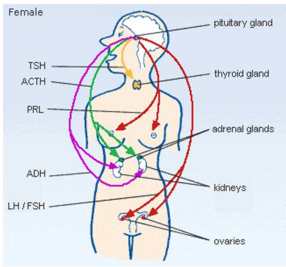
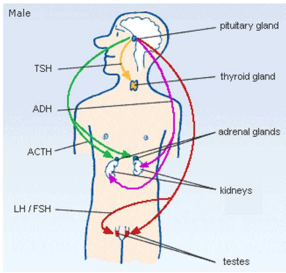
Special pathophysiology of endocrine system

Thyroid and adrenal glands

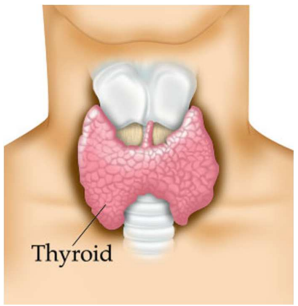
Mechanisms of endocrine diseases

- (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

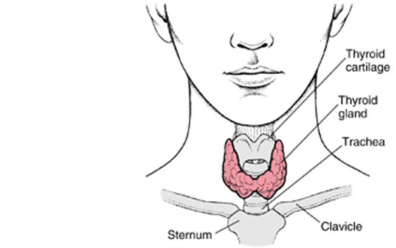


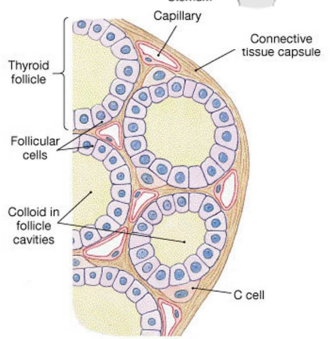


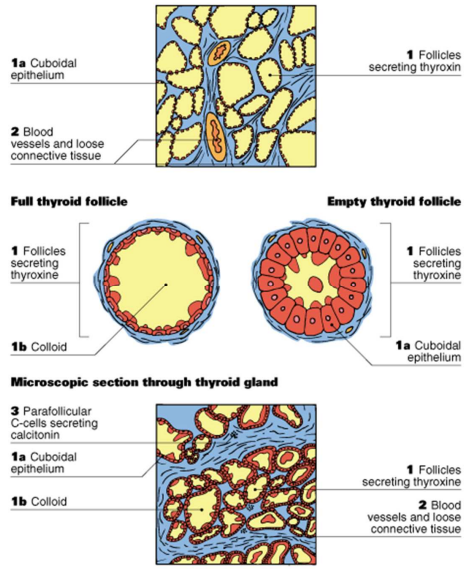
The Thyroid



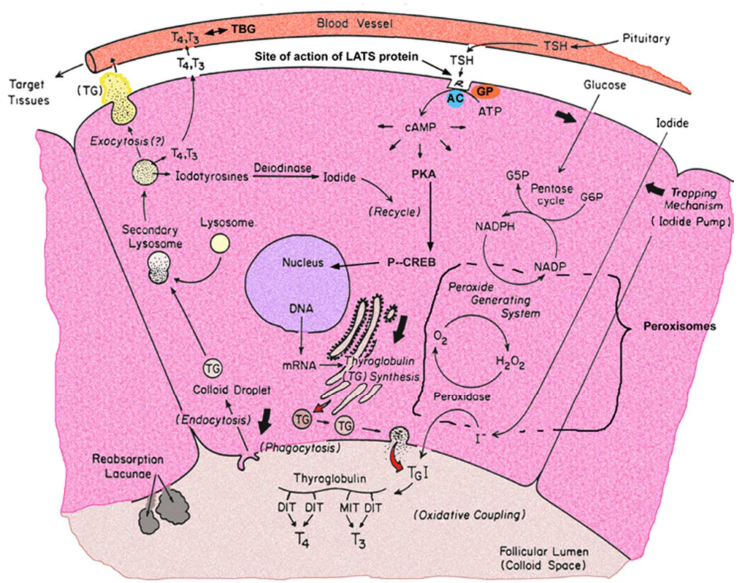
Pathophysiology of thyroid gland



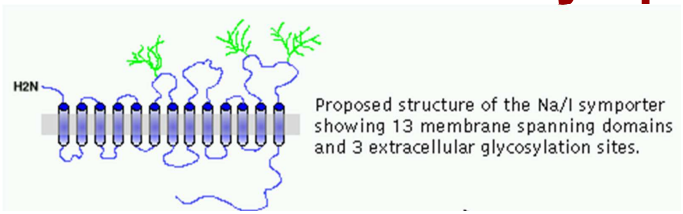


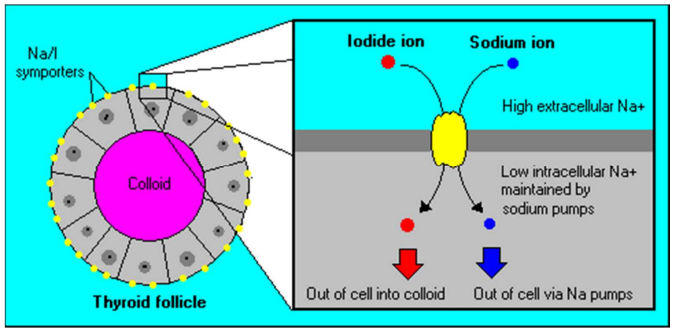


Hormone synthesis by follicular cell

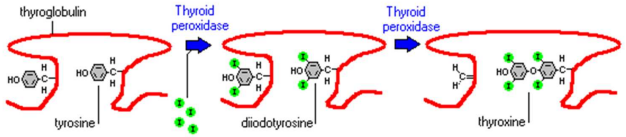


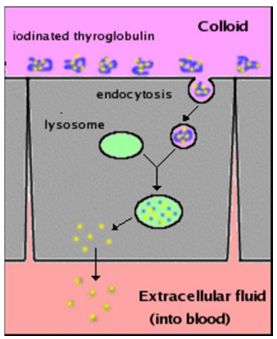
The sodium-iodide symporter

