Ppathophysiology of endocrine system III

Thyroid gland

Adrenal cortex na medulla

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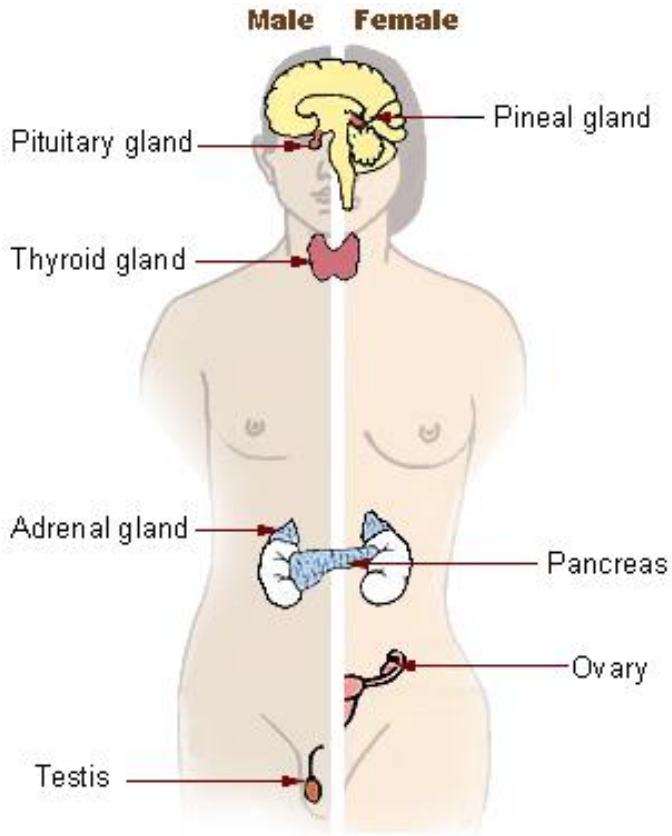
Endocrine system

- network of specialized endocrine **glands** in the body that make the **hormones**
- CAVE many more organs/tissues produce hormones
  - **discrete clusters of cells**
    - groups of hormone-producing cells are found in organs that have other functions, such as the **pancreas, ovary, placenta**, and **testis**
  - **DNES cells** (diffuse neuro-endocrine system, formerly APUD) in the gut, heart, kidney, liver, skin, …
    - Amine Precursor Uptake
      - for high uptake of amine precursors including 5-hydroxytryptophan (5-HTP) and dihydroxyphenylalanine (DOPA)
    - Decarboxylase
      - for high content of the enzyme amino acid decarboxylase (for conversion of precursors to amines)



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Survival of an organism is predicated upon the ability of:

- (1) to maintain homeostasis
  - = stable internal environment as a response to fluctuations in external or internal conditions
- (2) and to carry out important life-history functions, such as
  - growth and maturation
  - reproduction
  - repair, healing, remodeling
  - (migration)

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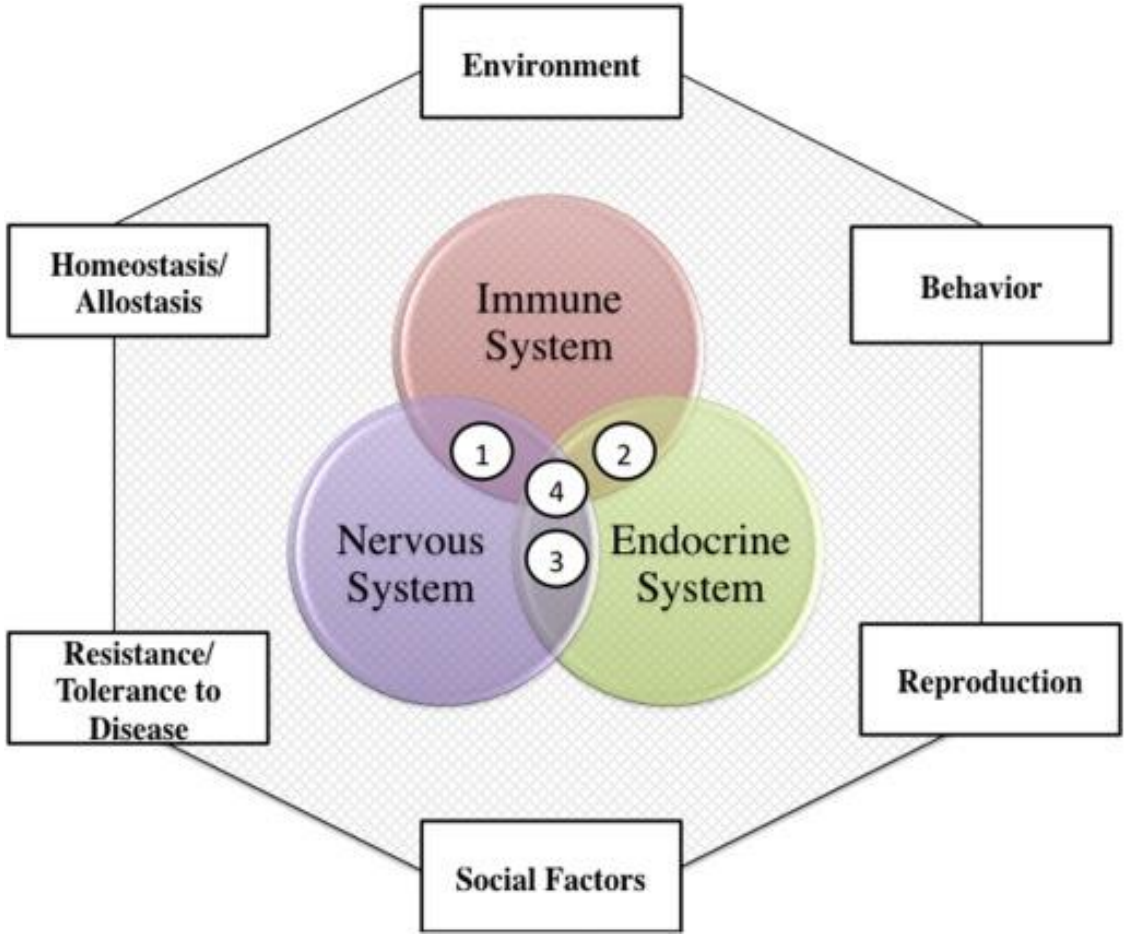
Neuro-endocrine-immune (NEI) network

- Neuro-endocrine-immune interactions involve multi-directional crosstalk that is mediated by extrinsic (environmental, social factors) and intrinsic (resistance/tolerance to disease, homeostasis and allostatic load, reproductive status, behaviour) factors
- First-order interactions involve
  - (1) direct interactions between the nervous and immune systems
    - e.g. sympathetic innervation of immune tissue
    - activation of microglia or specific nuclei in brain from cytokines
  - (2) endocrine-immune interactions
    - e.g. hormonal regulation of immunity
    - cytokine/ chemokine activation of endocrine cells)
  - (3) classic interactions between the nervous and endocrine systems
    - e.g. activation and modulation of hypothalamic-pituitary units
    - neuromodulation by hormones
  - (4) second-order interactions involve all three systems interacting to produce a physiological effect(s)



Horm Behav. 2017. Neuroendocrine-immune circuits, phenotypes, and interactions. Ashley NT, Demas GE.

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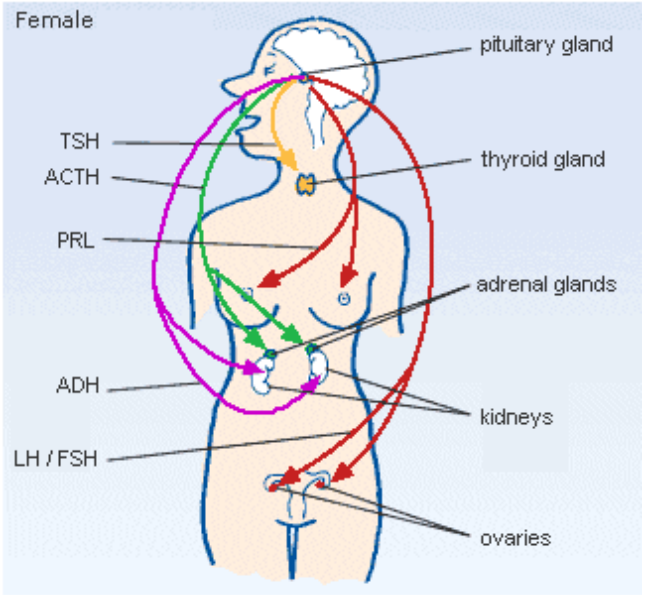
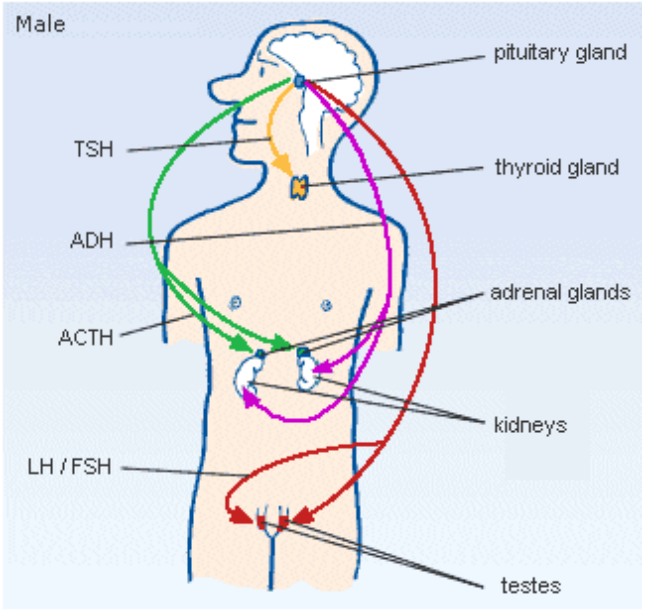
Mechanisms of endocrine diseases

- (1) hormone deficiency
  - destruction process in the gland
    - hereditary
      - genetic defect
    - acquired
      - infection
      - infarction
      - compression by tumour
      - autoimunity (type II hypersensitivity mostly – cellular or antibody cytotoxicity)
- (2) hormone excess
  - autotopic – in the very gland
    - tumours (adenomas)
    - immunopathologic (type V hypersensitivity – stimulatory anti-receptor Ig)
  - ectopic – elsewhere
    - tumours
  - exogenous (iatrogenic) – therapeutic use
- (3) hormone resistance
  - abnormal hormone
  - antibodies against hormone or receptor
  - receptor defect
  - post-receptor defect





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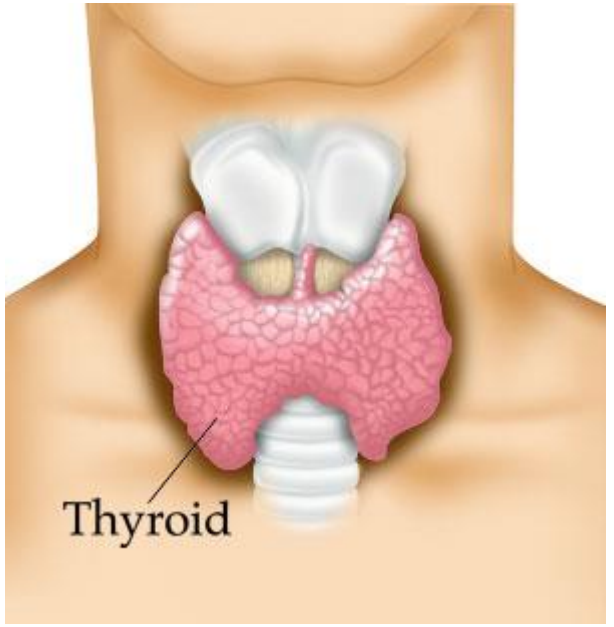
The Thyroid



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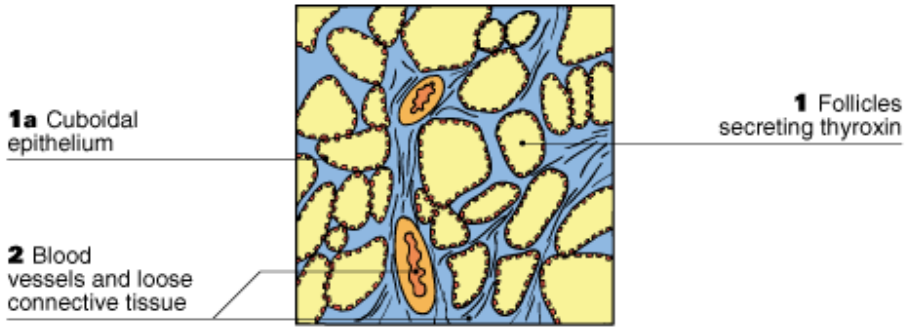
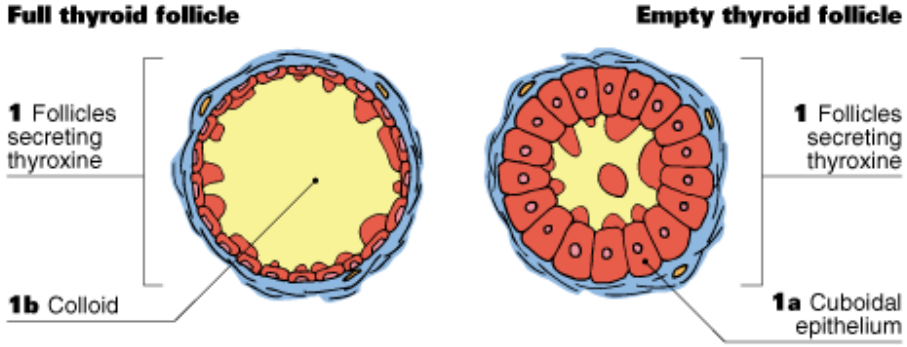
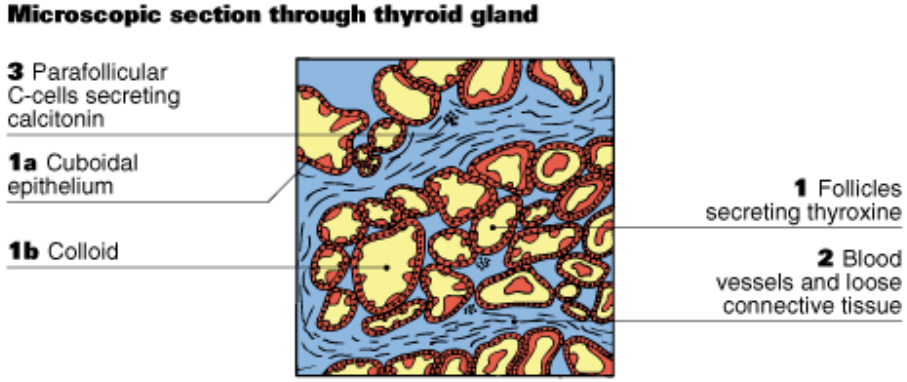
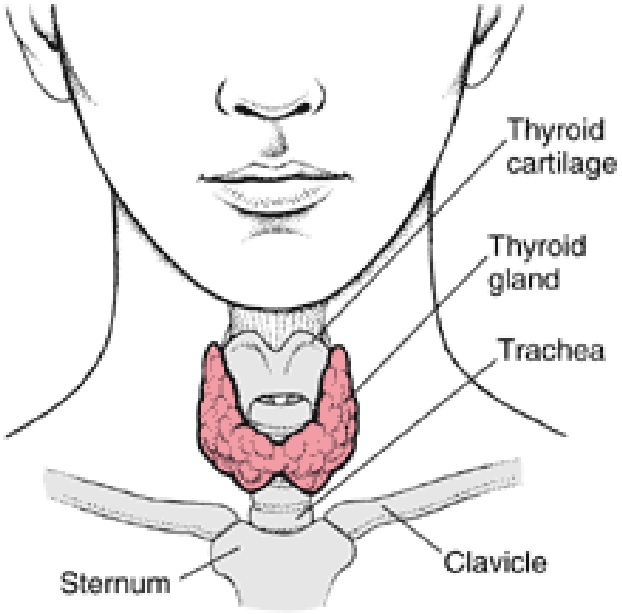
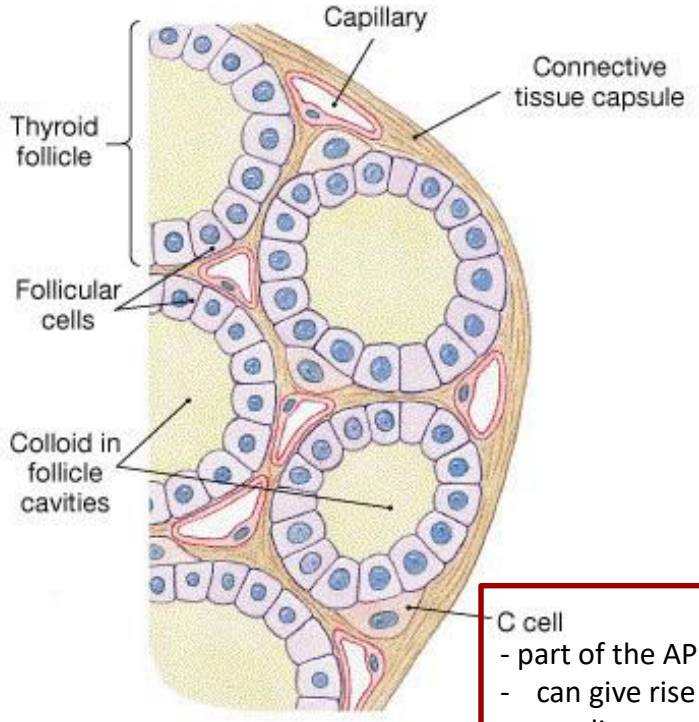
Pathophysiology of thyroid gland











- part of the APUD system (calcitonin)
- can give rise to medullary carcinoma
- no clin. consequences of deficiency/removal

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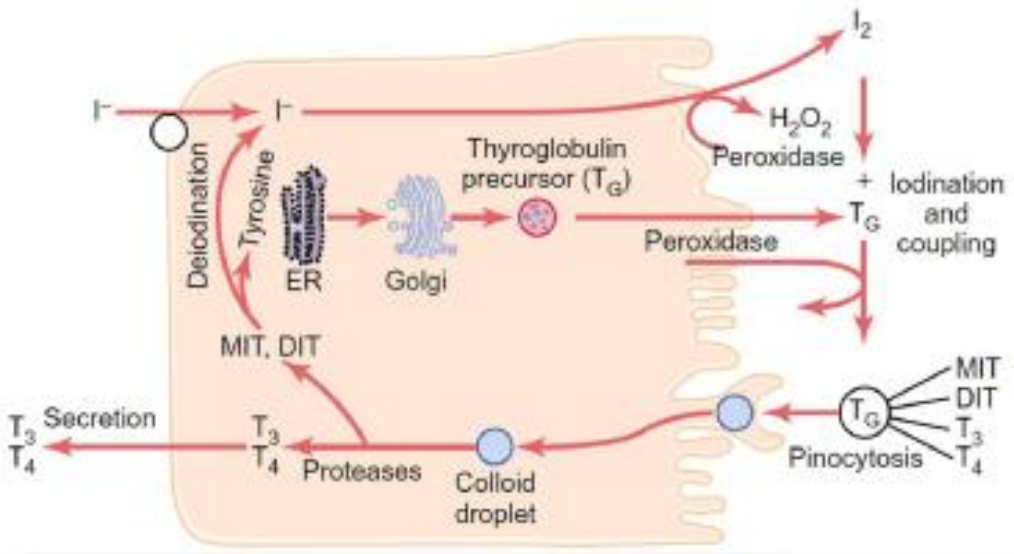
Hormone synthesis by follicular cell



- upon nutritional iodide intakein thyrocytes by the sodium-iodide symporter (NIS), it is transported into the follicular lumen
- fabrication of thyroid hormones is conducted by the enzyme thyroid peroxidase (TPO), an integral membrane protein present in the apical (colloid-facing) plasma membrane of thyroid epithelial cells
  - TPO catalyzes two sequential reactions:
    - iodination of tyrosines on thyroglobulin (also known as "organification of iodide") resultong in formation of mono- and diiodotyrosines
    - synthesis of thyroxine (T4) or triiodothyronine (T3) from two iodotyrosines
    - a molecule of thyroglobulin contains 134 tyrosines, although only a handful of these are actually used to synthesize T4 and T3
- after pinocytosis of TG into thyrocytes, it fuses with lysosomes, becomes hydrolysed by proteases and T4, T3 diffuse into the cytoplasm and then are released into the bloodstream where they quickly bind to carrier proteins for transport to target cells
  - TBG – thyroid binding globulin (produced in liver)

