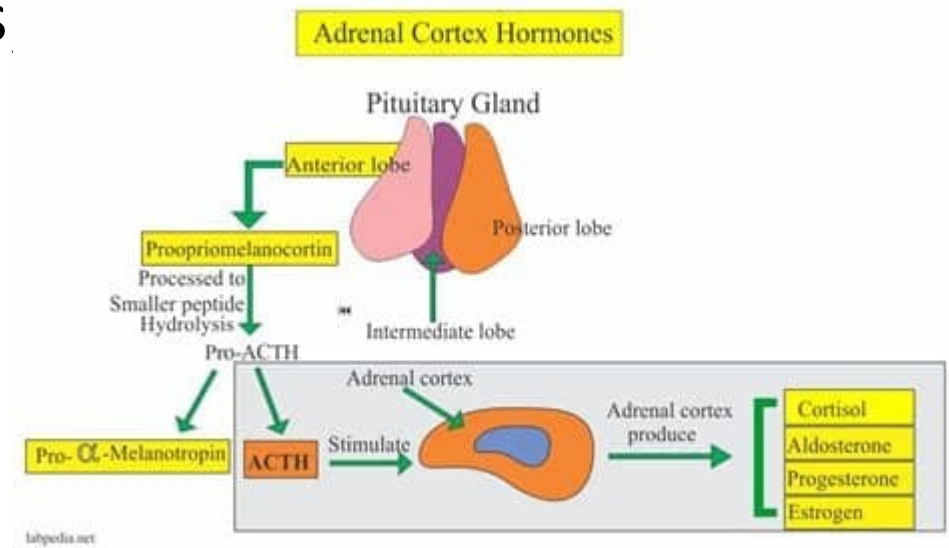
Poruchy sekrece ADH

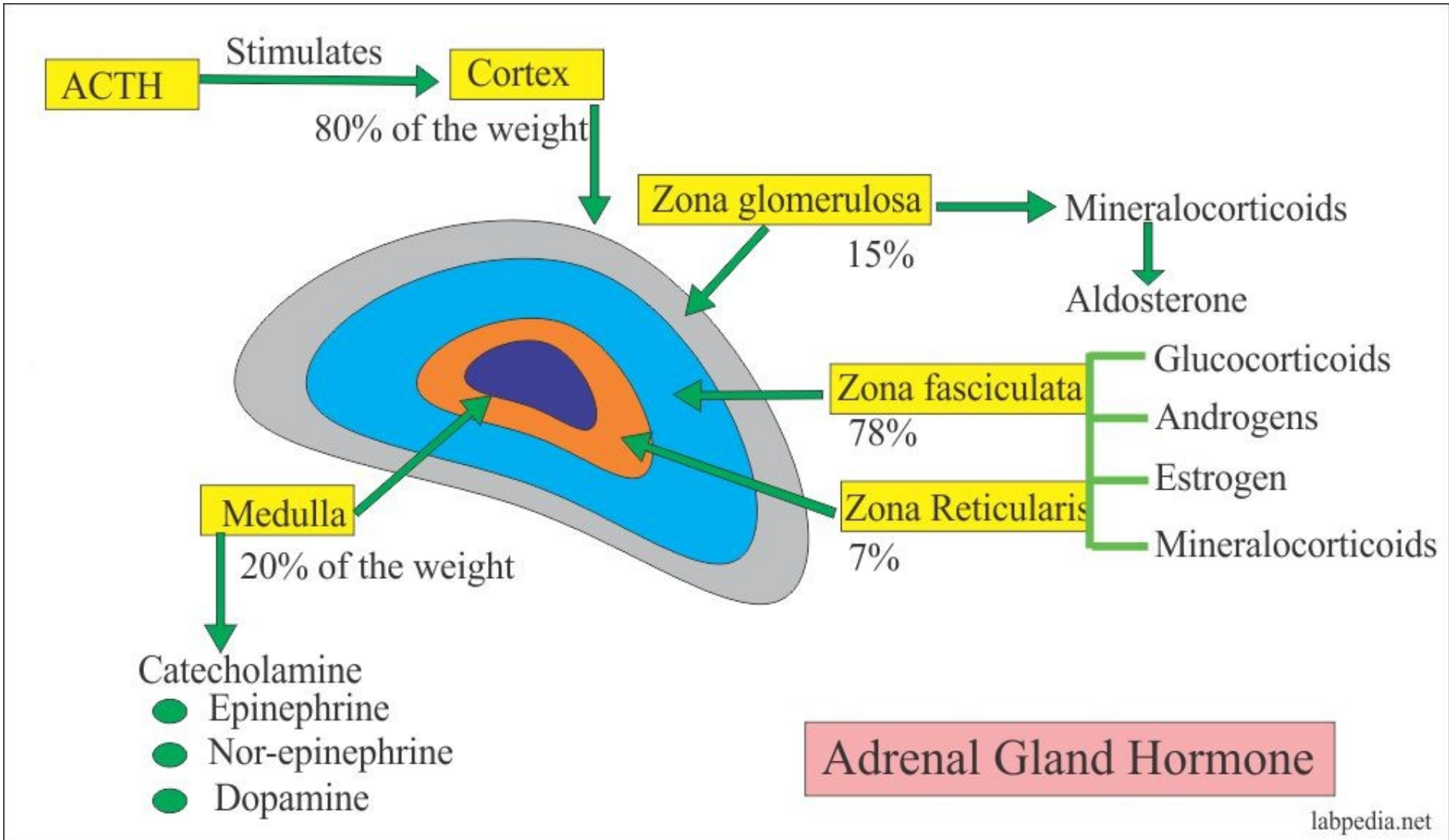
- ADH insufficiency
 - Diabetes insipidus
 - Polydipsia, polyuria
- Overproduction ADH
 - Syndrome of IADH
 - Hypoosmolarity of plasma, hyponatremia, oliguria

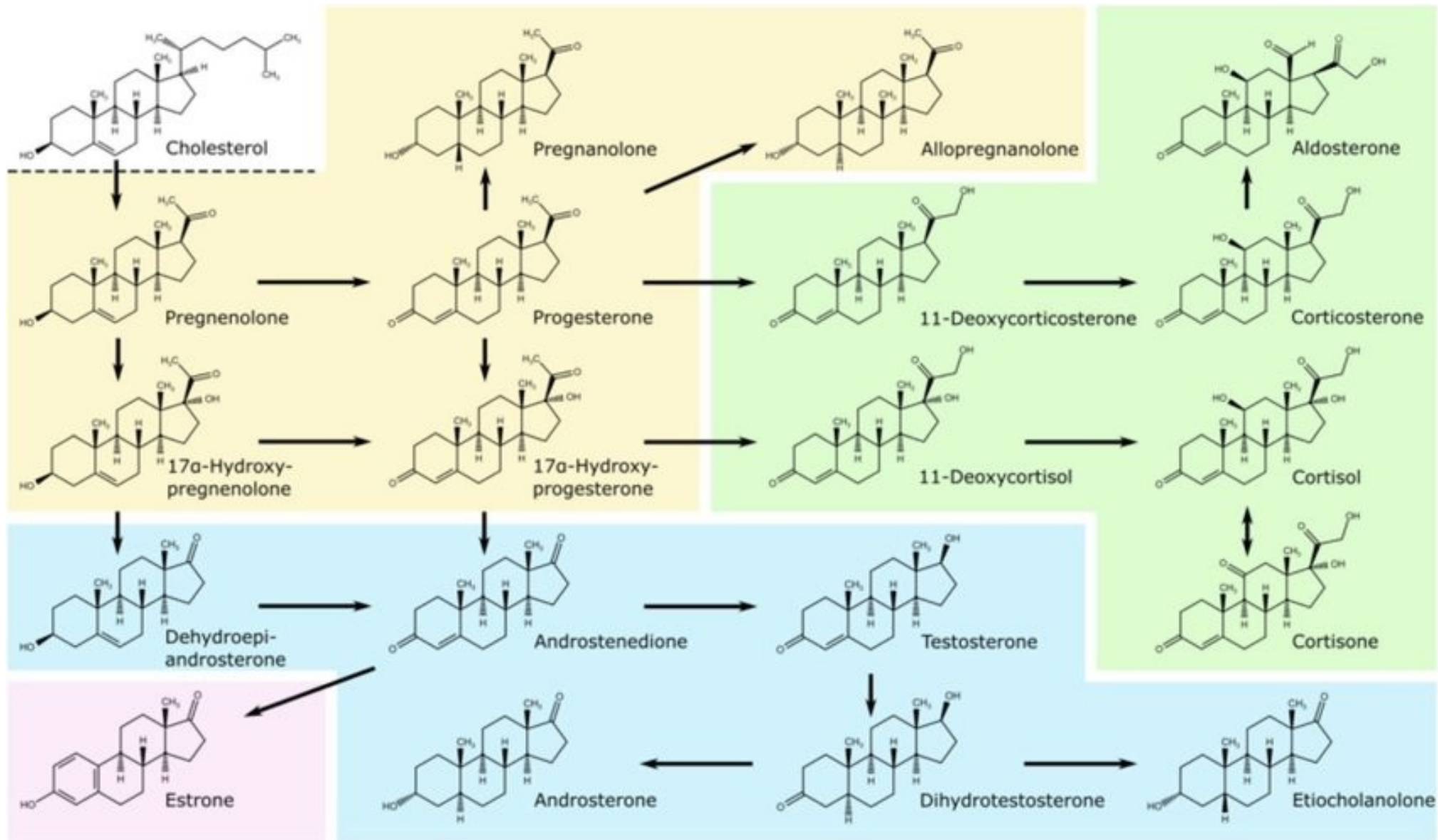
Adrenal glands



- Cortex
 - Zona glomerulosa (mineralocorticoids)
 - Zona fasciculata (glucocorticoids)
 - Zona reticularis (androgens)
- Medulla
 - catecholamines







Disorders of the adrenal glands

- Insufficiency
 - Primary – Addison's disease
 - Autoimmune, tuberculosis, hemorrhage (Waterhouse-Friderichsen syndrome in meningococcal infections)
 - Secondary – pituitary disorders, discontinuation of glucocorticoid therapy

Addison's disease

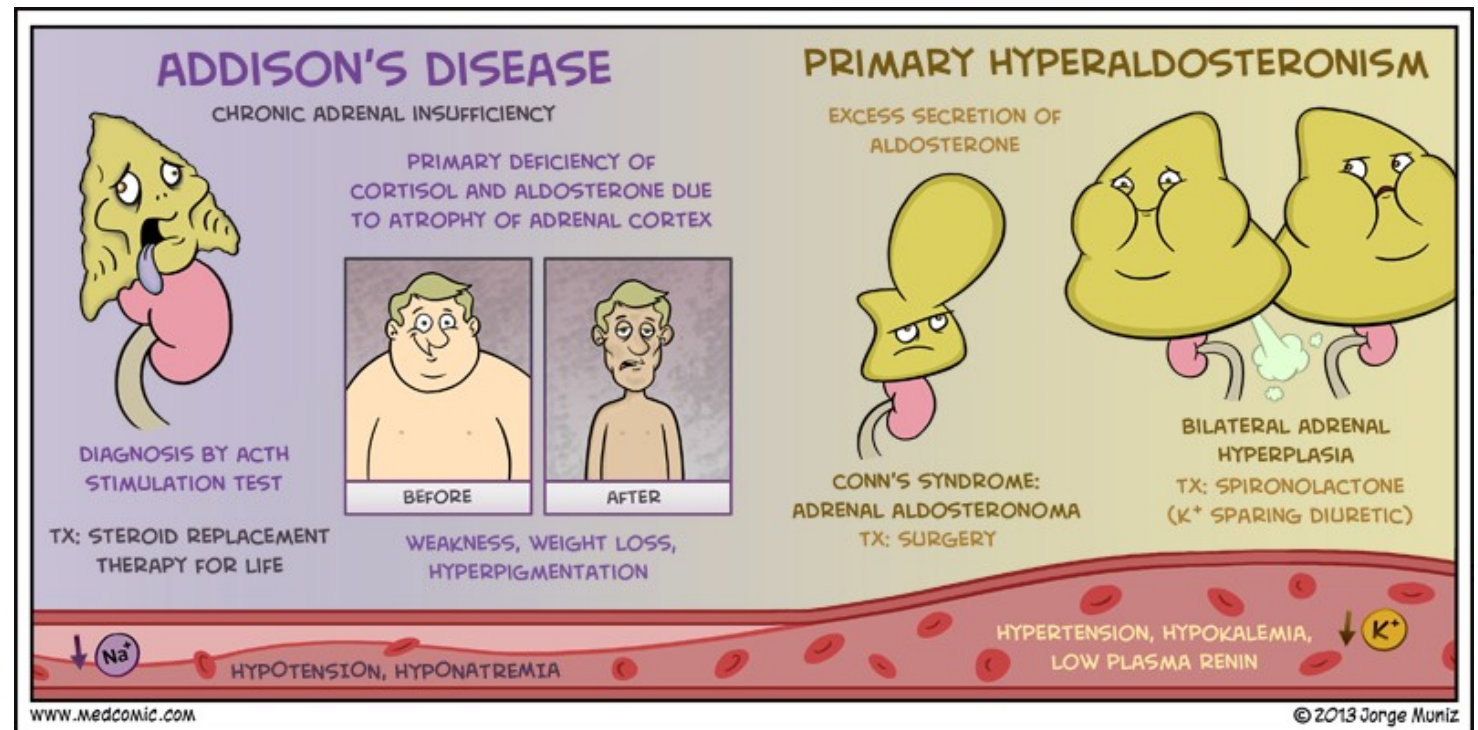
- Aldosterone insufficiency
 - Hypotension, hyponatremia, hyperkalemia
- Skin pigmentation
 - Pro-Opioid-Melanoma-Cortico-Tropin
- ACTH increased (diff-dg secondary adrenal insufficiency)



