Ppathophysiology of endocrine system I

HPA and HPT axis and chronobiology

Circadian rhythm

Adrenal cortex and medulla

Thyroid gland

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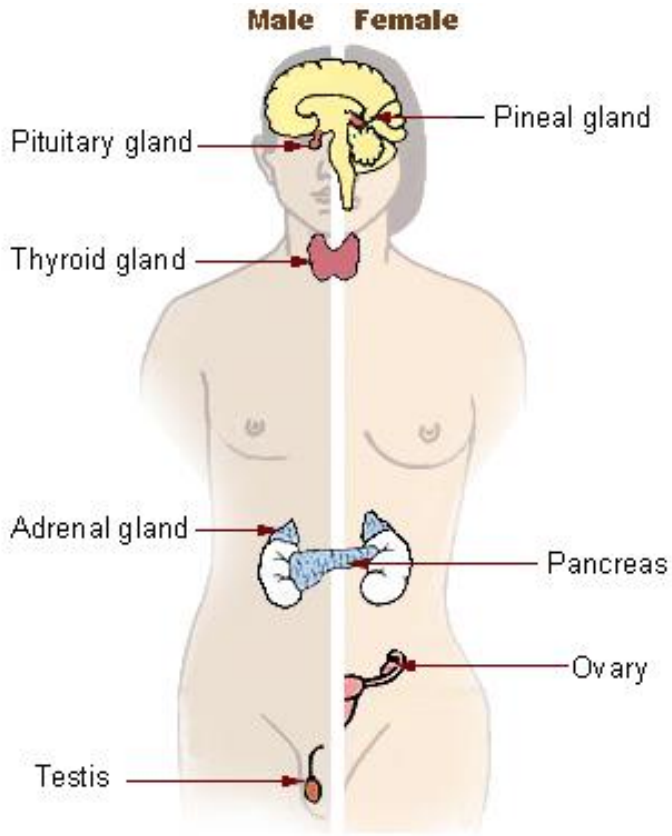
Endocrine system

- 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 in some species)

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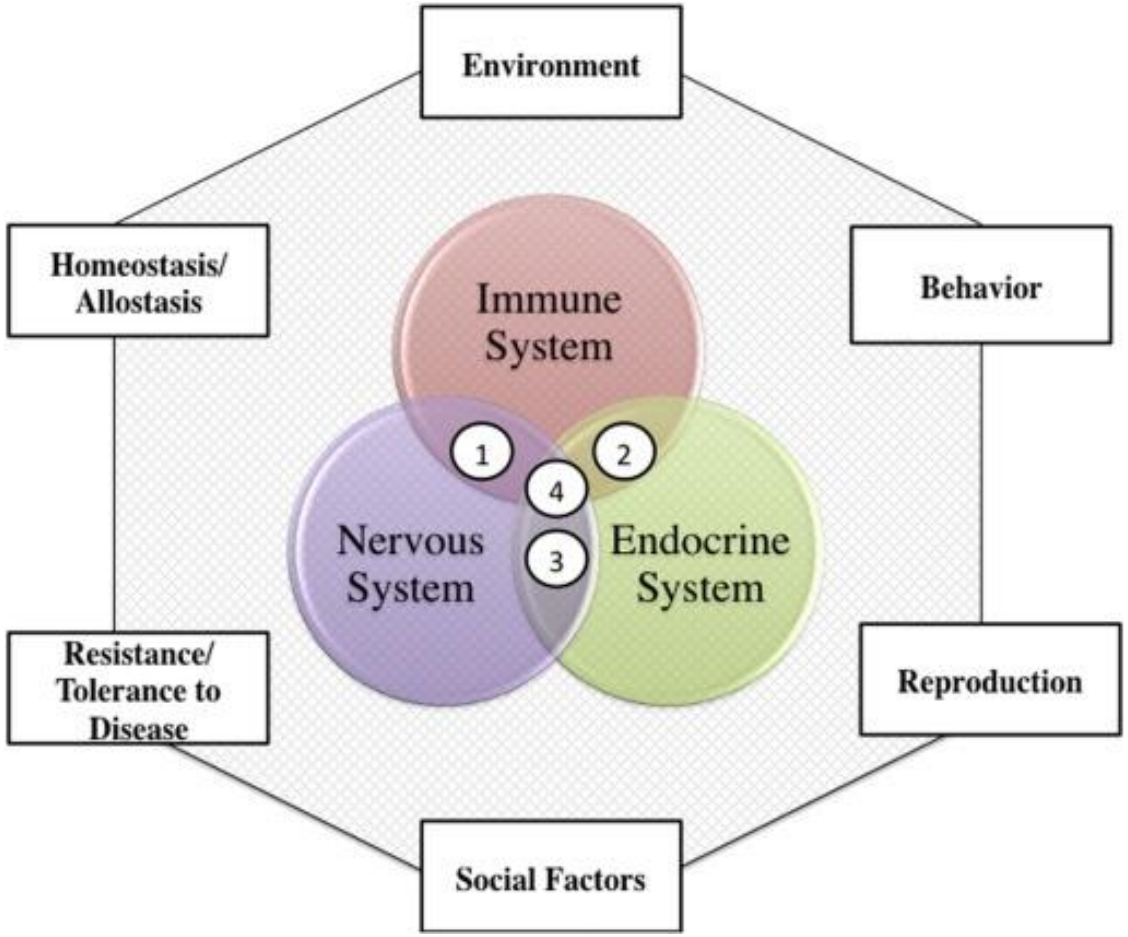
Neuro-endocrine-immune (NEI) network

- 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 the brain by cytokines
  - (2) endocrine-immune interactions
    - e.g. hormonal regulation of immunity
    - cytokine/ chemokine activation of endocrine cells)
  - (3) classical 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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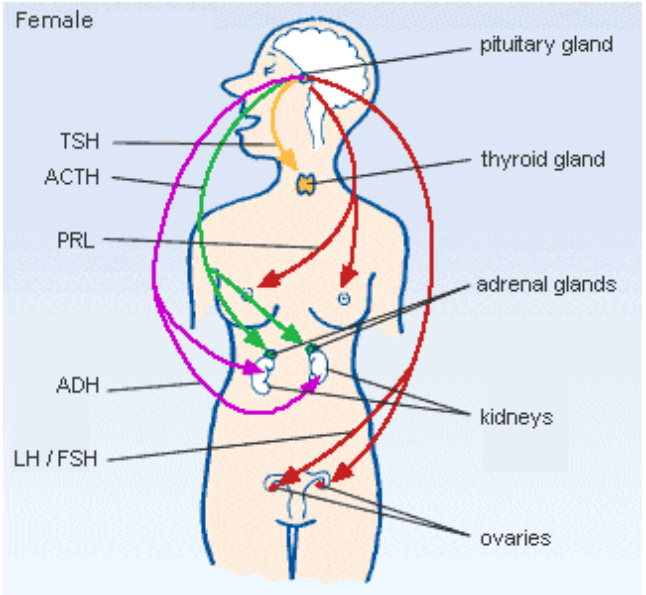
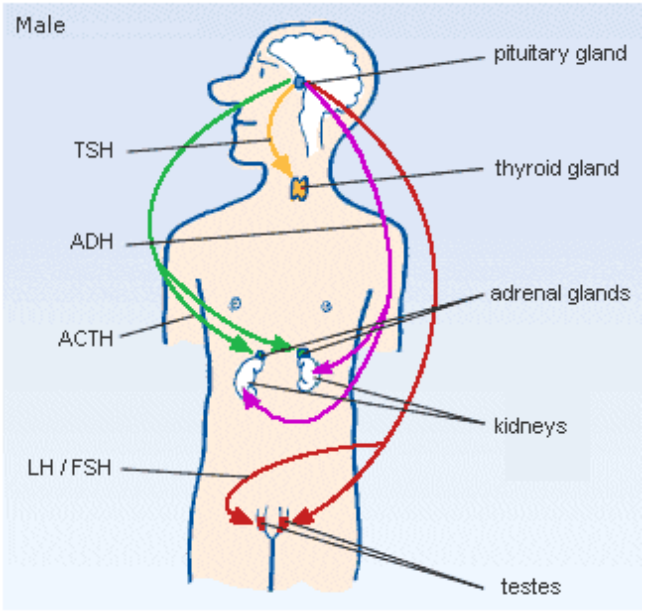
Mechanisms of endocrine diseases