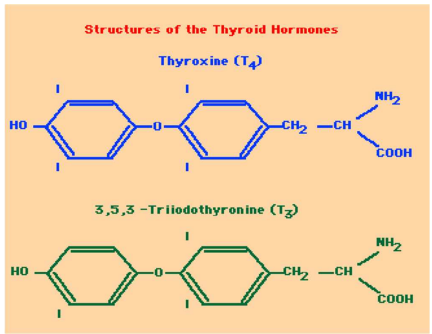




"Organification" of TG & coupling of thyrosines, liberation of T3/T4

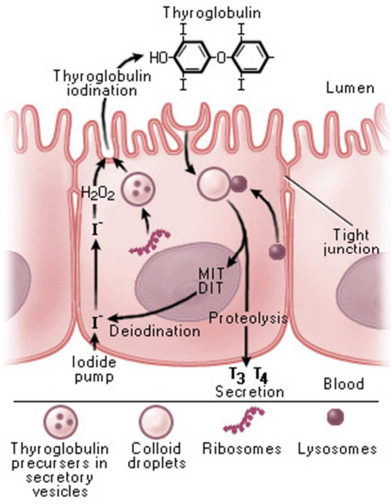






Secretion of thyroid hormones

- 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
  - bound to TBG (75%), transthyretin (15%) and albumin (10%)
- MIT and DIT are liberated into the cytoplasm, the iodines are removed by a **deiodinase**, and they and the tyrosines are reused
- peripheral de-iodination
  - liver, kidneys, others



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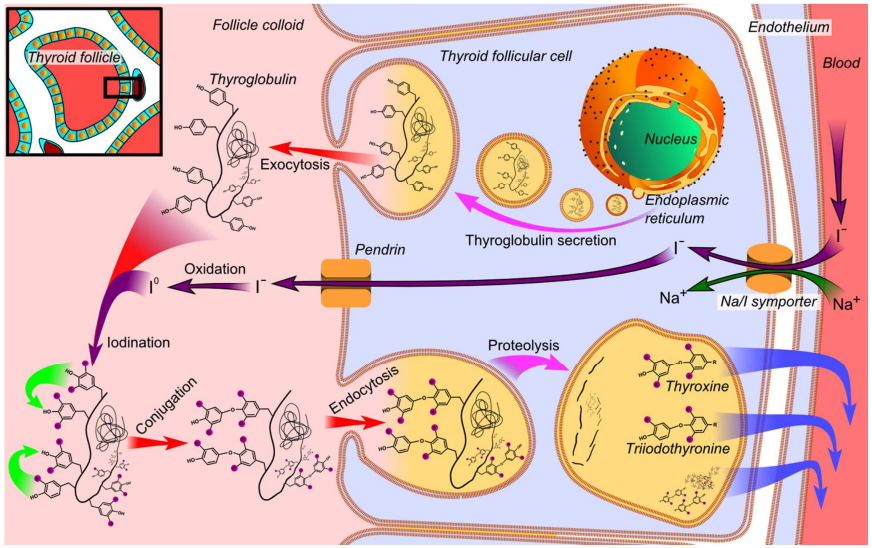
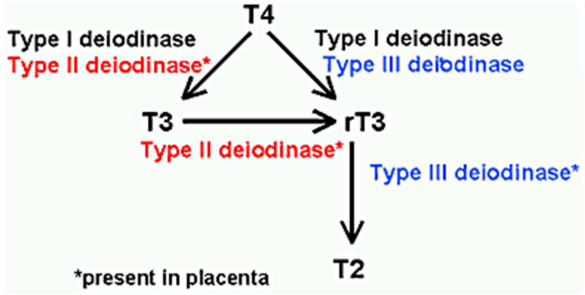
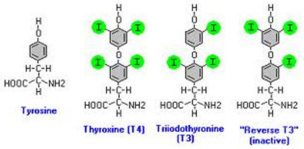


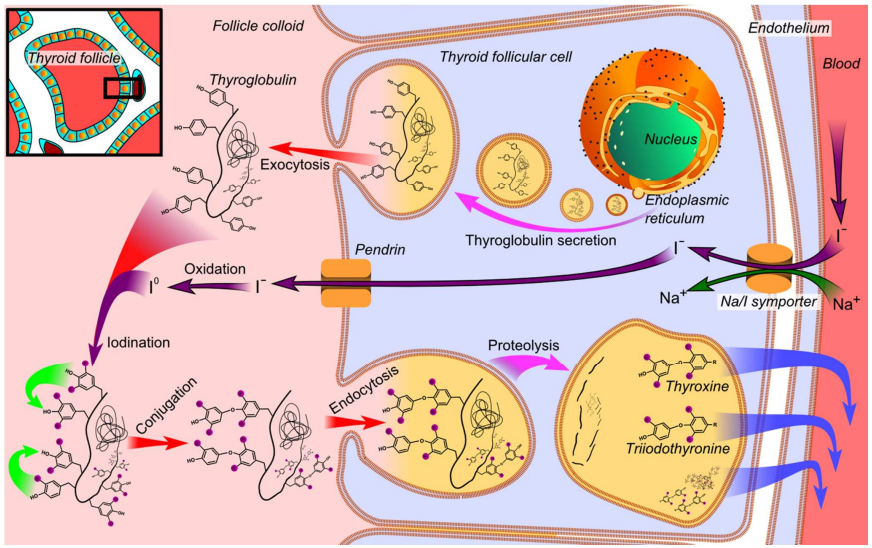
Peripheral modulation of T4 and T3 levels