Conn's disease

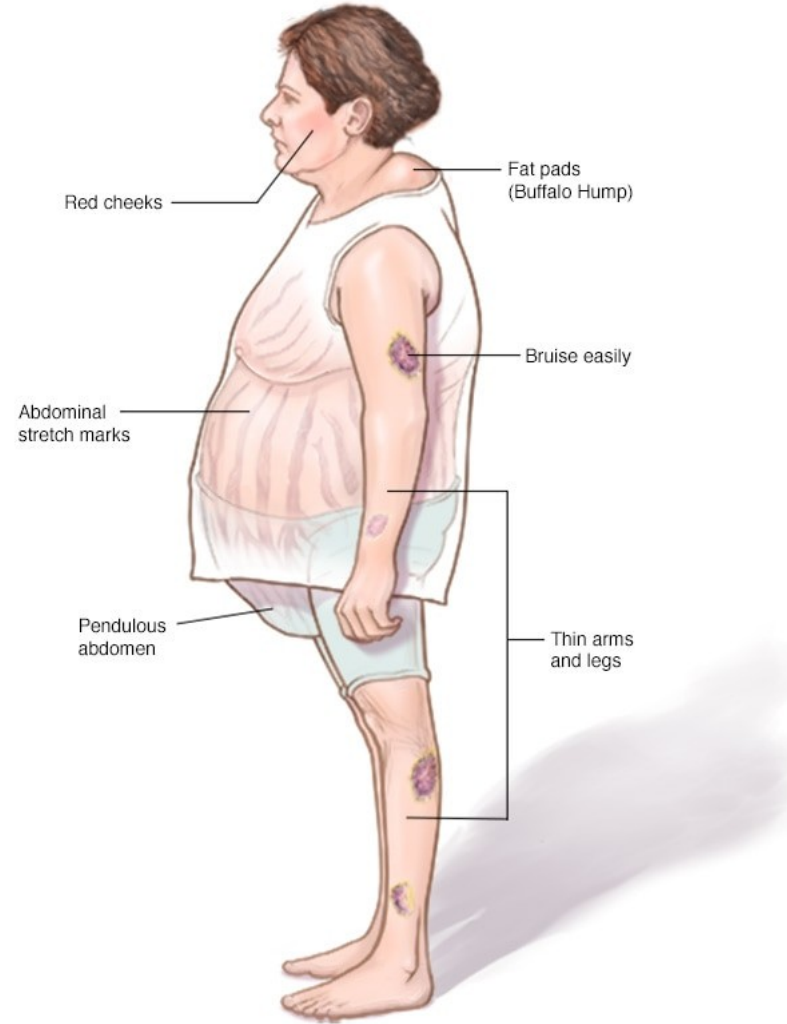
- Primary hyperaldosteronism
 - Mostly unilateral endocrine active tumor

- Hypertension
- Hypernatremia
- Hypokalemia



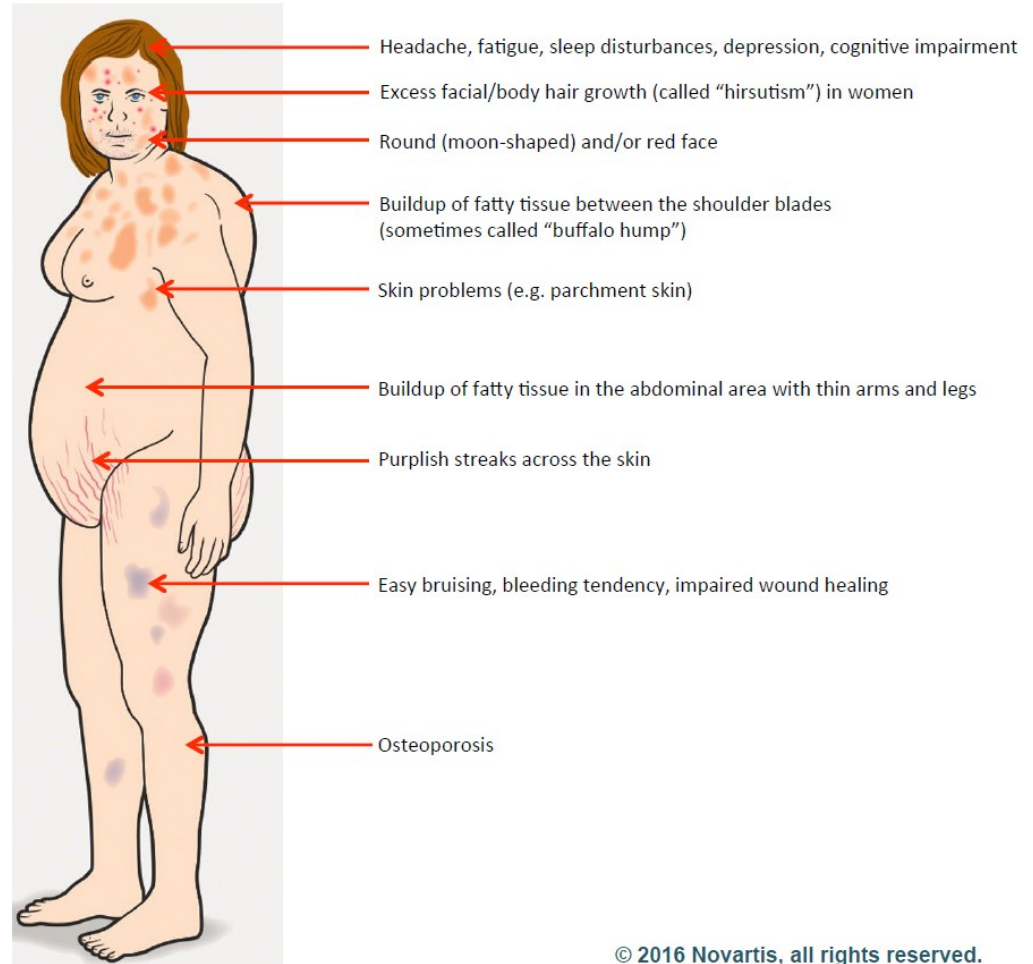
Cushing's syndrome

- **Hypercortisolism**
 - Primary
 - Adrenal adenoma
 - Secondary
 - Cushing's disease - overproduction of AC
 - Ectopic production - lung ca
 - Iatrogenic



Cushing's syndrome

- Central obesity
- Hypertension
- Osteoporosis
- Reduced growth
- Mental changes

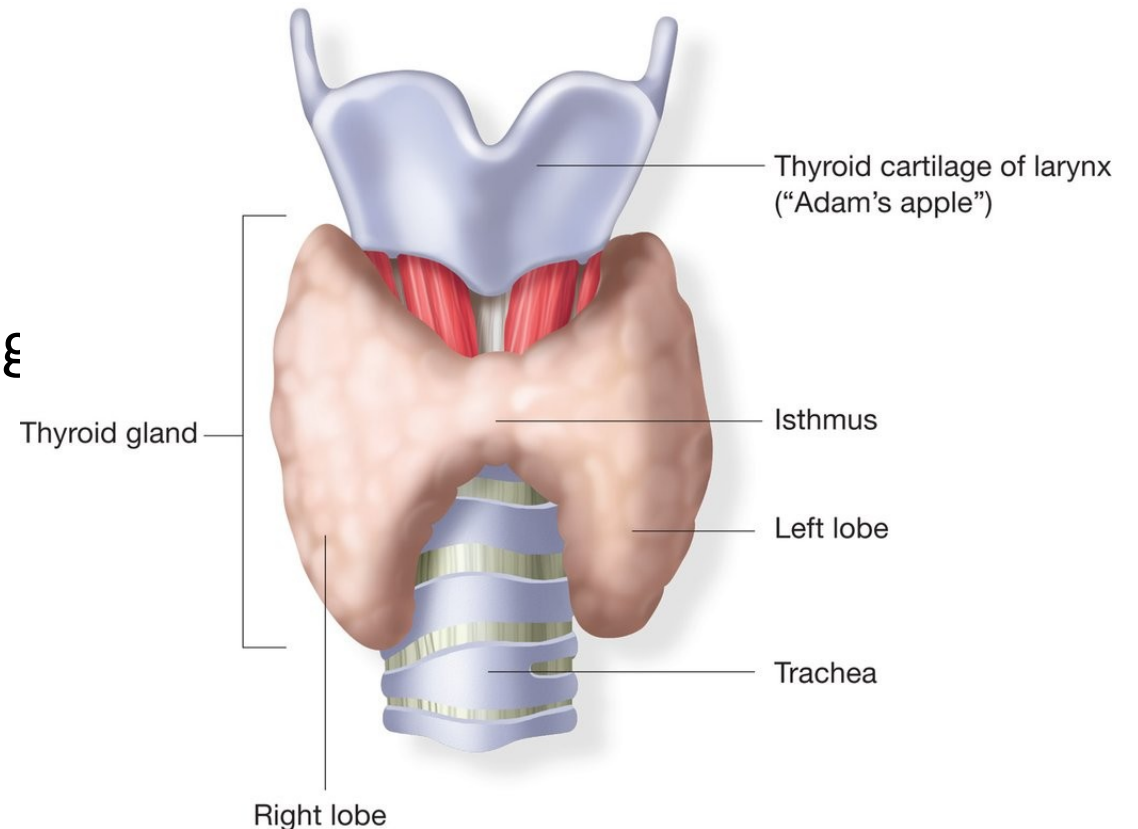


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- Hirsutism, acne, oligomenorrhea

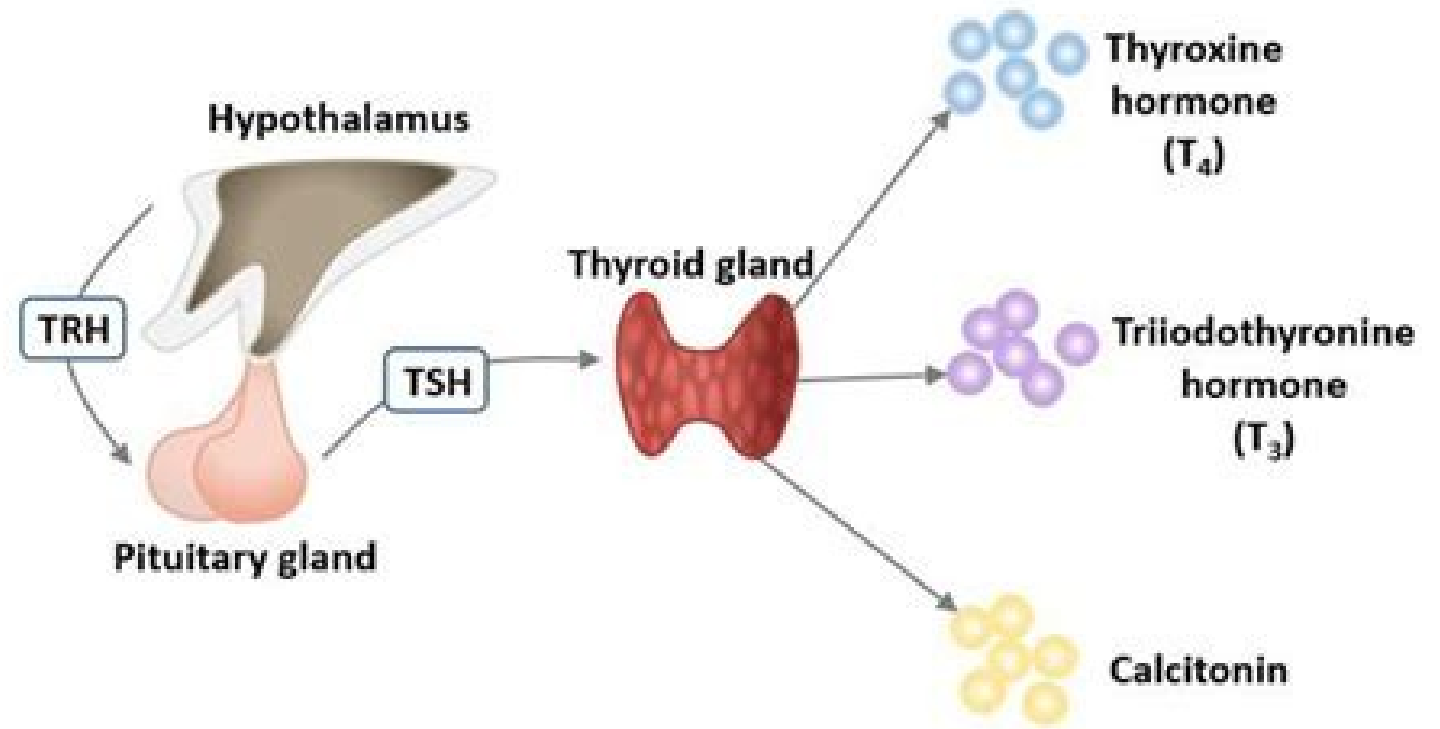
Thyroid gland – physiology

- Actions of the thyroid
 - Controls body temperature
 - How body burns calories
 - Controls how fast food moves through digestive tract
 - Muscle strength
- Thyroid hormones
 - T4-thyroxine
 - T3-triiodothyronine
 - Calcitonin

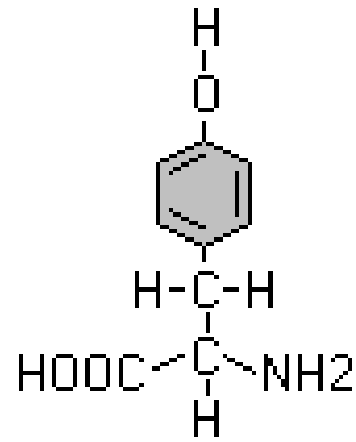


Thyroid

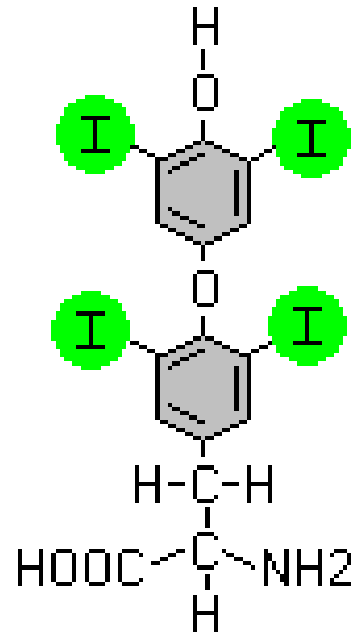
- Iodine is rare
- Ubiquitary receptors
- Highly potent action
- Very common disorders
 - 5% women
 - 0,5% men



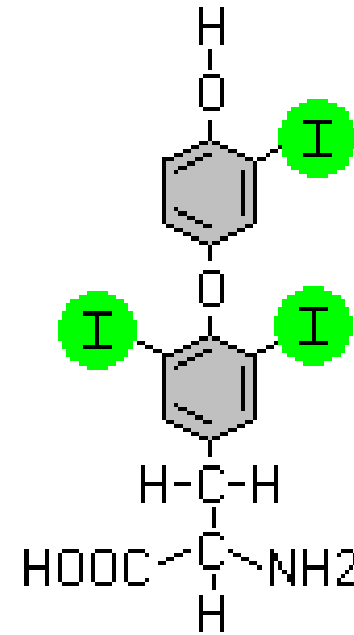
Thyroid hormones



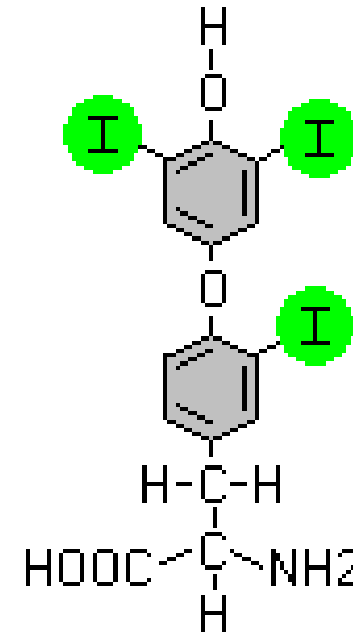
Tyrosine



Thyroxine (T4)