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





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CHRONOBIOLOGY

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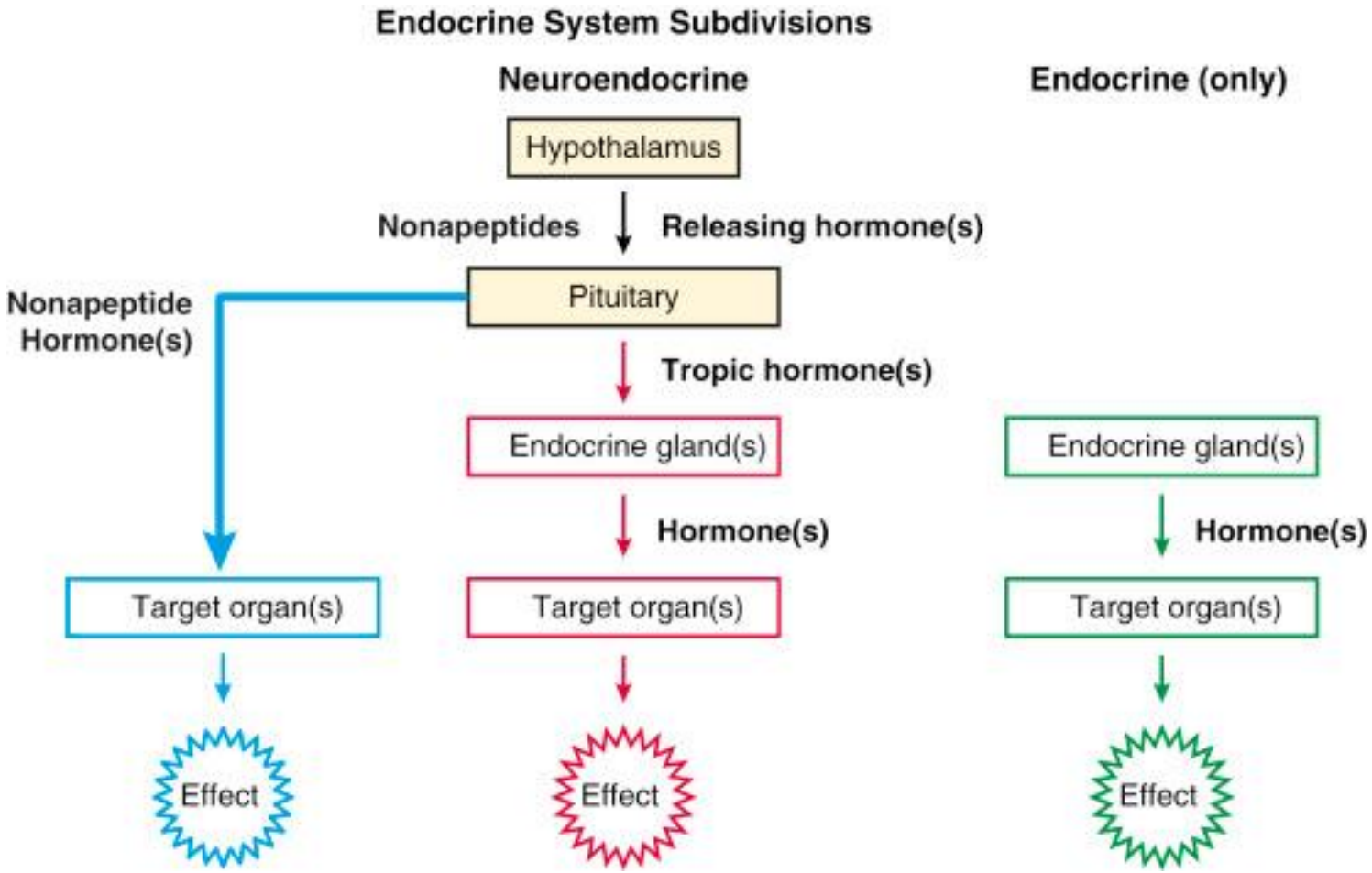
Homeostasis – feedback regulation – hierarchy



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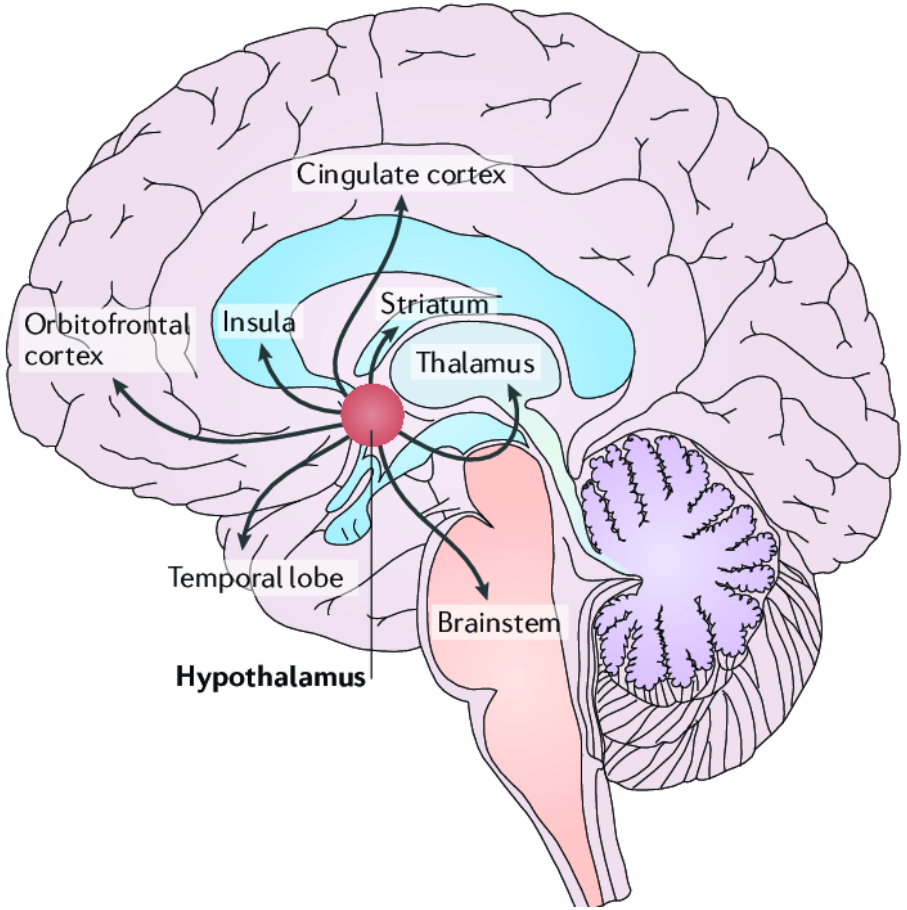
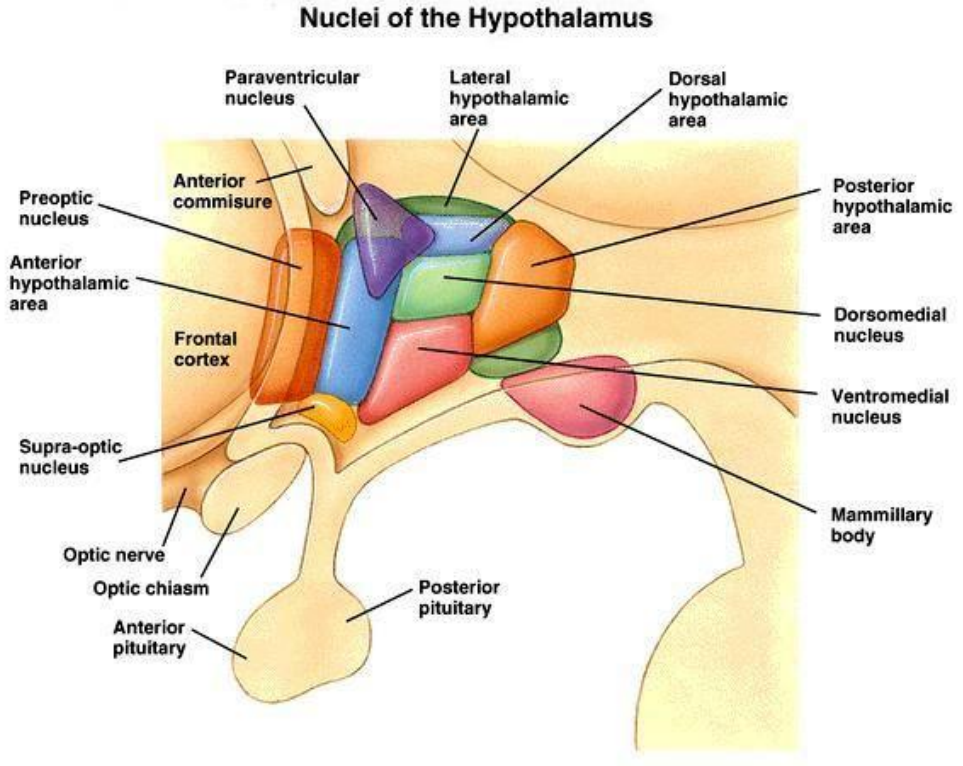
Hypothalamus – integration of signals form different parts of CNS