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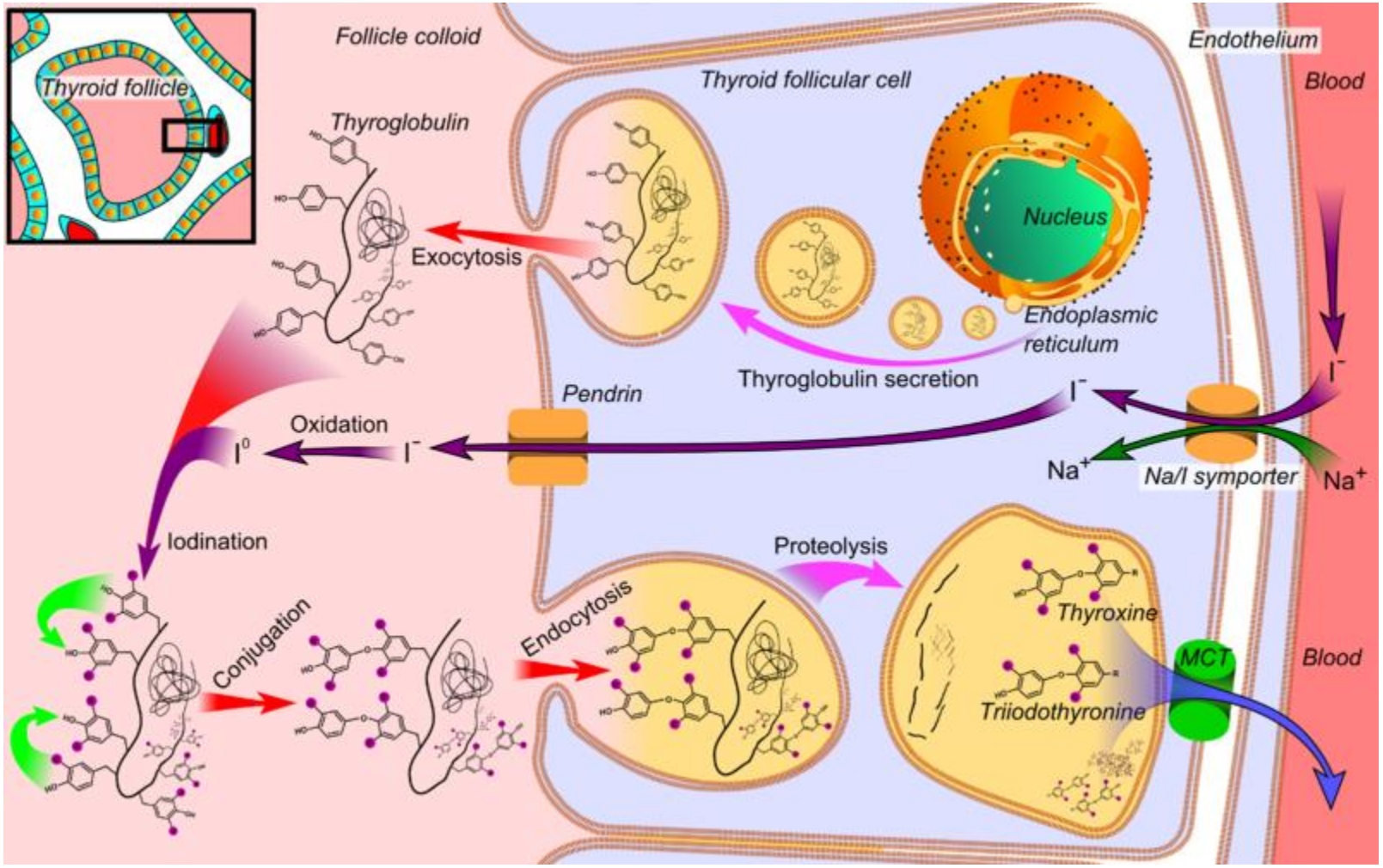
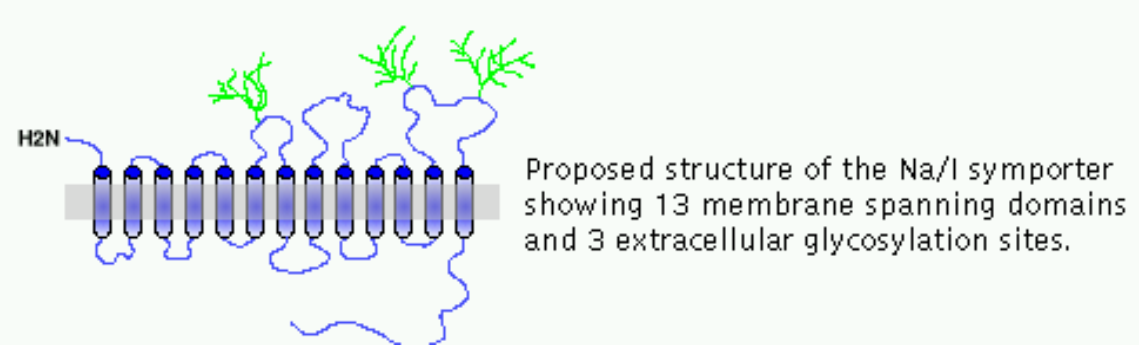
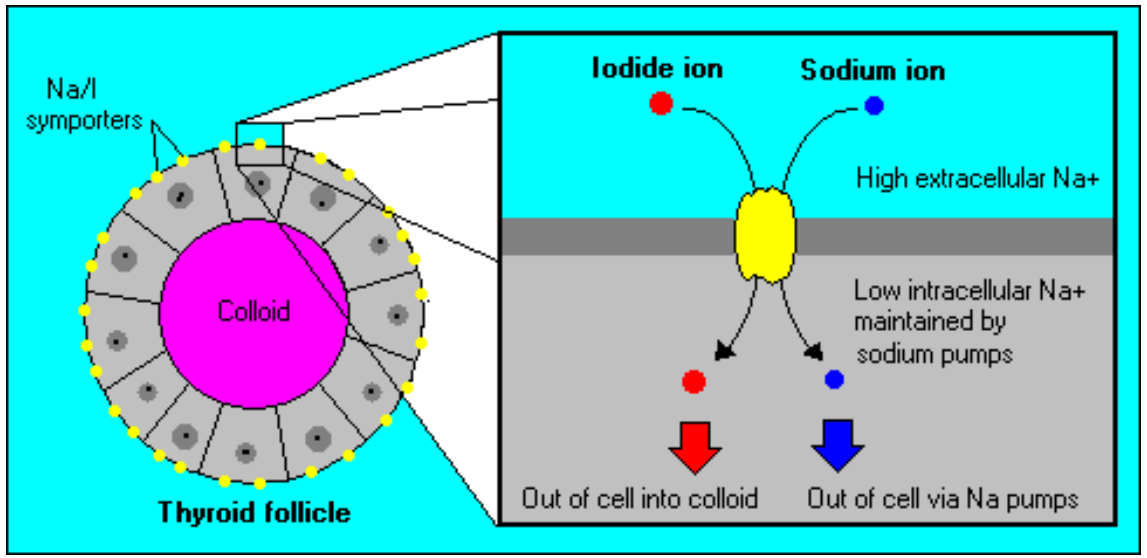
Hormone synthesis by follicular cell - detail

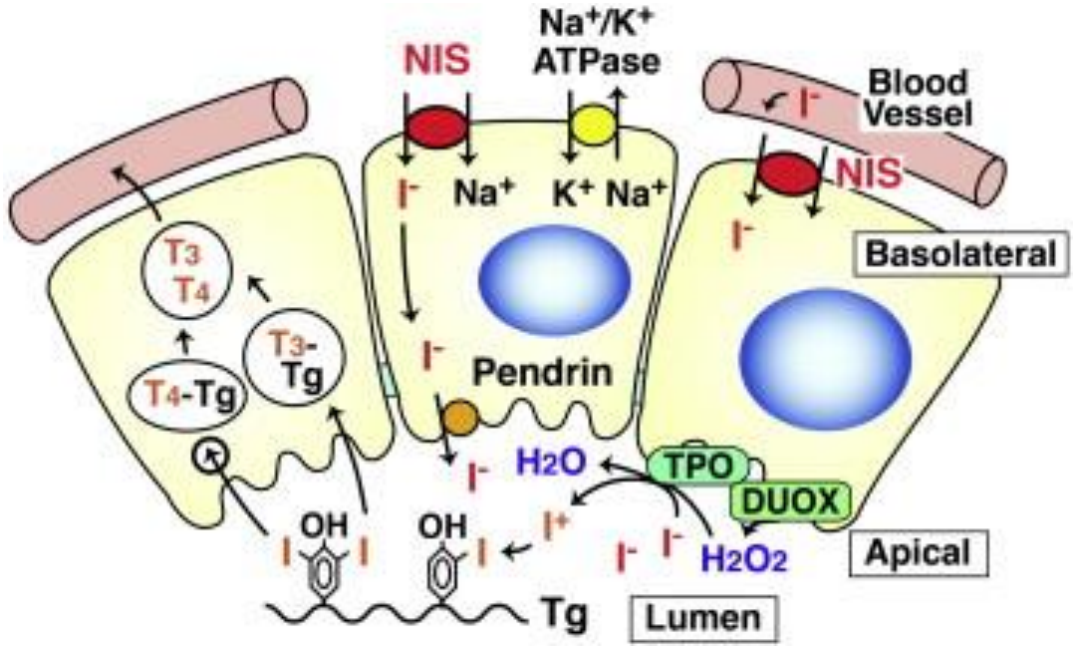


The sodium-iodide symporter



Proposed structure of the Na/I symporter showing 13 membrane spanning domains and 3 extracellular glycosylation sites.





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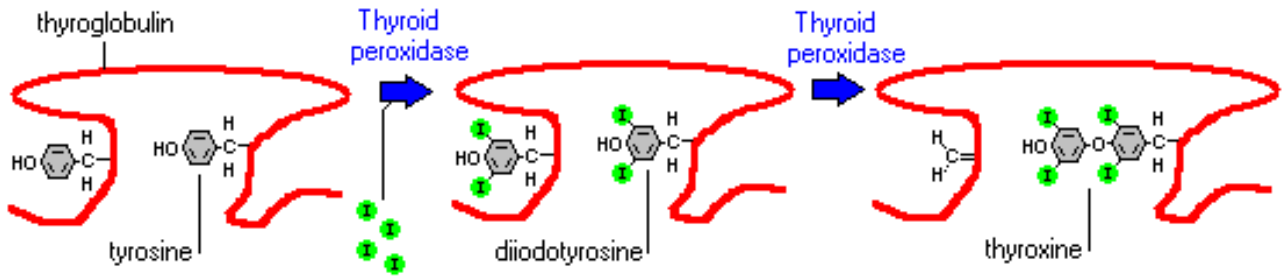
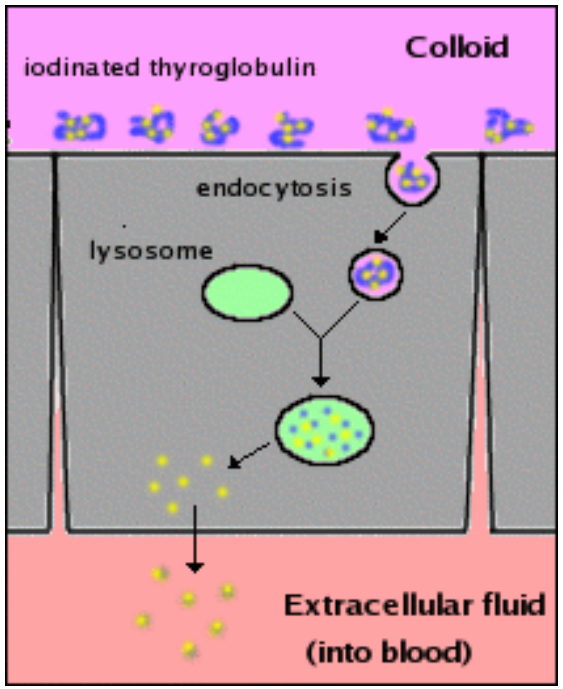
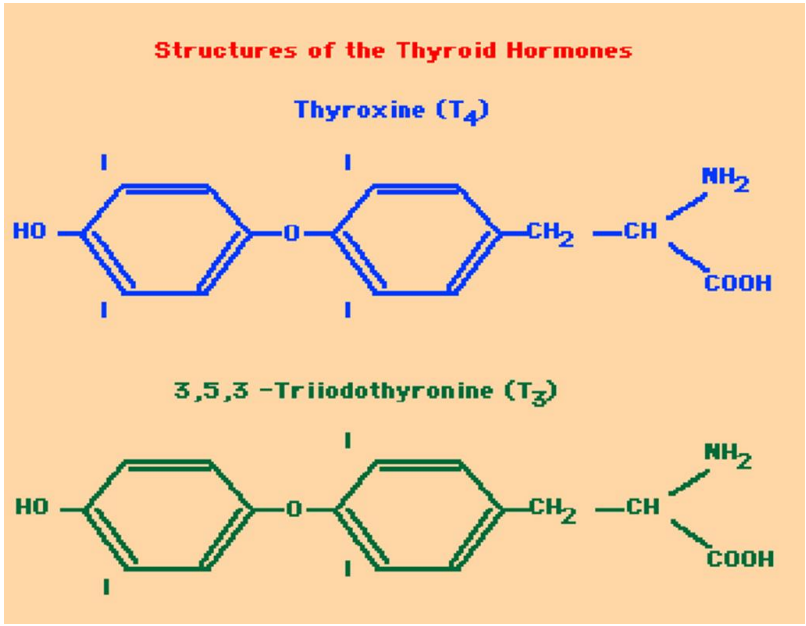
“Organification” of TG & coupling of thyrosines, liberation of T3/T4

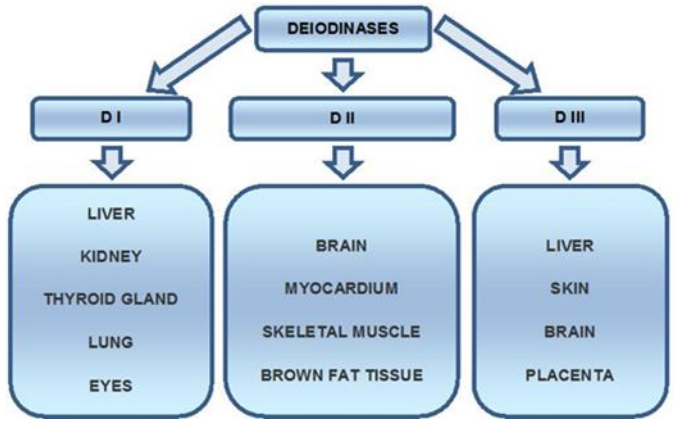


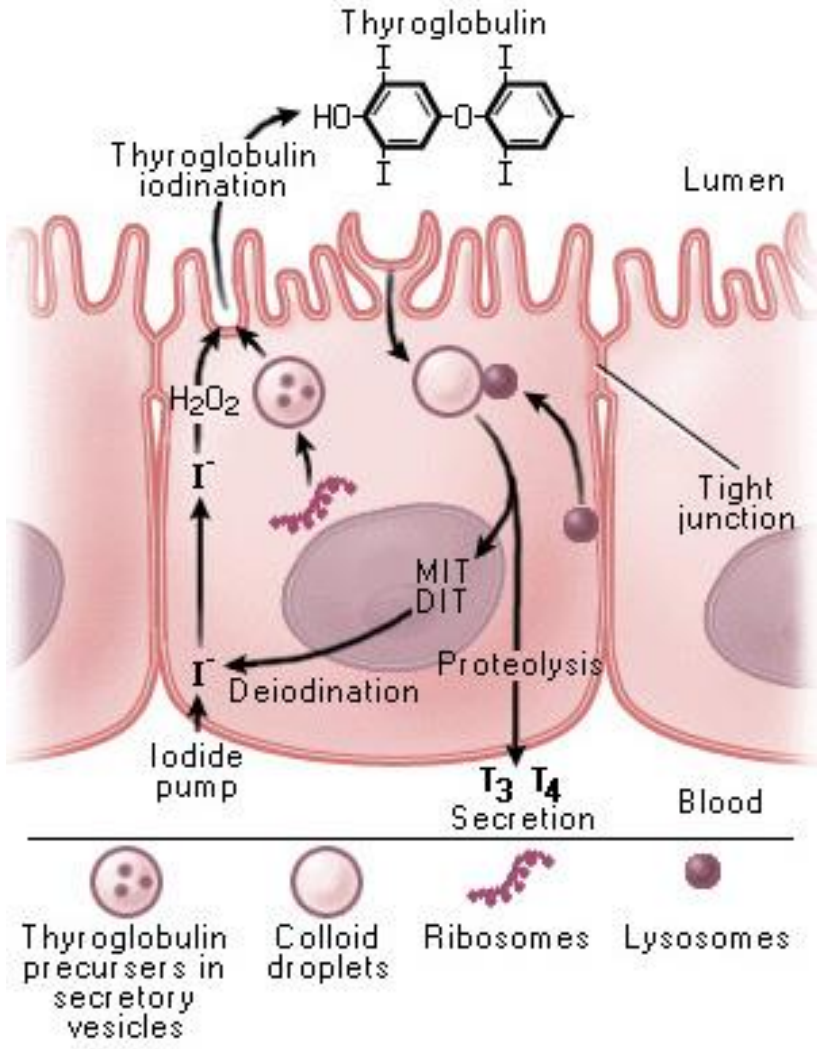




Secretion of thyroid hormones

- upon stimulation by TSH, droplets of iodinated thyroglobulin return to the follicular cell by **endocytosis**
  - the droplets fuse with lysosomes, forming an endosome
- proteases from the lysosomes breakdown peptide bonds between the iodinated residues and thyroglobulin molecules to yield **T3, T4, MIT** and **DIT**
- free T3 and T4 cross the cell membrane and are discharged into the capillaries
  - T4 limitedly de-iodinated
    - 99.9% bound to TBG (75%), transthyretin (15%) and albumin (10%)
  - T3 free fraction 0.3%
- MIT and DIT are liberated into the cytoplasm, the iodines are removed by a **deiodinases** (selenium-dependent enzymes), and they and the tyrosines are reused
- **free fraction** of T4 and T3 is metabolically active, while bound fraction is a 'reserve'
  - **peripheral de-iodination** (e.g. liver, kidneys, placenta, …)





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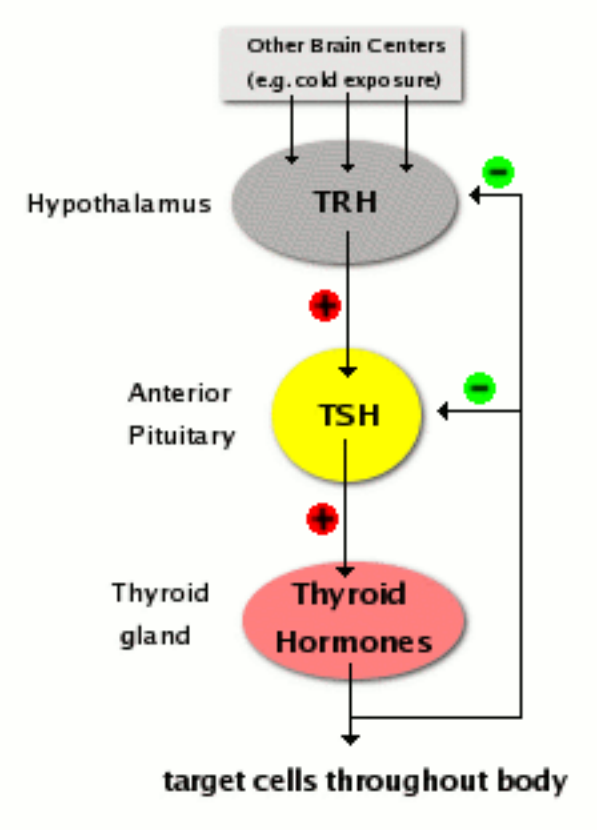
Control of the T3/T4 production



- hypothalamus:
  - TRH
  - somatostatin
- pituitary:
  - TSH
    - binding of TSH to TSH-R stimulates:
      - synthesis of the iodide transporter
      - thyroid peroxidase
      - synthesis of thyroglobulin
      - rate of endocytosis of colloid
- thyroid autoregulation
  - iodide uptake and transport

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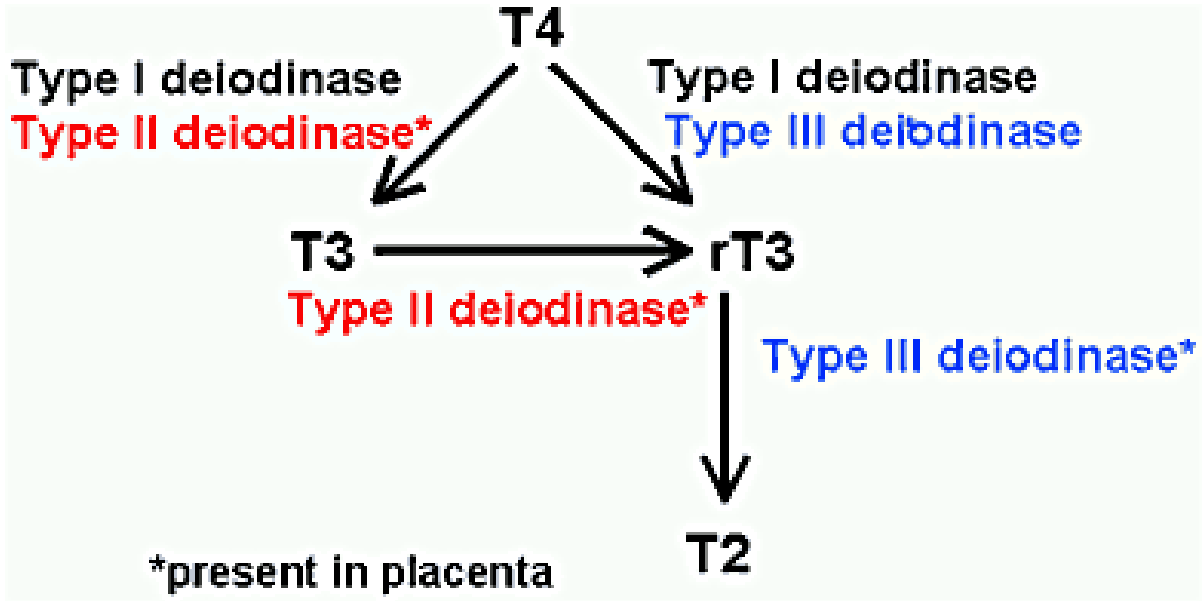
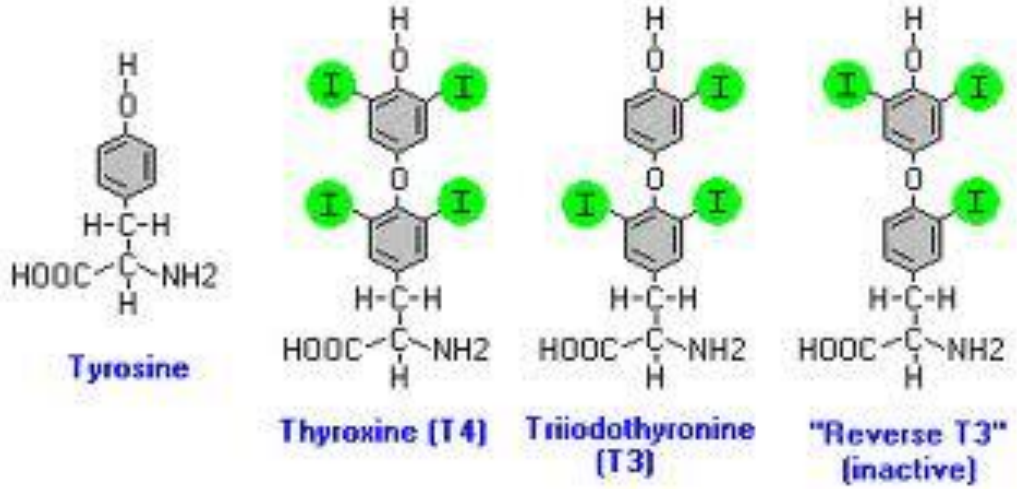
Peripheral modulation of T4 and T3 levels

- activity: T3 10× >> T4 > rT3
- enzymatic conversion by deiodinases
  - activation (by D1 and D2): T4 → T3
  - inactivation (by D3):T4 → rT3 (→ T2)
- tissue and organ specificity