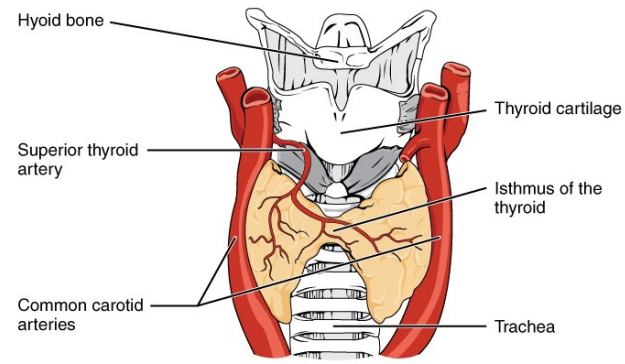


Triiodothyronine (T3)

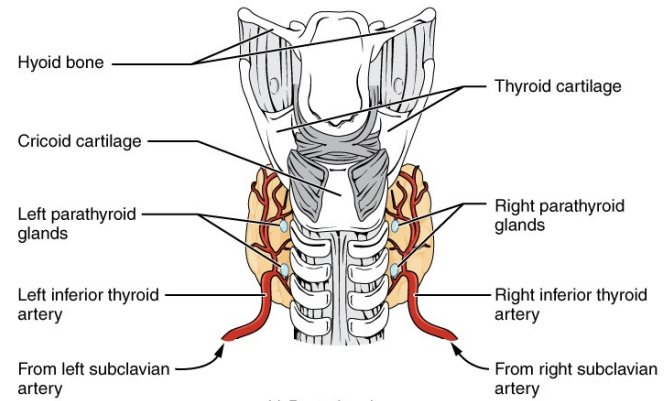


**"Reverse T3"
(inactive)**

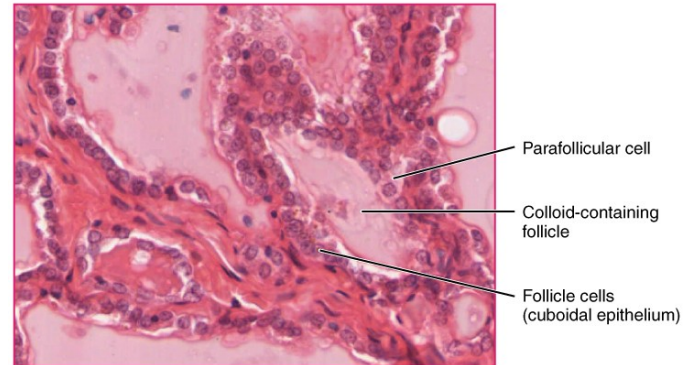
Thyroid gland



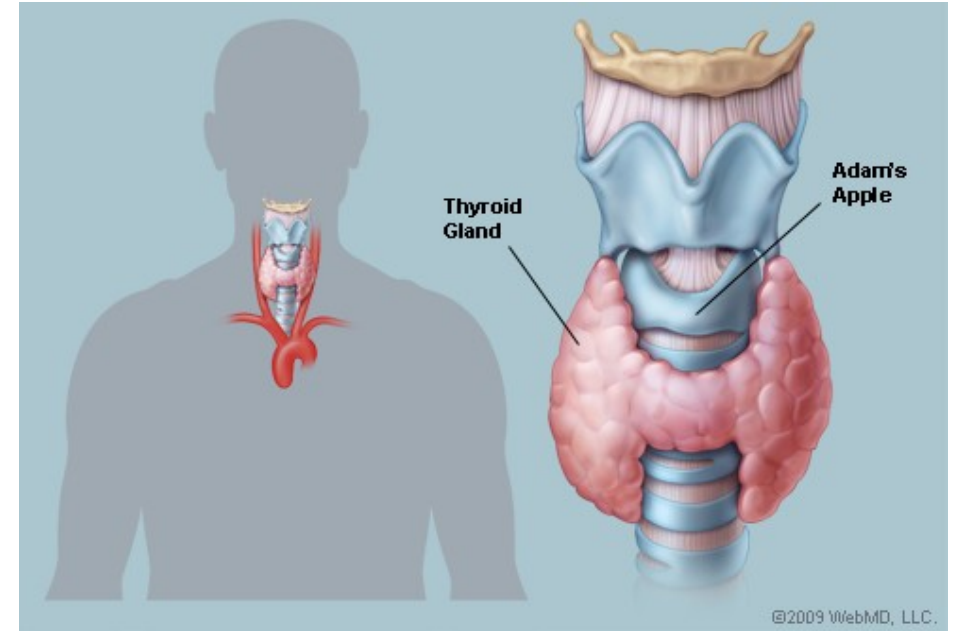
a) Anterior view



b) Posterior view

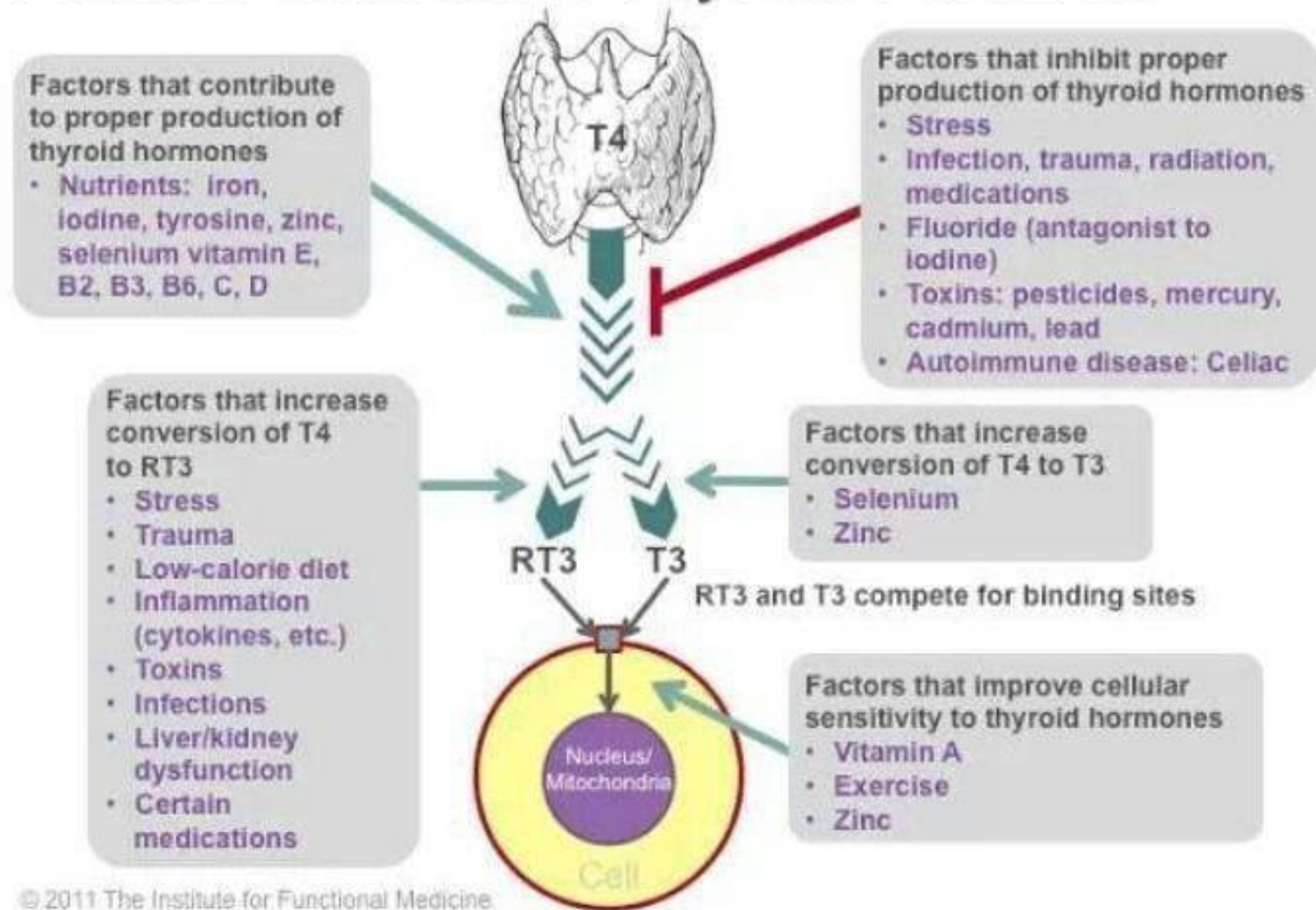


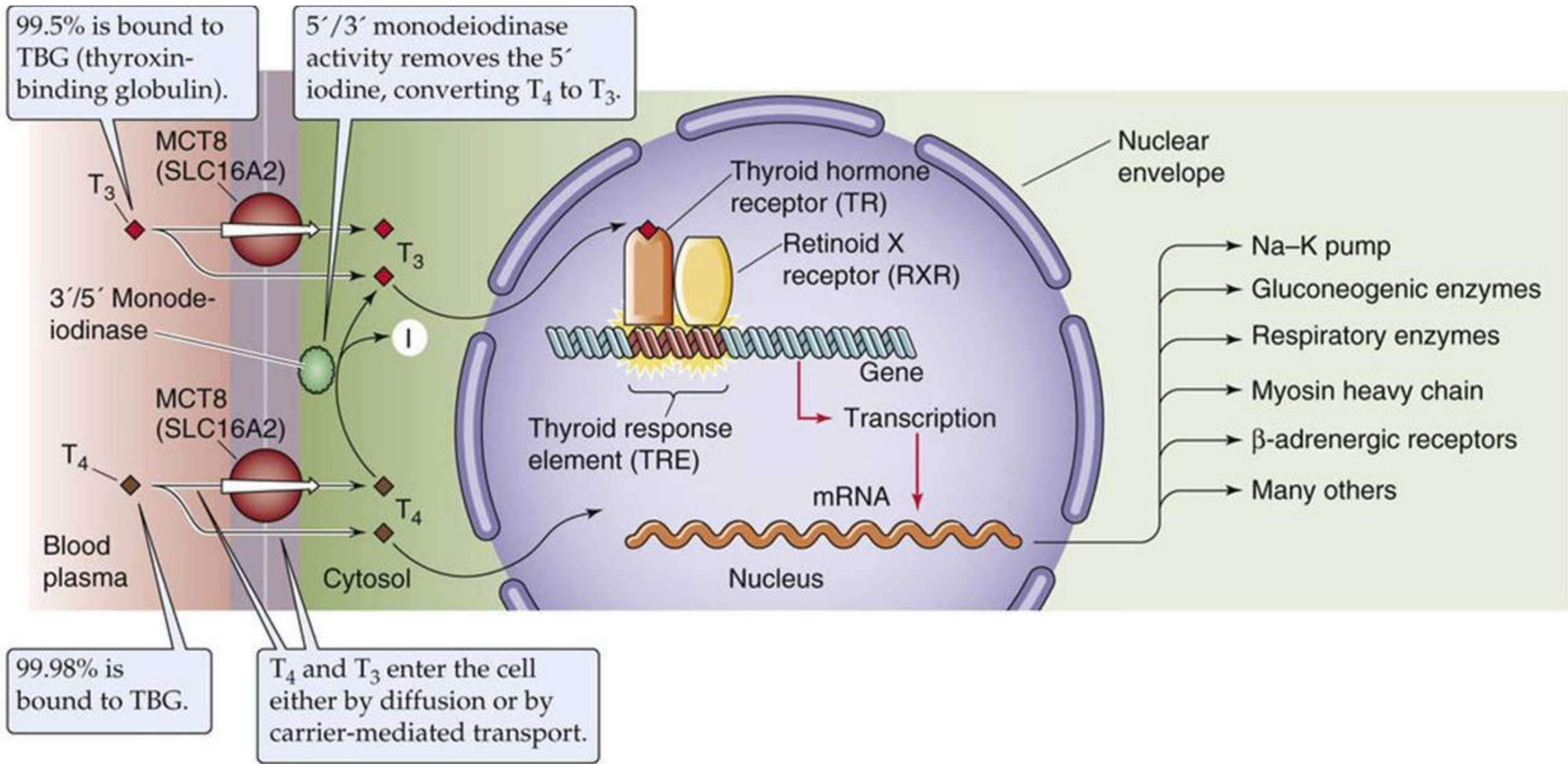
c) Thyroid follicle cells

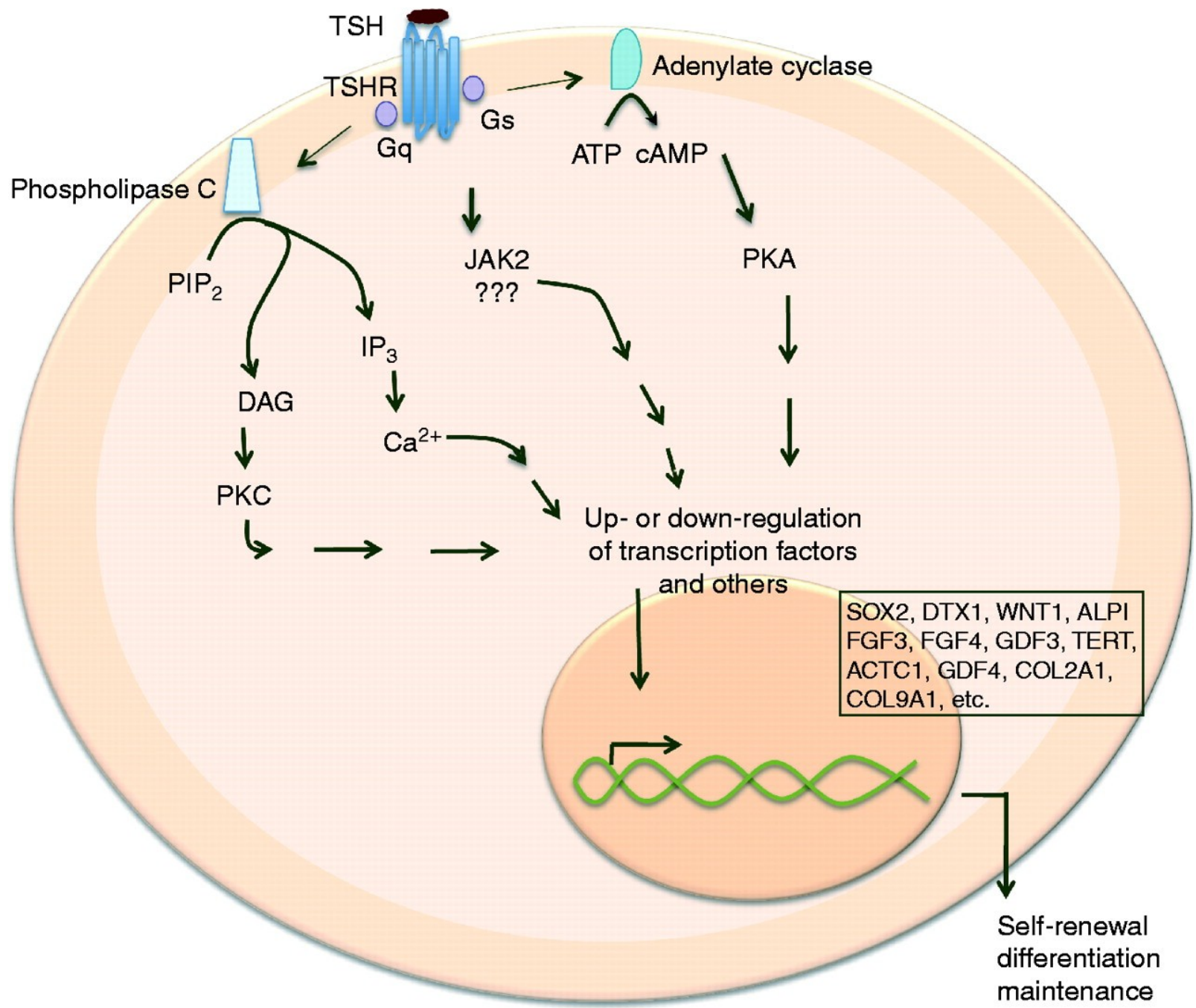


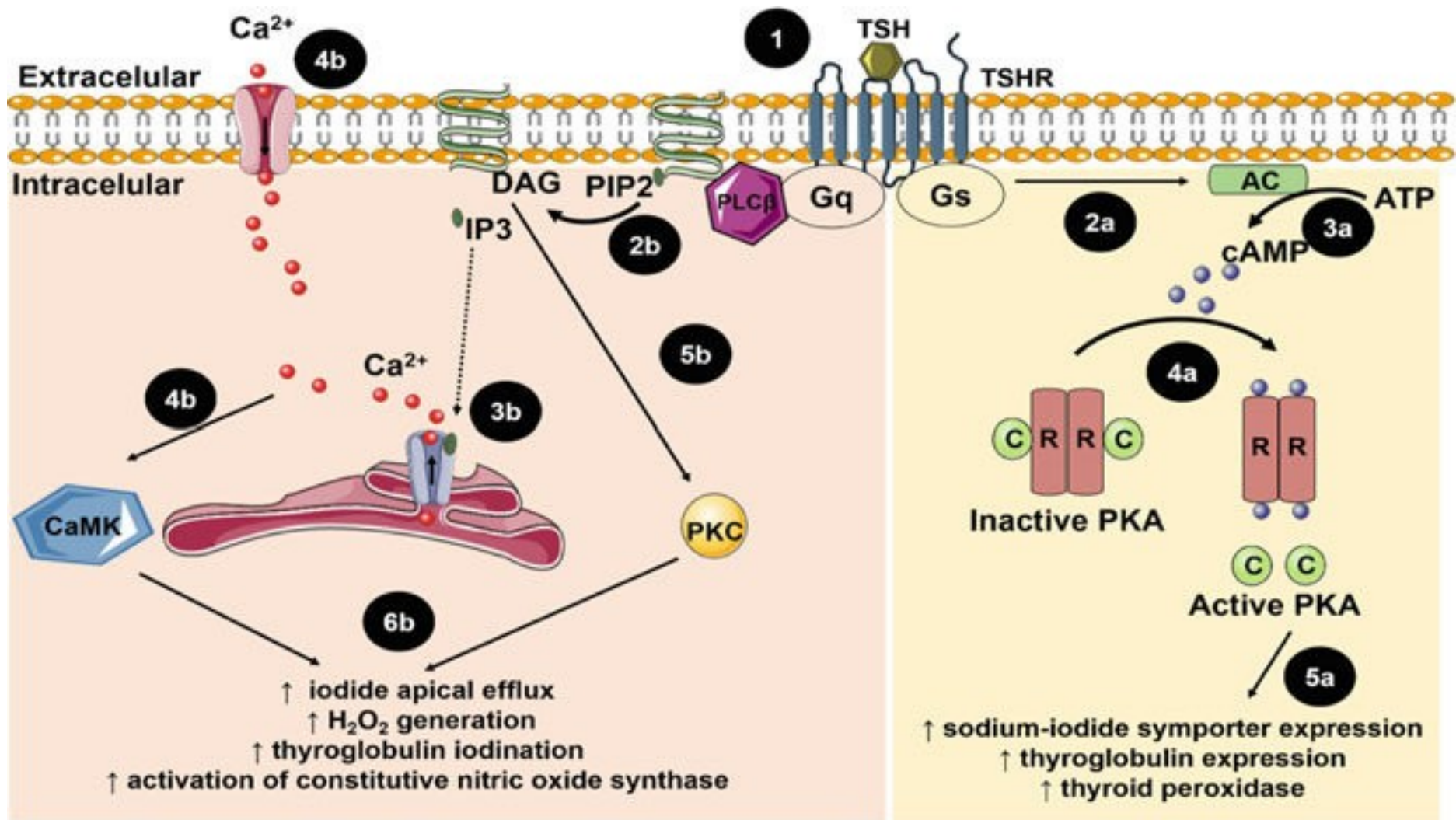
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Factors that Affect Thyroid Function



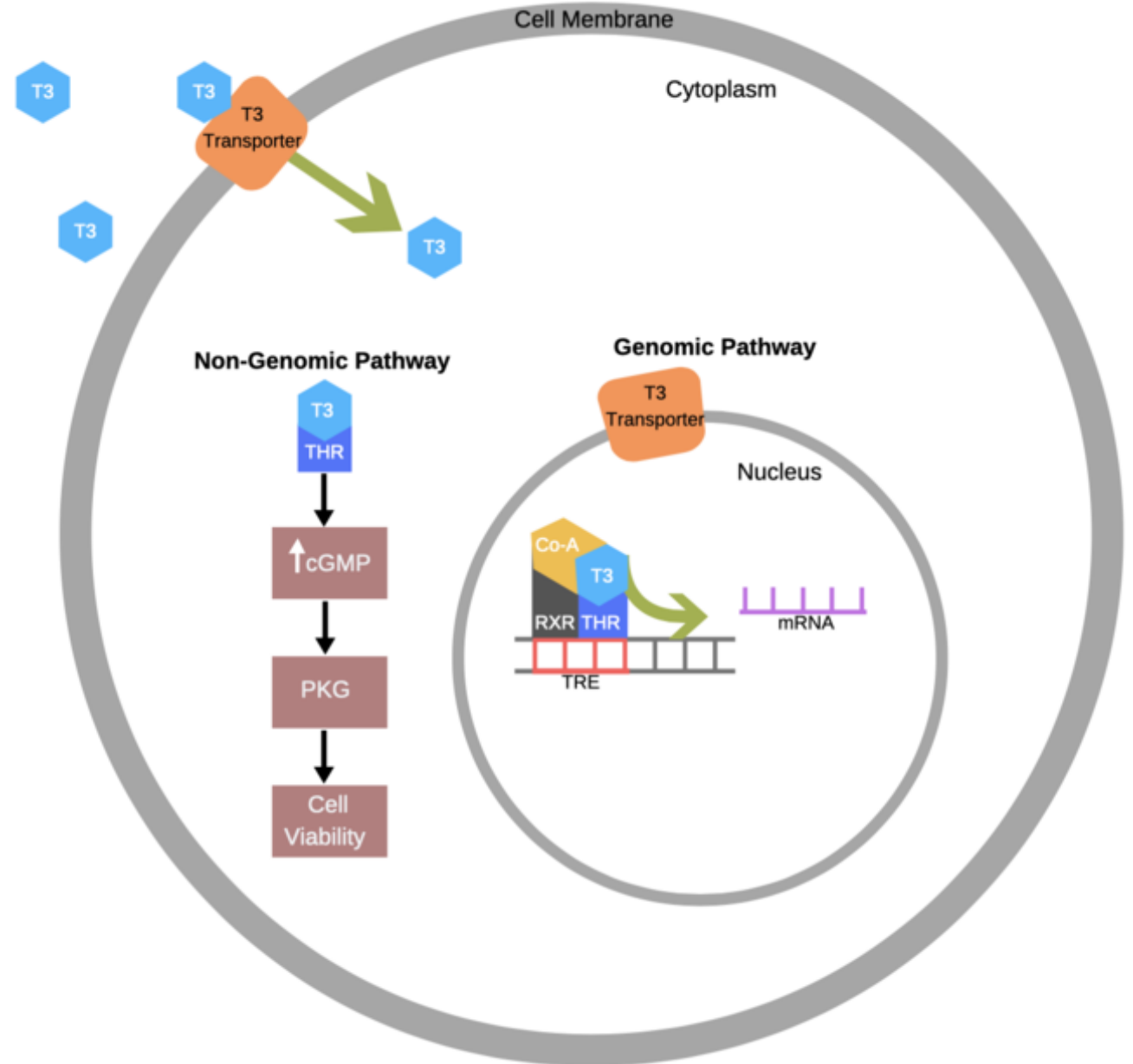






Repression of TR

- Depression
- Loss of vision
- Heart problems
- Weight gain
- Fatigue
- Hearing loss
- Sensitivity to cold
- Weakness
- Issues with digestion
- Cognitive impairment



Hyperthyroidism vs hypothyroidism

Hypothyroidism **Hyperthyroidism**

Symptoms:

Extreme Tiredness/Lethargy/
Lack of Stamina/Motivation
Memory Loss/'Brain Fog'
Depression/
Mood Swings
Hearing Loss

Weight
Gain

3pm
crash

Broken
Sleep

Brittle/
Ridged
Nails

Joint/
Muscle
Pain

Hair
Loss

Constipation

Prmenstrual Tension

Intolerance to Cold/Heat/
Sweating/Low Body Temperature

Tingling & Numbness in Extremities

Signs:

Sparse Eyebrows
Especially outer ends

Swelling of the Face
Especially around Eyes
(Oedema)

Changes at the back of
the Eye (at Fundus Oculi)

Wasting of Tongue
Listless, dull to look Eyes
Hoarseness

Rapid Heart
Rate with
weak force
of contraction

Slow Thinking
Slow Pulse
Rate

Non pitting oedema of ankles

Cold/dry/sore/scaly skin/brittle nails
Low basal activity level temperature
Dry/course/brittle hair or hair loss
Unexplained Weight Gain

Pounding Heart Beat

Nervousness
Sluggish
Movement

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Symptoms:

Protusion of one or both
eyeballs (exophthalmos)

Breathlessness

Nervousness

Difficulty
Sleeping/
Insomnia

Fatigue

Itching
-overall

Heartbeat
Sensations
Palpitations

Weakness

Diarrhoea

Increased Bowel Movements

Heat Intolerance

Light or Absent
Menstruel Periods

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Signs:

Protruding Eyes
(exophthalmos)