- 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

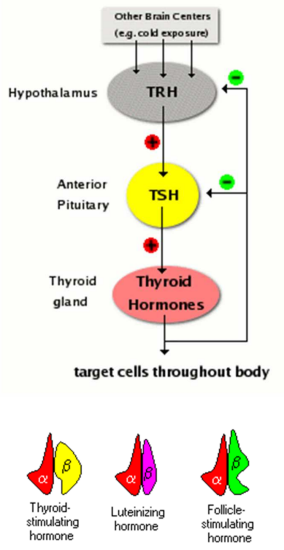




Summary …

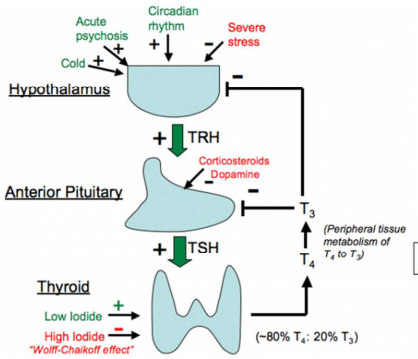


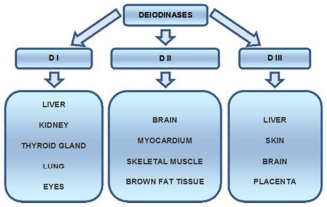
Control of the T3/T4 production

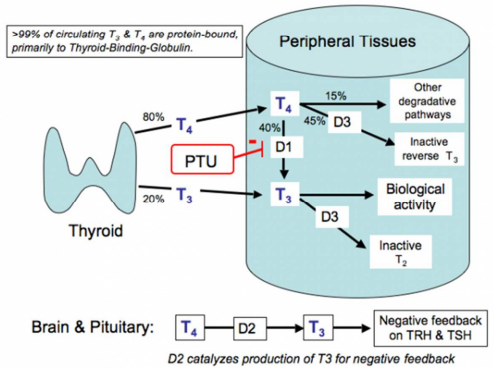


- hypothalamus:
  - TRH
  - somatostatin
- pituitary:
  - TSH
    - binding of TSH to TSH-R stimulates:
      - synthesis of the iodide transporter
      - thyroid peroxidase
      - synthesis of thyroglobulin
      - rate of endocytosis of colloid
- thyroid autoregulation
  - iodide uptake and transport

Quantitatively

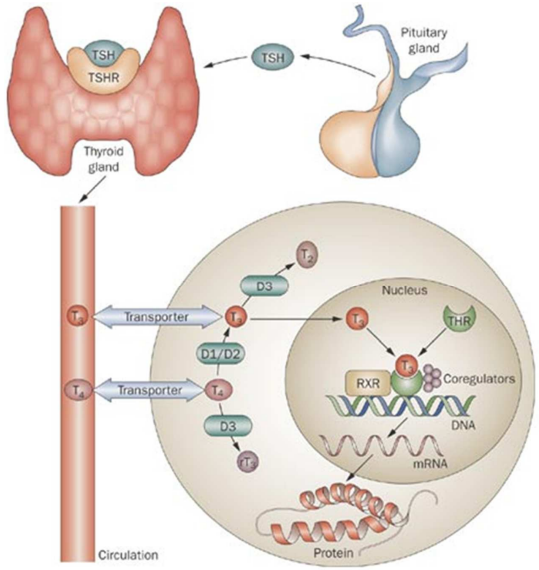






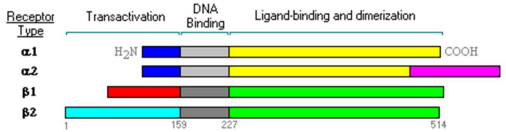
Molecular basis of T3/T4 action

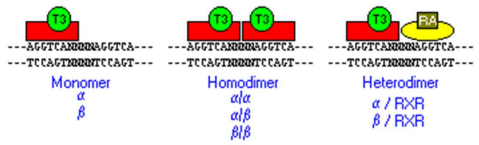
- complexes thyroid hormone/hormone-activated nuclear receptors act as transcription factors
  - modulation of gene expression
- in contrast to steroid hormone receptors, thyroid hormone receptors bind DNA already in the absence of hormone, usually leading (in inactive state) to transcriptional repression



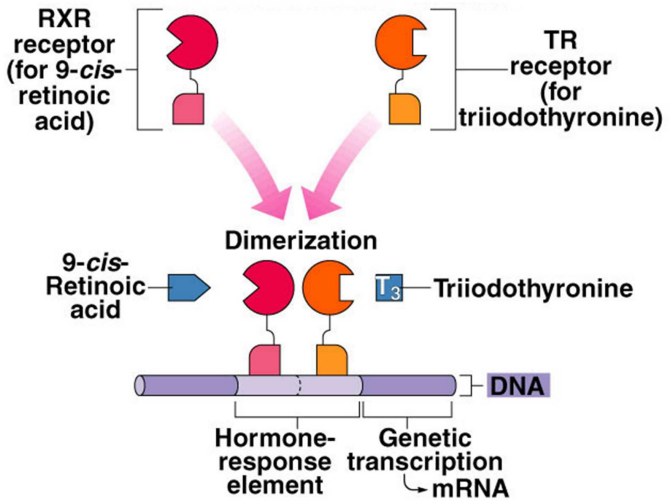
Thyroid hormone receptors

- 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)



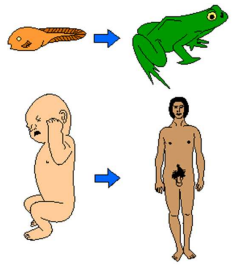


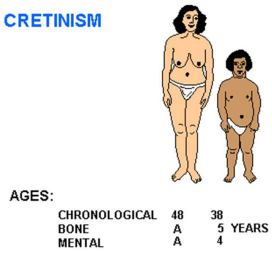
T3 action on gene transcription



Physiologic effects of T3/T4

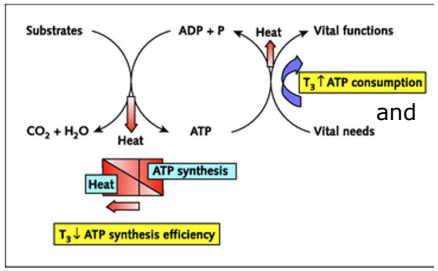
- (1) development
  - profound effects on the terminal stages of brain differentiation, including synaptogenesis, growth of dendrites and axons, myelination and neuronal migration (esp. in the fetal period)
  - the net effect of pregnancy is an increased demand on the thyroid gland
    - in the normal 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 clinicial 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