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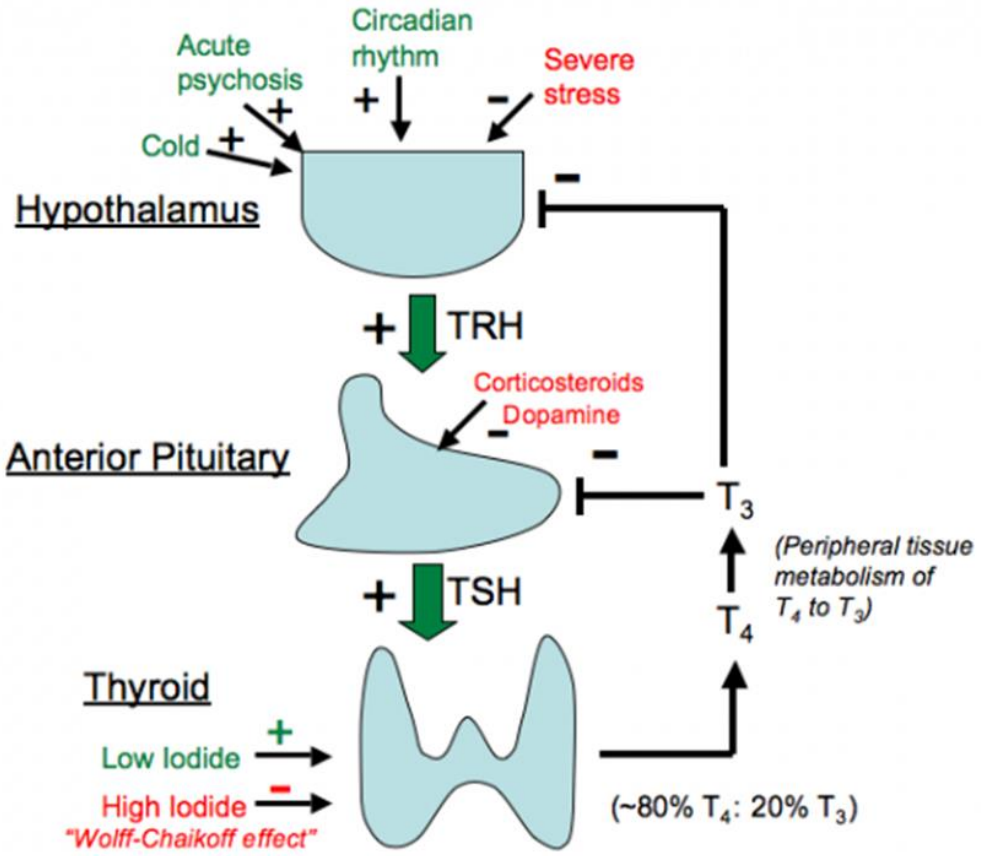
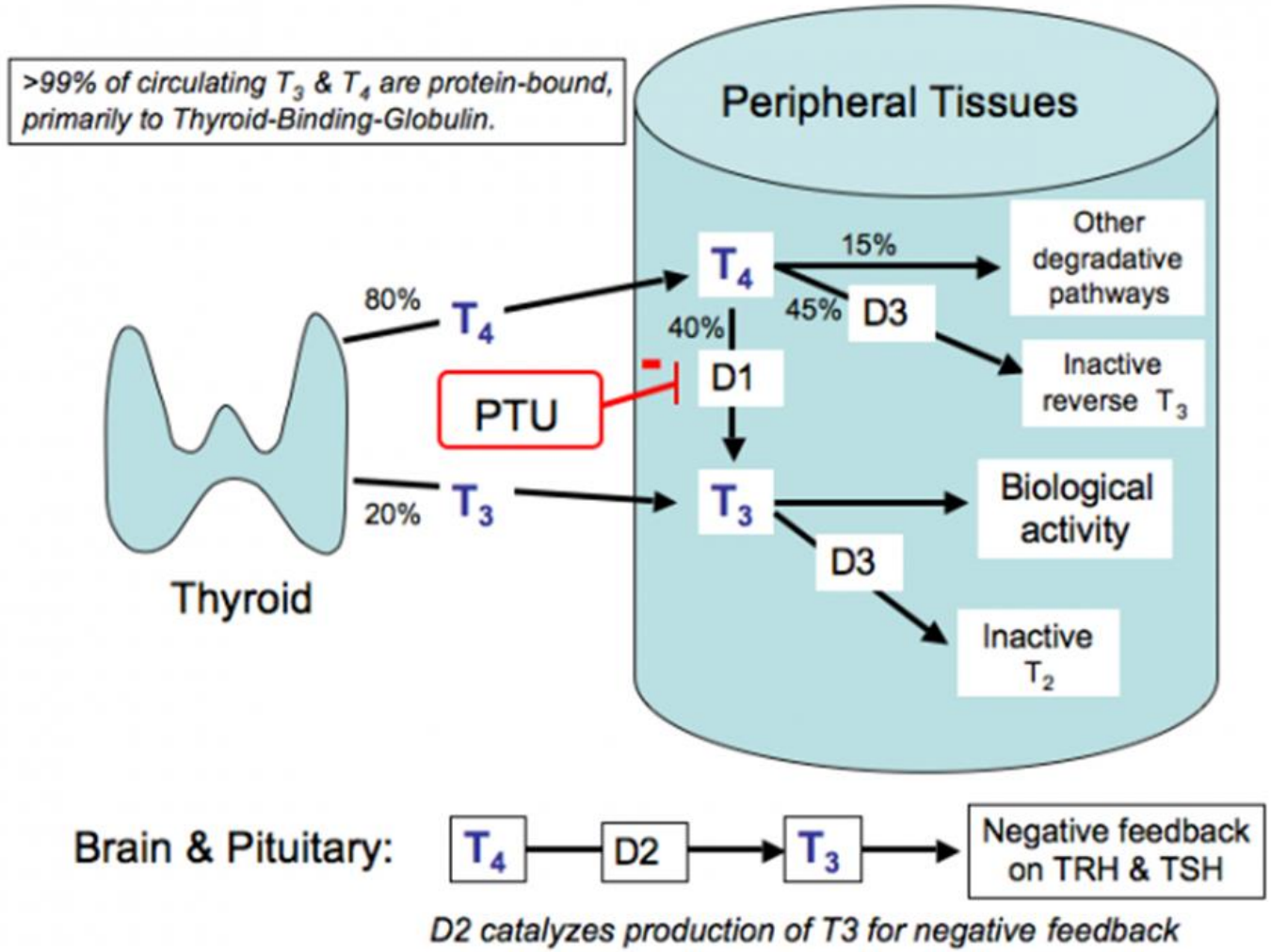
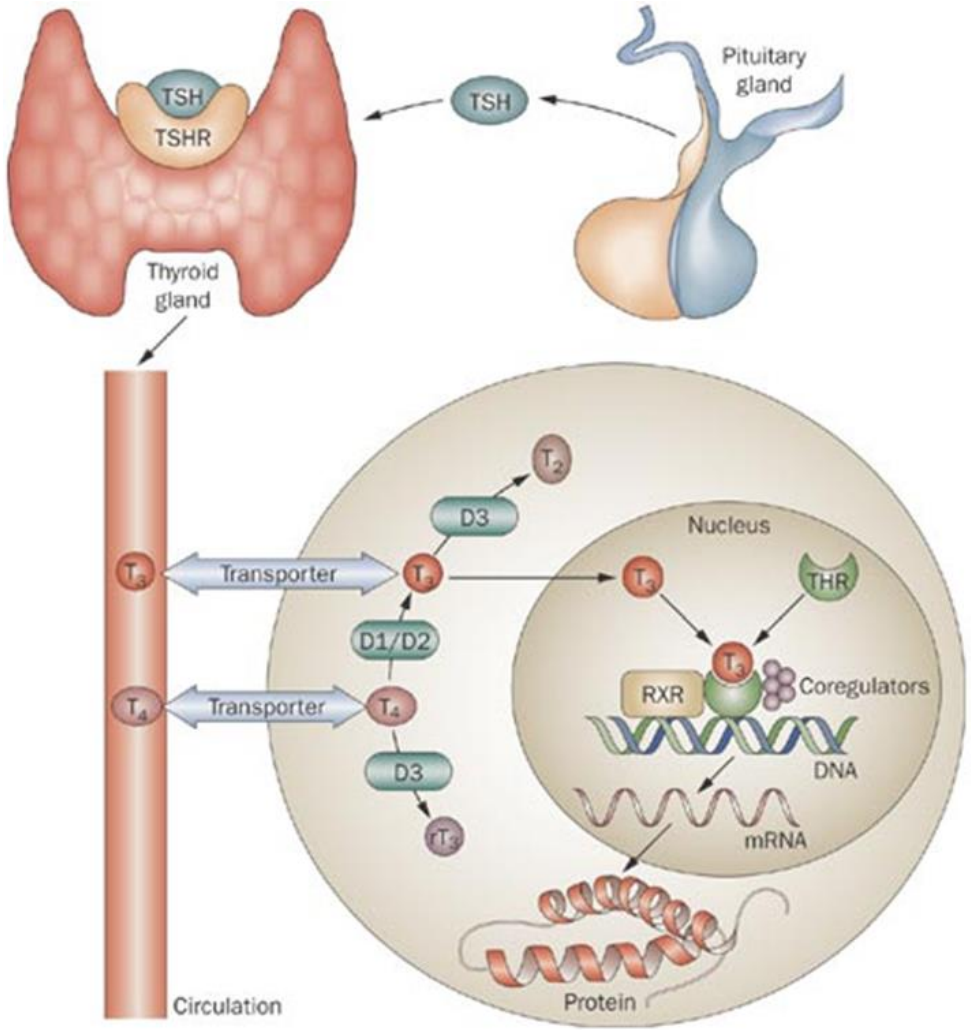
Quantitatively





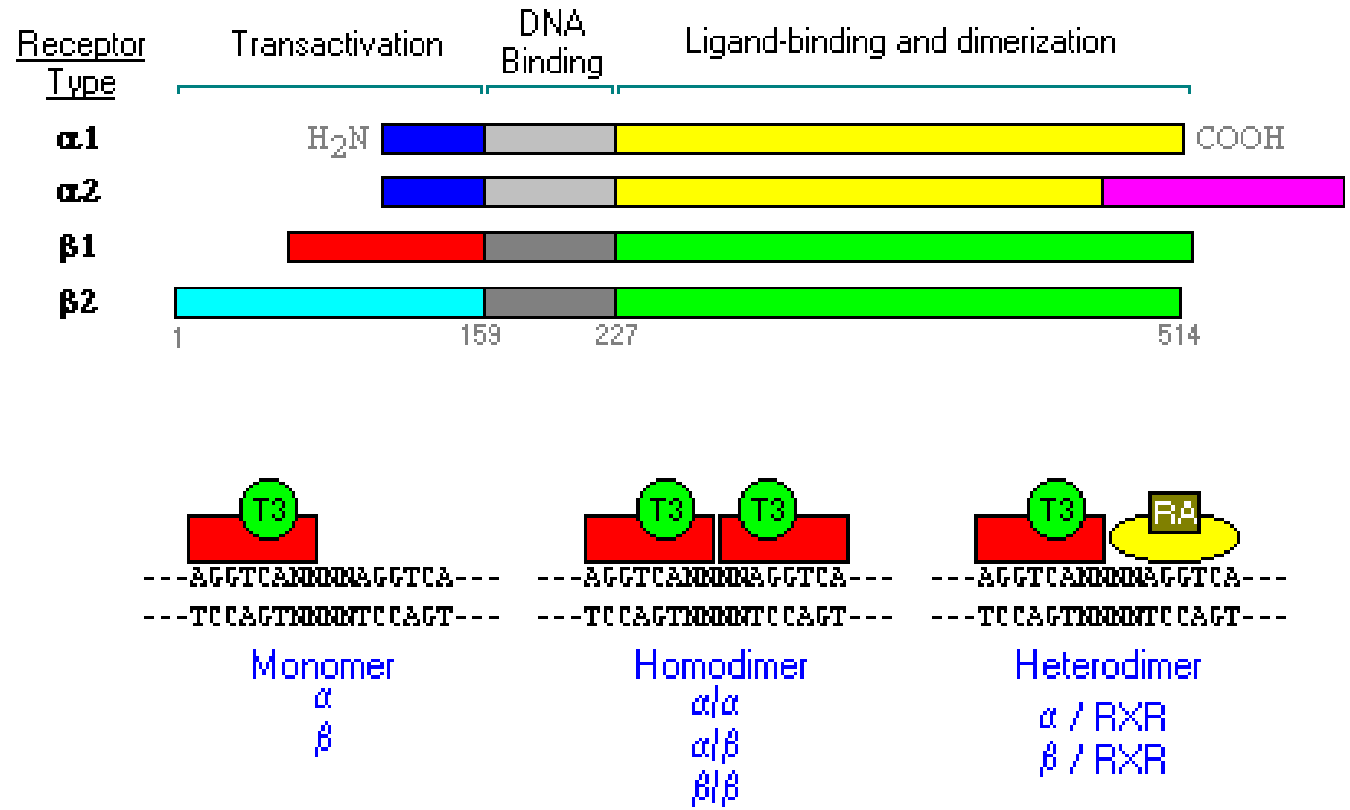
Molecular basis of T3/T4 action

- (1) genomic effects
  - complexes thyroid hormone/hormone-activated **nuclear receptors** act as transcription factors
    - modulation of gene expression
  - in contrast to steroid hormone receptors, thyroid hormone receptors bind DNA already in the absence of hormone, usually leading (in inactive state) to transcriptional repression
- (2) fast immediate effects
  - mitochondria?
  - plasma membrane

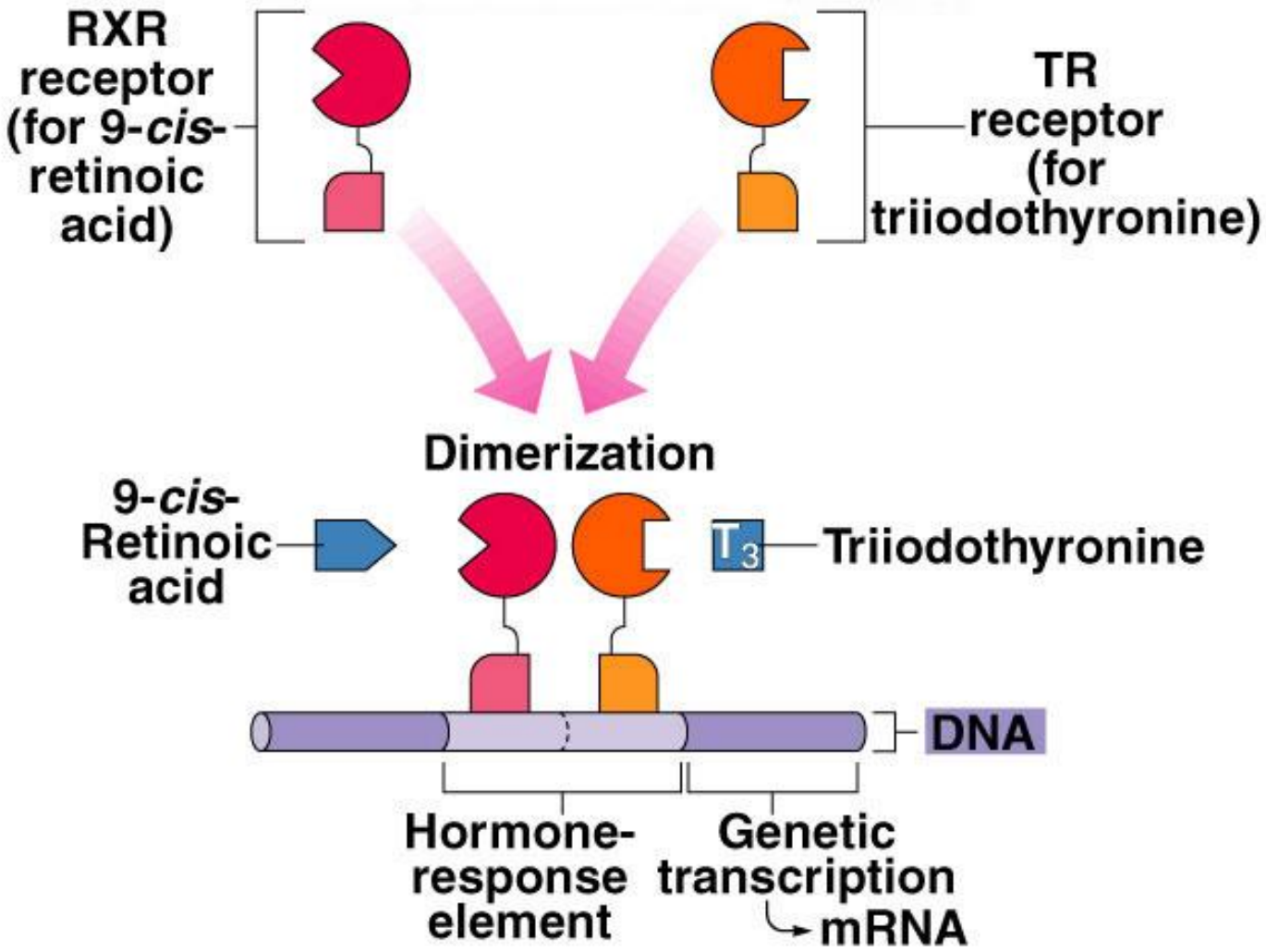


Thyroid hormone receptors

- encoded by two genes, designated alpha and beta
  - further, the primary transcript for each gene can be alternatively spliced, generating 4 different alpha and beta receptor isoforms): α-1, α-2, β-1 and β-2
    - different forms of thyroid receptors have patterns of expression that vary by tissue and by developmental stage
- THR bind to a short, repetitive sequences of DNA called thyroid or T3 response elements (TREs)
  - T3 bind to a TRE as monomers, as homodimers or as heterodimers with the retinoid X receptor (RXR)
    - the heterodimer affords the highest affinity binding - the major functional form of the receptor
  - change from co-repressor complex binding (T3 absence) to co-activator complex binding (T3 presence)



T3 action on gene transcription



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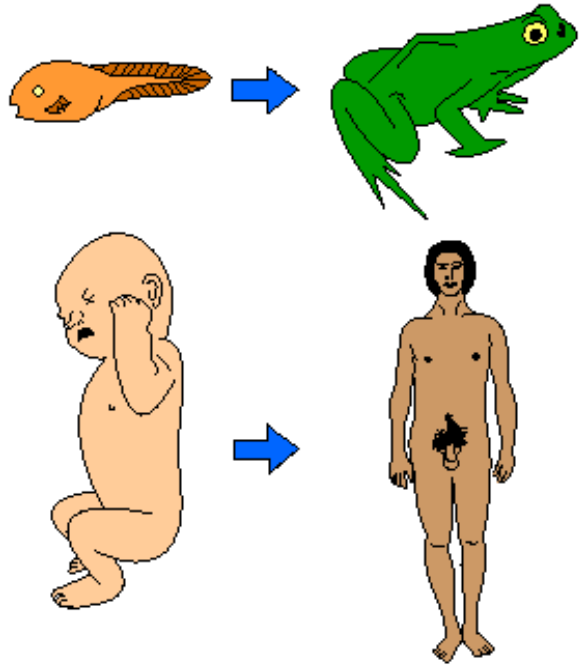
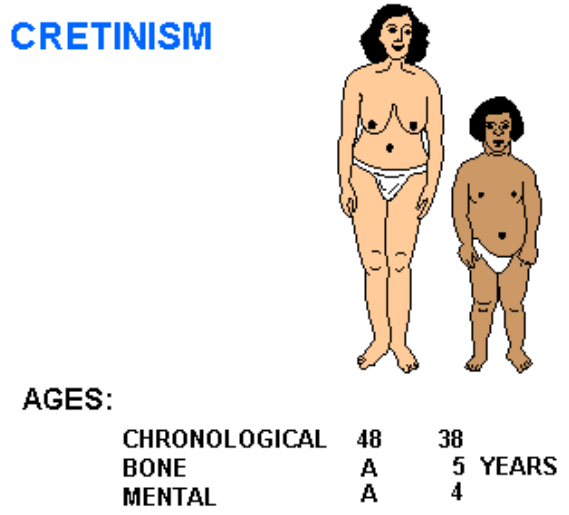
Physiologic effects of T3/T4

- (1) development
  - profound effects on the terminal stages of brain differentiation, including synaptogenesis, growth of dendrites and axons, myelination and neuronal migration (esp. in the fetal period)
  - the net effect of pregnancy is an increased demand on the thyroid gland
    - in the normal individuals, this does not appear to represent much of a load to the thyroid gland, but in females with subclinical hypothyroidism, the extra demands of pregnancy can precipitate clinical disease
- (2) growth
  - T3 is a critical determinant of postnatal linear bone growth and mineralisation
  - growth-retardation observed in thyroid deficiency
    - the growth-promoting effect of thyroid hormones is intimately intertwined with that of growth hormone and IGF





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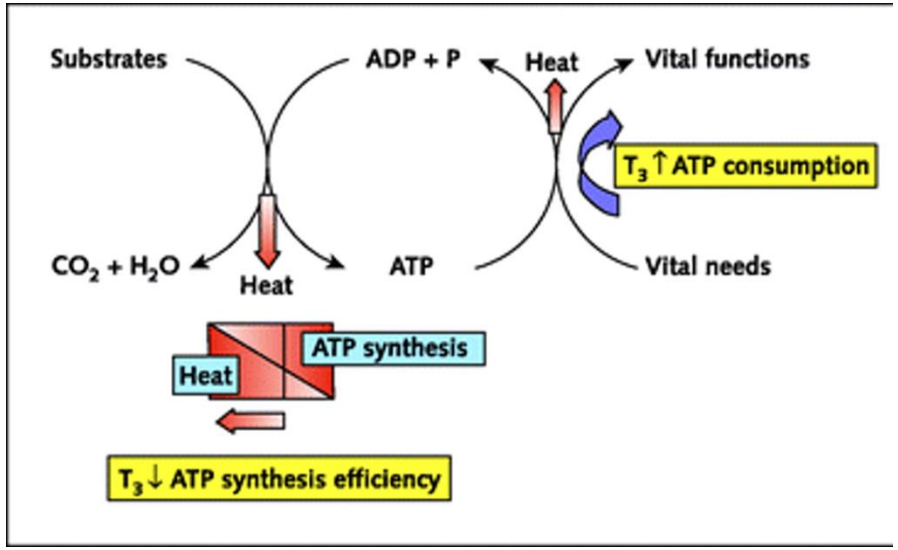
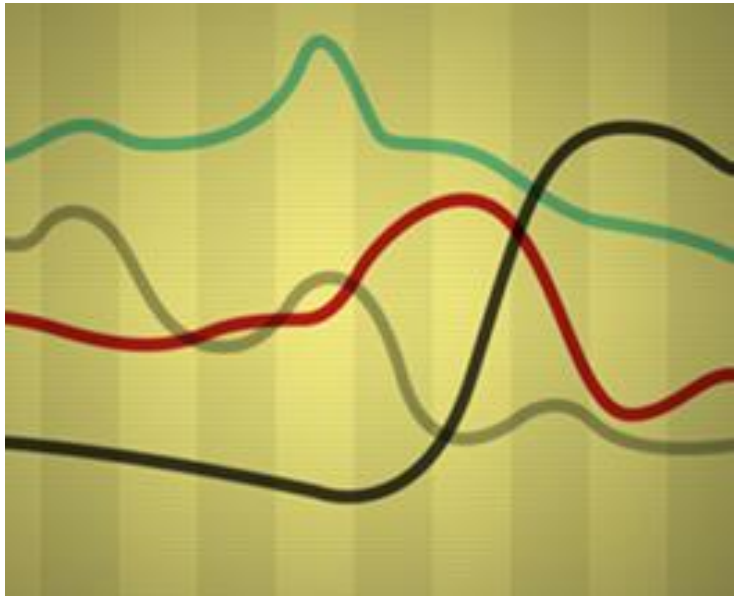
Physiologic effects of T3/T4

- (3) metabolism
  - increase in basal metabolic rate and thermoregulation
    - increase body heat production from increased O2 consumption and rate of ATP hydrolysis
  - lipid metabolism
    - fat mobilization → increased concentrations of FFA in plasma
    - oxidation of FFA
    - plasma concentrations of cholesterol and triglycerides are inversely correlated with thyroid hormone levels
  - carbohydrate metabolism
    - stimulate almost all aspects of carbohydrate metabolism, including enhancement of insulin-dependent entry of glucose into cells (via GLUT4) and increased gluconeogenesis and glycogenolysis to generate free glucose
  - protein metabolism
- (4) other effects
  - cardiovascular, CNS, reproductive system