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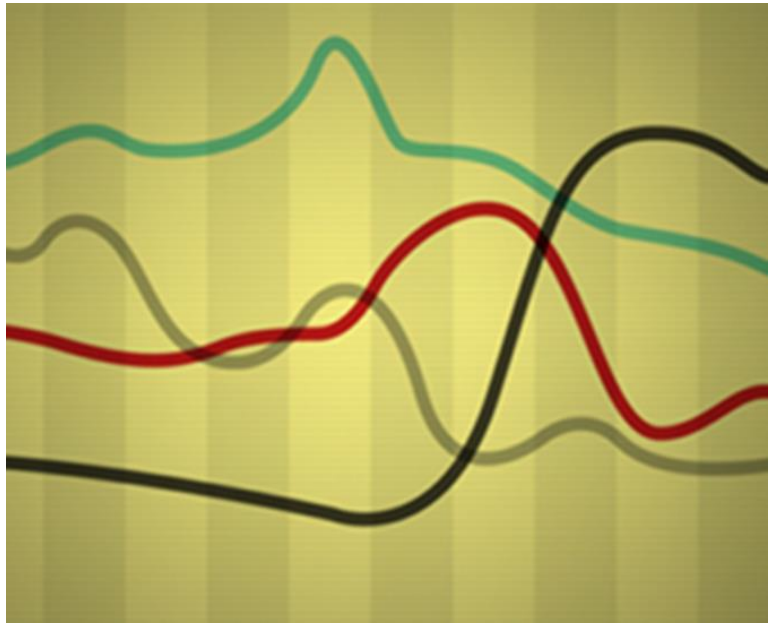
Biological rhythms



- most processes in the body has some cyclic character, however, the length of the biological cycle is various
  - circadian rhythm
    - production of hormones throughout the day and regulation of respective processes
  - ultradian – shorter than 24 hrs.
    - e.g. appetite/satiety cycles, respiration adjustment, …
  - infradian – longer than 24 hrs.
    - lunar, seasonal, …
- principal biological rhythm – circadian – is generated autonomously by inner "biological clock"
  - **nucleus suprachiasmaticus** (SCN) in hypothalamus
  - **glandula pinealis** – guiding the production of melatonin in cooperation with SCN
  - **nucleus paraventricularis** (PVN) in hypothalamus
    - releasing hormones
    - tractus hypothalamo-hypophysialis (oxytocin and ADH)
    - orexins
- mediators influenced by periodical activity of biological clock direct the activity of peripheral endocrine glands and other organs incl.
  - awakeners/sleep
  - alertness
  - feeding and energy homeostasis
  - reproduction
  - immune functions and repair
  - growth
  - etc.
- synchronization depends on external cues via sensory receptors and cognition
  - dark/light signals from the retina (and also skin)
  - food intake – nutrient levels
  - temperature – season
    - less important in a man

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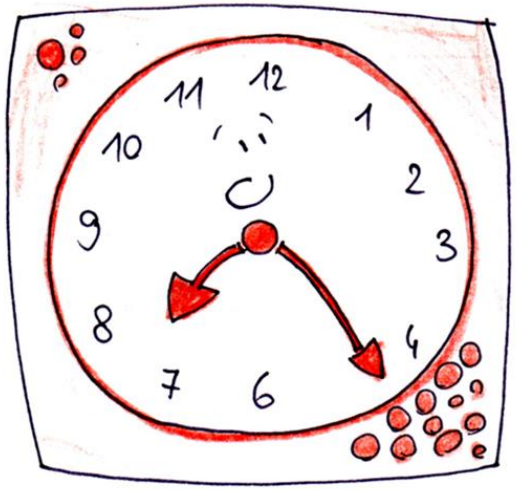
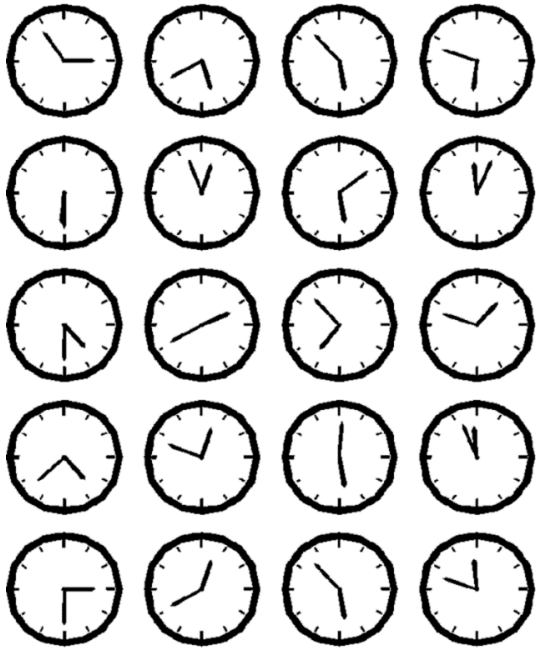
Circadian clock systems





- Circadian clock systems are present in all cells and organs and their timing is determined by a **transcriptional-translational feedback loop** of circadian genes which form proteins
  - the key genes involved are *CRY1*, *CRY2*, *PER1*, *2*, and *3*, *BMAL*, and *CLOCK*
    - CLOCK and BMAL1 form cytoplasmic heterodimers which, once within the nucleus start the transcription of clock genes (*PER1*, *PER1*, *PER3*, *CRY1*, and *CRY2*)
    - gene transcription is switched off by negative feedback of PER:CRY heterodimers which inhibit the action of the CLOCK/BMAL1 heterodimers
    - this cycle lasts approx. 24 hrs
- Individual cellular clocks are synchronized by the central body clock (situated in the suprachiasmatic nucleus), which communicates with them through humoral and neural signals including melatonin
- The circadian system controls both
  - the circadian period, i.e., the length of the intrinsic clock
  - the circadian phase, i.e., the clock timing
- An important determinant of the circadian system is **light exposure**
  - in most humans, the circadian period is slightly longer than 24 hrs and without regular resetting it tends to drift, leading to progressively later bedtimes and wake times