Hair Loss

Staring Gaze
Nausea & Vomiting
Warm Moist Skin

Goitre

Fast
Heart
Rate

Trembling
Hands

Skin Blushing/ Flushing

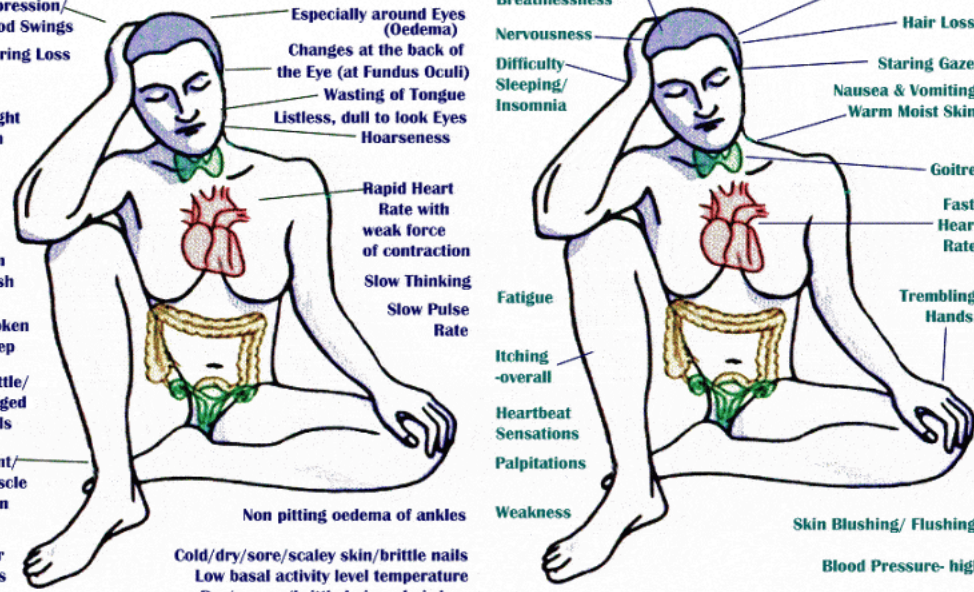
Blood Pressure- high

Pulse- Pounding

Weight Loss

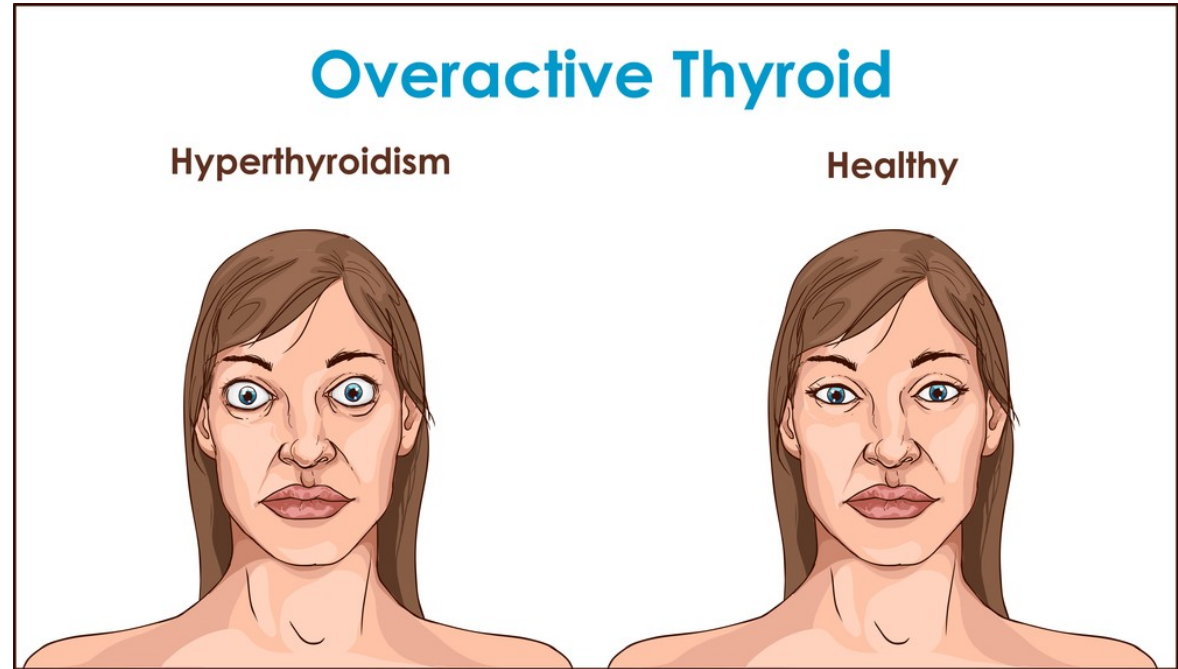
Muscle Weakness

Breast Development in Men



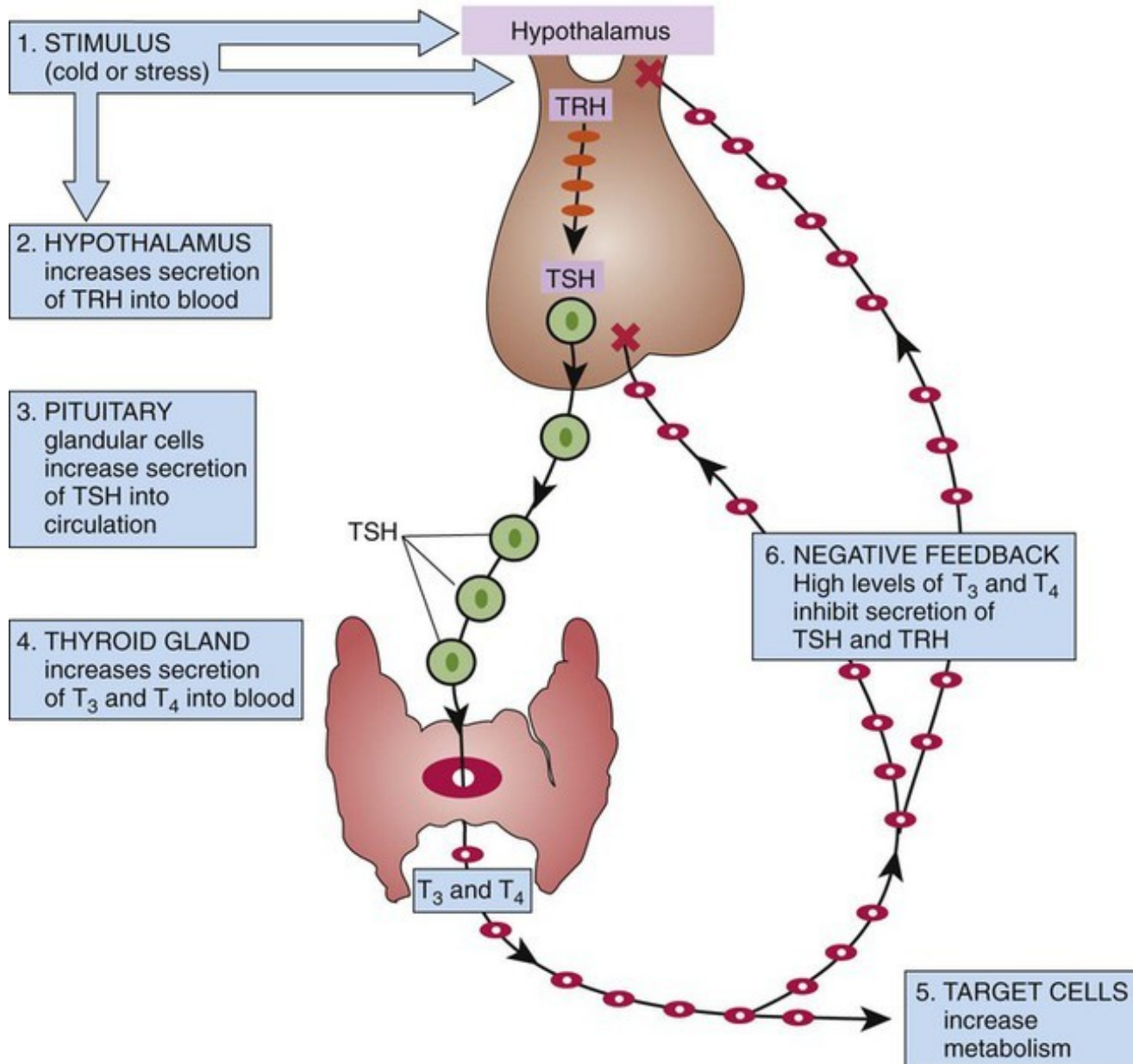
Hyperthyroidism

- Emotional symptoms
 - Nervousness
 - Restlessness
 - Anxiety
 - Irritability
 - Sleeplessness or insomnia
 - Exhaustion



Causes of hyperthyroidism

- Grave's disease
- A benign nodule on the thyroid
- Thyroiditis
- Taking too much of the synthetic thyroid hormone



Hyperthyroidism DiffDg

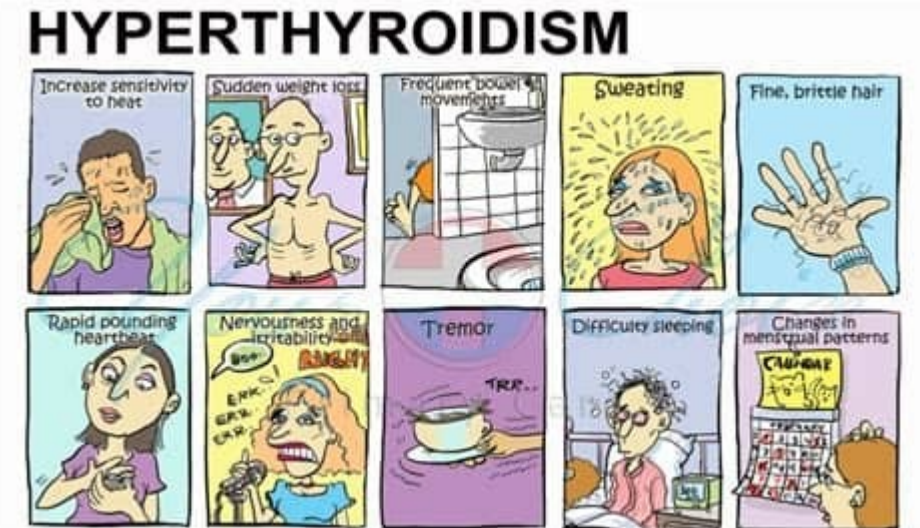
- Graves' Disease
- Toxic Multinodular Goiter
- Toxic Adenoma
- Thyroiditis
 - silent (Hashimoto's) – painless, often post partum
 - subacute (de Quervain's) – painful, post viral
 - drug-induced – amiodarone, lithium, interferon
- Thyrotoxicosis factitia
 - ingestion

Thyroid storm (crisis)

- Sudden onset
- Fever
- Profuse diaphoresis
- Flushed warm skin
- Tachycardia
- Weakness, lethargy and confusion
- Coma
- Nausea, vomiting, diarrhea

Treatment of hyperthyroidism

- Causative
- Radioactive iodine
 - Supplementation
- High-dose iodine – Wolff-Chaikoff effect
- Beta-blockers
- Antithyroid treatment
 - Propylthiouracil (PTU)
- Thyroidectomy