CHRONOBIOLOGY OF THE THYROID

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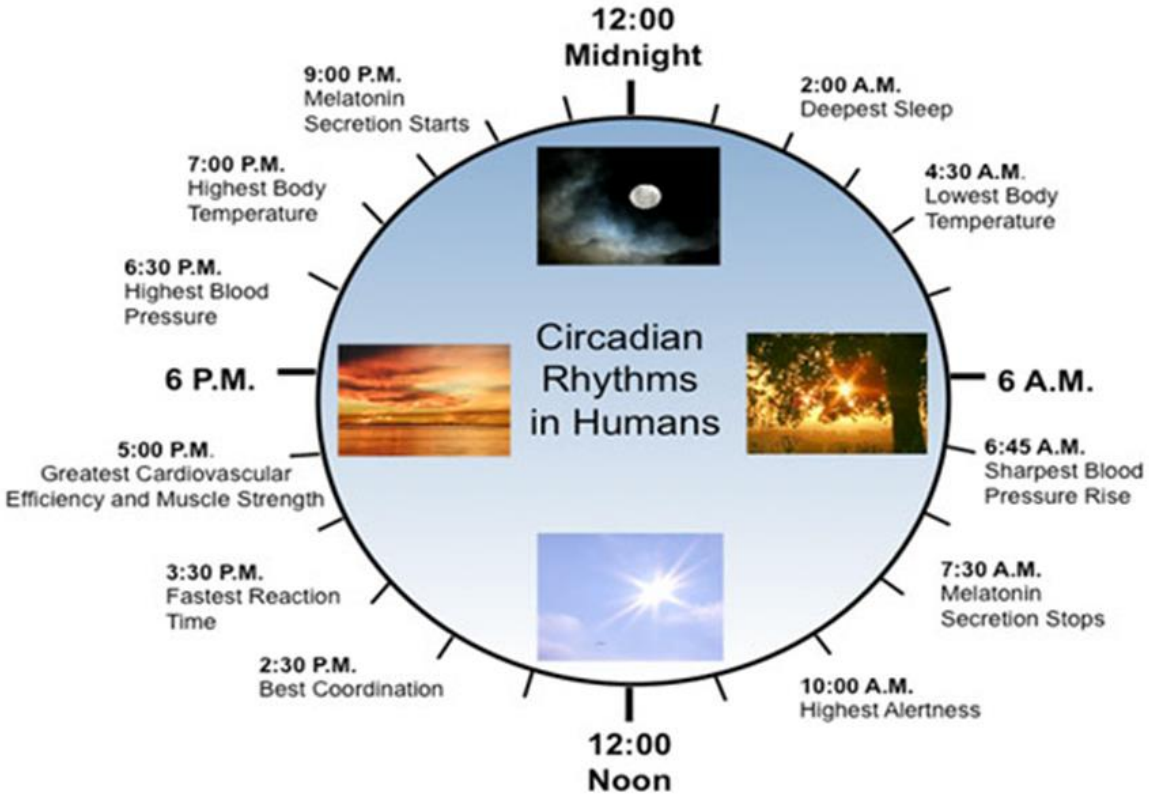
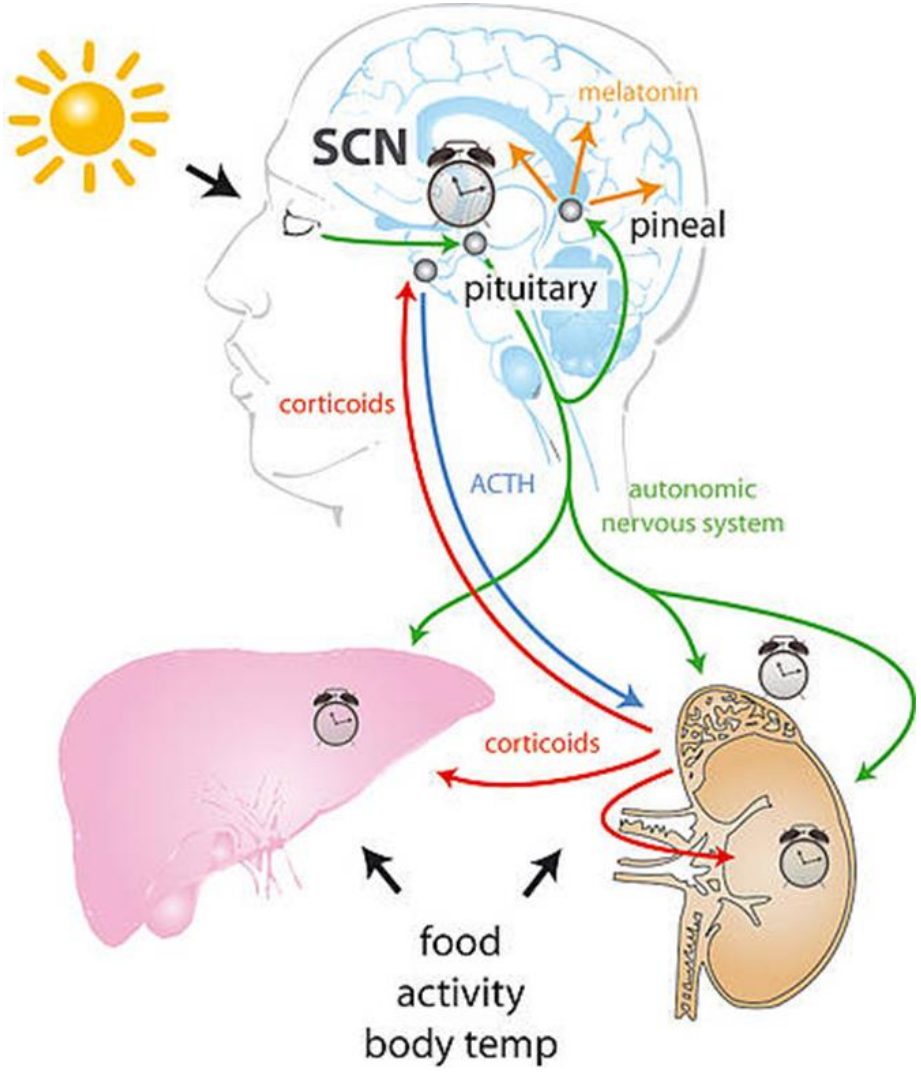
Circadian rhythm





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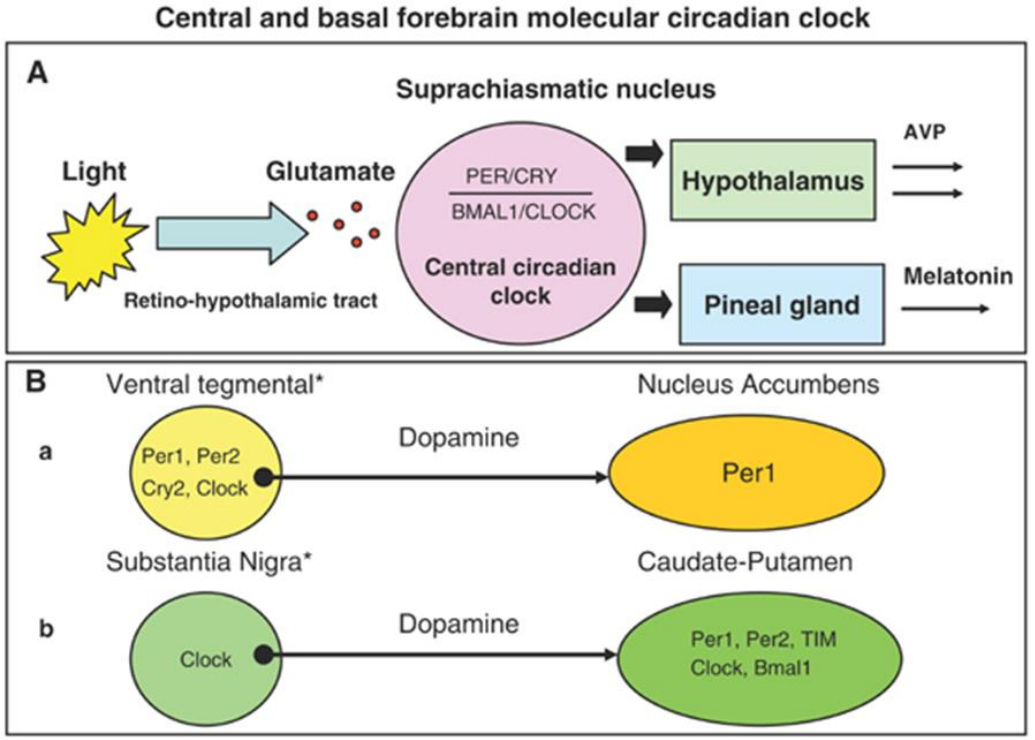
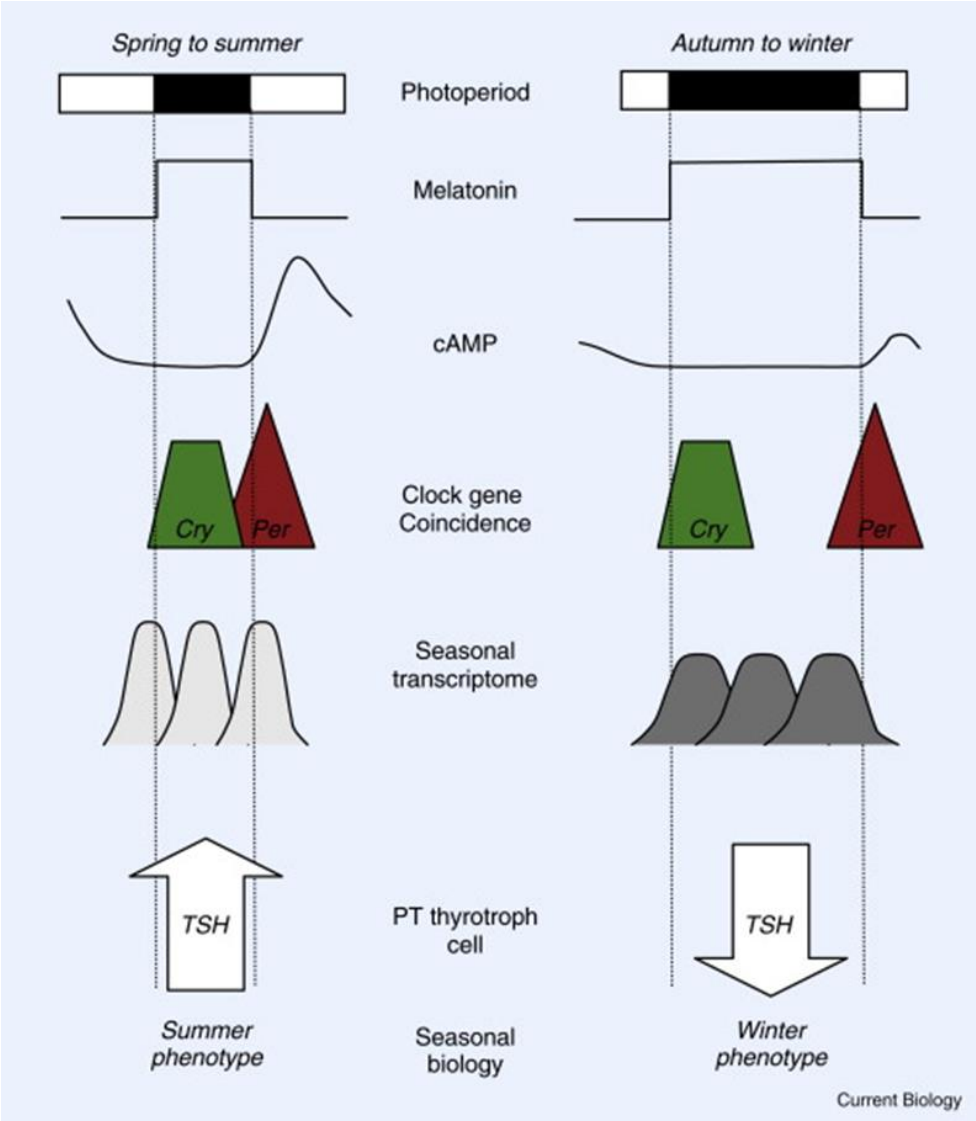
„Molecular clock“

- inner biological rhythmicity is caused by negative and positive feedbacks between transcription of clock genes (CGs), their translation, postransl. modification and degradation
- their products - proteins – then serve as transcription factors of other hundreds of genes (CCGs) n n. suprachiasmaticus and peripherally
  - they synchronize the body according to external environment
- hypothalamus
  - clock genes (CGs)
    - Clock
    - BMal1 (Mop3), BMal2
    - Per1, Per2 (Period)
    - Cry1, Cry2 (Cryptochrome)
    - Rev – Erb-α
    - CK1Є CK1δ (caseinkinase)
  - clock-controlled genes (CCGs)
    - Per 3
    - AVP (arginin vasopresin)
    - Dbp (D-element binding
- peripheral organs



Seasonal clocks - analogy with circadian clocks

- in long-lived species there is evidence for the existence of self-sustained circannual oscillators
  - migratory restlessness
  - hibernation
  - seasonal moulting
  - seasonal breeding



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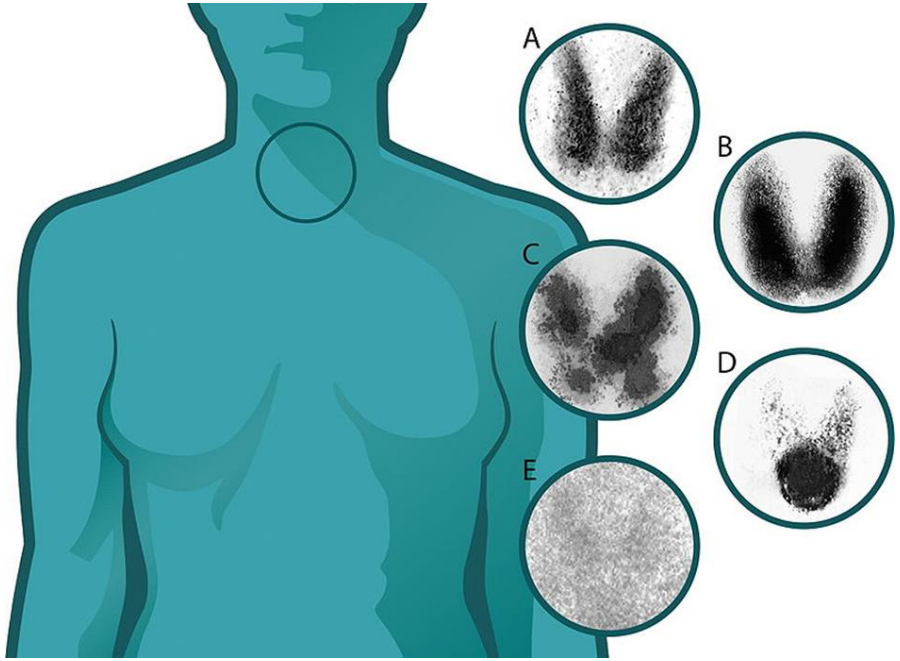
Thyroid function assessment

- serum
  - hormones
    - TSH, T4, T3, fT4, fT3, rT3
  - antibodies
    - anti-thyroglobulin (anti-TG), anti-thyroid peroxidase antibodies (anti-TPO)
  - calculated indexes
    - fT4/fT3, fT3/rT3
  - ioduria (morning urine)
- thyroid ultrasound
- radionuclide thyroid scan – iodine (^{123}I) or pertechnatate (Tc-99)
  - detection of nodules and to assess thyroid function
- fine needle aspiration



- Thyroid scintigramms (marker 99Tc)
  - A) normal thyroid
  - B) Graves disease, diffuse increased uptake in both thyroid lobes,
  - C) Plummers disease (TMNG, toxic multinodular goitre)
  - D) toxic adenoma
  - E) thyroiditis

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DISEASES OF THE THYROID GLAND

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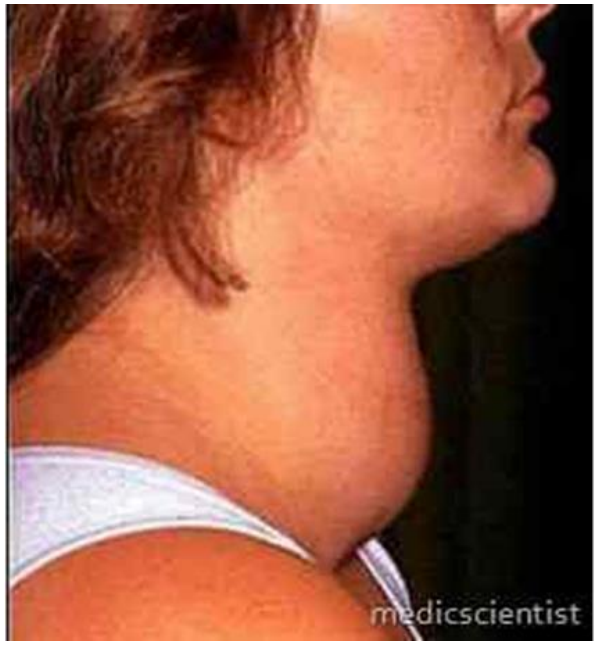
Goiter (struma)

- abnormal enlargement of the thyroid gland that is not associated with inflammation or cancer
- presence of a goiter does not necessarily mean that the thyroid gland is malfunctioning
  - gland that is producing too much hormone (hyperthyroidism)
  - too little hormone (hypothyroidism)
  - or the correct amount of hormone (euthyroidism)
- presence of goiter indicates there is a condition present which is causing the thyroid to grow abnormally



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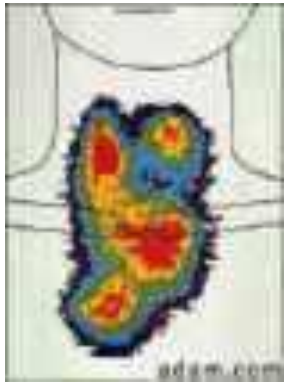
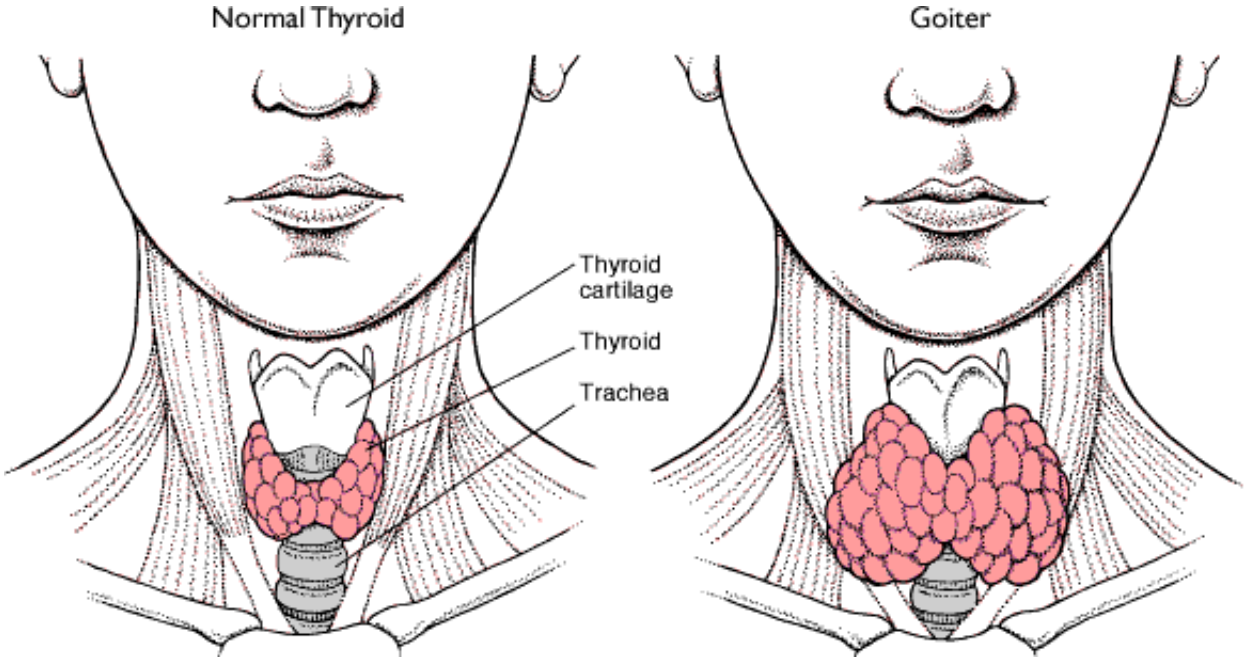
Types of goiter





- simple (non-toxic, euthyroid)
  - causes
    - endemic
      - caused by a deficiency of iodine in the diet (inland and highland areas of all continents)
    - sporadic
      - "strumigens" in the diet (e.g. cabbage, soybeans, peanuts, peaches, strawberries, spinach, and radishes)
  - usually diffuse form
- toxic (hyperthyroidism, thyrotoxicosis)
  - nodular or diffuse form

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Endemic goiter

- inland, mountainous districts all over the world
  - affects almost 13% of population
  - another 30% are in a risk of a manifest deficit
    - Himalayas – Pakistan, India and Nepal, China, Thailand and Vietnam, Indonesia, New Zealand, Europe, Andes, Africa
- cretinism
  - neurologic form
  - myxedematous form
- iodine prophylaxis !!!

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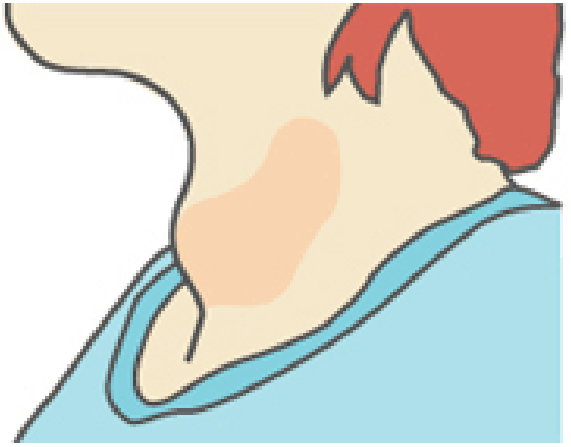
Thyroid endocrinopathies from the functional point of view

- Hyperthyroidism
  - Graves' disease (toxic diffuse goitre)
    - autoimmune
  - toxic nodular goitre (Plummer's disease)
    - toxic adenoma
  - thyroiditis
  - primary and/or metastatic follicular carcinoma
  - TSH-producing tumour of the hypophysis
- Hypothyroidism
  - hypothalamic or pituitary
  - autoimmune thyroiditis (Hashimoto)



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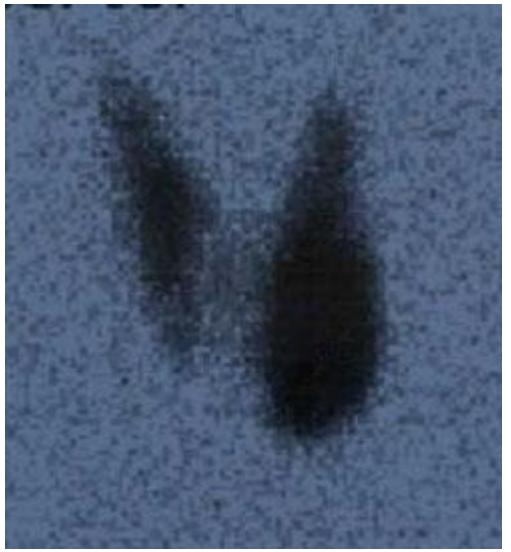
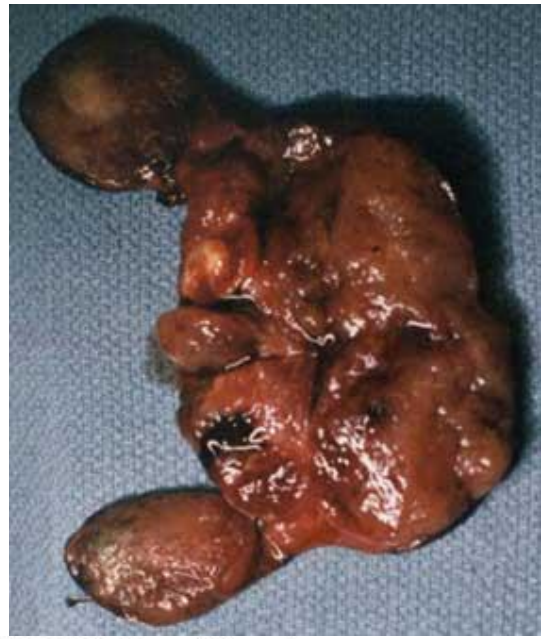
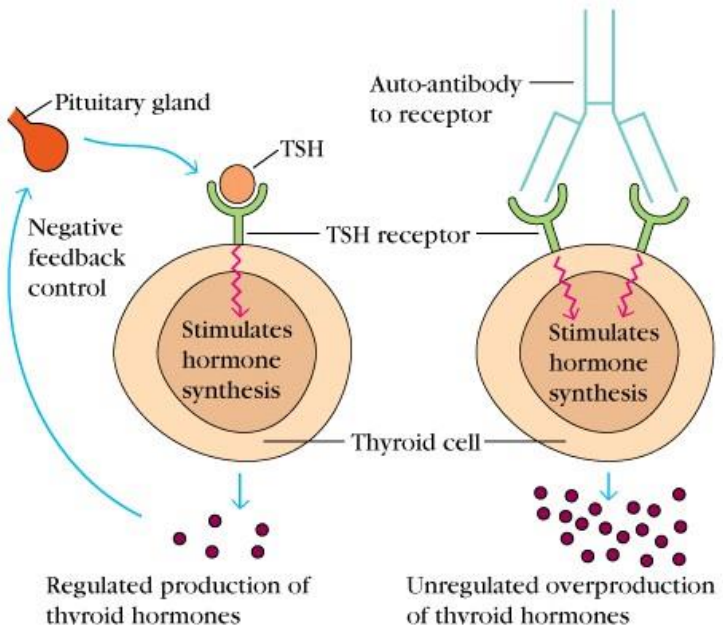
Toxic goiter