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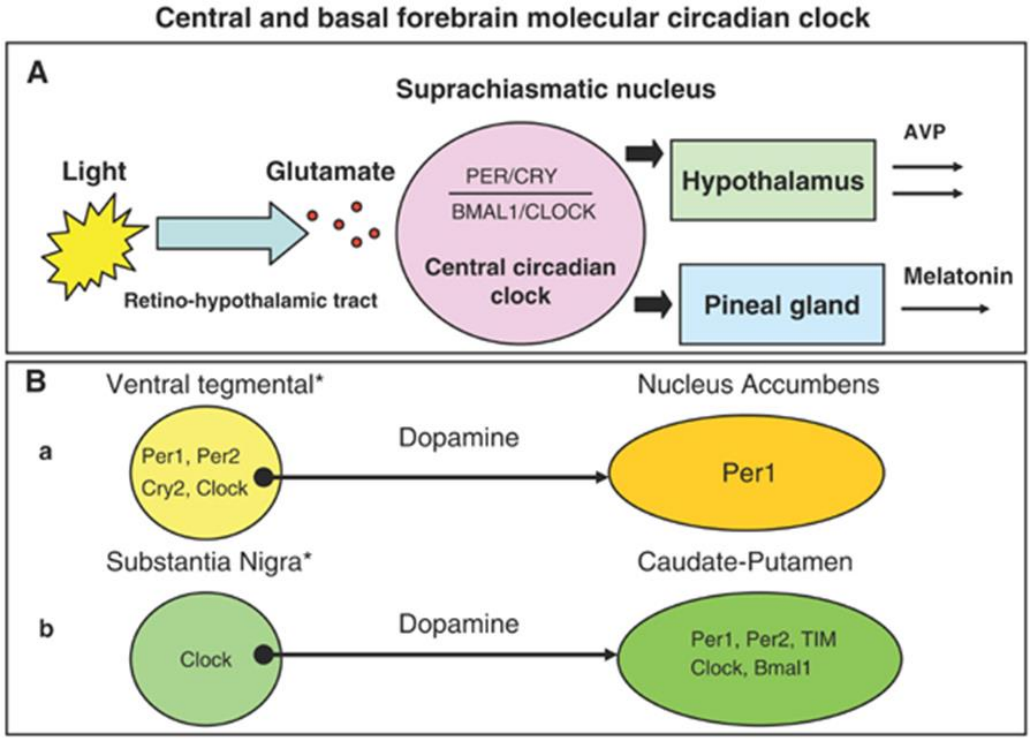
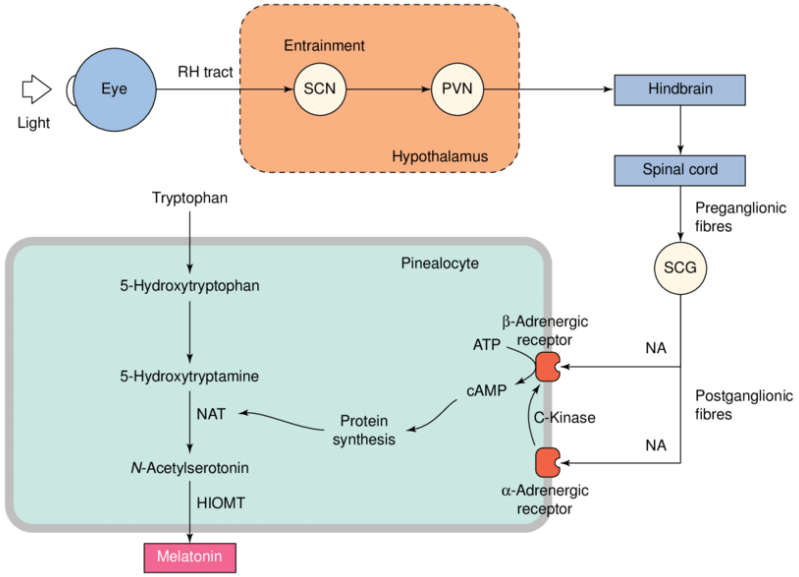
„Molecular clock“

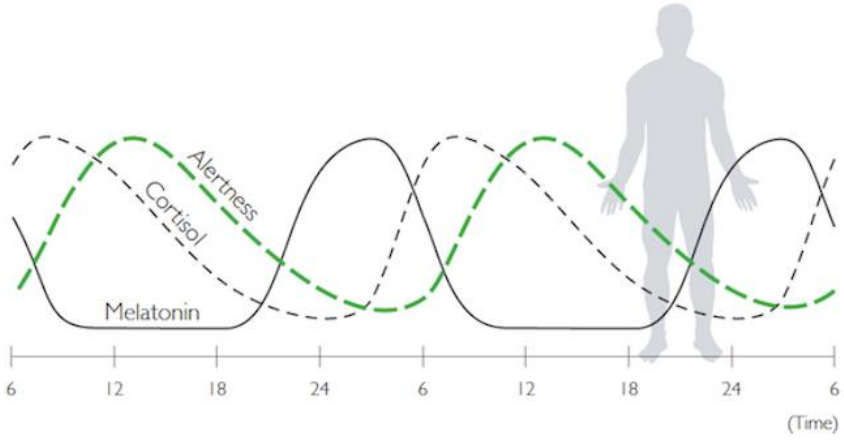
- inner biological rhythmicity is caused by negative and positive feedbacks between transcription of clock genes (CGs), their translation, postransl. modification and degradation
- their products - proteins – then serve as transcription factors of other hundreds of genes (CCGs) in n. suprachiasmaticus 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

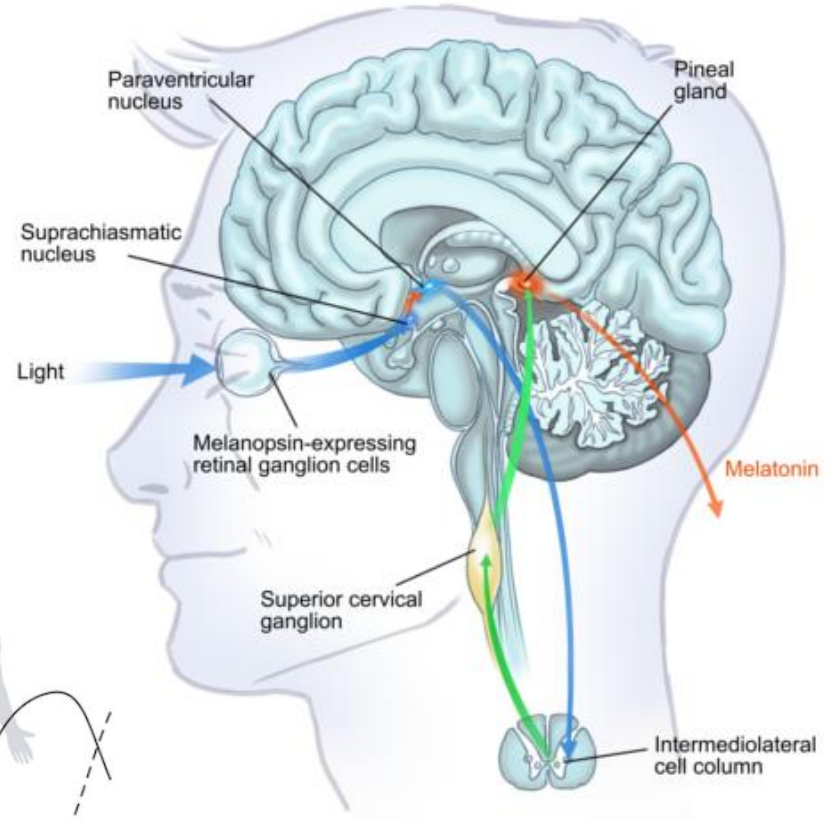


Light is the most powerful external cue synchronising the circadian rhythm

- light perception includes 3 types of retinal photoreceptors:
  - classical cones and rods
  - and specialised retinal ganglion cells (RGCs) producing a photopigment melanopsin
  - this controls the production of melatonin