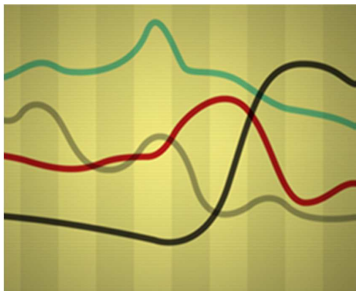




Physiologic effects of T3/T4

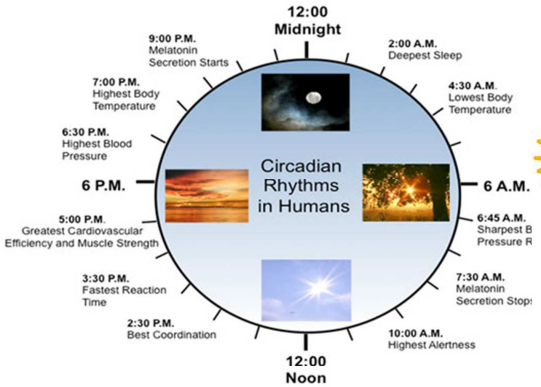
- (3) metabolism
  - increase in basal metabolic rate and thermoregulation
    - increase body heat production from increased O2 consumption rate of ATP hydrolysis
  - lipid metabolism
    - fat mobilization → increased concentrations of FFA in plasma
    - oxidation of FFA
    - plasma concentrations 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

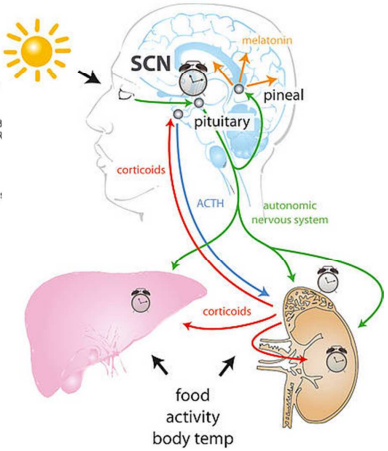




CHRONOBIOLOGY OF THE THYROID

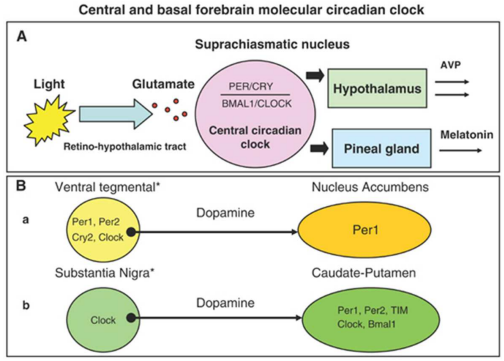
Circadian rhythm





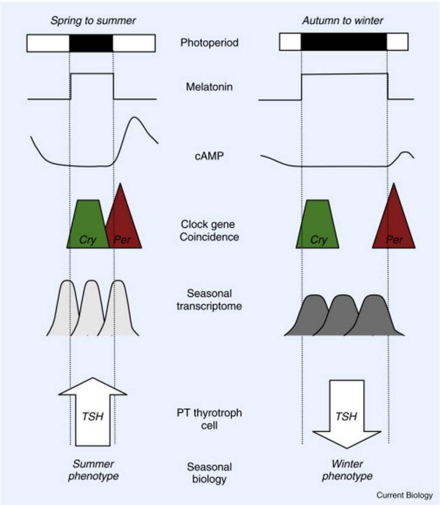
„Molecular clock“

- 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 protein)
- peripheral organs



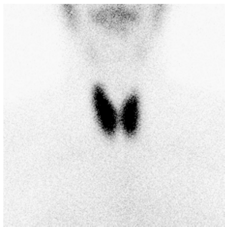
Seasonal clocks - analogy with circadian clocks

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



Thyroid function assessment

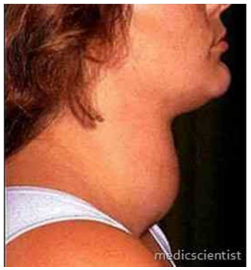
- serum
  - hormones
    - TSH, T4, T3, fT4, fT3, rT3
  - antibodies
    - anti-thyroglobulin (anti-TG), anti-thyroid peroxidase antibodies (anti-TPO)
  - calculated indexes
    - fT4/fT3, fT3/rT3
- thyroid ultrasound
- radionuclide thyroid scan – iodine (^{123}I) or pertechnatate (Tc-99)
  - detection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



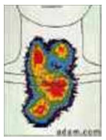
DISEASES OF THE THYROID GLAND

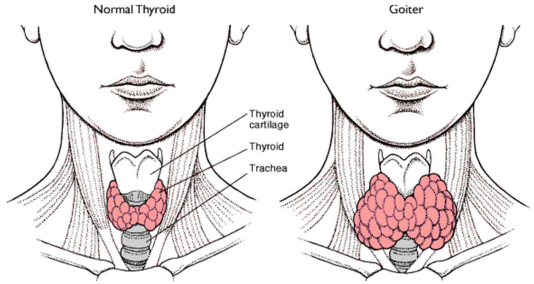
Goiter (struma)

- 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



Types of goiter





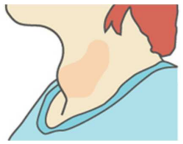
- simple (non-toxic, euthyroid)
  - causes
    - endemic
      - caused by a deficiency of iodine in the diet (inland and highland areas of all continents)
    - sporadic
      - "strumigens" in the diet (e.g. cabbage, soybeans, peanuts, peaches, strawberries, spinach, and radishes)
  - form
    - usually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

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 !!!