- nodular (Plummer's disease)
  - autonomous function of one or more thyroid adenomas in a part of the gland
- diffuse (Graves-Basedow's disease)
  - stimulation by anti-TSH antibodies (type V hs) [LATS = long-acting thyroid stimulators]







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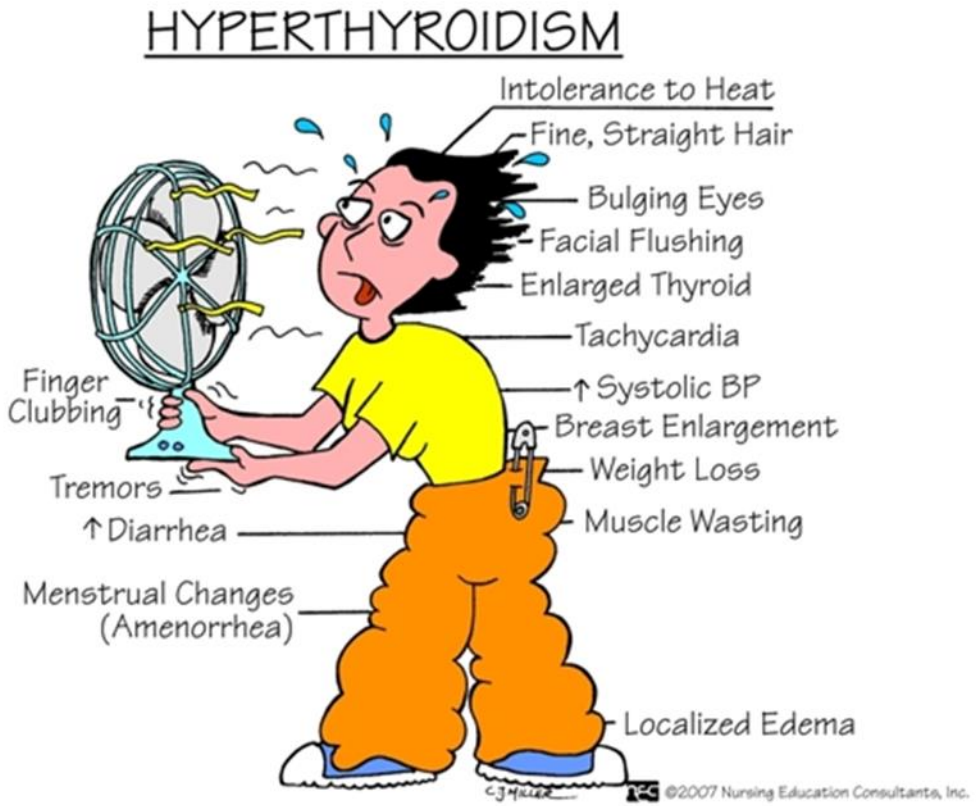
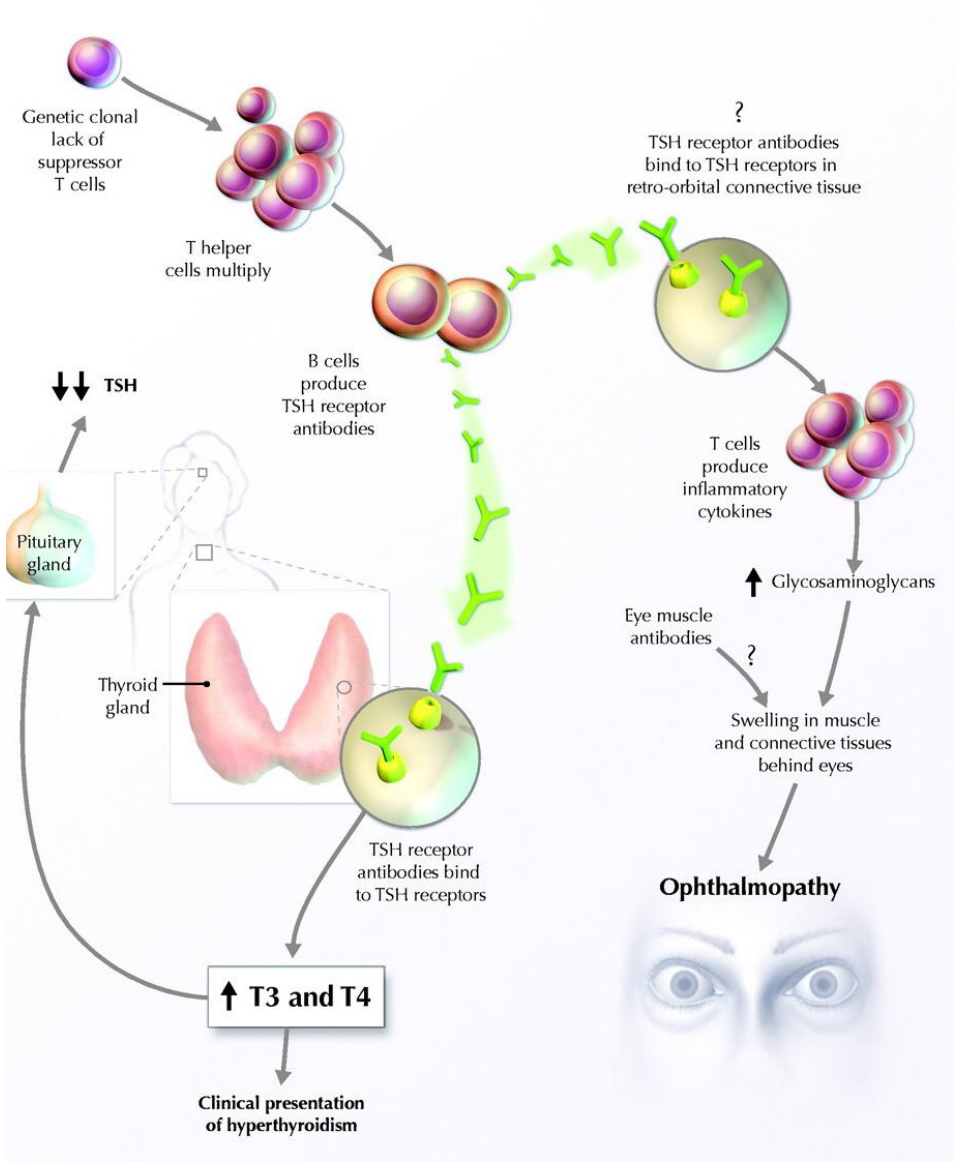
Hyperthyroidism (thyrotoxicosis)

- predominance of women, middle age

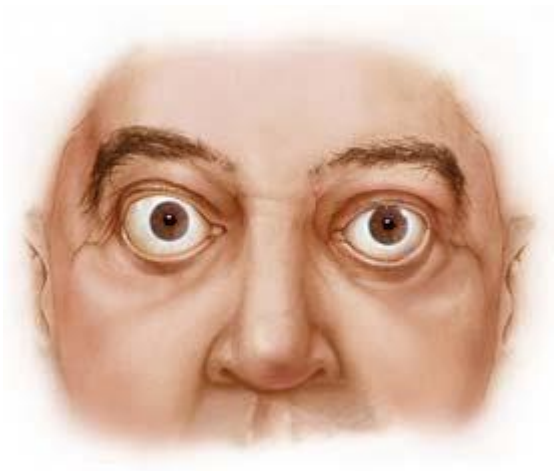


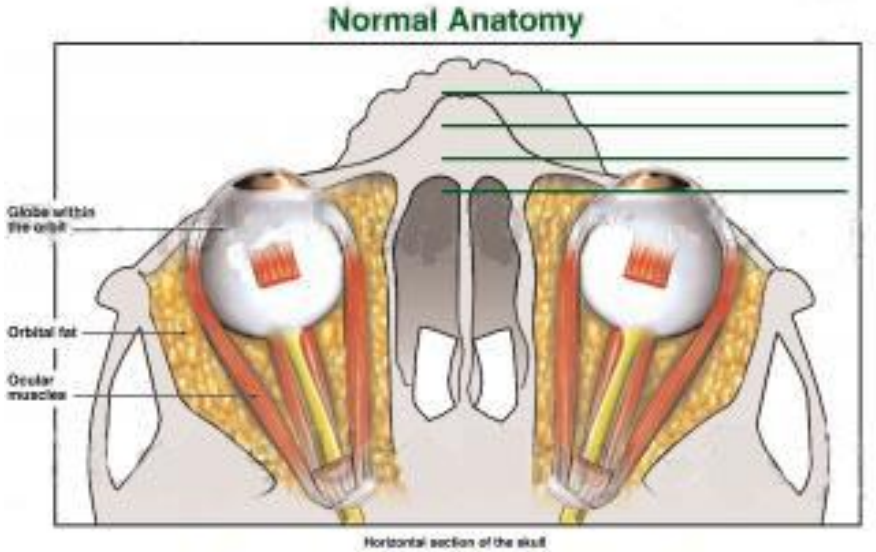
Grave's disease

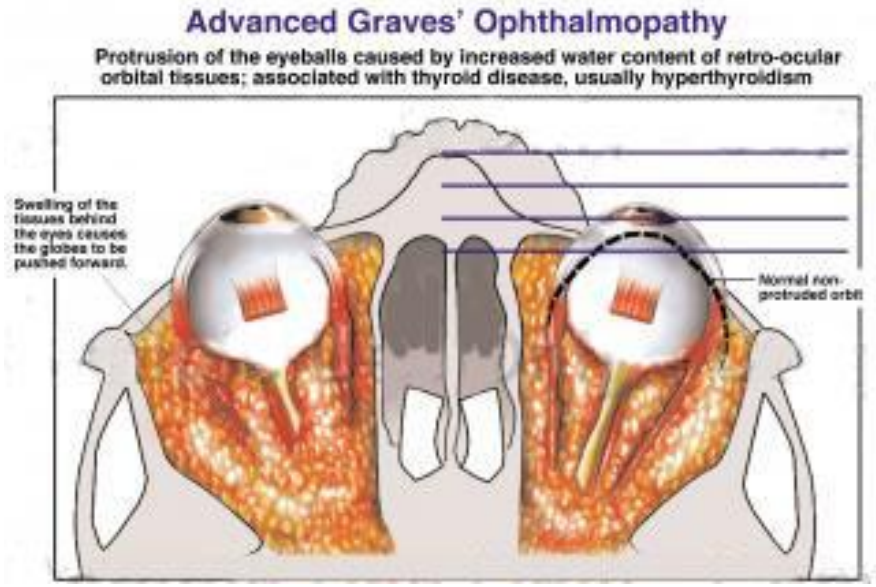
- hyperthyroidism +
- infiltrative ophthalmopathy
  - ~1/2 od the cases, independent on hyperthyroidism
  - involves periorbital connective tissue, ocular muscles and fat
- infiltrative dermopathy
  - ~1/5 of cases
  - pretibial myxedema



Ophthalmopathy







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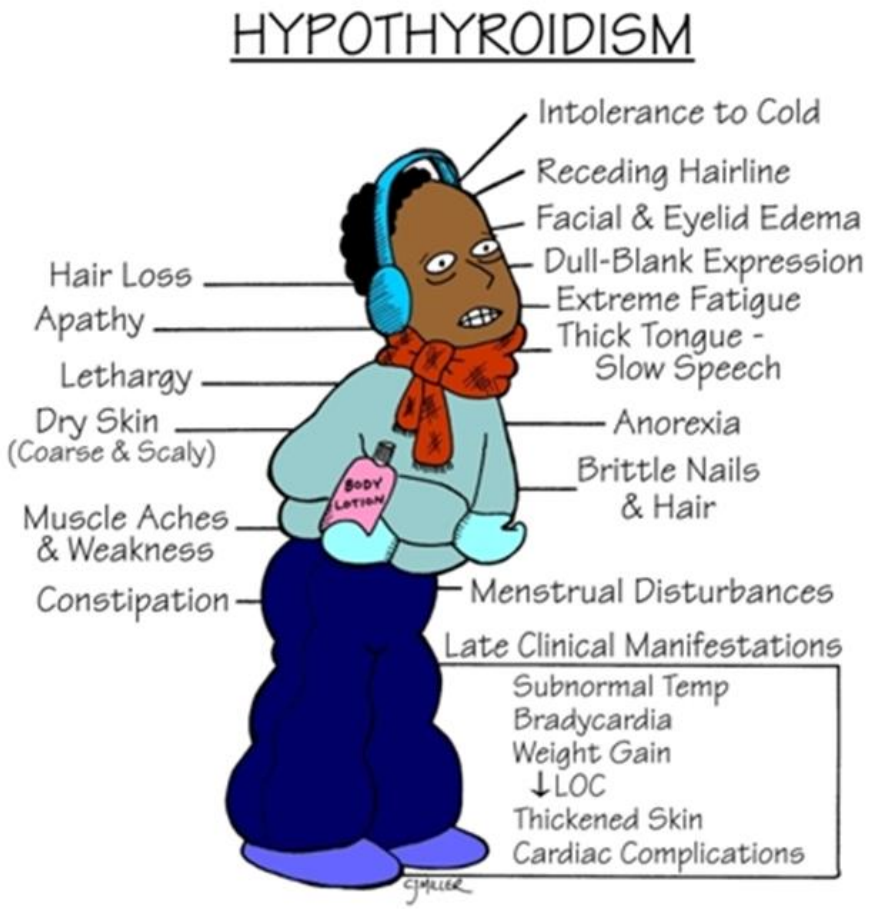
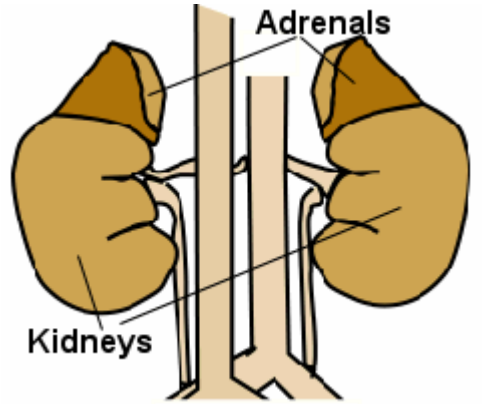
Hypothyroidism

- often results of (auto)immune destruction of the thyroid
  - de Quervain thyroiditis
  - Hashimoto thyroiditis
- usually transitory hyperthyroidism in acute phase, then cessation of function
- predominance of women, middle age



The Adrenals



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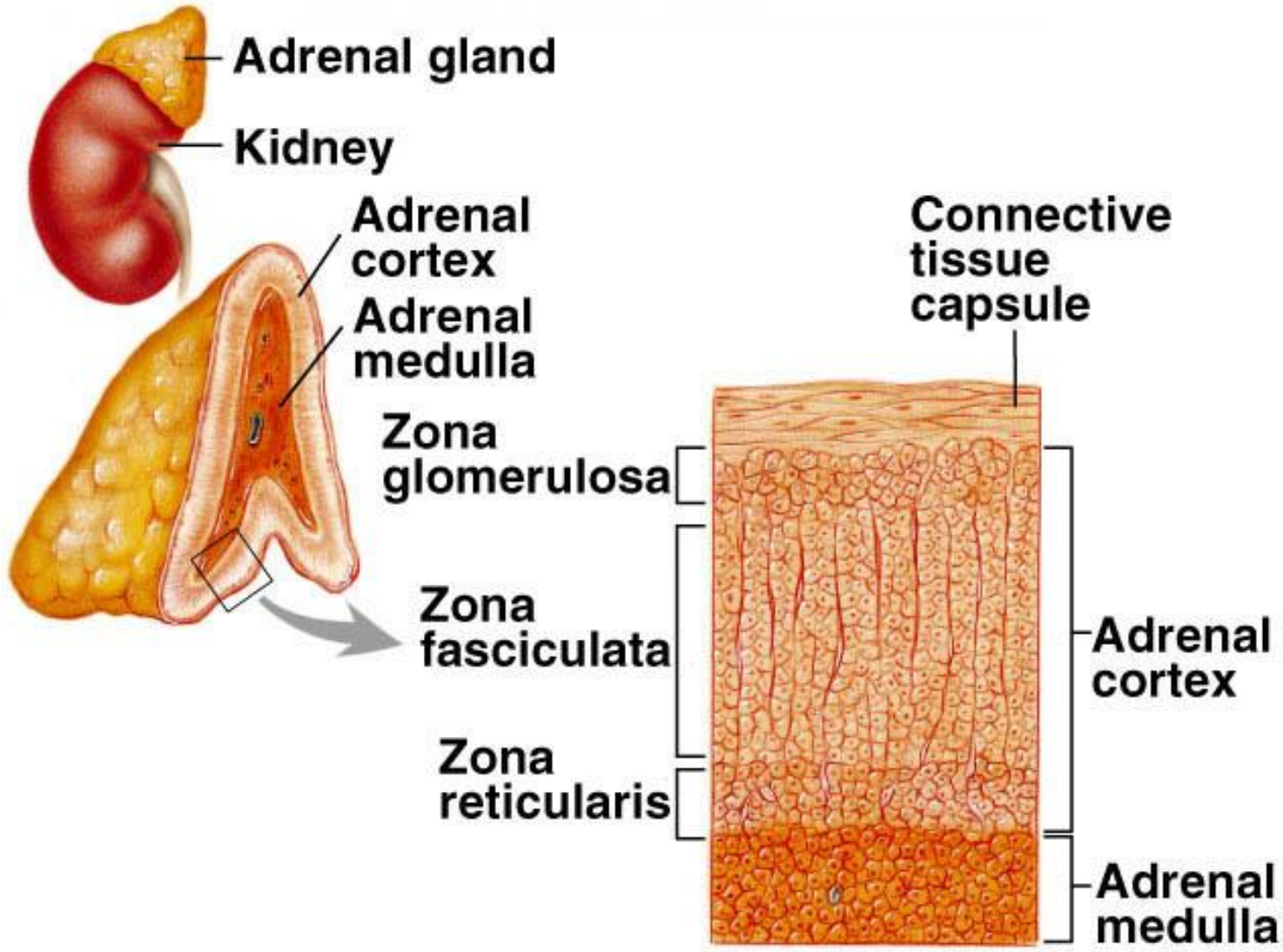
Pathophysiology of adrenals



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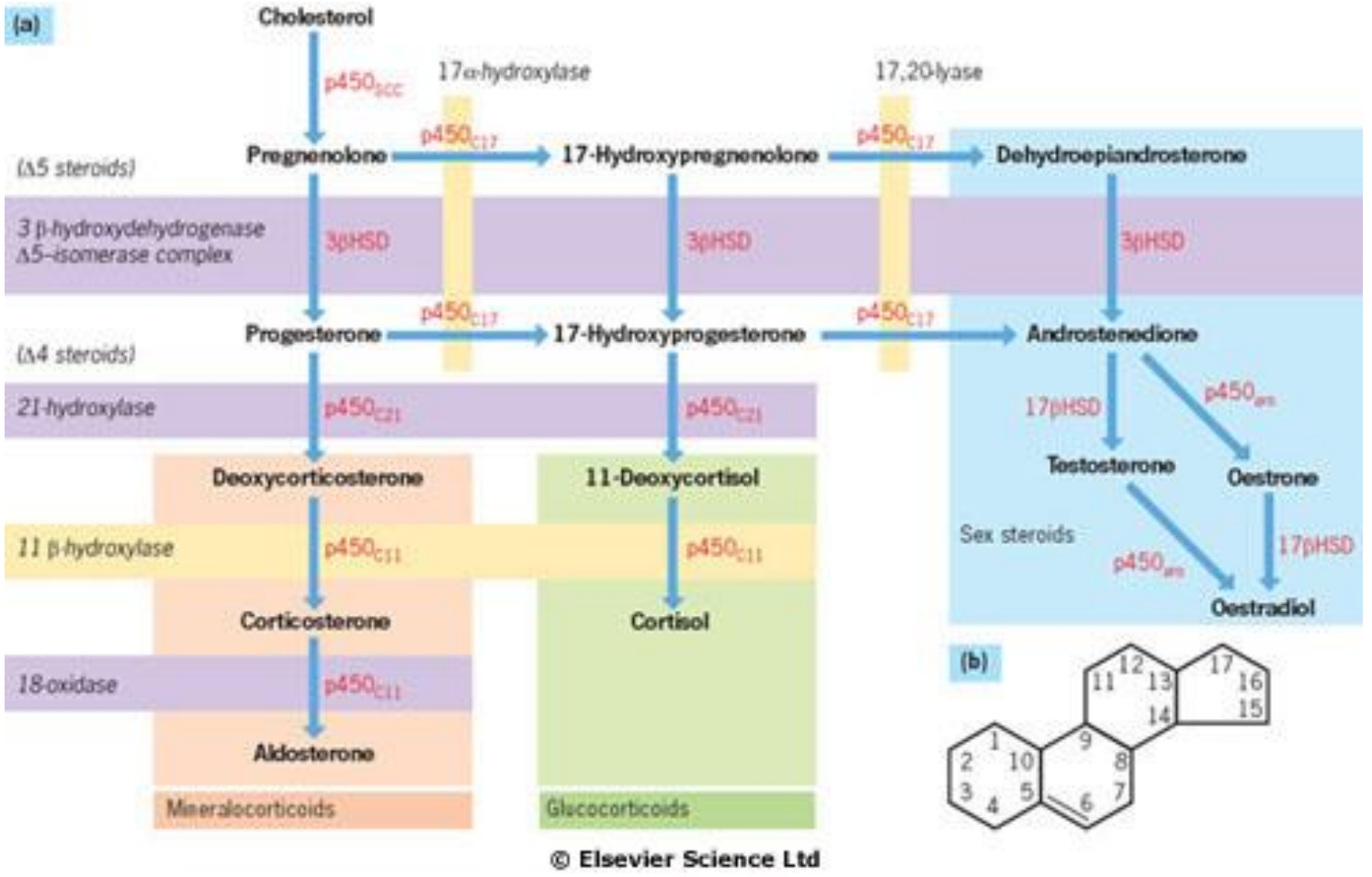
Major steroid biosynthetic pathways



- p450 enzymes are in mitochondria, each catalyses several reaction steps
- 3βHSD (hydroxysteroid dehydrogenase) is in cytoplasm, bound to endoplasmic reticulum
- 17βHSD and p450aro are found mainly in gonads