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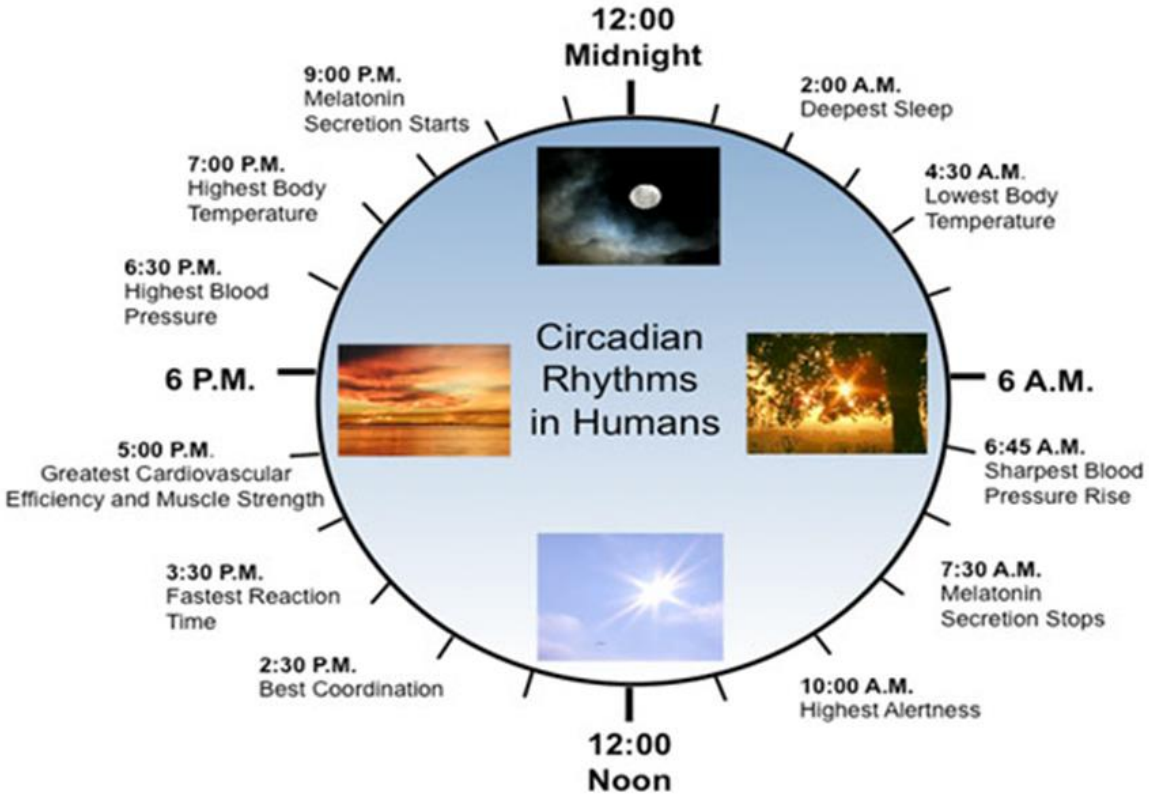
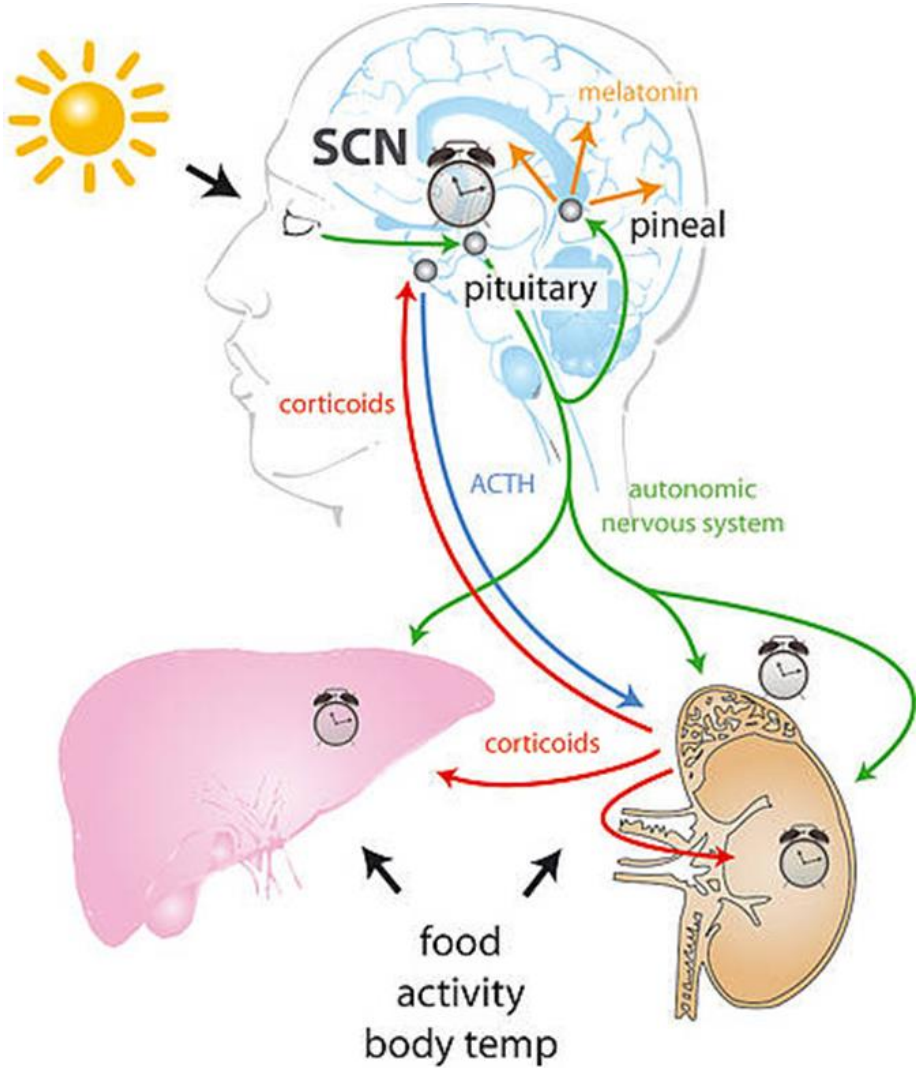
Circadian rhythm