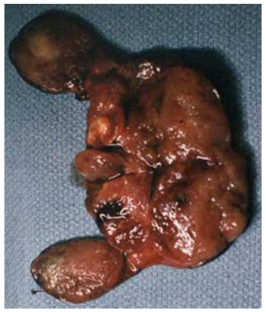
Thyroid endocrinopathies from the functional point of view

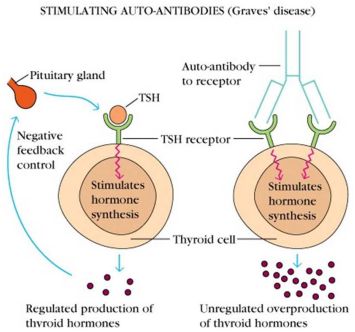
- Hyperthyroidism
  - Graves' disease (toxic diffuse goitre)
    - autoimmune
  - toxic nodular goitre (Plummer's disease)
    - toxic adenoma
  - thyroiditis
  - primary and/or metastatic follicular carcinoma
  - TSH-producing tumour of the hypophysis
- Hypothyroidism
  - hypothalamic or pituitary
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



Toxic goiter

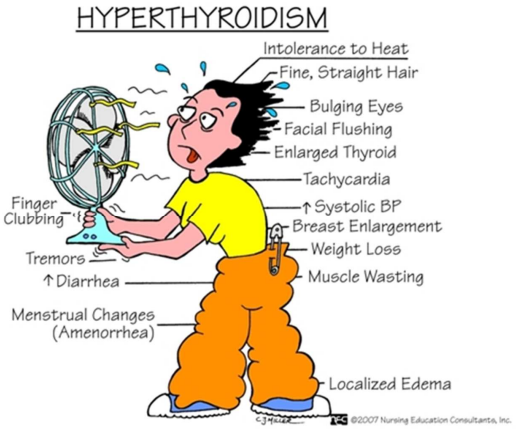
- nodular (Plummer's disease)
  - autonomous function of one or more thyroid adenomas in a part of the gland
- diffuse (Graves-Basedow's disease)
  - stimulation by anti-TSH antibodies (type V hs) [LATS = long-acting thyroid stimulators]





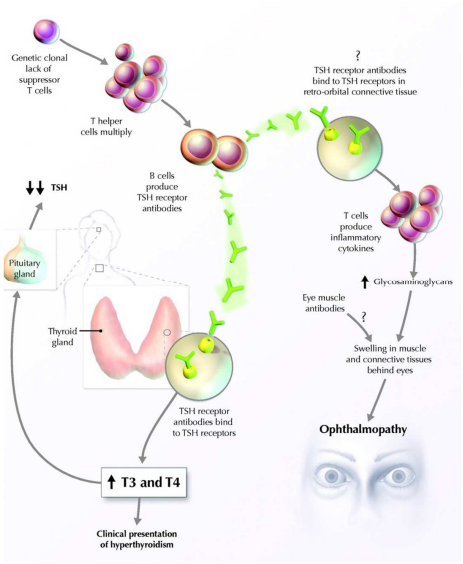
Hyperthyroidism (thyrotoxicosis)

- predominance of women, middle age

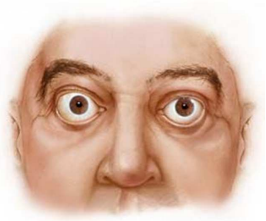


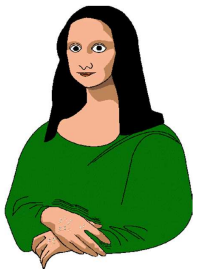
Grave's disease

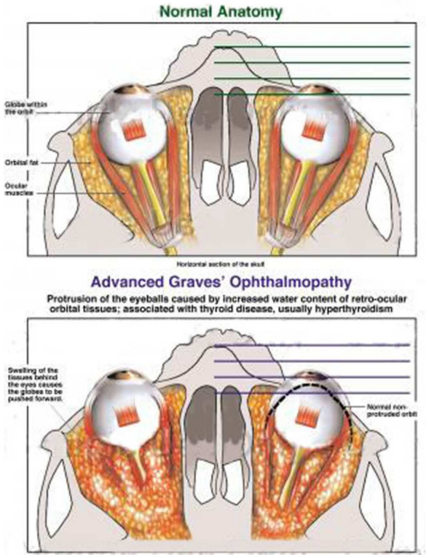
- hyperthyroidism +
- infiltrative ophthalmopathy
  - ~1/2 od the cases, independent on hyperthyroidism
  - involves periorbital connective tissue, ocular muscles and fat
- infiltrative dermopathy
  - ~1/5 of cases
  - pretibial myxedema