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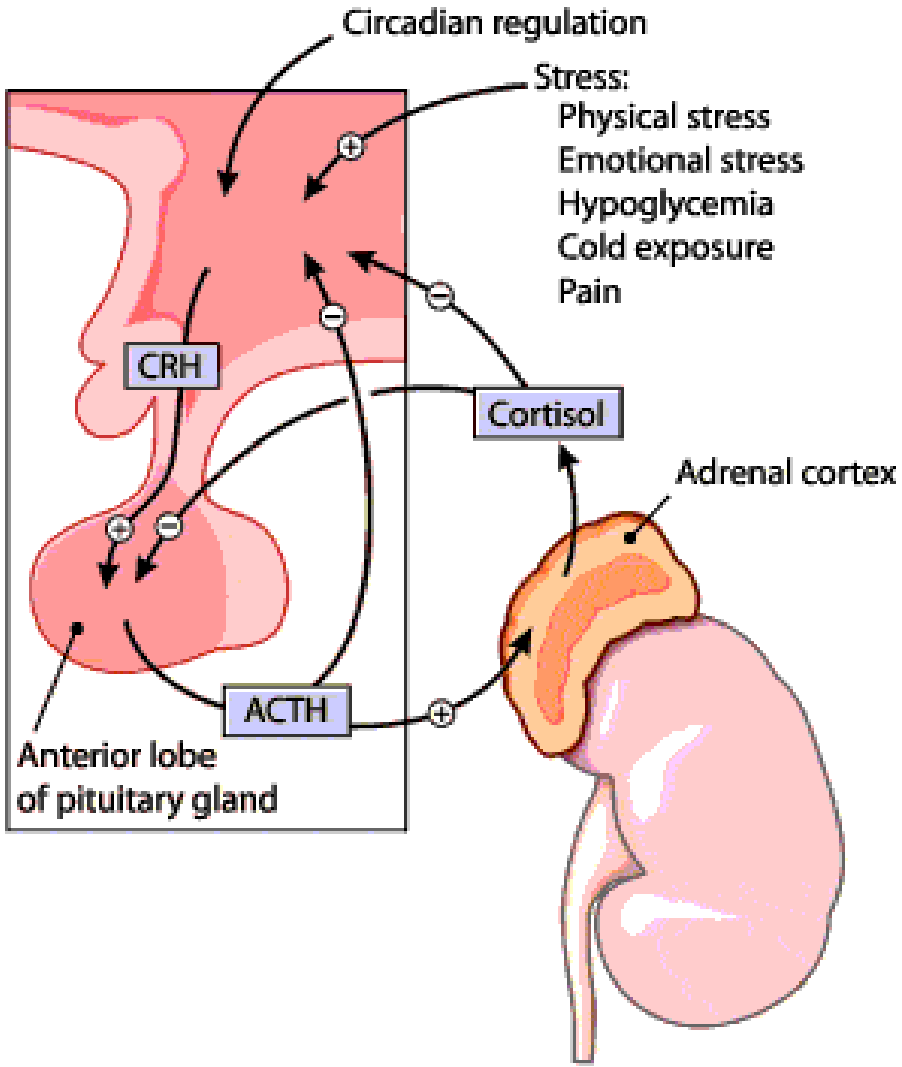
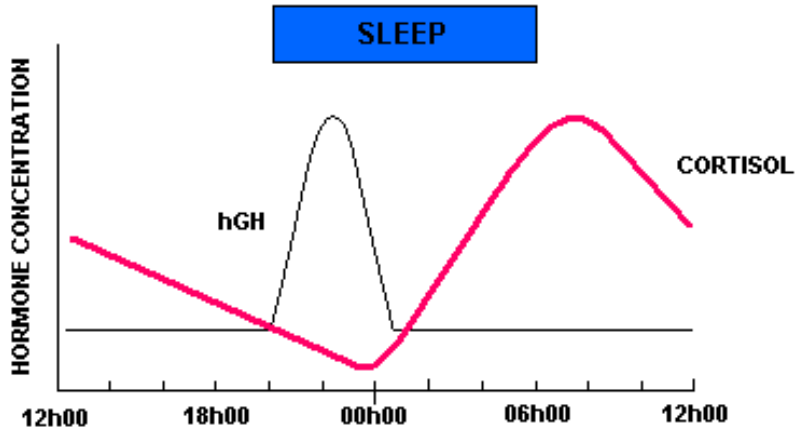
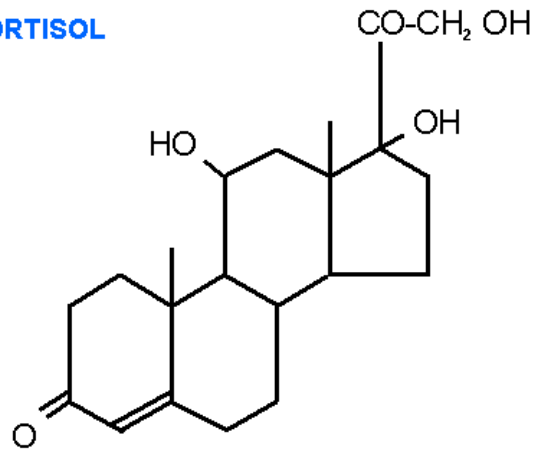
Cortisol profile & regulation





CORTISOL



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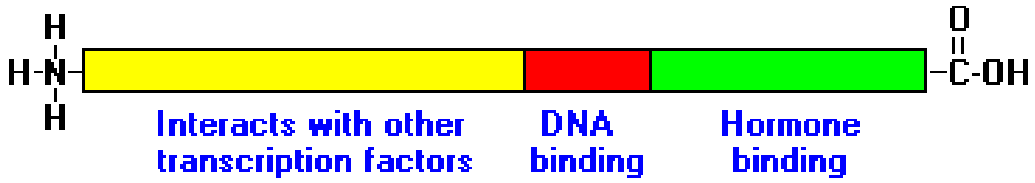
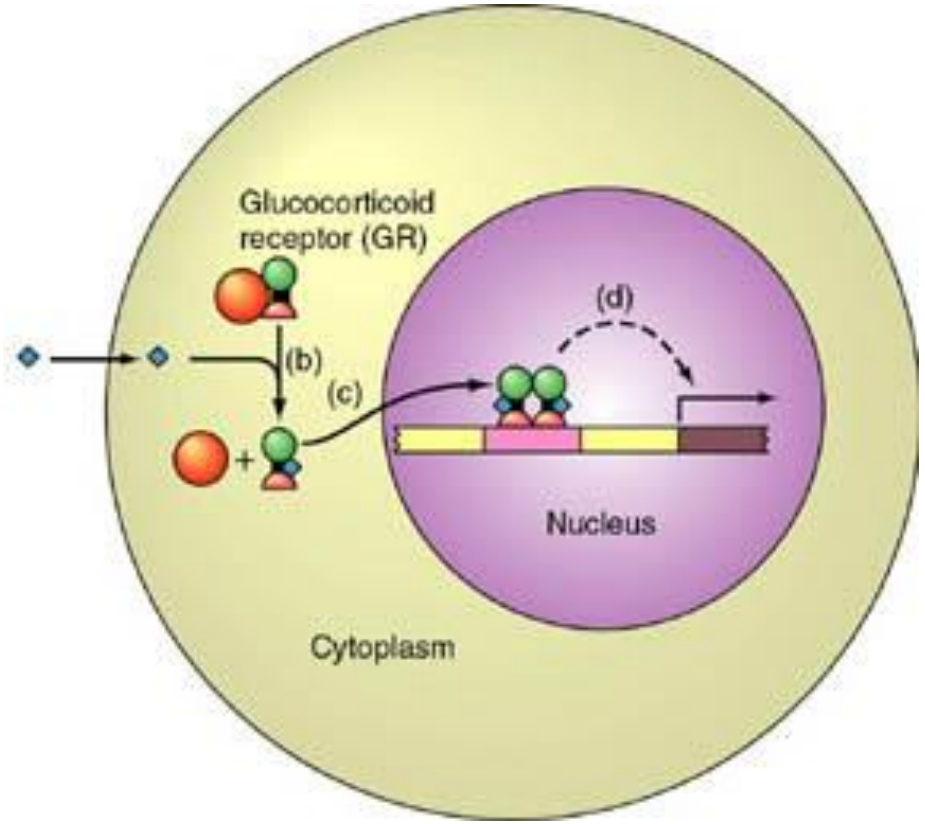
Glucocorticoid (GC) receptor





- GCs have receptor (GR) existing in two isoforms
  - cytoplasmic (cGR)
  - membrane bound (mGR)
- therefore, GCs have several modes of action
  - (1) genomic – mediated by cytosolic receptors (cGR) upon binding to GC responsive elements (GREs)
  - (2) fast non-genomic – mediated by cGR, mGR and non-specific effects by interaction with other proteins and cell membranes
- receptor activation
  - cGR has 3 domains: N-terminal transactivation domain / DNA-binding domain / ligand-binding domain
  - following synthesis GRs are located in the cytoplasm in the complexes with molecular chaperons
    - Hsp-70 – newly synthesized, helps further folding of the nascent GR
    - Hsp-90 – helps to full maturation and achieving hormone-activavable state
  - GR/Hsp (+ other proteins) complexes
    - protect GRs from degradation by proteasome
    - increase affinity of GRs for GCs (~100×)
    - blocking action of other proteins (e.g. MAPK) bound to complex
  - upon binding of GC in cytoplasm → conformational changes and release from inhibitory complexes with Hsp → translocation to nucleus and homodimerisation
- binding to hormone responsive elements (HREs)
  - short specific sequences of DNA located in promoters
  - phosphorylation
- induction of transcription
  - binding to HRE facilitate binding of TF to TATA box
    - complex hormone-receptor - HRE thus function as an enhancer

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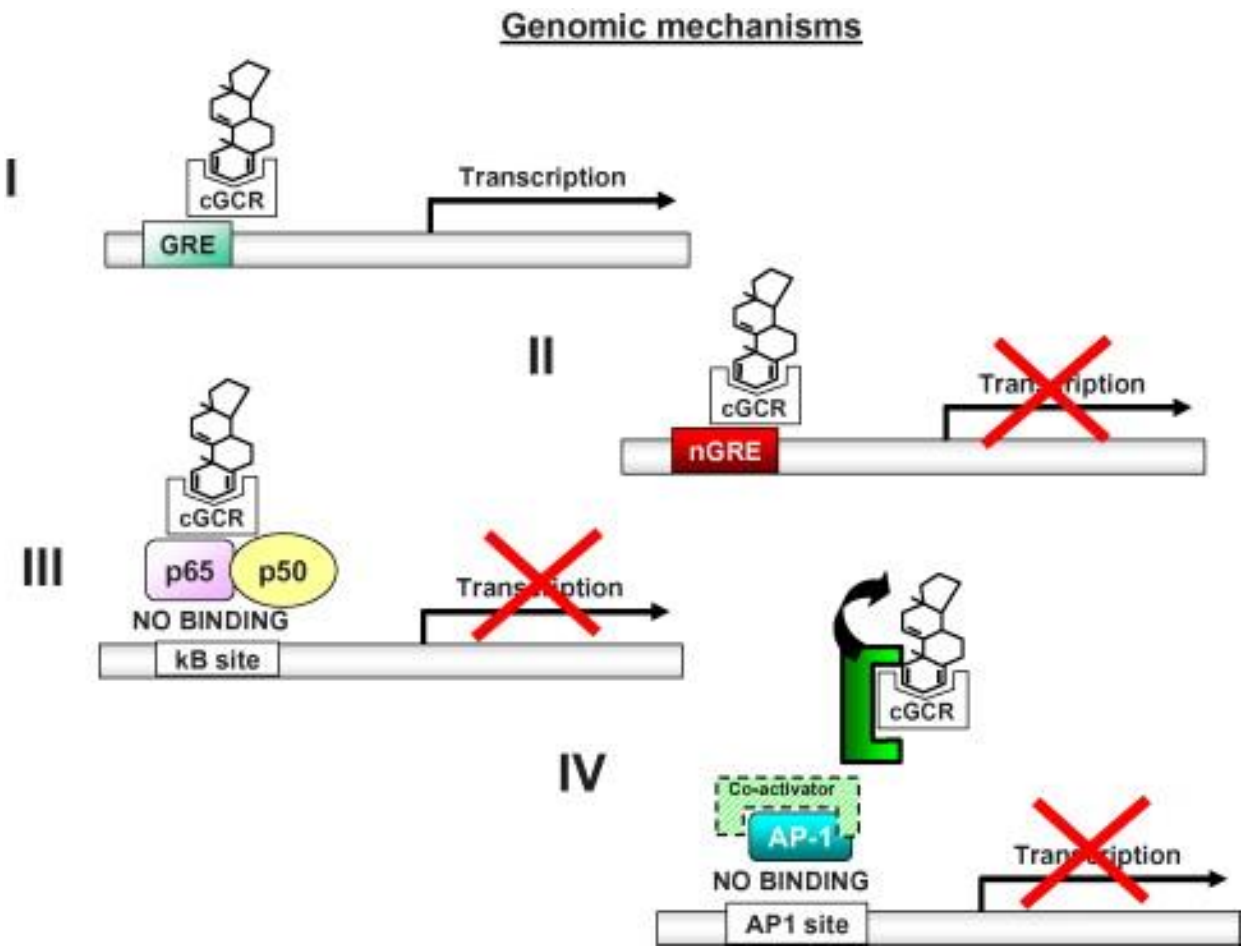
GC action – genomic effects



- (A) genomic effects – via cGR – majority of metabolic effects are achieved by genomic effects
  - GC responsive genes represent ~ 20% of all coding genes, indispensable for life
    - GR knock-out animals are not viable!!
  - effects:
    - (1) transactivation = binding to GREs
      - short specific sequences of DNA located in promoters → gene transcription [I]
    - (2) transrepression = binding to negative GRE (nGRE) [II] or interaction with other TF [III] or their coactivators [IV]
      - repression of transcription or blocking action of other TF on gene transcription (such as AP-1, NFkB, ...)
  - the whole sequence of events following binding of GCs to cGRs takes at least 20-30min – late effects compared to the action of peptide hormones or non-genomic action of GCs
  - affinity of steroid receptors (for GC, aldosteron, estradiol) is not specific!!
    - e.g. GCs bind avidly to MR in brain, not in kidney though (degraded)
- (B) non-genomic effects – many of anti-inflammatory and immunosuppressive effects

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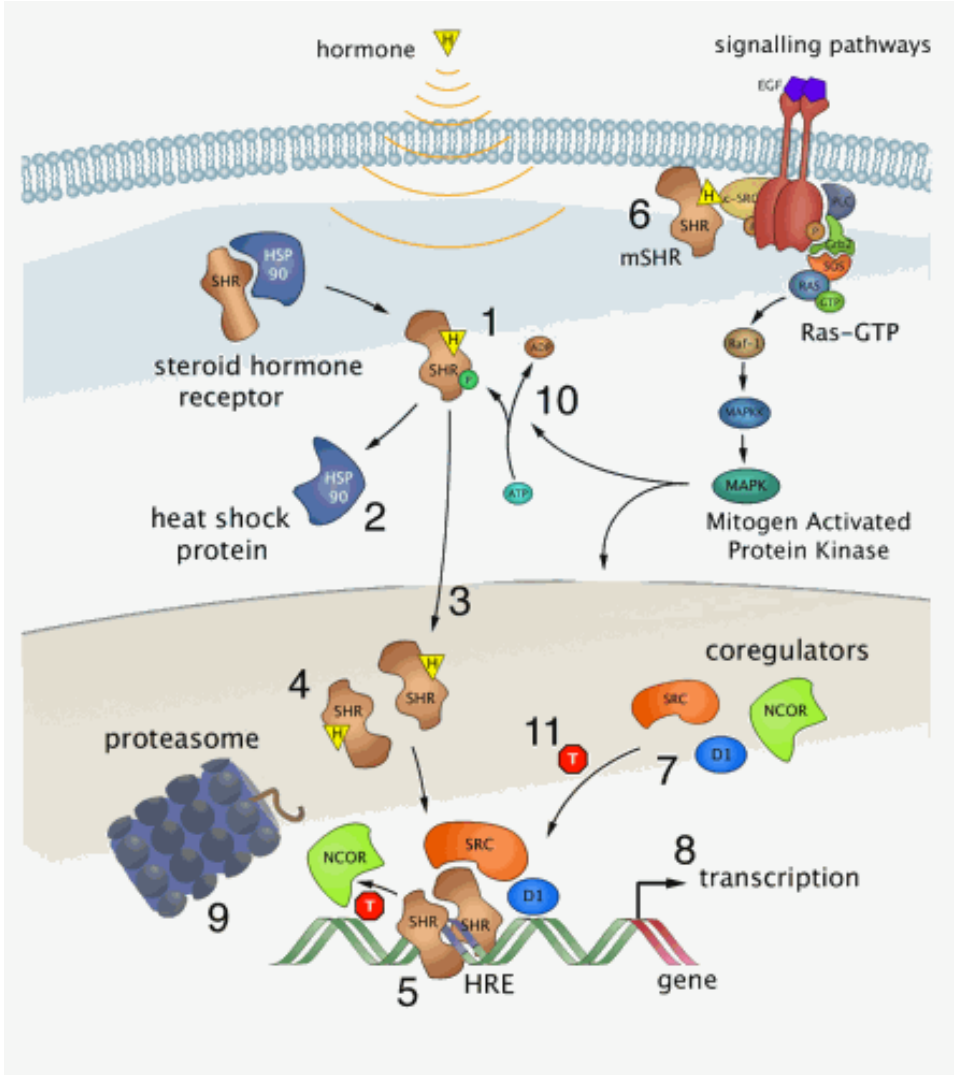
Steroid hormone receptor signalling

- GR act as hormone dependent nuclear transcription factor
- upon entering the cell by passive diffusion, the hormone (H) binds the receptor[1], which is subsequently released from heat shock proteins [2], and translocates to the nucleus [3]
- there, the receptor dimerizes [4], binds specific sequences in the DNA [5], called Hormone Responsive Elements or HREs, and recruits a number of co-regulators [7] that facilitate gene transcription
- this latter step can be modulated by certain cellular signaling pathways [10] or receptor antagonists (like tamoxifen [11])
- subsequent gene transcription [8] represents a genomic effect of GC
- action is terminated by proteasomal degradation [9],
- other, non-genomic effects are mediated through putative membrane-bound receptors [6]



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Metabolic effects of GC – increased turnover of free and stored substrates (i.e. lipids and proteins)

Tissue/organ	Physiologic effects	Effects of overproduction
Liver	↑**hepatic gluconeogenesis (↑ Glc)** (stimulation of key enzymes – pyruvate carboxylase, PEPCK, G6Pase)	impaired glucose tolerance/diabetes mellitus
	hepatic lipogenesis (↑ FA and VLDL) (stimulation of key enzymes acetyl-CoA-carboxylase and FA synthase)	steatosis/steatohepatitis
Adipose tissue	↑**lipolysis in subscutaneous fat (↑ FFA)** (activation of HSL and inhibition of LPL)	insulin resistance in the muscle (competition of FFA with Glc for oxidation)
	↓**Glc uptake** (down-regulation of IRS, inhibition of PI3K, Glut4 translocation)	insulin resistance by interference with insulin post-receptor signalling
	↑**adipocyte differentiation in visceral fat** (expression of GR and 11βHSD1 different in adipose and visceral fat)	truncal (abdominal) obesity, metabolic syndrome
Skeletal muscle	↓ **Glc uptake** (down-regulation of IRS, inhibition of PI3K, Glut4 translocation)	insulin resistance by interference with insulin post-receptor signalling
	↑**proteolysis,** ↓ **proteosynthesis (↑ AA)** (counteracting effect of IGFs, activation of ubiquitin-mediated degradation, induction of myostatin and glutamine synthetase)	muscle atrophy, weakness, steroid myopathy
Pancreas (β cells)	↓ **insulin secretion** (supression of GLUT2 and K^+ channel, apoptosis)	impaired glucose tolerance/diabetes mellitus

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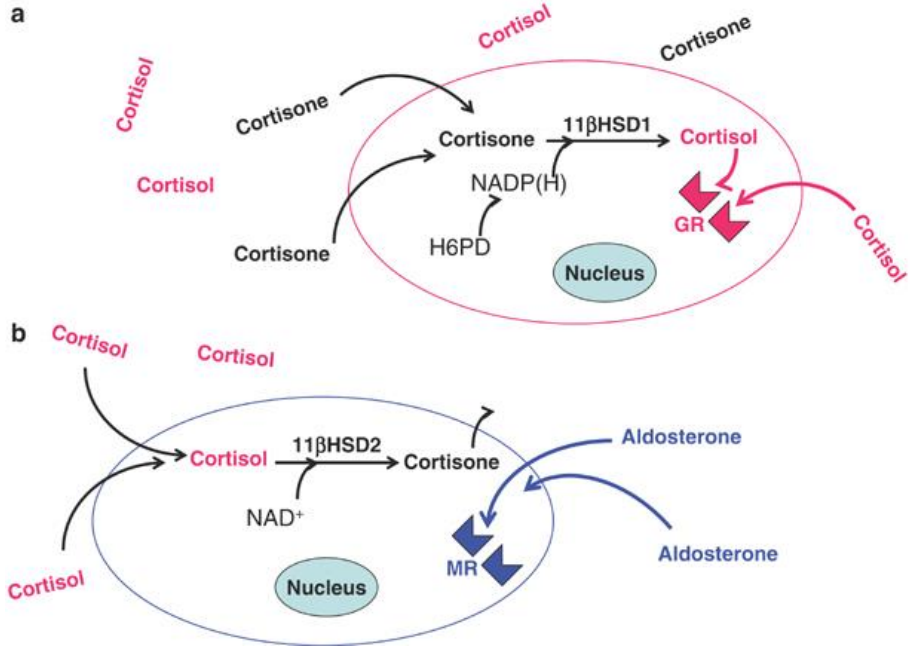
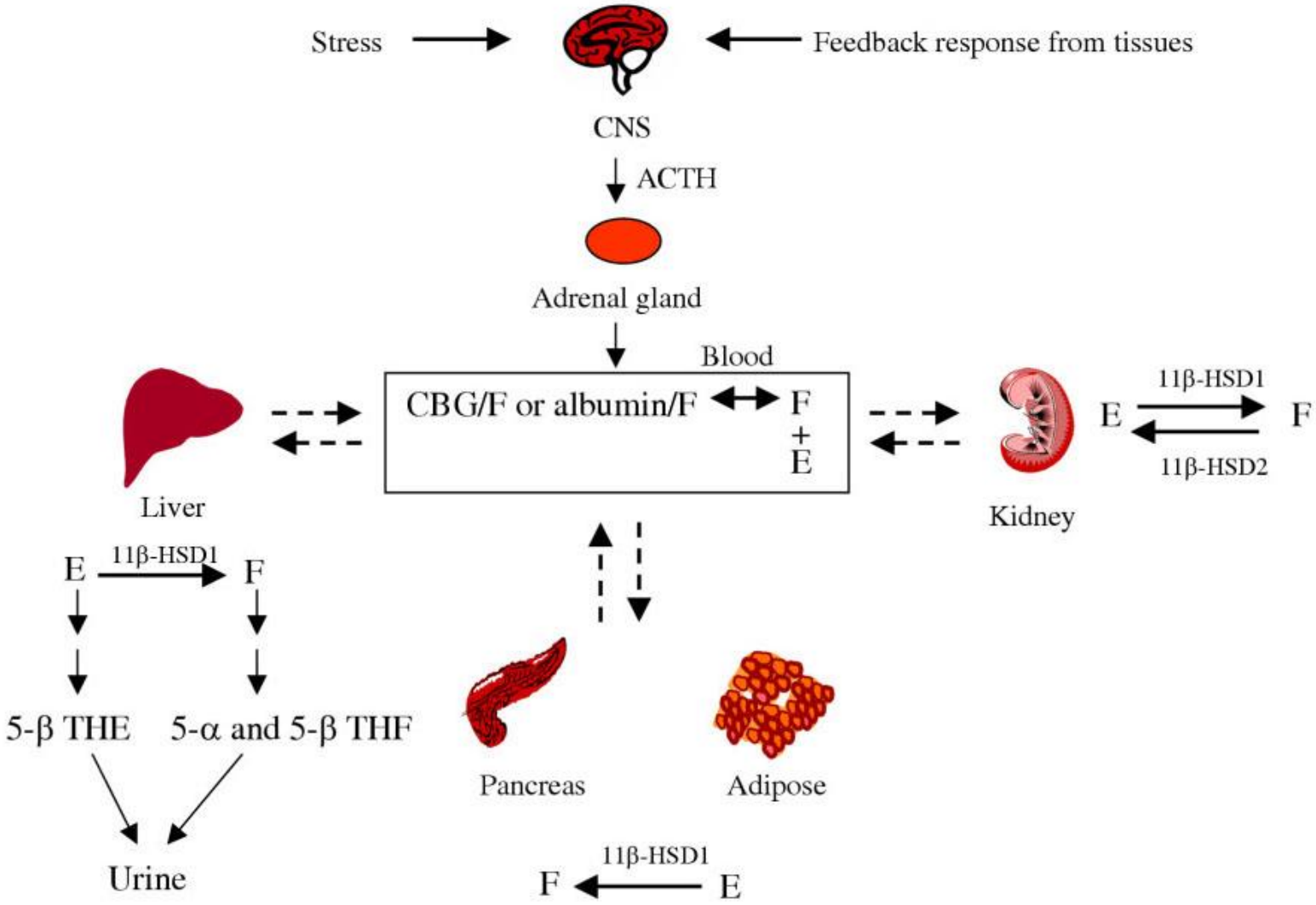
Peripheral modulation of GC availability