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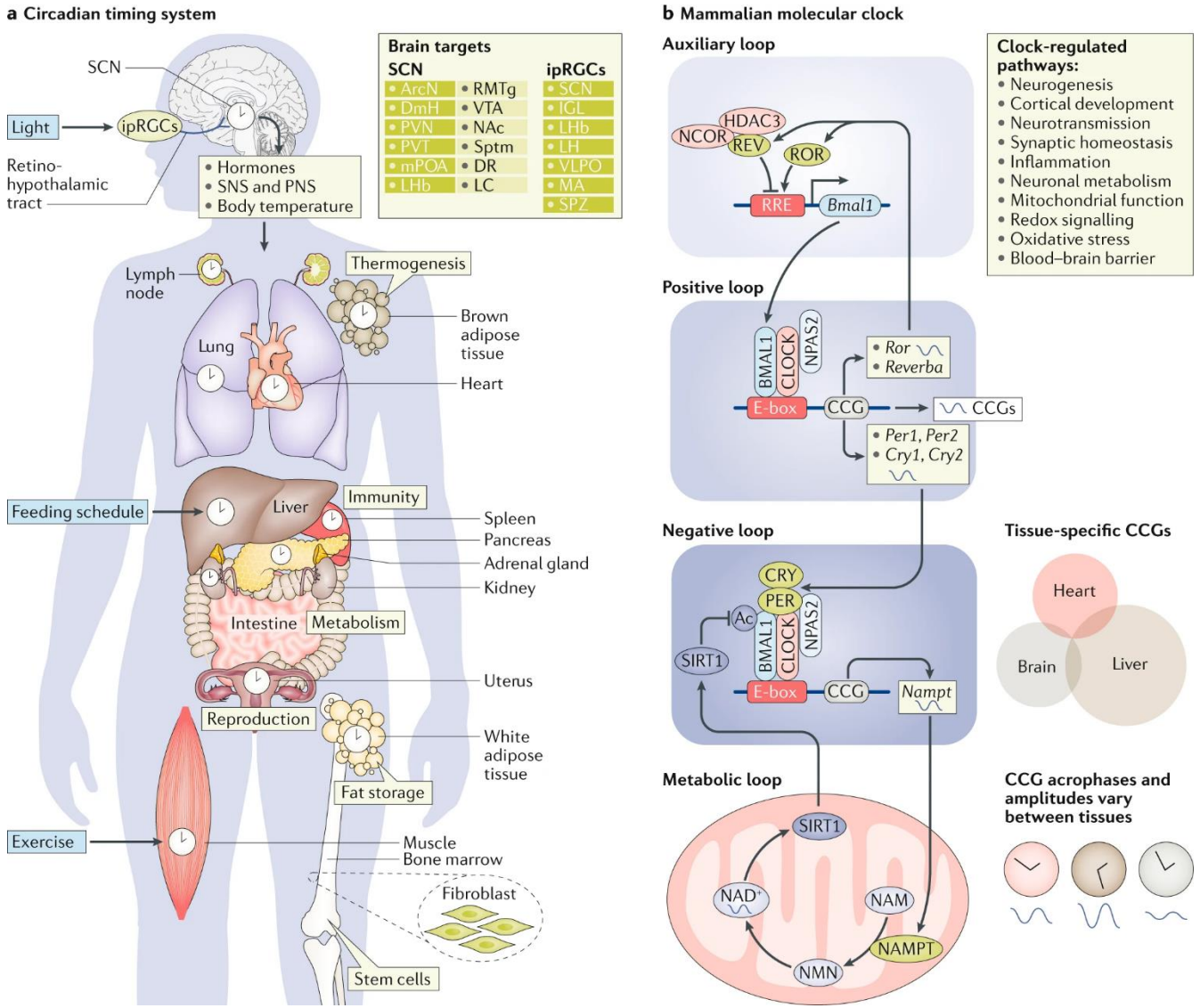
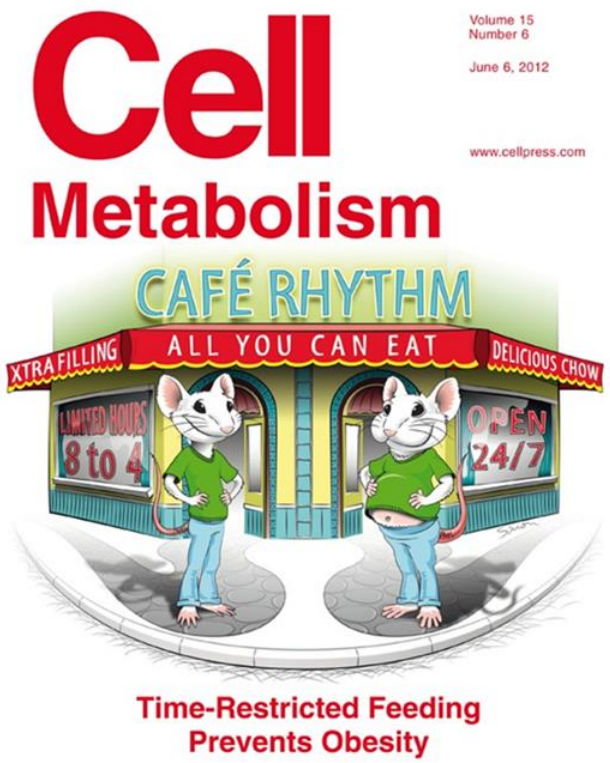
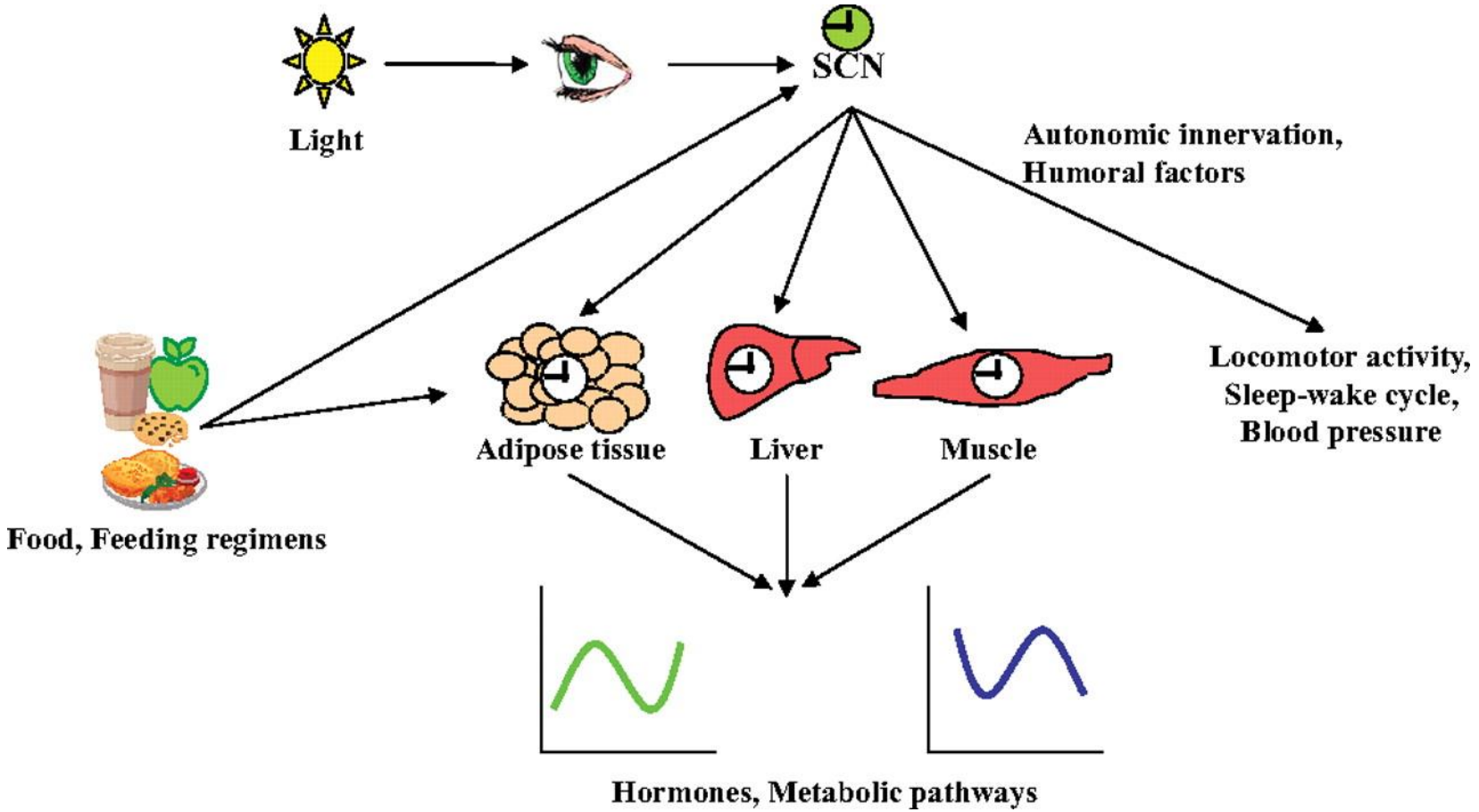
Molecular mechanisms of circadian rhythm