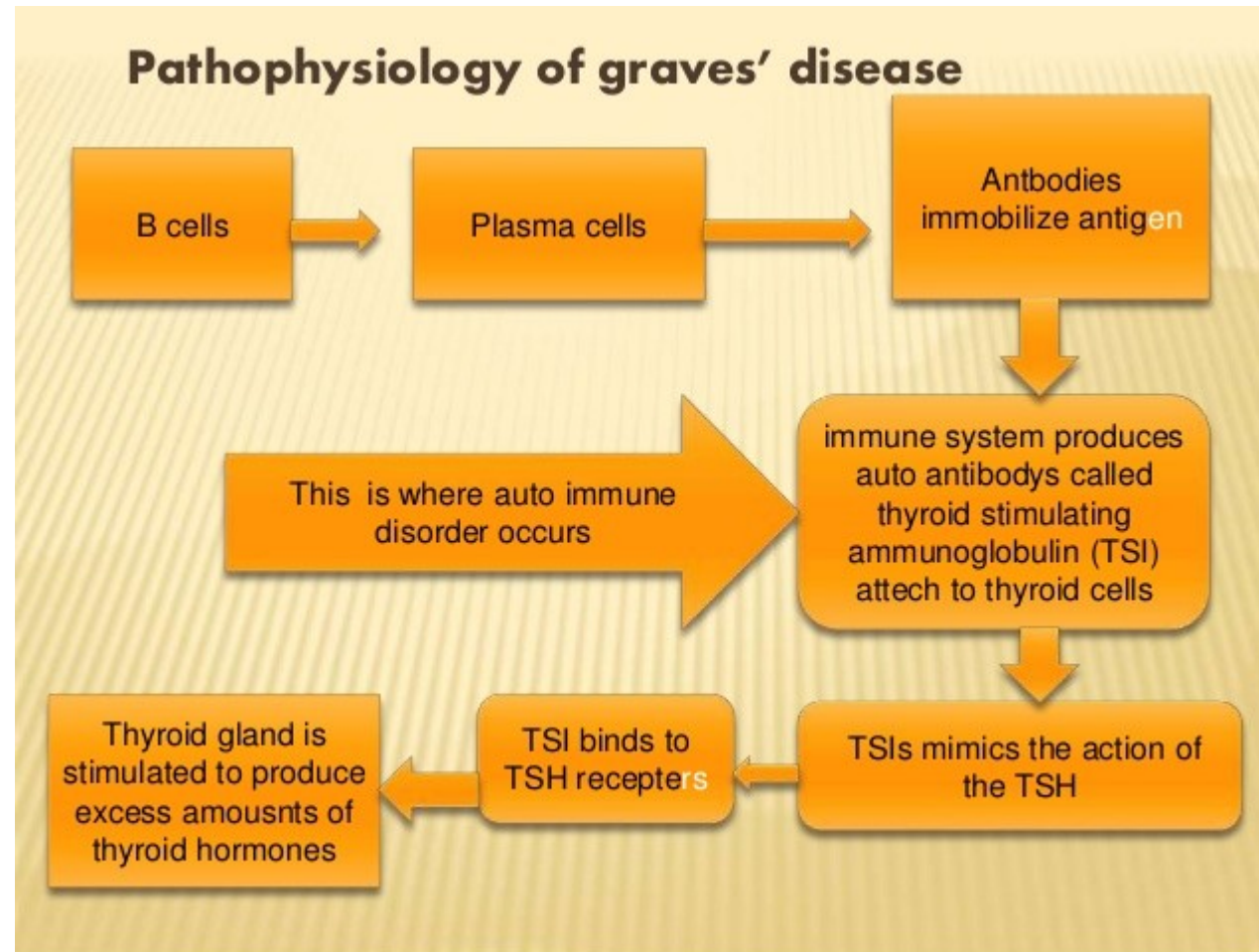


Grave's disease

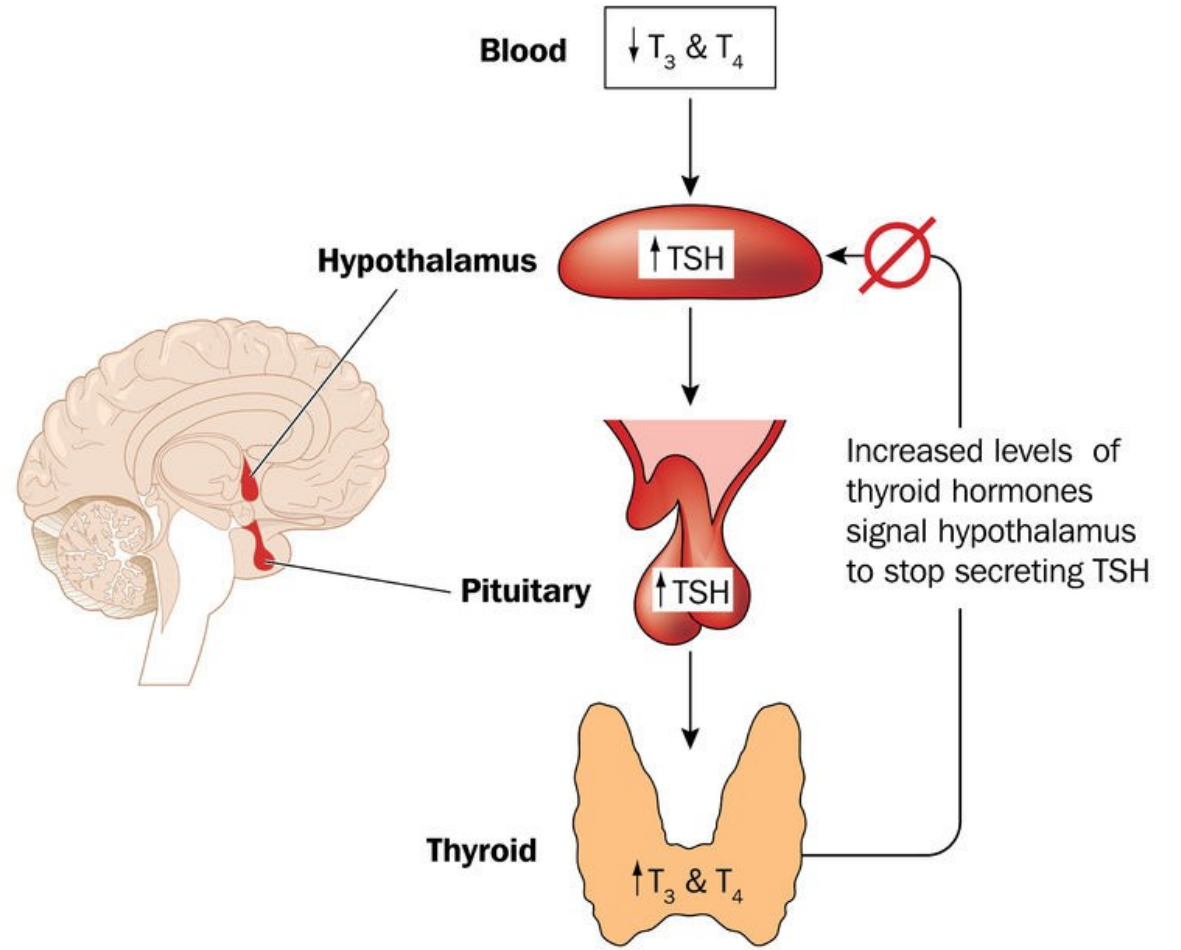
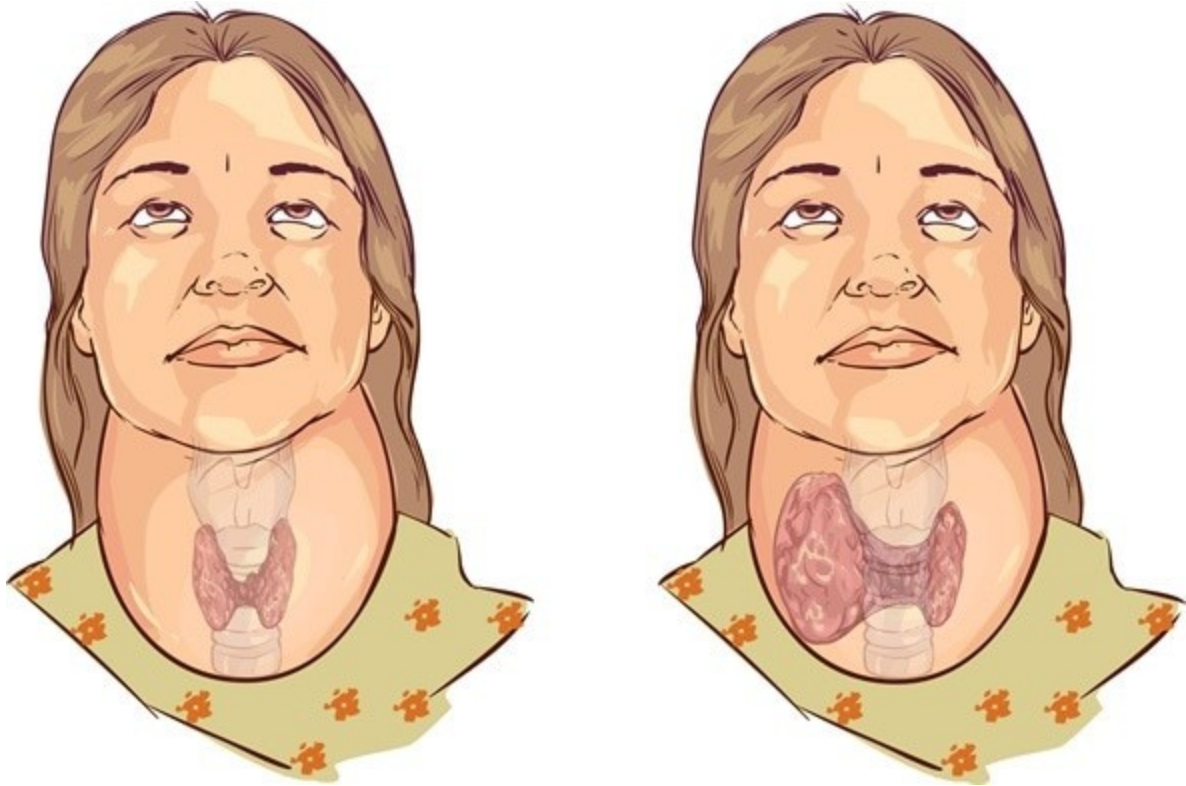
SIGNS	SYMPTOMS
<ul style="list-style-type: none">• Resting tremor• Hyperreflexia• Atrial tachyarrhythmias (including atrial fibrillation)• Enlarged painless thyroid with thrill and bruit• Warm, moist, and smooth skin• Hair loss• Onycholysis (Plummer's nails)• Gynecomastia• Localized dermatopathy (pretibial myxedema)• Thyroid acropachy (clubbing)• Stare, eyelid lag, proptosis	<ul style="list-style-type: none">• Irritability• Tremor• Proximal-muscle weakness• Difficulty sleeping• Palpitations• Heat intolerance• Weight loss• Increased appetite• Increased frequency and loose stools• Menstrual irregularity (oligomenorrhea, amenorrhea)• Decreased libido and erectile dysfunction• Photophobia, gritty eye sensation, xerophthalmia, blurry vision, diplopia



Pathophysiology of Graves diseases



Goiter



Hypothyroidism

Hypothyroidism: Clinical Symptoms and Signs

Endocrine

- Infertility and subfertility
- Menstrual disturbances
- Galactorrhea
- Goiter
- Glucose metabolism dysregulation
- Sexual dysfunction
- Increased prolactin
- Pituitary hyperplasia

Skeletal

- Muscle weakness
- Muscle cramps
- Arthralgia
- Creatine phosphokinase elevation
- Ruffian's syndrome (hypothyroid myopathy)
- Osteoporotic fracture (due to over treatment)

Electrolytes and kidney function

- Deterioration of kidney function
- Decreased estimated glomerular filtration rate
- Hyponatremia

Skin and Hair

- Dry skin
- Hair loss
- Coarse skin
- Loss of lateral eyebrows (rare)
- Yellow palms of the hand
- Alopecia areata

General Metabolism

- Weight gain (increased BMI)
- Cold intolerance / Hypothermia
- Fatigue
- Low metabolic rate
- Myxedema



Chaker L et al., Lancet 2017

Neurological

- Impaired memory
- Parosmia
- Mood impairment
- Impaired cognitive function
- Delayed relaxation of tendon reflexes
- Depression
- Dementia
- Hoarseness of voice, decreased taste, vision, or hearing
- Ataxia
- Carpal tunnel syndrome and other nerve entrapment syndromes
- Myxedema coma

Cardiovascular

- Fatigue or exertion shortness of breath
- Dyslipidemia
- Bradycardia
- Hypertension
- endothelial dysfunction or increased intima-media thickness
- Diastolic dysfunction
- Pericardial effusion
- Hyperhomocysteinemia
- ECG changes

GI/hepatic

- Constipation
- Reduced esophageal motility, non-alcoholic fatty liver disease
- Acute liver rare

Haematological

- Bleeding
- Fatigue
- Mild anemia
- Acquired von Willebrand disease
- Decreased protein C and S
- Increased red cell distribution width
- Increased mean platelet volume

Hyposekrece T3, T4 v dětství

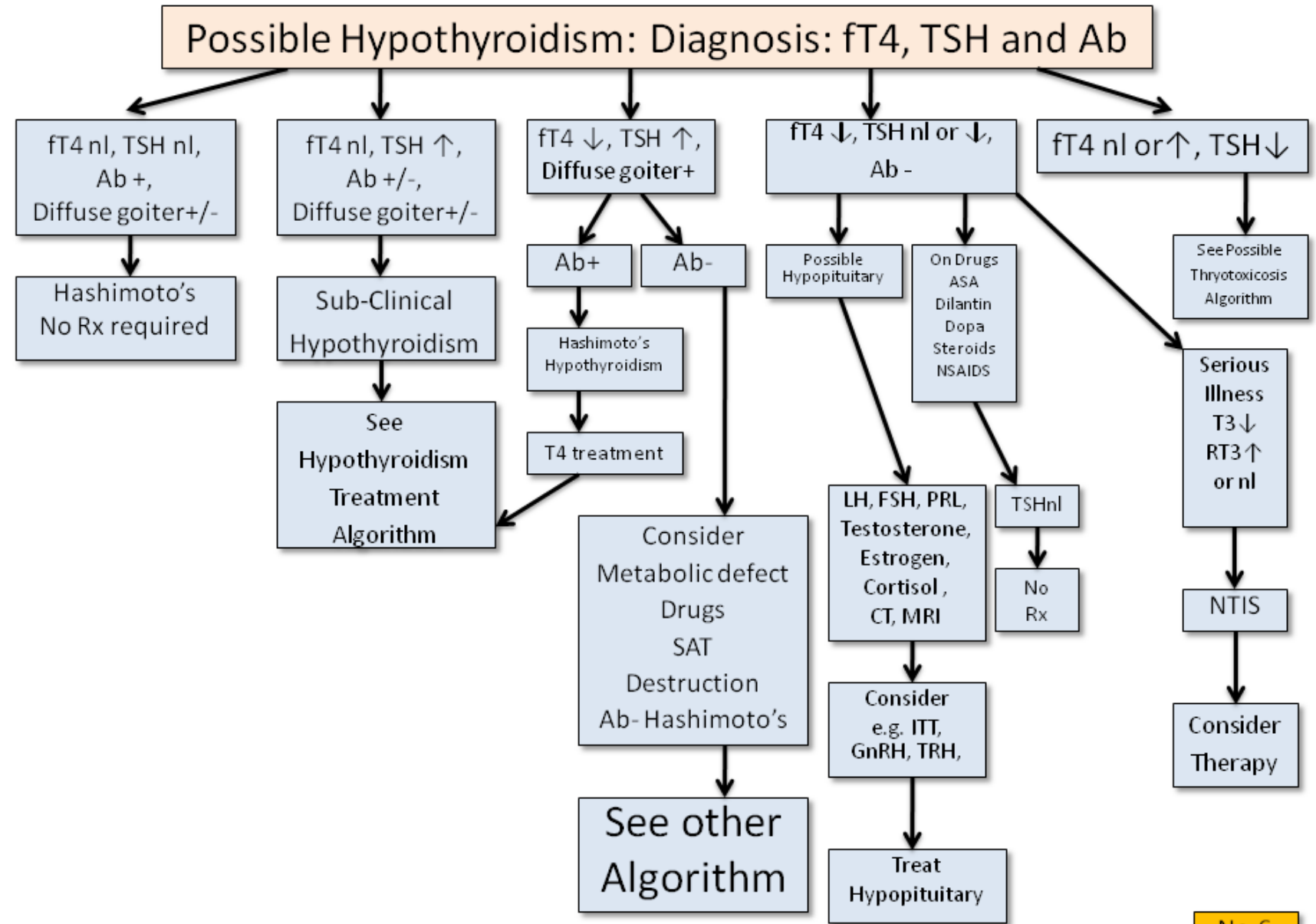
Kretenismus

nedostatek T3 a T4 již intrauterinně,
porucha vývoje žlázy nebo endemický
nedostatek jodu

- poruchy růstu, kratší končetiny
- poruchy intelektu, spavost
- únava, svalová slabost
- zácpa, velké břicho



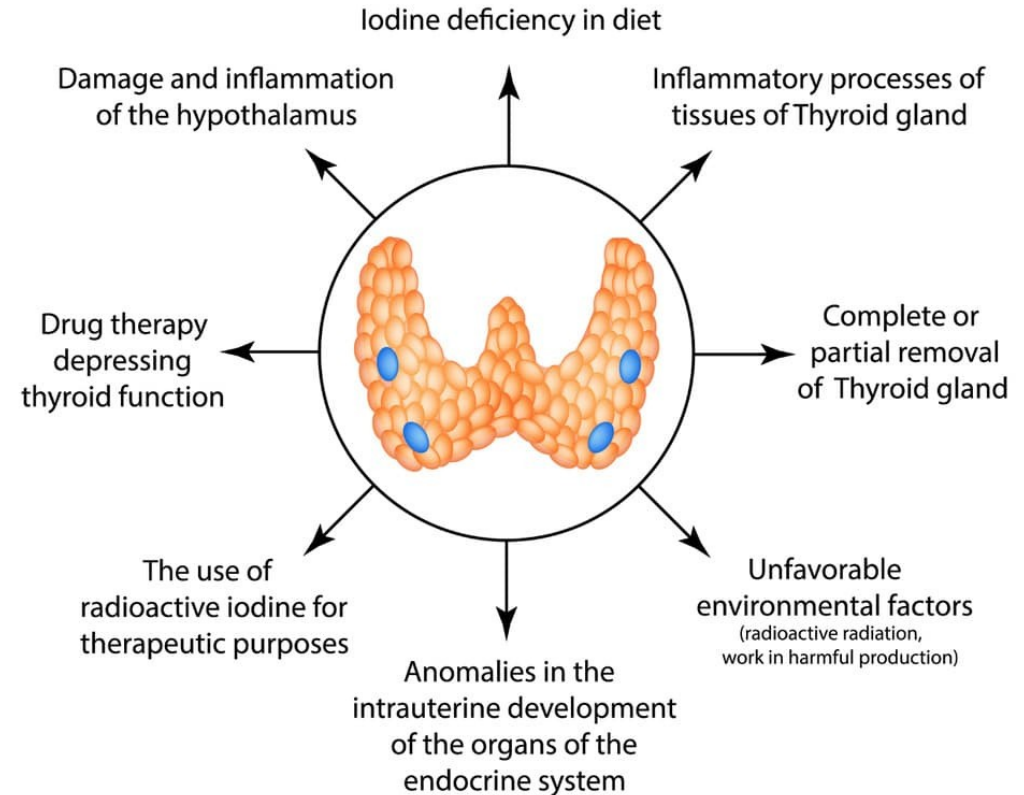
Hypothyroidism



Hypothyroidism

- Primary
 - Thyroid gland
 - Hashimoto's disease
 - Autoimmune thyroid destruction
 - Creteinism
 - Neonatal screening
- Secondary
 - Pituitary gland