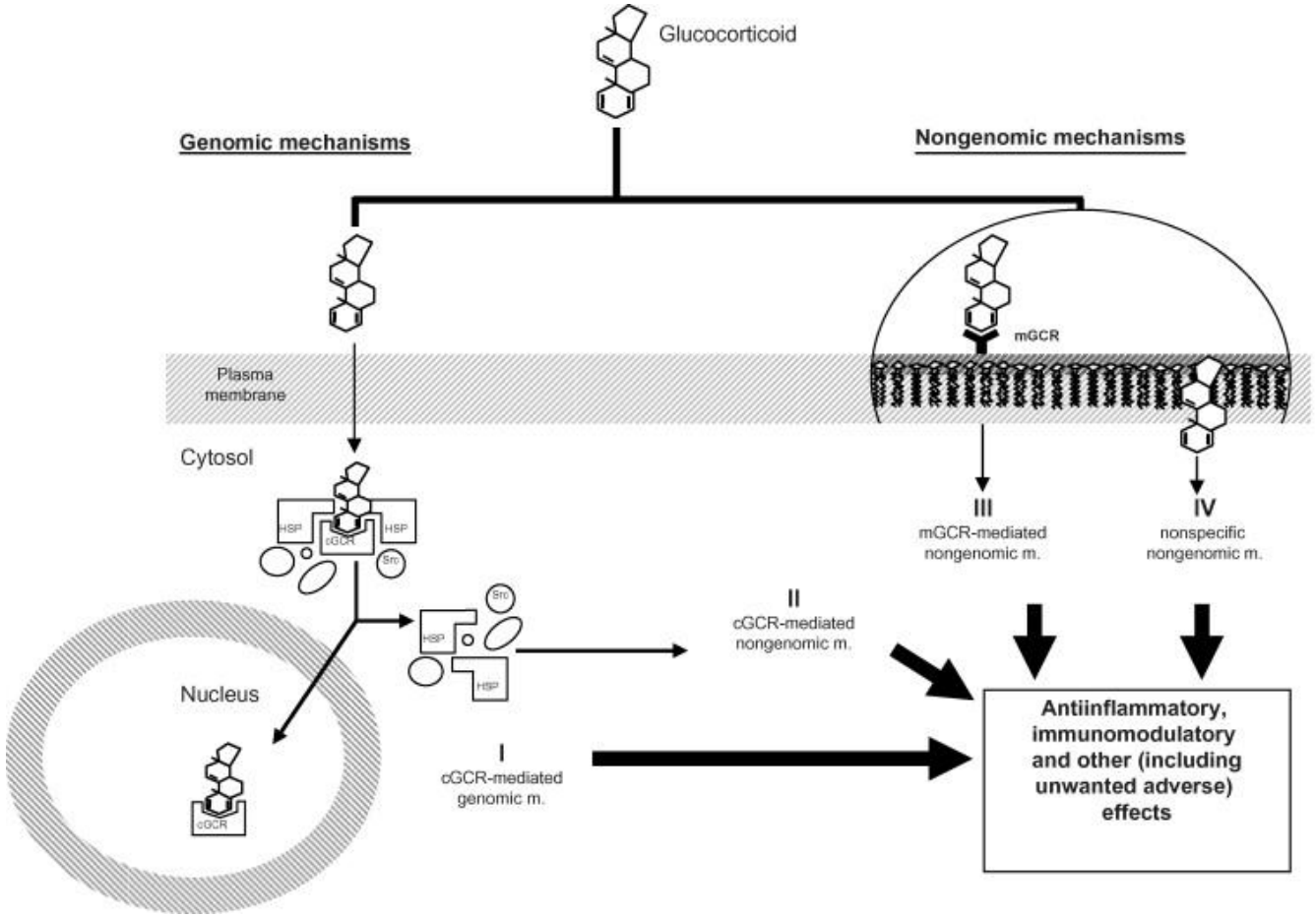
- peripheral tissue-specific modulation of cortisol availability by enzymes catalysing interconversions of active and inactive forms of GCs
- **(a) 11β hydroxysteroid dehydrogenase type 1 (11βHSD1)**
  - act as a reductase regenerating cortisol from cortisone → ↑ intracellular cortisol concentration
    - mainly in liver and adipose tissue
      - expression of 11βHSD1 is higher in visceral than subcutaneous fat! → visceral fat is therefore more flexible pool of energy substrate
  - often co-localises with GR (e.g. in liver and adipose tissue) and thus locally amplifies the GC action
    - 11βHSD1 overexpressing mice develop obesity, while 11βHSD1 knock-out mice are protected from overeating-induced obesity
    - liver and fat-tissue specific inhibitors of 11βHSD1 could be used for treatment of metabolic syndrome and obesity
  - pathology associated with 11βHSD1
    - Cushing syndrome – higher expression of 11βHSD1 in visceral fat – normally first source of substrate, but higher suppression with GC, while enhanced GC action leads to lipolytsis in adipose tissue, the fat cumulates in visceral
    - congenital deficiency of 11βHSD1 (apparent cortison reductase deficiency) → compensatory over-activation of HPA axis → adrenal androgen excess, oligomenorhea, hirsutism in women
    - overexpression of 11βHSD1 in subcutaneous tissue (congenital or acquired) leads to lipodystrophy
    - 11βHSD1 plays a role in the pathogenesis of polycystic ovary syndrome
  - regulation: starvation, cortisol, other hormones
- **(b) 11β hydroxysteroid dehydrogenase type 2 (11βHSD2)**
  - act as a dehydrogenase degrading cortisol to cortisone → ↓ intracellular cortisol concentration
    - mainly in kidney
  - by degrading cortisol 11βHSD2 enables tissue-specific preferential action of aldosterone on MR even though concentration of plasma cortisol >>> aldosterone
  - pathology associated with 11βHSD2
    - congenital deficiency of 11βHSD2 (apparent mineralocorticoid excess) → monogenic form hypertension
    - 11βHSD2 is expressed in placenta (maintains lower cortisol in fetal circulation than in maternal) – deficient action contributes to pregnancy pathologies (preeclampsia, IUGR, ...) and possibly to fetal metabolic programming



Summary – availability of GCs



GC action on immunity



- suggested to be mediated via:
  - genomic effects [I]
    - transactivation and transrepression of many immunoproteins
  - non-genomic effects
    - cGR by sequestering proteins [II]
      - e.g. kinases (MAPK) → blockade of action
    - mGR [III] - multi-protein complexes with other membrane receptors → blockade of action
      - e.g. growth factors
      - alternatively, induction of apoptosis
    - direct interactions of GC with cellular membranes [IV] → intercalation into membrane → stabilisation
      - inhibition of Na/Ca exchange
      - increase of proton leak in mitochondria → less ATP
        - ↓ATP-dependent processes in immune system (cytokinesis, migration, phagocytosis, antigen processing and presentation, Ig synthesis, cytotoxicity, …)

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GCs and immune system

Glucocorticoid effects on primary and secondary immune cells	
Monocytes / macrophages	↓ Number of circulating cells (↓ myelopoiesis, ↓ release)
	↓ Expression of MHC class II molecules and Fc receptors
	↓ Synthesis of pro-inflammatory cytokines (e.g. IL-1, -2, -6, TNFα) and prostaglandins
T cells	↓ Number of circulating cells (redistribution effects)
	↓ Production and action of IL-2 (most important)
Granulocytes	↑ Number of circulating neutrophils
	↓ Number of eosinophile and basophile granulocytes
Endothelial cells	↓ Vessel permeability
	↓ Expression of adhesion molecules
	↓ Production of IL-1 and prostaglandins
Fibroblasts	↓ Proliferation
	↓ Production of fibronectin and prostaglandins

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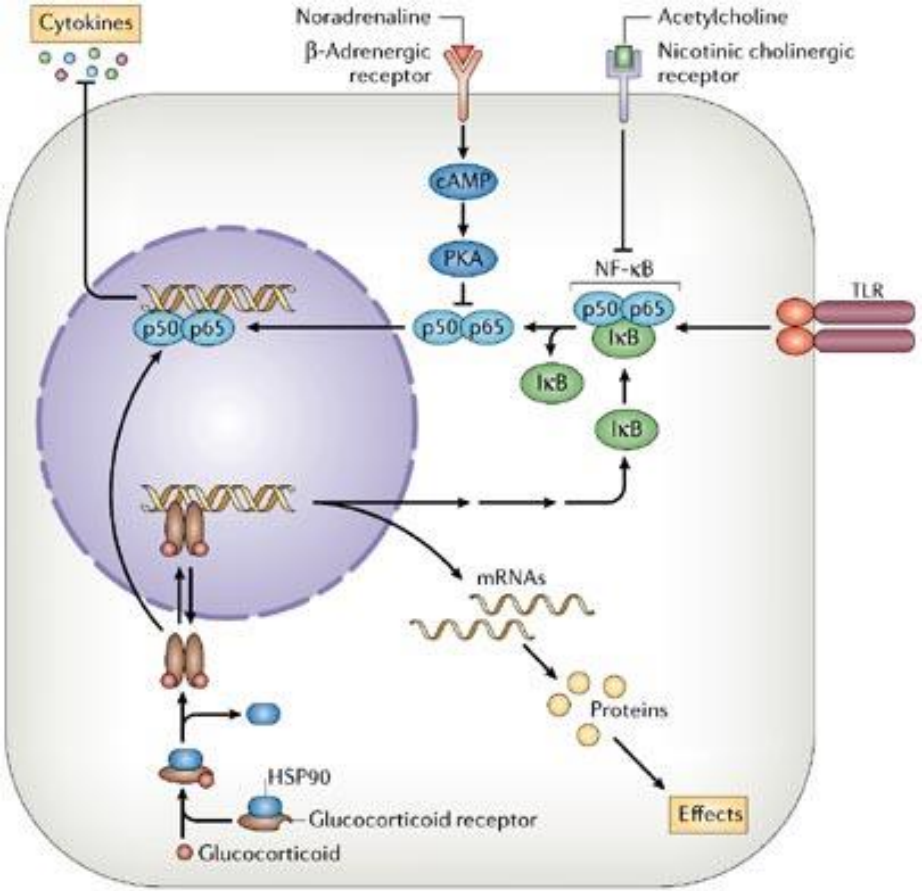
Examples of multiple action of GCs on immunity



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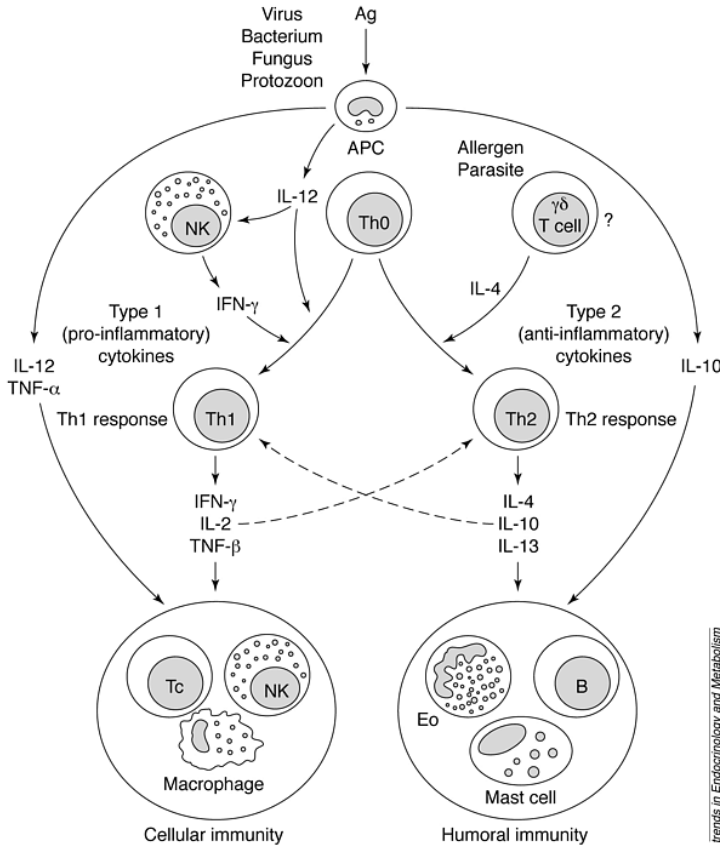
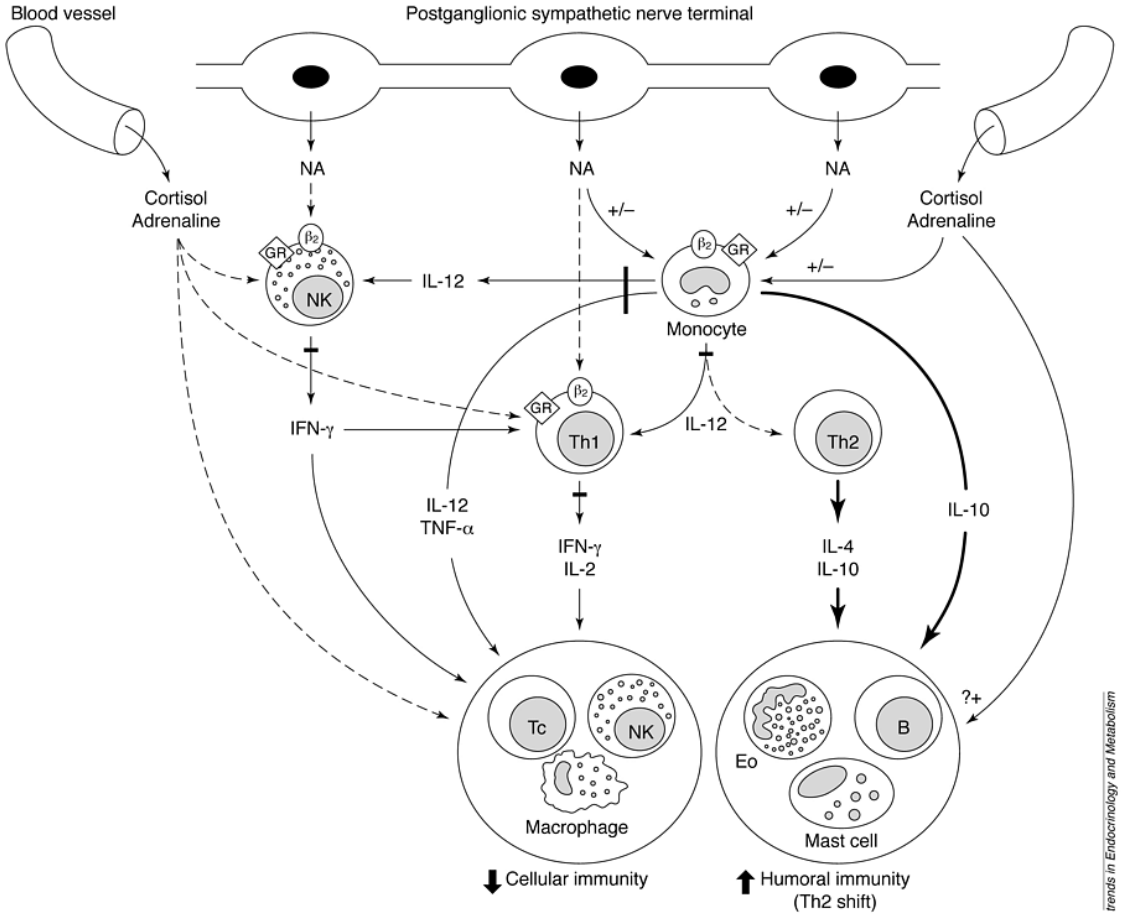
Balance of Th1/Th2 immune responses - Th2 shift as a consequence of stress





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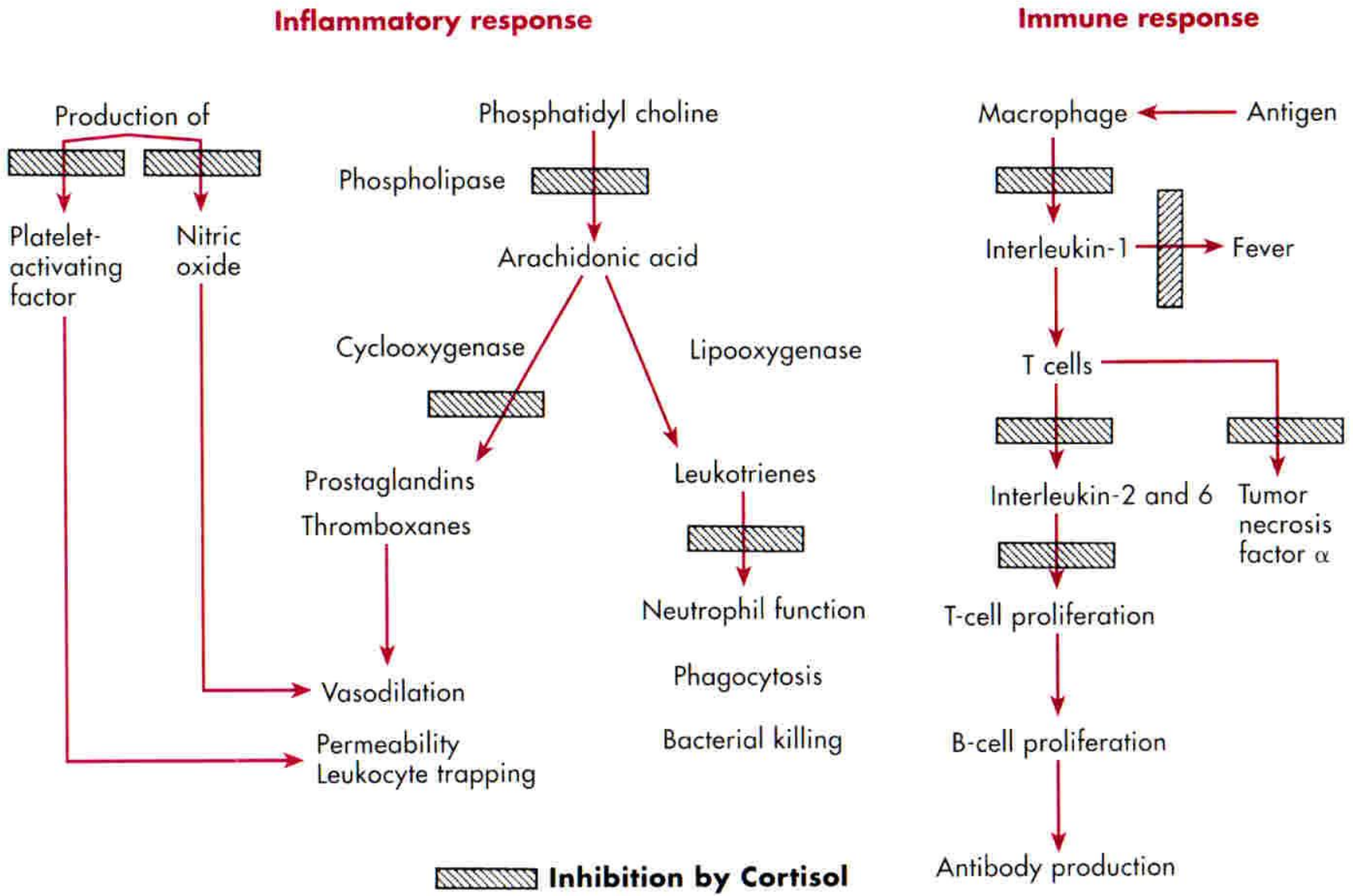
Summary – effects of GC on immunity

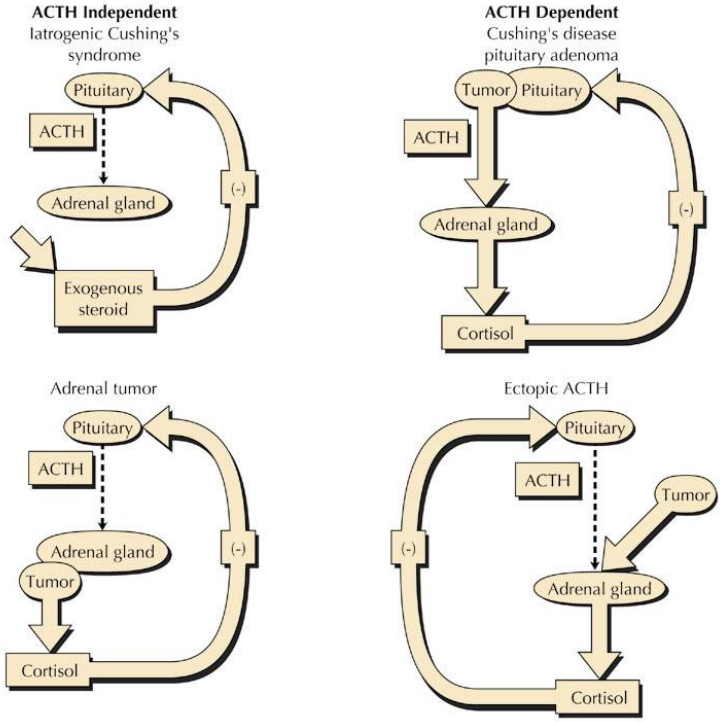


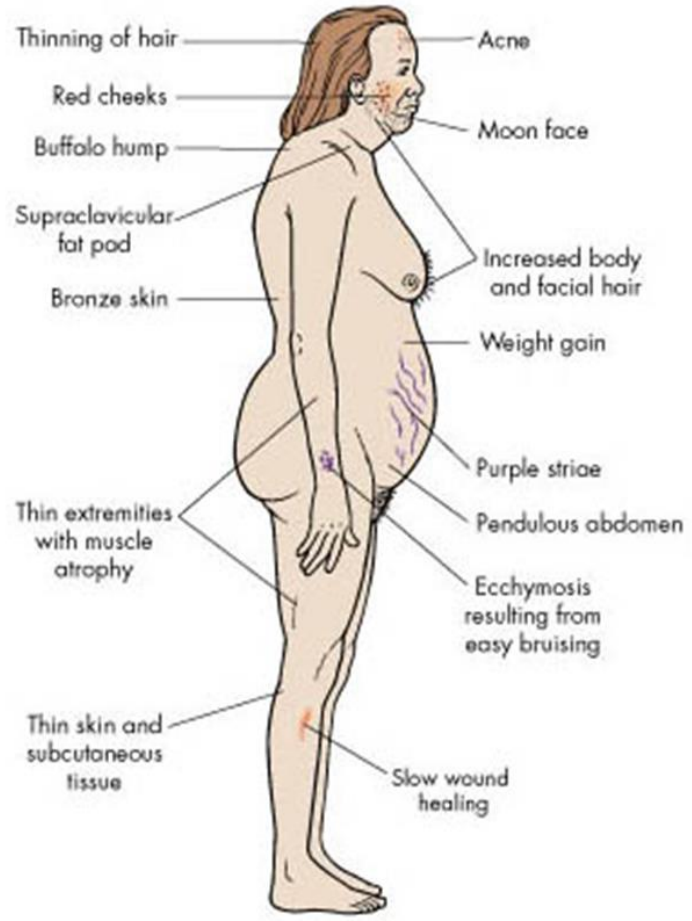
Disorders of adrenal gland

- hyper-corticalism
  - usually selective
  - primary vs. secondary
  - Cushing syndrome
  - Conn syndrome
  - adrenal hyperandrogenism
    - DHEA producing adrenal adenoma
- hypo-corticalism
  - usually generalised
  - Addison syndrome
- dissociation of adrenal function
  - abnormality of steroid biosynthesis
  - if serious – CAH (congenital adrenal hyperlasia)