- **a** | The circadian timing system synchronizes clocks across the entire body to adapt and optimize physiology to changes in our environment. Light is received by specialized melanopsin-producing photoreceptive retinal ganglion cells (ipRGCs) in the eye. These ipRGCs project through the retinohypothalamic tract to the suprachiasmatic nucleus (SCN), among other brain regions. The SCN relays timing information to other areas of the brain via direct projections (dark green boxes) and indirect projections (light green boxes). Humoral signals and the peripheral nervous system (that is, the sympathetic nervous system (SNS) and parasympathetic nervous system (PNS)) convey information from the SCN to orchestrate peripheral clocks. Feeding schedules and exercise can also entrain central and peripheral clocks. Circadian rhythms are key regulators of thermogenesis, immune function, metabolism, reproduction and stem cell development. **b** | The mammalian molecular clock is composed of transcriptional and translational feedback loops that oscillate with a near-24-hour cycle. The positive loop is driven by the heterodimerization of either circadian locomotor output cycles protein kaput (CLOCK) or neuronal PAS domain-containing protein 2 (NPAS2) with brain and muscle ARNT-like 1 (BMAL1) in the nucleus. The resulting heterodimers bind to enhancer boxes (E-boxes) in gene promoters to regulate the transcription of clock-controlled genes (CCGs), including those encoding period (PER) proteins and cryptochrome (CRY) proteins. PER and CRY proteins accumulate in the cytoplasm during the circadian cycle, eventually dimerizing and shuttling to the nucleus to inhibit their own transcription, thus closing the negative-feedback loop. The auxiliary loop includes the nuclear retinoic acid receptor-related orphan receptors (RORα and RORβ) and REV-ERBs (REV-ERBα and REV-ERBβ), which are also transcriptionally regulated by CLOCK–BMAL1 heterodimers. REV-ERBα (REV in the figure) and RORα repress and activate the transcription of *Bmal1*, respectively, by inhibiting and activating the ROR or REV-ERB response elements (RREs). CLOCK–BMAL1 complexes also control the expression of nicotinamide phosphoribosyltransferase (NAMPT), which is the rate-limiting enzyme of NAD^+ biosynthesis from nicotinamide (NAM). NAM is modified by NAMPT to produce nicotinamide mononucleotide (NMN), which in turn is converted to NAD^+ by several adenyltransferases. Thus, NAMPT oscillations control circadian fluctuations in NAD^+ levels, which in turn modulate sirtuin 1 (SIRT1) activity and signalling. High levels of NAD^+ promote SIRT1 activation. SIRT1 interacts directly with CLOCK–BMAL1 to deacetylate BMAL1 and inhibit CLOCK-driven transcription. Between tissues and cell types, CCGs and other molecular and cellular rhythms may be expressed with different acrophases (phase of peak expression), amplitudes and even periodicities. ArcN, arcuate nucleus; DmH, dorsomedial hypothalamus; DR, dorsal raphe; IGL, intergeniculate leaflet; LC, locus coeruleus; LH, lateral hypothalamus; LHb, lateral habenula; MA, medial amygdala; mPOA, medial preoptic area; NAc, nucleus accumbens; PVN, paraventricular nucleus of the hypothalamus; PVT, paraventricular nucleus of the thalamus; RMTg, rostromedial tegmental nucleus; Sptm, septum; SPZ, subparaventricular zone; VLPO, ventrolateral preoptic nucleus; VTA, ventral tegmental area.

Coordination of signals from central and peripheral „clocks“





Froy O Endocrine Reviews 2010;31:1-24

ENDOCRINE REVIEWS

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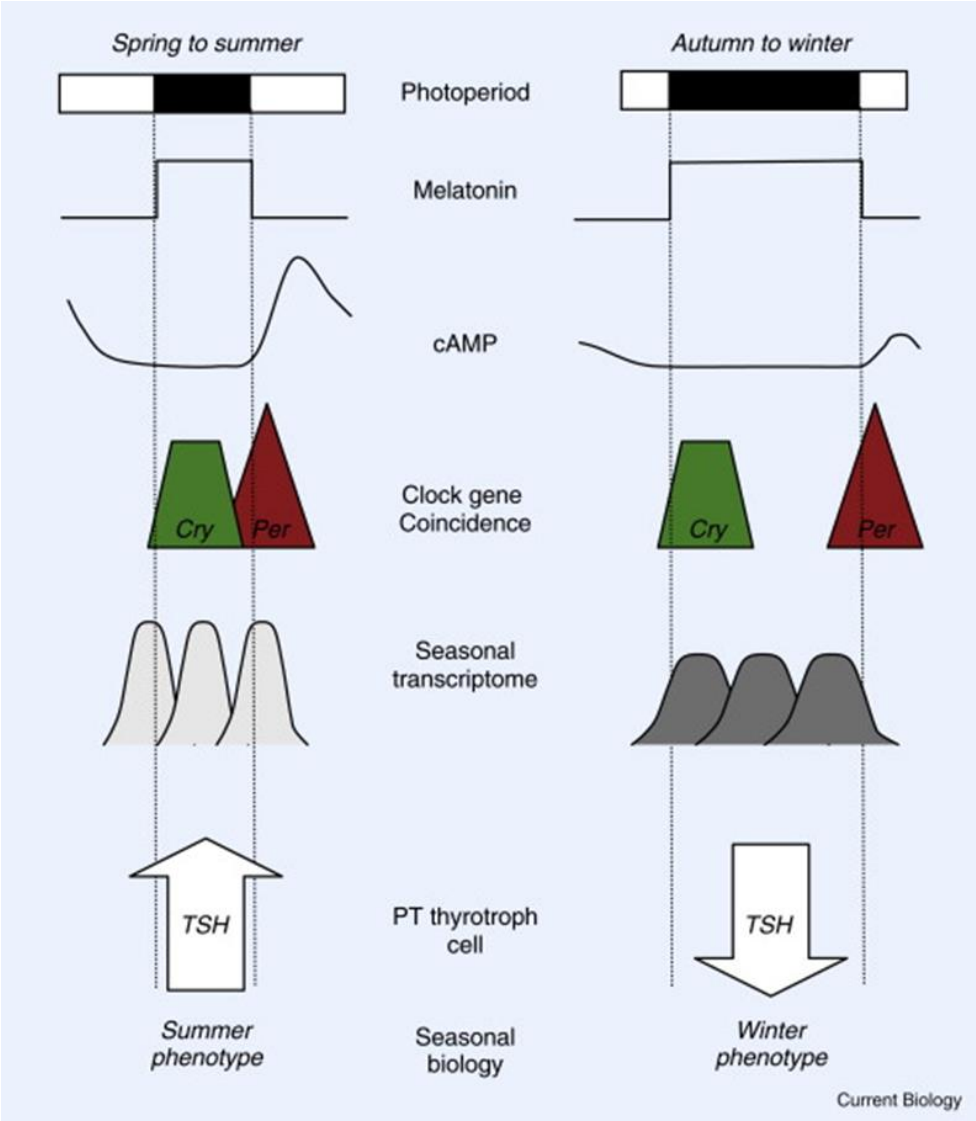
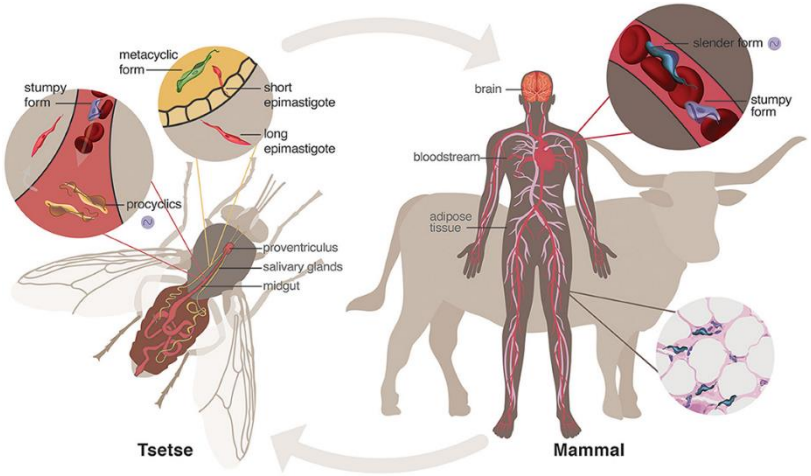
Seasonal clocks - analogy with circadian clocks