Ophthalmopathy

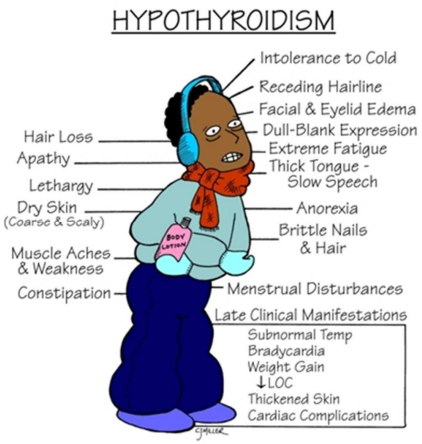




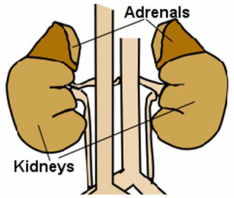


Hypothyroidism

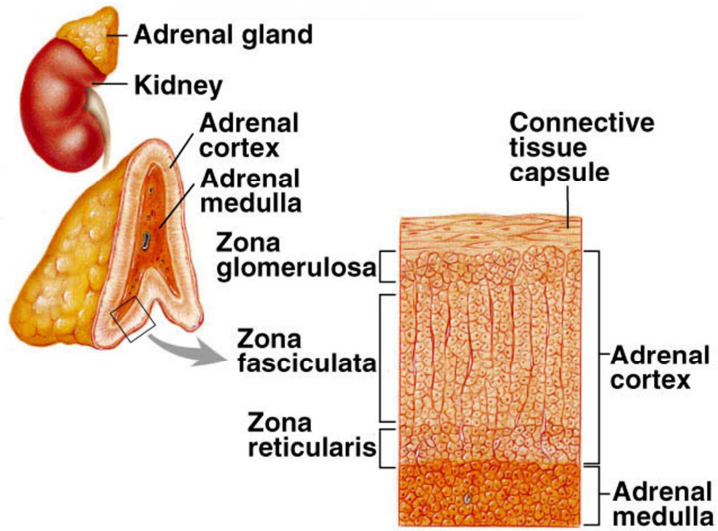
- often results of (auto)immune destruction of the thyroid
  - de Quervain thyroiditis
  - Hashimoto thyroiditis
- usually transitory hyperthyroidism in acute phase, then cessation of function
- predominance of women, middle age



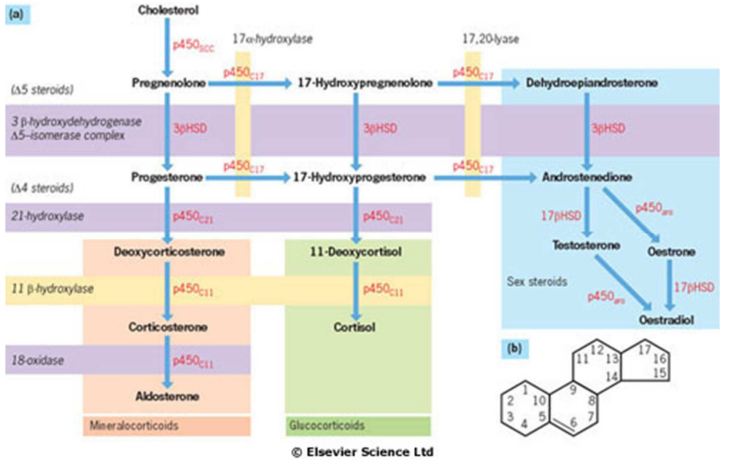
The Adrenals



Pathophysiology of adrenals

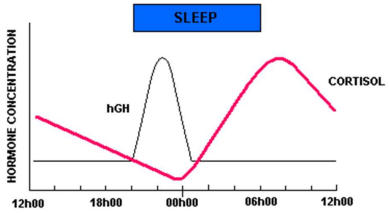


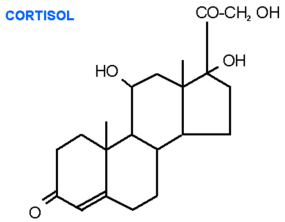
Major steroid biosynthetic pathways

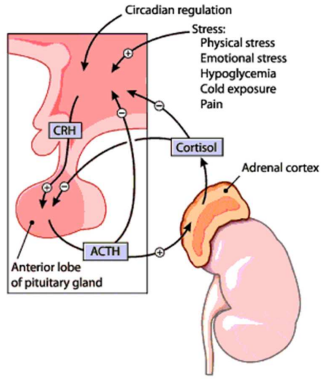


- p450 enzymes are in mitochondria, each catalyses several reaction steps
- 3βHSD (hydroxysteroid dehydrogenase) is in cytoplasm, bound to endoplasmic reticulum
- 17βHSD and p450aro are found mainly in gonads

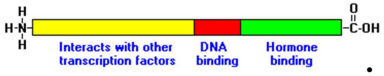
Cortisol profile & regulation

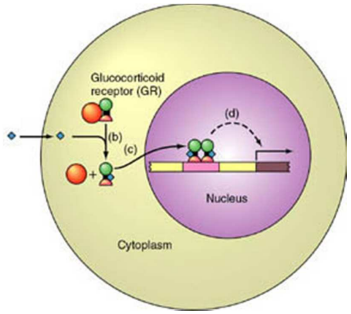






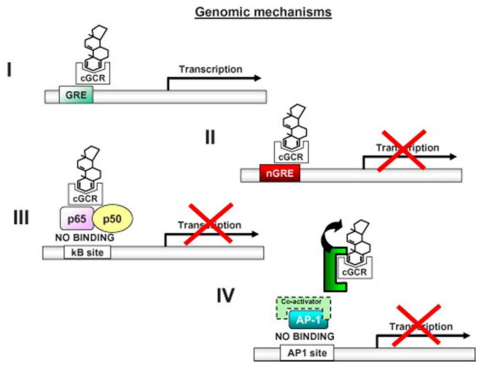
Glucocorticoid (GC) receptor





- GCs have receptor (GR) existing in two isoforms
  - cytoplasmic (cGR)
  - membrane bound (mGR)
- therefore, GCs have several modes of action
  - genomic – mediated by cytosolic receptors (cGR) upon binding to GC responsive elements (GREs)
  - 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

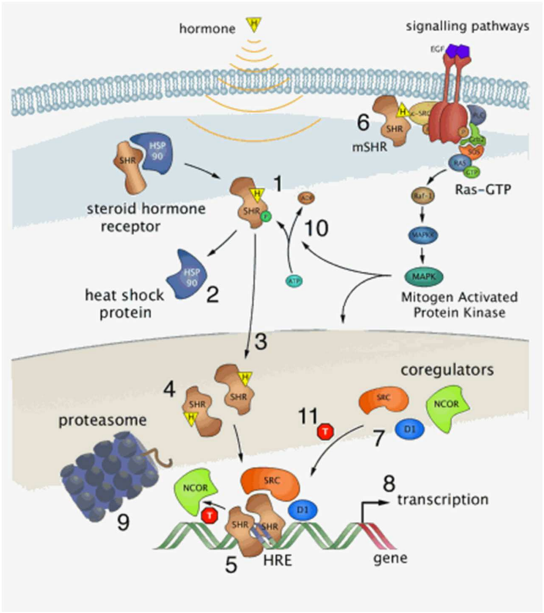
GC action – genomic effects



- (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

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 signalling 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]