Glucocorticoid excess: Cushing's syndrome

- Etiology
  - primary
    - GC overproduction by adrenal tumor (adenoma or carcinoma)
    - GC overproduction by ectopic tissue (embryonic origin, commonly ovary or testes)
  - secondary
    - ACTH-producing pituitary tumor (Cushing's disease)
    - excess CRH from the hypothalamic tumor
    - extra-hypophyseal/ectopic ACTH production
      - typically mediastinum (i.e. small cell lung carcinoma)
    - low CBG
  - iatrogenic





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Adrenocortical insufficiency - etiology

- destructive process usually affecting all zones of the cortex
  - decreased production of cortisol, aldosterone and adrenal androgens
    - adrenal insufficiency occurs when at least 90% of the adrenal cortex has been destroyed
    - prior to that can be latent and manifest in stress
- (1) primary generalized (Addison's disease)
  - chronic or acute manifestation (Addison’s crisis)
  - ↑ ACTH
  - causes
    - autoimmune destruction (type II hs) - gradual destruction of the adrenal cortex
    - TBC
    - necrosis (Waterhouse-Friderichsen syndrome)
      - acute adrenal insufficiency due to massive haemorrhage into the adrenal gland, more often bilateral, caused by meningococcus infection
    - rare: congenital, haemochromatosis, adrenalectomy, X-linked adrenoleukodystrophy (X-ALD), amyloid, thrombosis, …
- (2) primary in dissociation of adrenal function
  - see further
- (3) secondary to inadequate secretion of ACTH
    - hypopituitarism
    - Sheehan's syndrome
      - after severe postpartum hemorrhagic or infectious shock, ischemic damage to the pituitary
- symptoms
  - weakness (↑K)
  - anorexia, hypotension (↓Na)
  - nausea, diarrhea or constipation (↑Ca)
  - vomiting (hypoglycemia)
  - abdominal pain (lymphocytosis)
  - weight loss
  - hyperpigmentation (POMC → MSH → melanocytes)
    -

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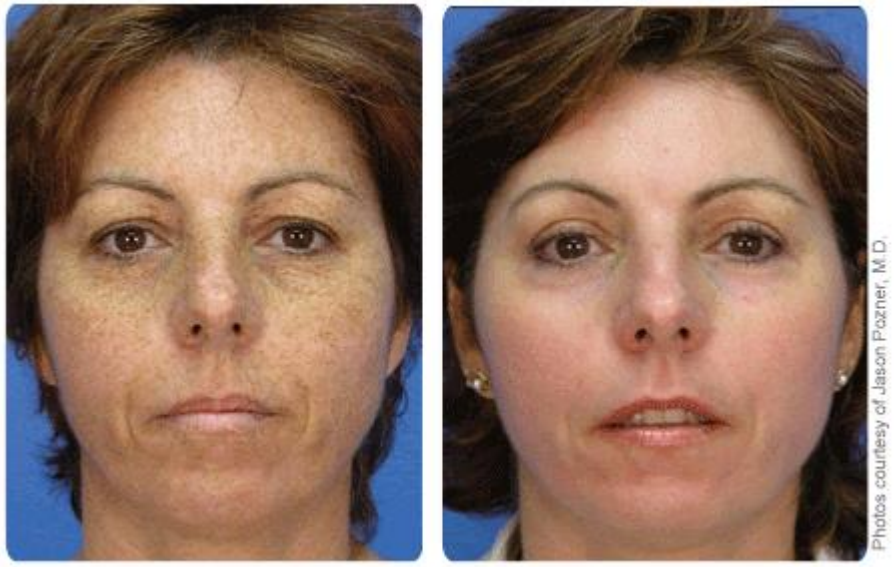
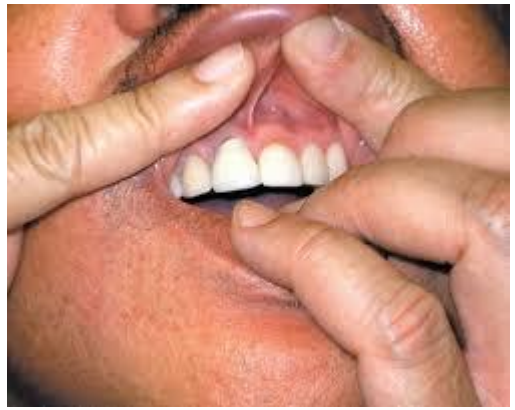
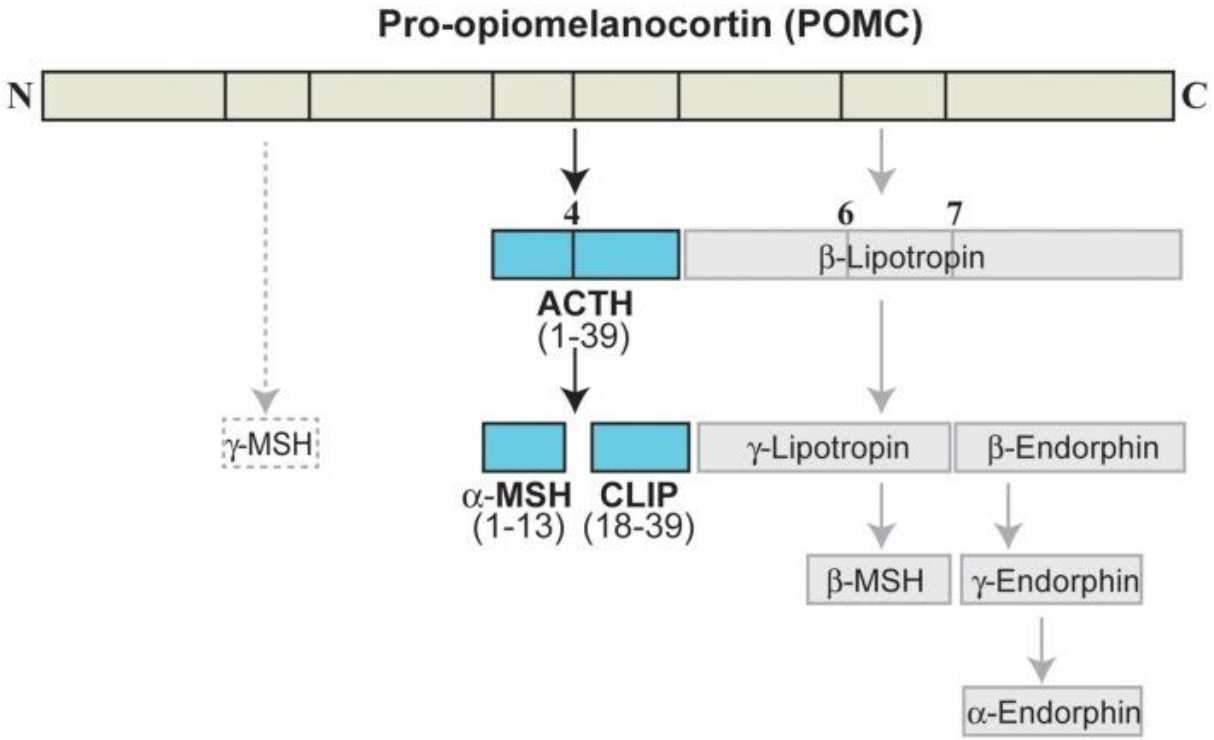
Addison's disease







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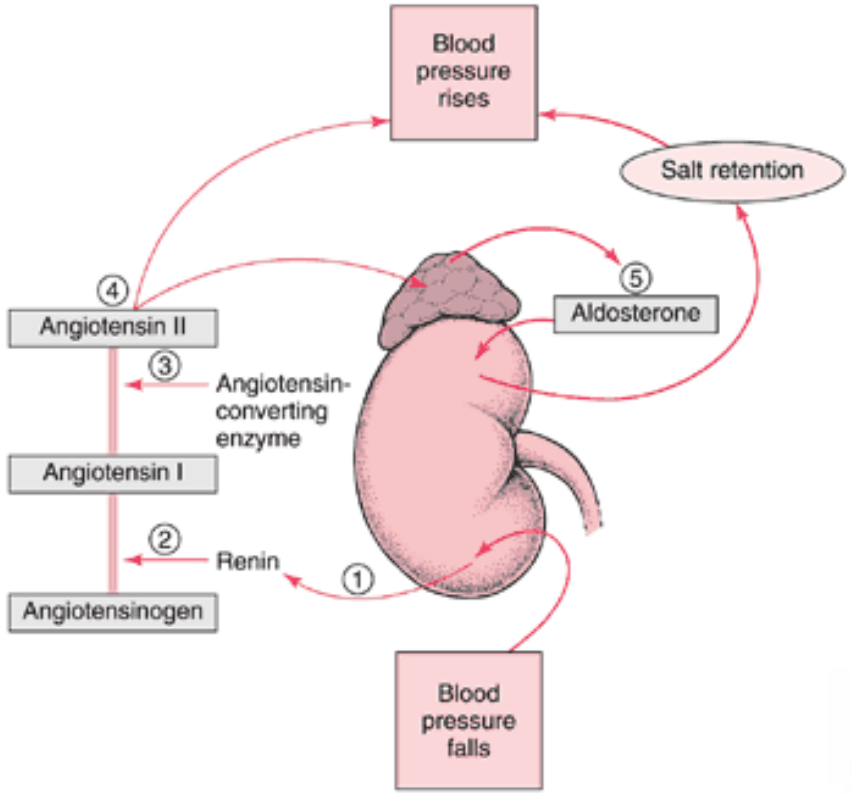
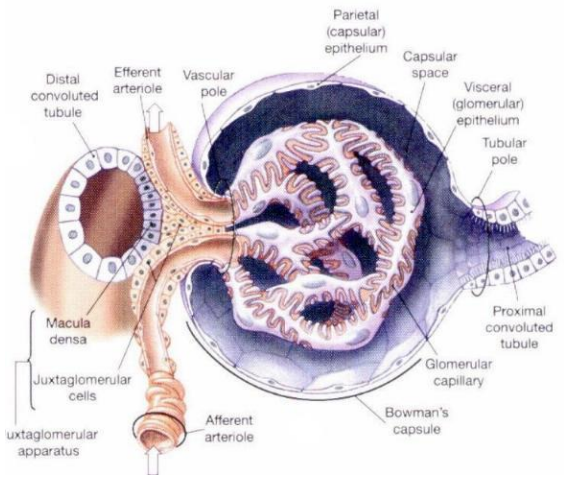
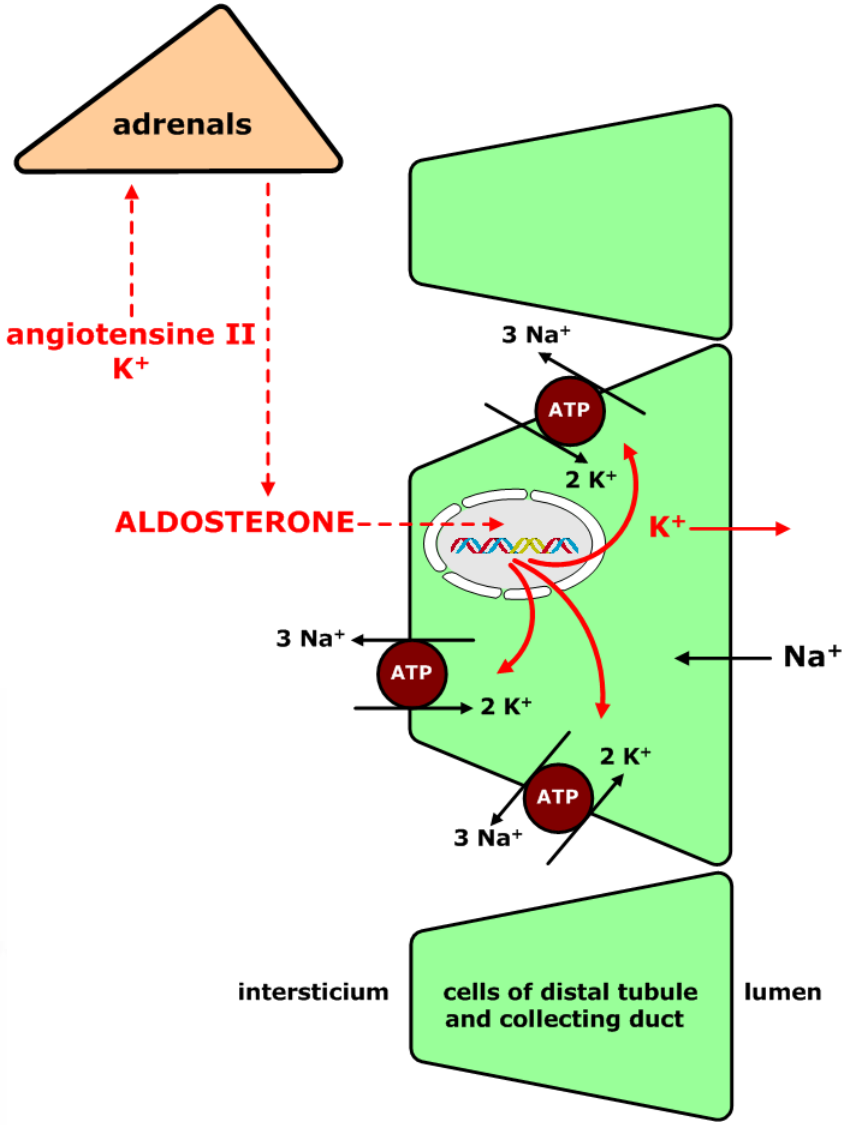
Mineralocorticoid regulation

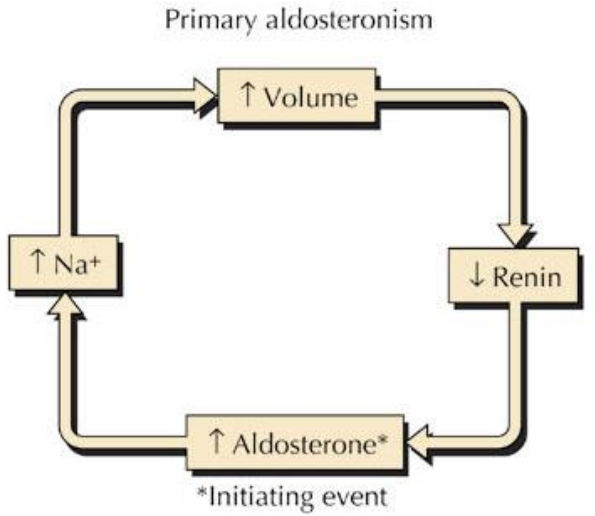


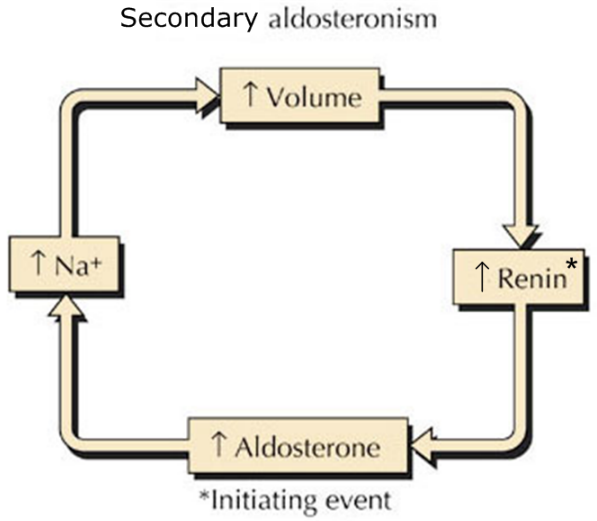




Hyperaldosteronism

- increased secretion of aldosterone
- etiology
  - primary hyperaldosteronism
    - unilateral adenoma (Conn's disease)
      - 70%, benign tumor
    - bilateral adrenal hyperplasia
  - secondary hyperaldosteronism
    - ↑ RAAS
    - ↑ ACTH
  - tertiary hyperaldosteronism
    - decreased aldosterone clearance – liver disease





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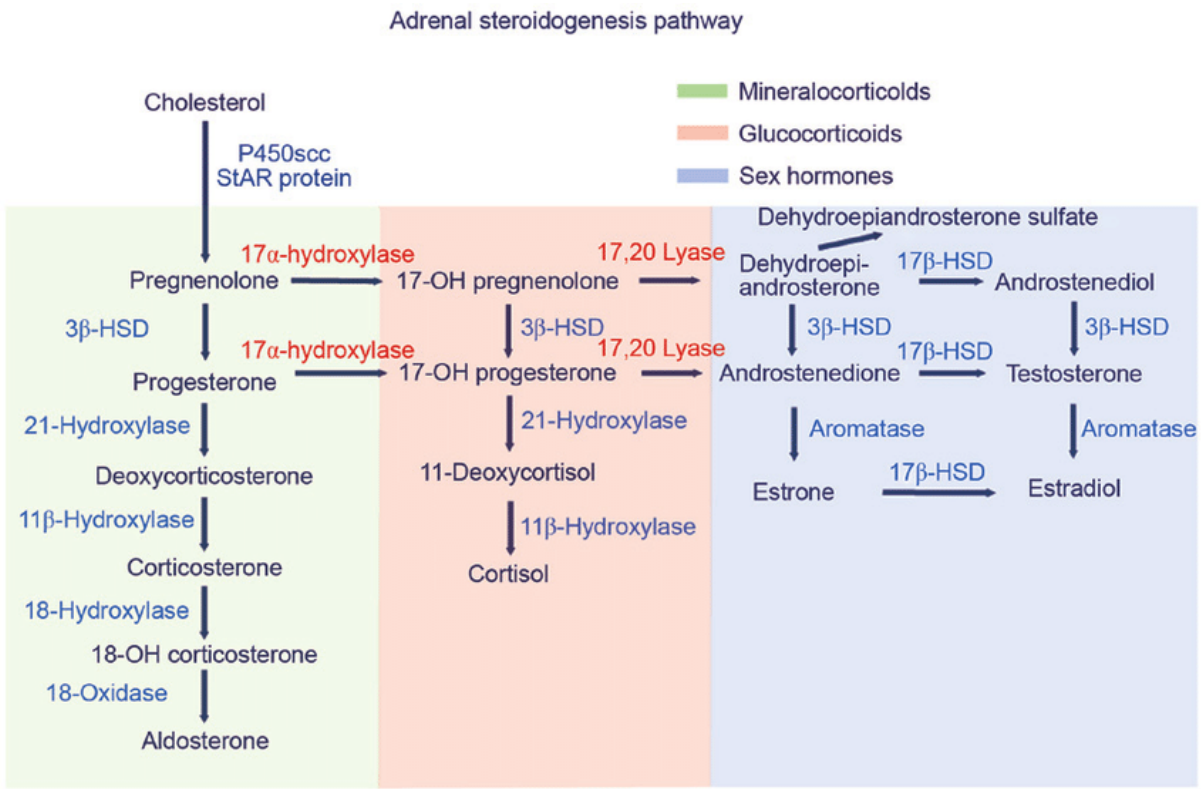
Congenital adrenal hyperplasia (CAH)



- frequency 1/8000 – 10000 new-borns – postnatal screening
- a group of inherited disease that impair cortisol synthesis, with compensatory increases in ACTH leading to hyperplastic adrenals
- spectrum of enzymatic deficiencies ranges from mild to complete and from a single activity to several activities
- steroid 21-hydroxylase deficiency (21OHD) accounts for over 90% of CAH cases
- much rarer
  - 11-Beta hydroxylase deficiency
  - 17a-hydroxylase deficiency
  - 3-Beta-hydroxysteroid dehydrogenase deficiency
  - congenital lipoid adrenal hyperplasia
  - p450 oxidoreductase deficiency
- abnormalities of primary and secondary sex differentiation
- for 21-hydroxylase deficiency:
  - females will most likely have ambiguous or atypical external genitalia (masculinization or virilization), although they are genetically female and will have normal internal reproductive organs
  - males will not have ambiguous genitalia
  - both genders can experience other symptoms such as early onset of puberty, fast body growth, and premature completion of growth leading to short stature, if they are not diagnosed and treated in early life

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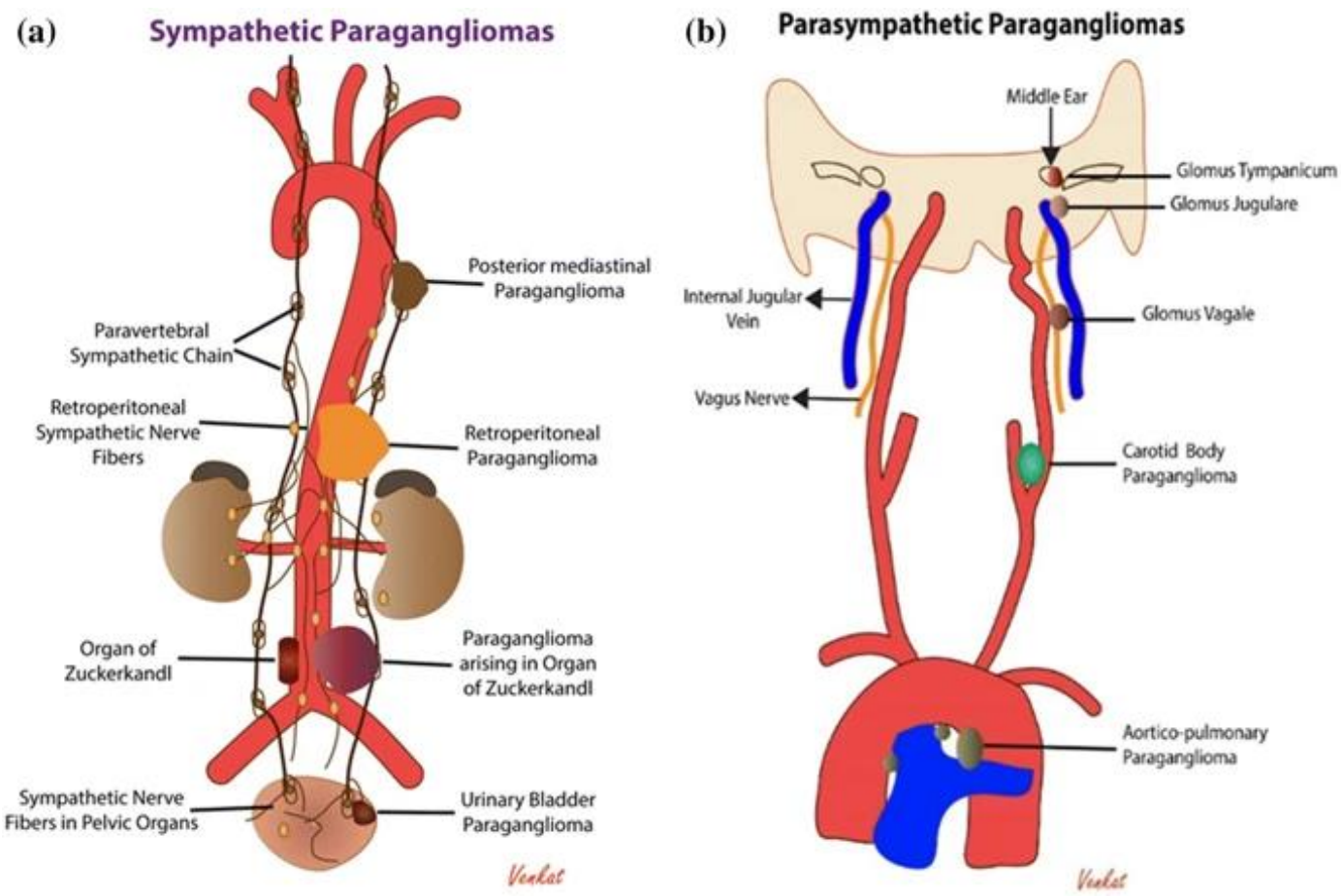
Adrenal medulla



- paragangliomas form in nerve tissue in the adrenal glands and near certain blood vessels and nerves
- paragangliomas that form in the adrenal glands are called heochromocytomas pheochromocytomas and paragangliomas may be benign or malignant cancer

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