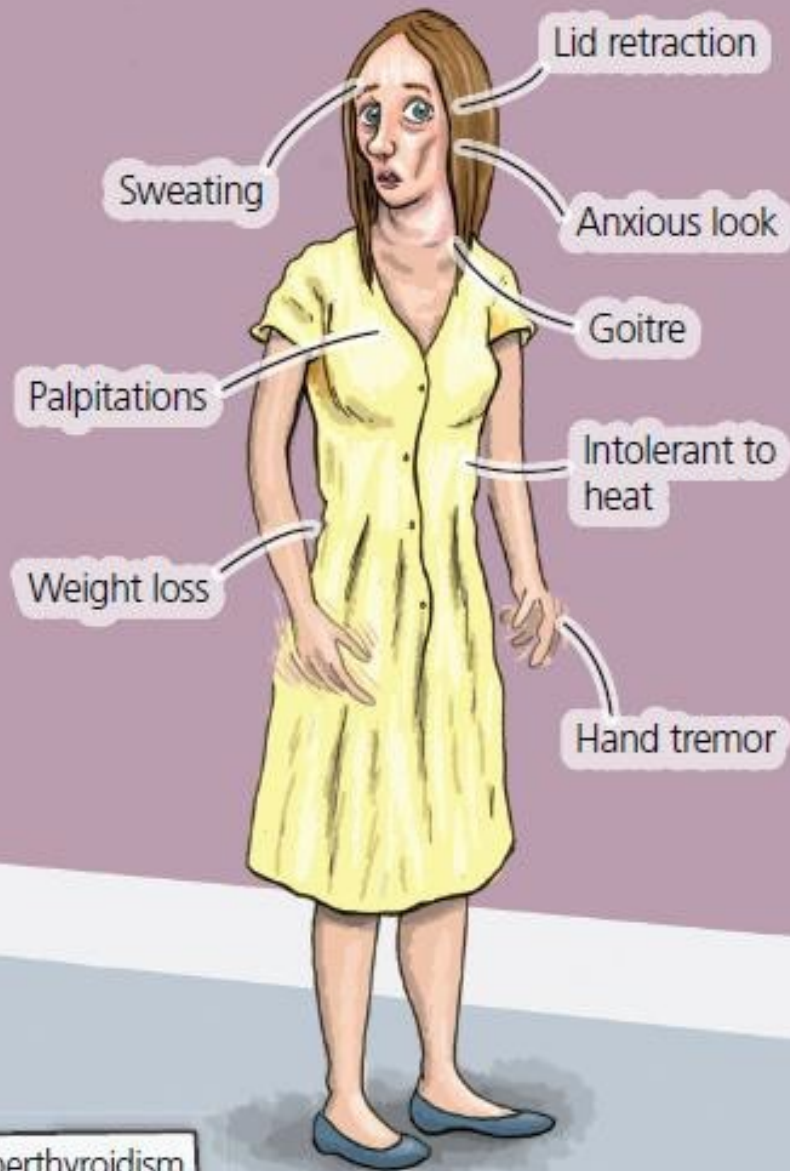
CAUSES OF HYPOTHYROIDISM

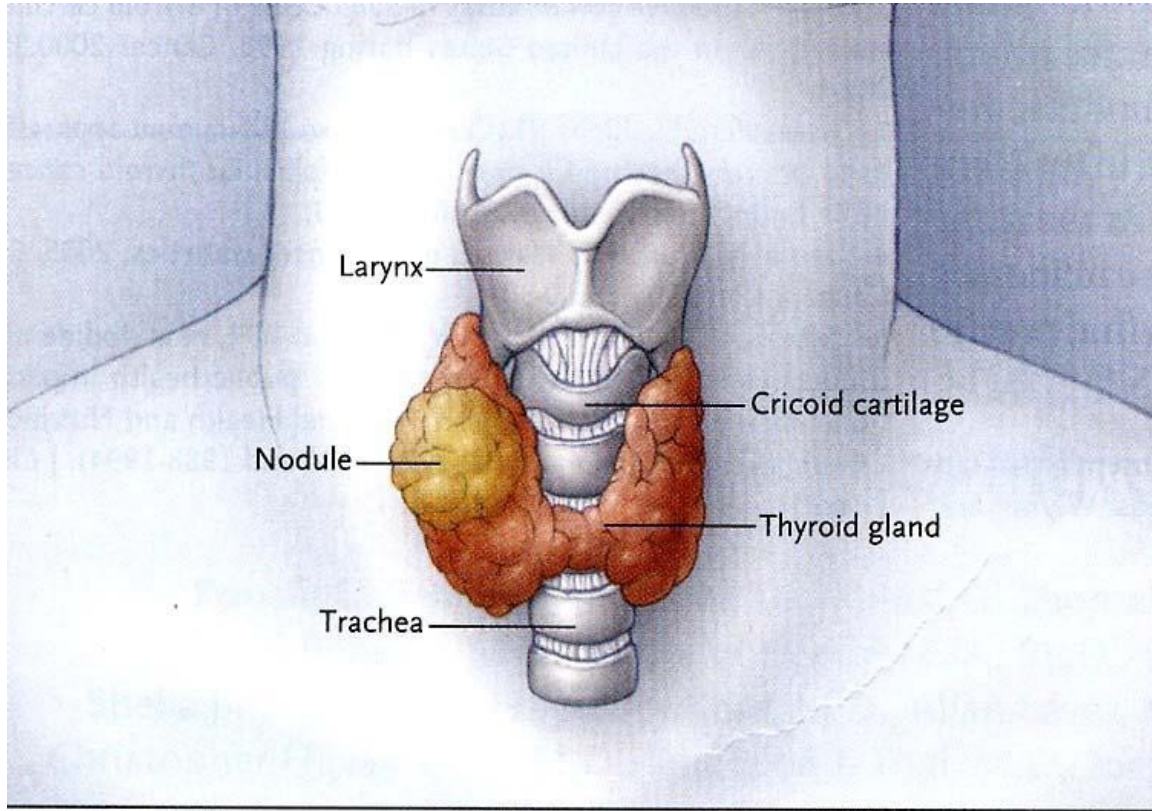


Hypothyroidism

- Treatment of hypothyroidism
 - Causative
 - Thyroid hormone replacement
 - Iodine
 - Jod-Basedow effect

Features of hypothyroidism and hyperthyroidism





Benign Nodules (95%)

Hyperplastic nodules (85%)
 Adenomas (15%)
 Cysts (<1%)

Carcinomas (5%)

Papillary (81%)
 Follicular and Hürthle-cell (14%)
 Medullary (3%)
 Anaplastic (2%)

Common Varieties of Thyroid Nodules.

HASHIMOTO'S DISEASE

Normal Thyroid ✓

Hashimoto's Disease ✗

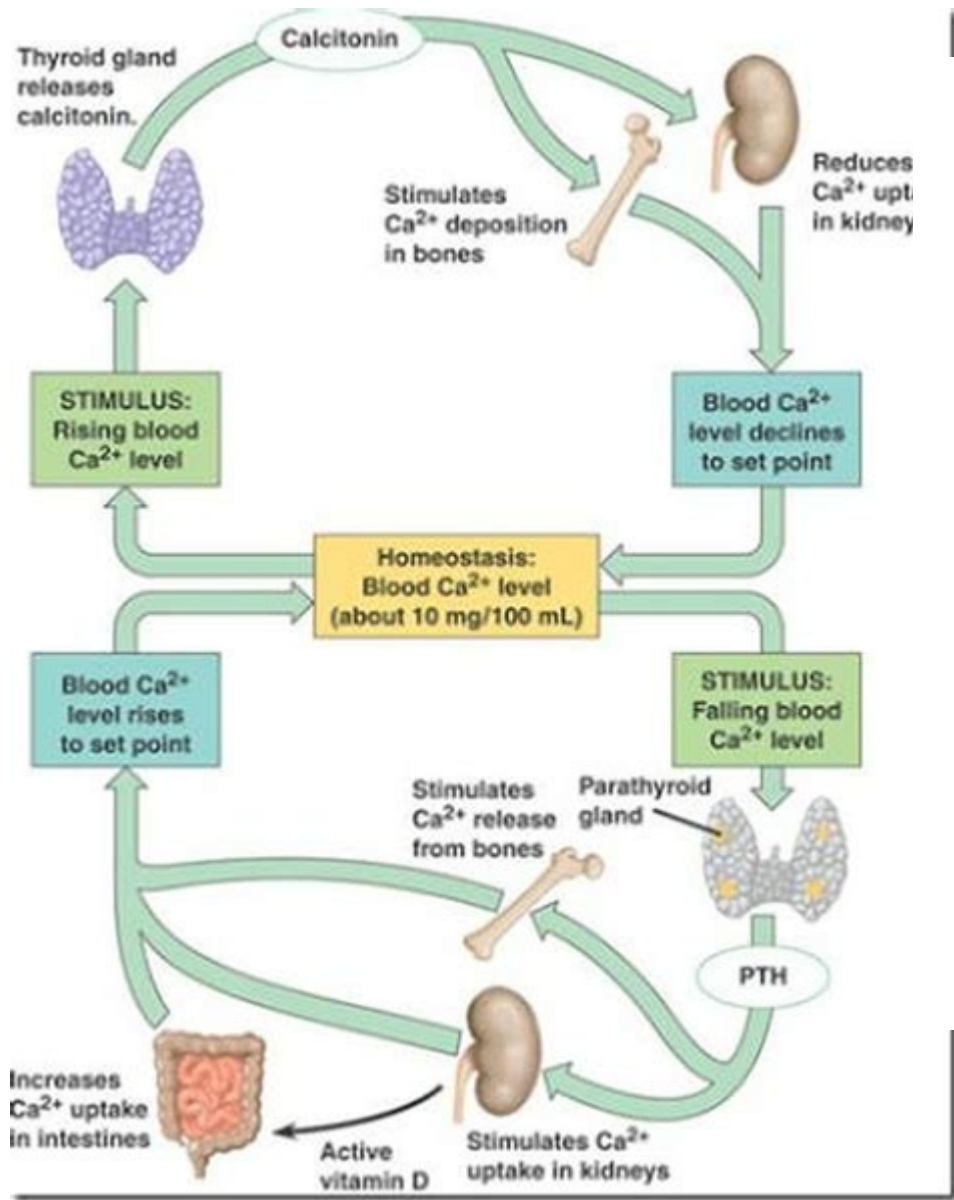
Enlarged and Inflamed Underactive Thyroid (Goiter)

Hashimoto's Disease, is an Autoimmune Disease in Which the Thyroid Gland is Gradually Destroyed

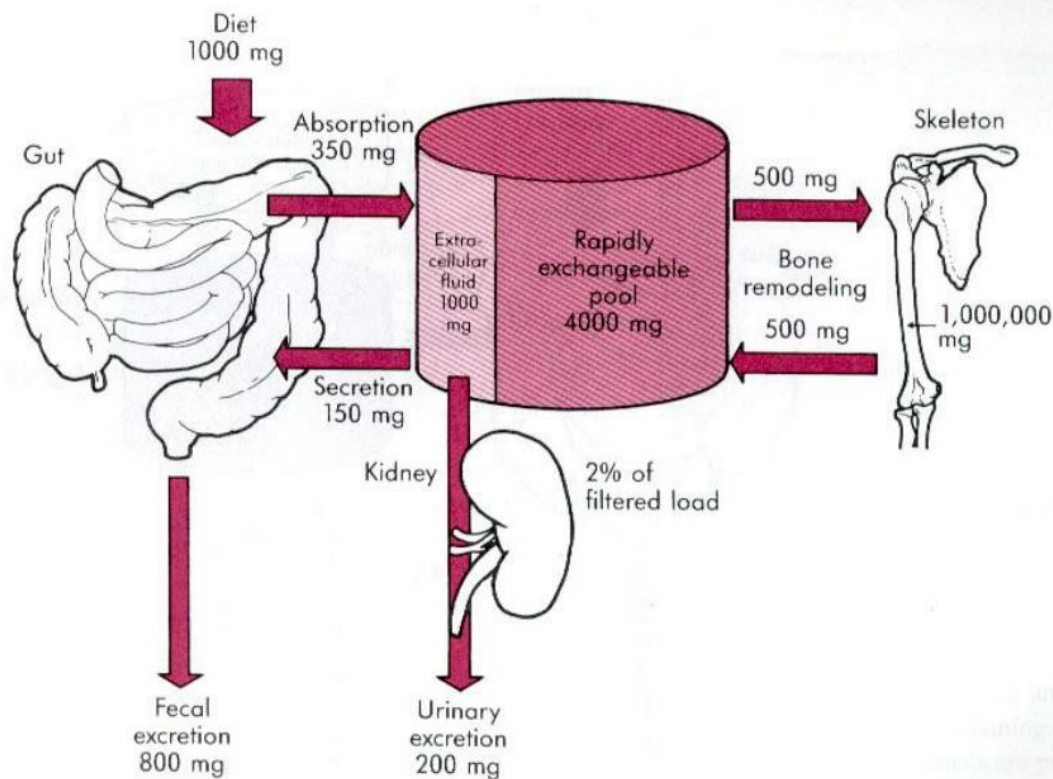
Fatigue and Sluggishness
Increased Sensitivity to Cold
Unexplained Weight Gain

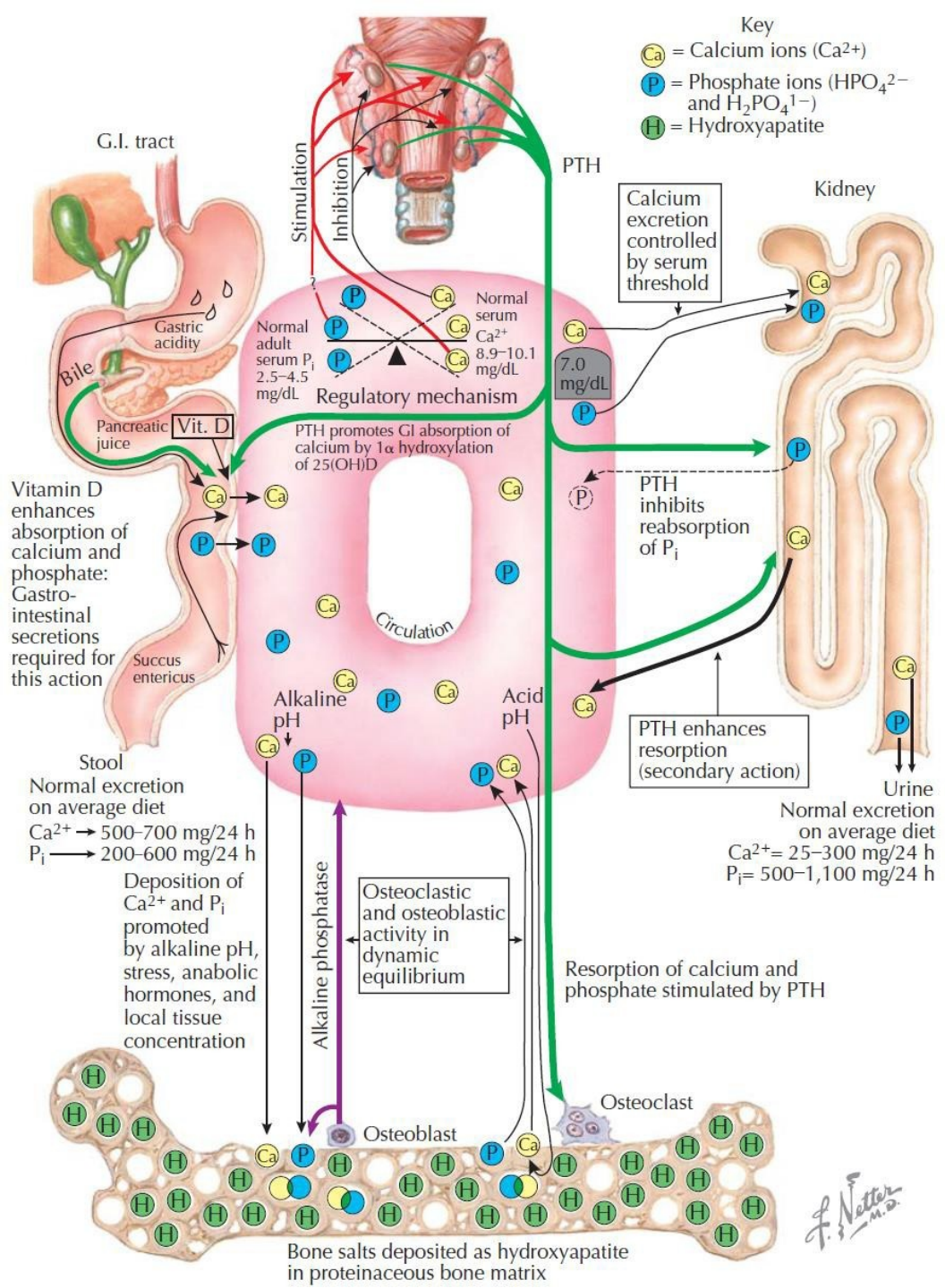
Symptoms:

- Enlargement of the Tongue
- Memory Lapses Depression
- Goiter A puffy Face Brittle Nails Hair Loss
- Pale, Dry Skin
- Excessive or Prolonged Menstrual Bleeding
- Joint Pain and Stiffness
- Muscle Aches, Weakness, Tenderness and Stiffness
- Constipation



Calcium Turnover





Hypercalcemia

- Symptoms
 - Renal (stones, polydipsia, polyuria)
 - Bones (pain)
 - Gut (constipation)
 - Brain (depression, fatigue, anorexia)
- Signs
 - Hypertension, cognitive impairment, joint swelling, bone deformities

Hypercalcemia

• Causes

- Primary (tertiary) hyperparathyroidism
- Malignancies (parathyroid hormone-related protein)
- Hypervitaminosis D
- Renal failure

• Therapy

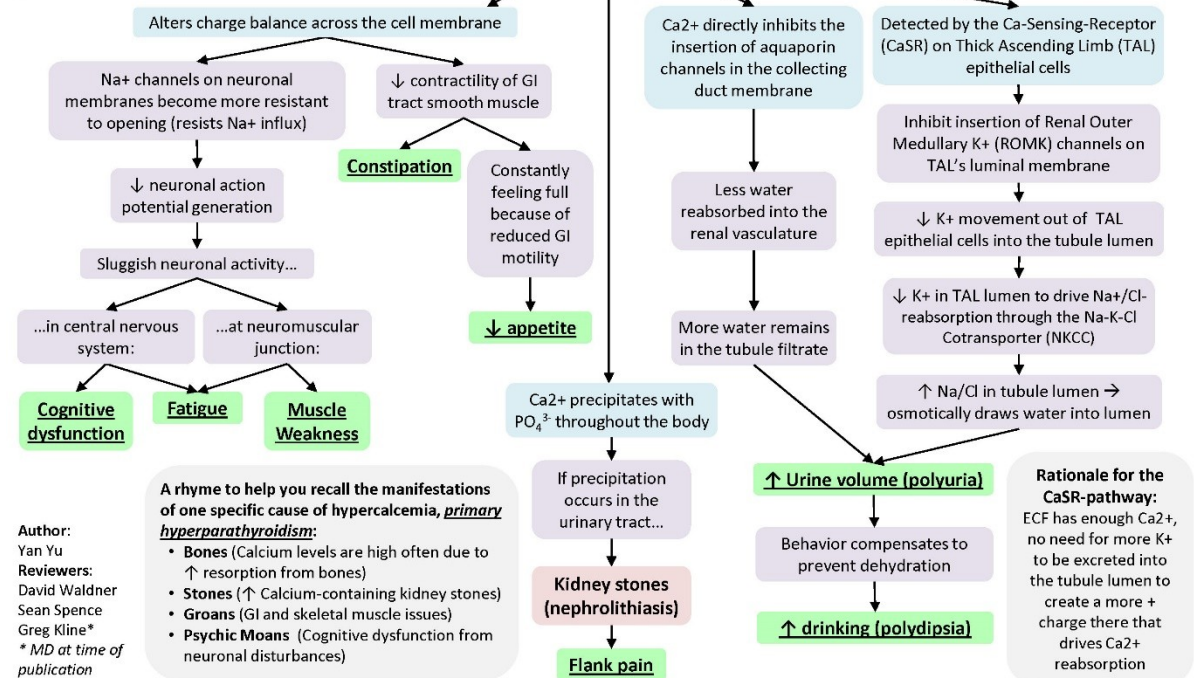
- Diuretics
- Bisphosphonates
- Calcitonin

Hypercalcemia: Clinical Findings

Note: "Total Ca²⁺" in the blood is either "free", or bound to albumin. The lab value measures the "Total Ca²⁺", but it is the "free Ca²⁺" that carries out Ca²⁺'s functions and determines if someone is hyper- or hypo-calcemic.

Hypercalcemia
(serum [Ca²⁺] > 2.5mmol/L)

Note: sick/ICU patients have ↓ serum albumin, due to ↓ synthesis from a sick liver. Their lab Ca²⁺ values can be "normal", but they may be truly hypercalcemic (more "free Ca²⁺", less "albumin-bound Ca²⁺").
Correct this by adding 0.2mmol/L to the lab Ca²⁺ value for every 10g/L drop of albumin below 40g/L

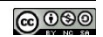


Author:
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Reviewers:
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Sean Spence
Greg Kline*
* MD at time of publication

A rhyme to help you recall the manifestations of one specific cause of hypercalcemia, primary hyperparathyroidism:

- **Bones** (Calcium levels are high often due to ↑ resorption from bones)
- **Stones** (↑ Calcium-containing kidney stones)
- **Groans** (GI and skeletal muscle issues)
- **Psychic Moans** (Cognitive dysfunction from neuronal disturbances)

Rationale for the CaSR-pathway:
ECF has enough Ca²⁺, no need for more K⁺ to be excreted into the tubule lumen to create a more + charge there that drives Ca²⁺ reabsorption

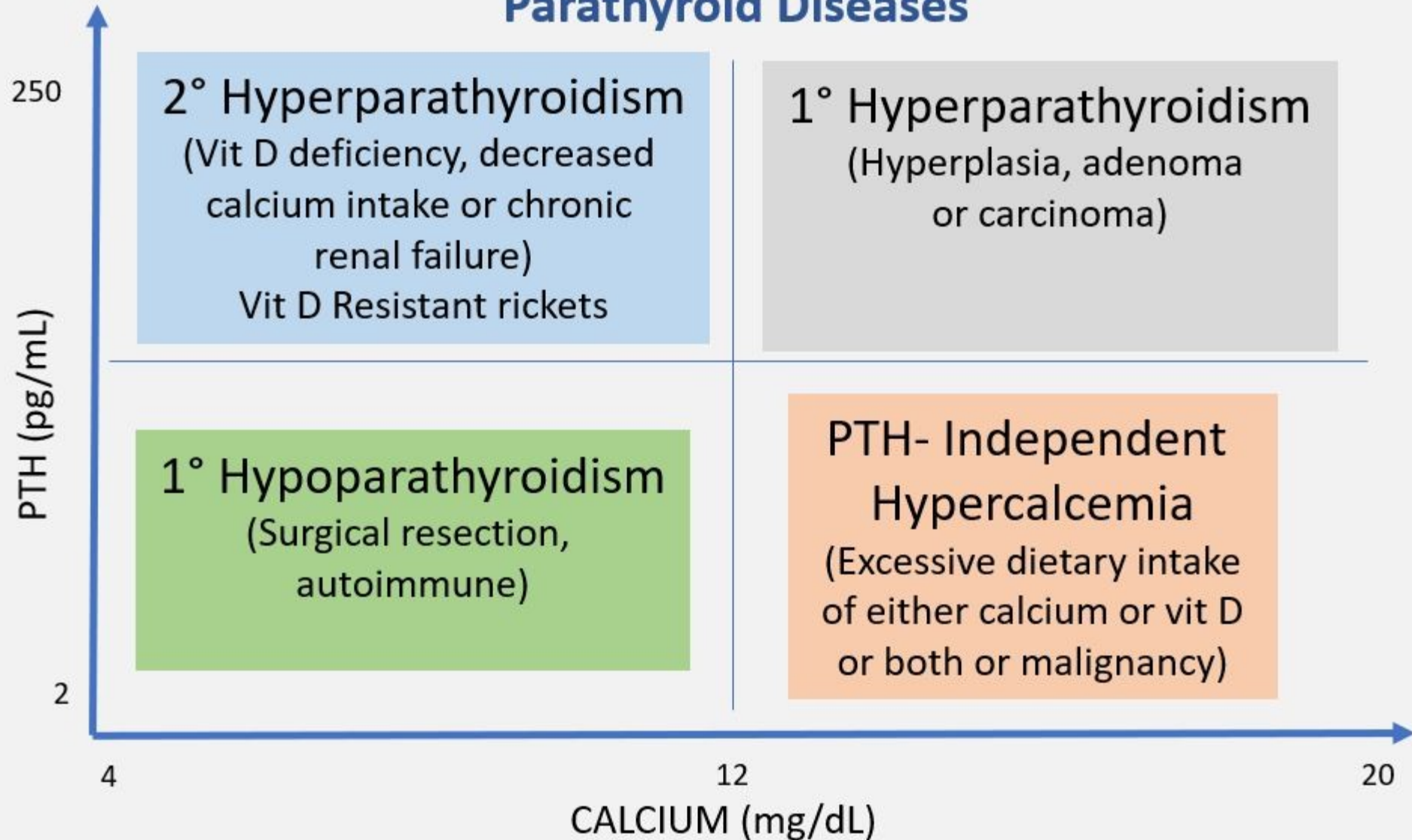


Hypocalcemia

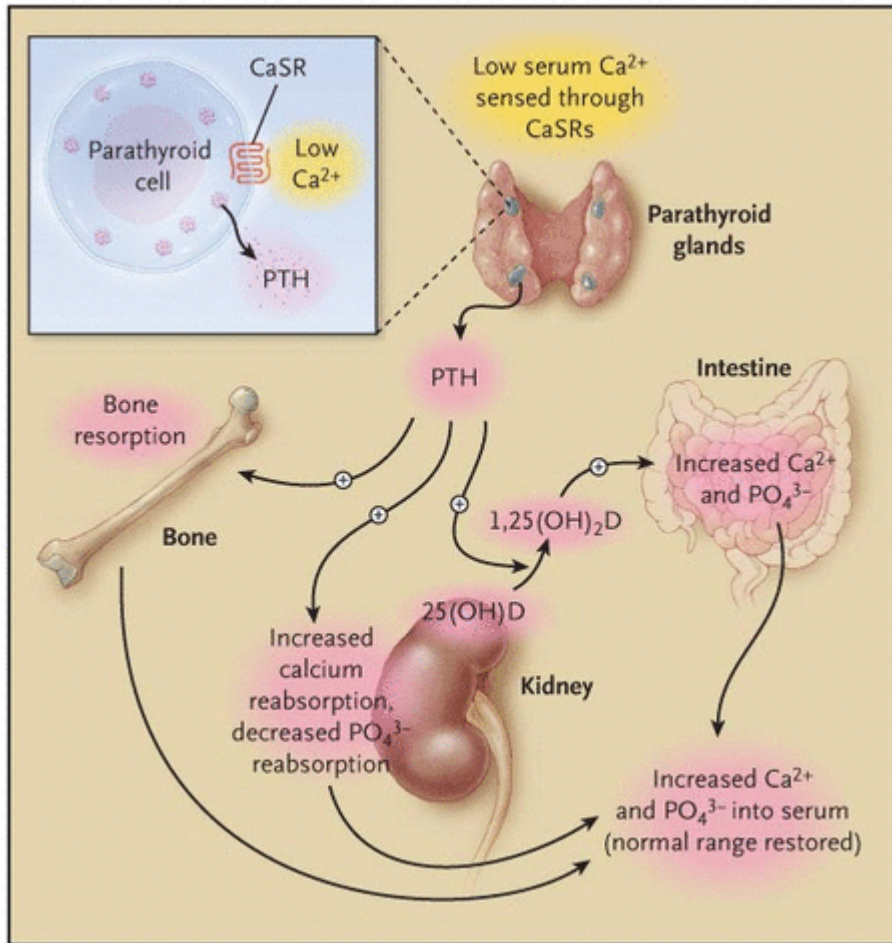
Table 1. Causes of hypocalcemia.

Low PTH levels (hypoparathyroidism)	High PTH levels (secondary hyperparathyroidism)
<p><i>Parathyroid Destruction</i></p> <ul style="list-style-type: none"> Surgery Auto-immune (isolated or polyglandular) Cervical irradiation Infiltration by metastasis or systemic diseases (Sarcoidosis, amyloidosis, hemochromatosis, Wilson's disease, thalassemia) <p><i>Reduced parathyroid function</i></p> <ul style="list-style-type: none"> Hypomagnesemia PTH gene defects Calcium sensing receptor mutations <p><i>Parathyroid agenesis</i></p> <ul style="list-style-type: none"> DiGeorge Syndrome Isolated x-linked hypoparathyroidism Kenny-Caffey syndrome Mitochondrial neuropathies 	<p><i>PTH resistance</i></p> <ul style="list-style-type: none"> Pseudohypoparathyroidism Hypomagnesemia <p><i>Vitamin D deficiency</i></p> <ul style="list-style-type: none"> Nutritional Lack of sunlight Malabsorption Vitamin D dependent rickets <ul style="list-style-type: none"> type I (lack of activity of 1α-hydroxylase) type II (Vitamin D receptor resistance) Chronic renal disease <p><i>Drugs</i></p> <ul style="list-style-type: none"> Bisphosphonates, cisplatin, ketoconazole, gallium nitrate, anticonvulsants <p><i>Hyperphosphatemia</i></p> <ul style="list-style-type: none"> Renal insufficiency Massive tumor lysis Acute rhabdomyolysis <p><i>Acute pancreatitis</i></p> <p><i>Hungry bone</i></p> <p><i>Toxic shock syndrome</i></p> <p><i>Acute severe illness</i></p> <p><i>Calcium chelators (citrate blood transfusions, phosphate)</i></p>

Parathyroid Diseases



Hypoparathyroidism



Mechanism	Risk Factor/Comorbidity	Etiology
Destruction or Removal	Surgery	Removal or damage to blood supply
	Disorder Dependent	Autoimmune
	Radiation therapy	Destruction of gland--Rare
	Cancer	Metastatic infiltration
	Transfusion dependent thalassemia	Iron Infiltration
	Wilson's Disease	Copper infiltration
	Amyloidosis	Amyloid deposition
Impaired PTH secretion or action	Malnutrition, Malabsorption, Alcoholism, Drugs, RTA	Severe Magnesium Deficiency
	Chronic Renal Failure, IV magnesium administration	Hypermagnesemia
Genetic Disorders of PTH synthesis or parathyroid gland development	Family History of hypocalcemia or hypoparathyroidism	Multiple and varied

Děkuji za pozornost