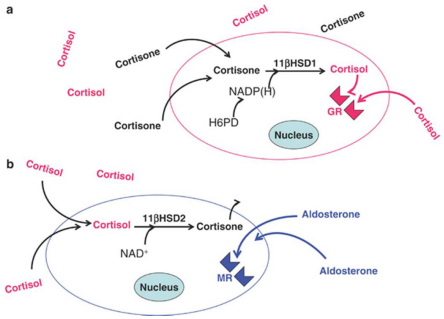


Metabolic effects of GC – increased turnover of free and stored substrates

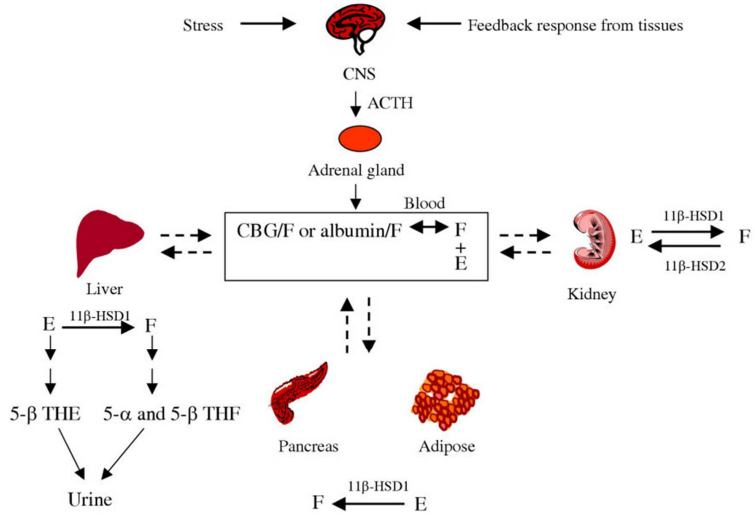
Tissue/organ	Physiologic effects	Effects of overproduction
Liver	–**hepatic gluconeogenesis (↑ Glc)** (stimulation of key enzymes – pyruvate carboxylase, PEPCK, G6Pase)	impaired glucose tolerabce/diabetes mellitus
	hepatic lipogenesis (↑ FA and VLDL) (stimulation of key enzymes acetyl-CoA-carboxylase 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 tolerabce/diabetes mellitus

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 corticol 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 corticol 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
    - 11βHSDě 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

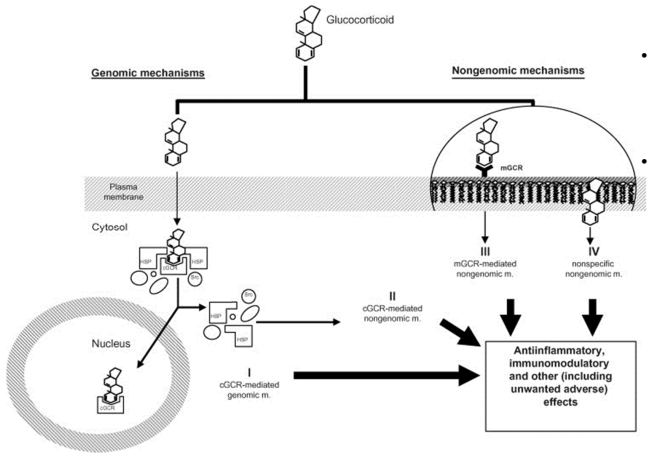


Summary – availability of GCs



GC action on immunity

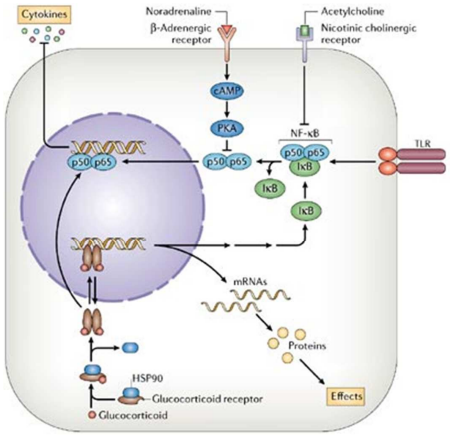
- suggested to be mediated via:
  - genomic effects [I]
    - transactivation and transrepression of many immunoproteins
  - non-genomic effects
    - cGR by sequestering proteins [II]
      - e.g. kinases (MAPK) → blockade of action
    - mGR [III] - multi-protein complexes with other membrane receptors → 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, …)



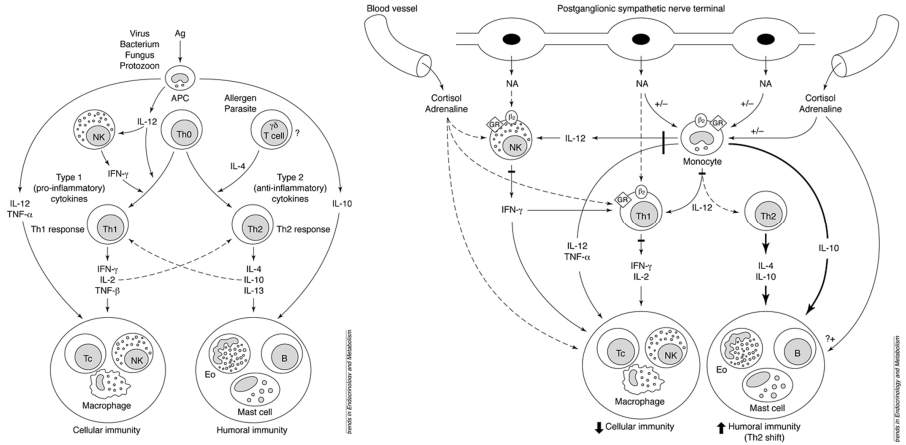
GCs and immune system

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

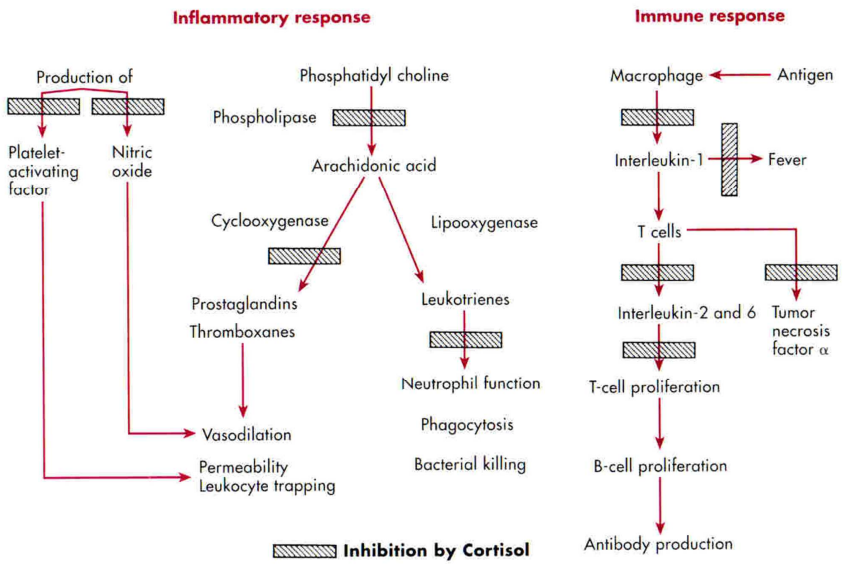
Examples of multiple action of GCs on immunity



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

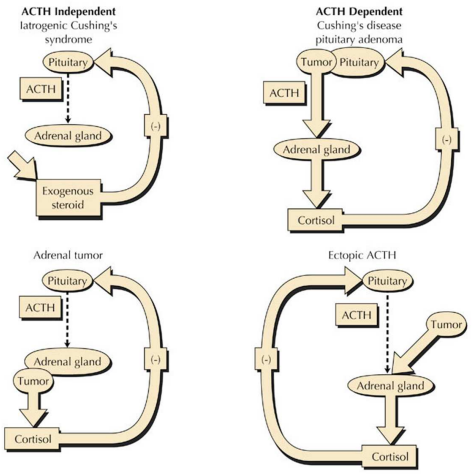


Summary – effects of GC on immunity

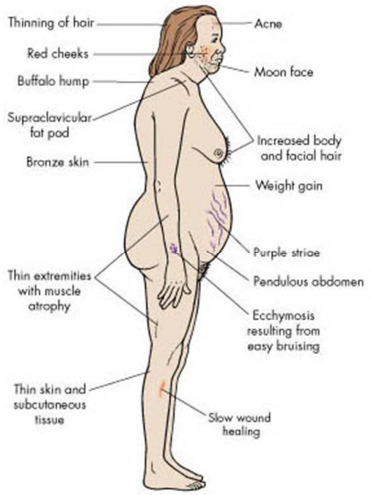


Glucocorticoid excess: Cushing's syndrome

- Etiology
  - primary adrenal tumor
  - ACTH-producing pituitary tumor (Cushing's disease)
  - ectopic ACTH production
    - small cell lung carcinoma
  - excess CRH from the hypothalamus tumor or by an ectopic CRH-producing tumor



Cushing's disease



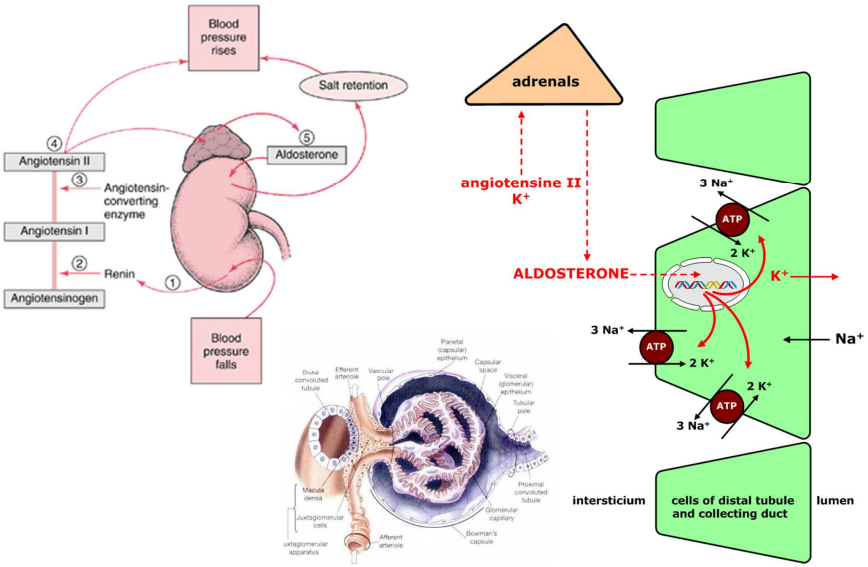
Adrenocortical insufficiency

- Etiology
  - primary adrenal disease (Addison's disease)
    - destructive process usually affecting all zones of the cortex
      - decreased production of cortisol, aldosterone and adrenal androgens
  - secondary to inadequate secretion of ACTH
    - 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)

Addison's disease

- autoimmune destruction (type II hs)
  - gradual destruction of the adrenal cortex
    - adrenal insufficiency occurs when at least 90% of the adrenal cortex has been destroyed
- TBC
- necrosis (Waterhouse-Friderichsen syndrome)
  - acute adrenal insufficiency due to massive haemorrhage into the adrenal gland, more often bilateral, caused by meningococcus infection

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