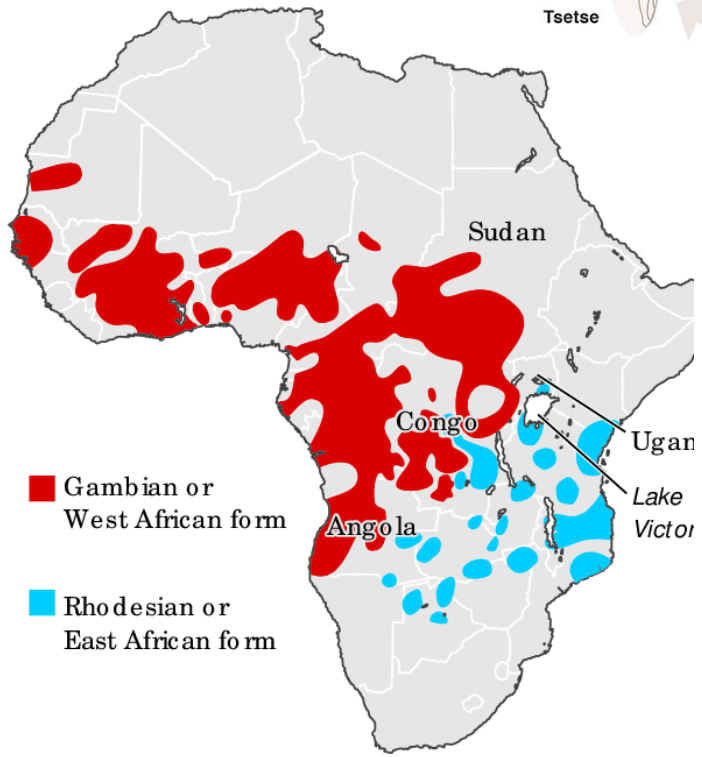
- in long-lived species there is evidence for the existence of self-sustained circannual oscillators
  - migratory restlessness
  - hibernation
  - seasonal moulting
  - seasonal breeding



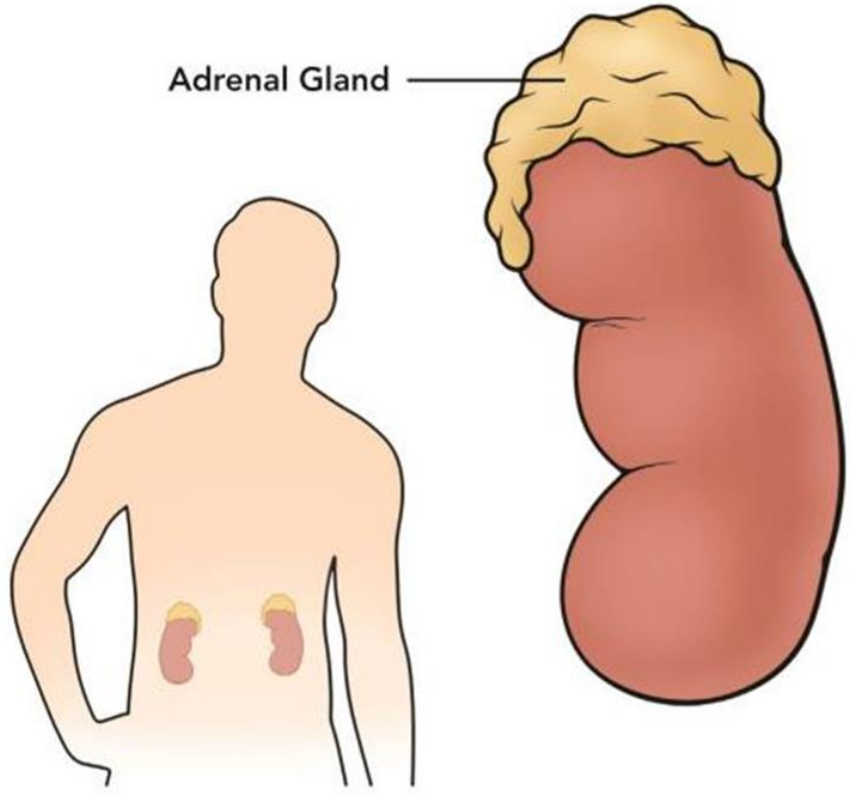
Disturbances of circadian rhythmicity

- aetiology/causes
  - mutations in clock genes
    - interindividual variability
      - chorotype "owls" vs. "larks"
  - aging
  - external factors
    - shift work
    - jet lag
    - exposure to light during evening and night
    - social factors
    - infection – sleeping sickness (Trypanozoma brucei)
  - psychiatric and neurological diseases
    - depression
    - neurodegenerative
  - obesity and abnormal food intake
  - blindness (total without light perception)
    - preserved circadian rhythm
      - perception of light by skin resp. subcutaneous fat cells?
      - ~50% subjects suffer from non-24-hour sleep-wake disorder (N24SWD, „free-running")
- consequences
  - T2DM, cardiovascular diseases, immunopathology, cancer
- a concept of chrono-pharmacology





THE ADRENALS



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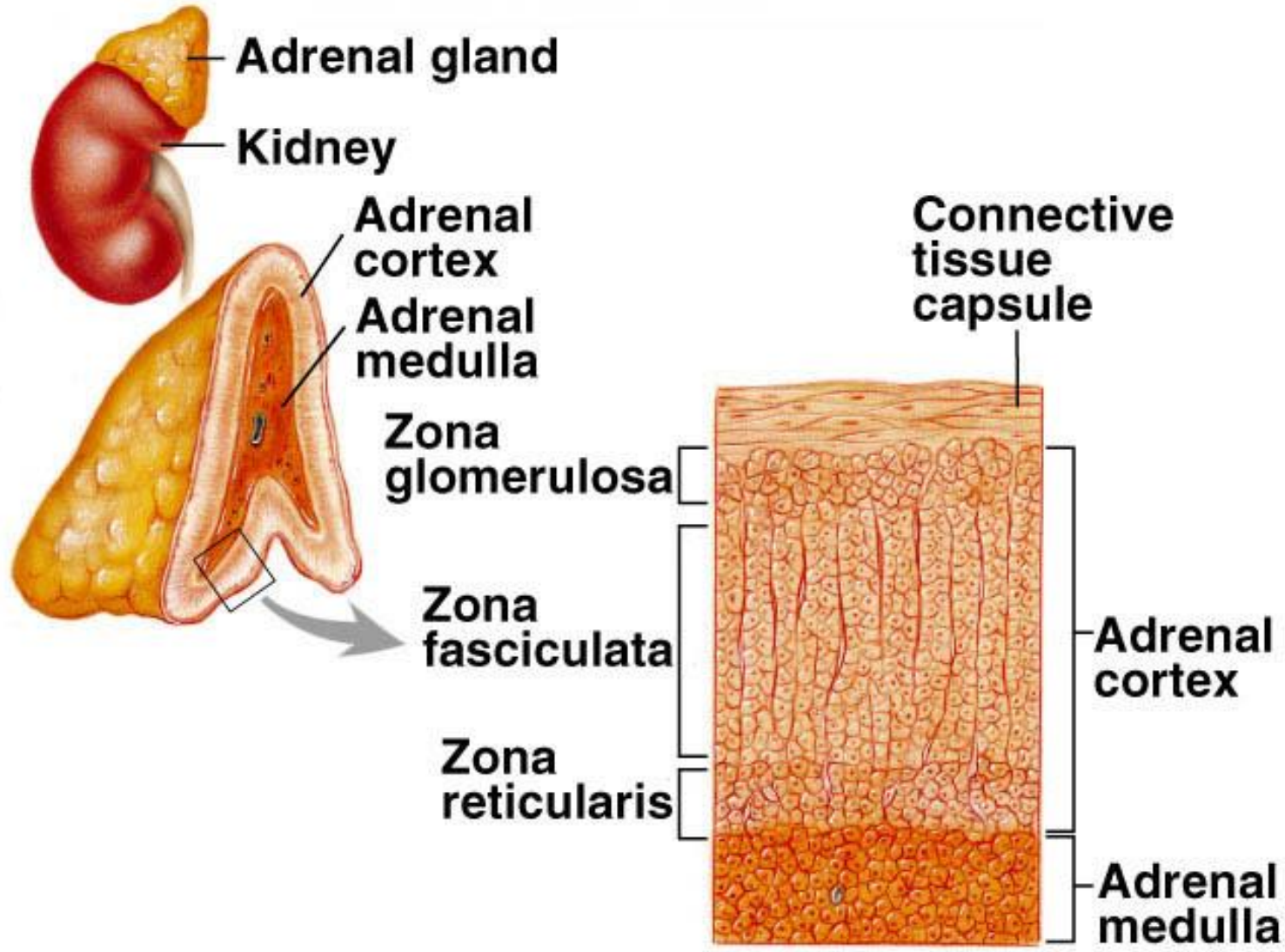
Anatomy and histology of adrenals



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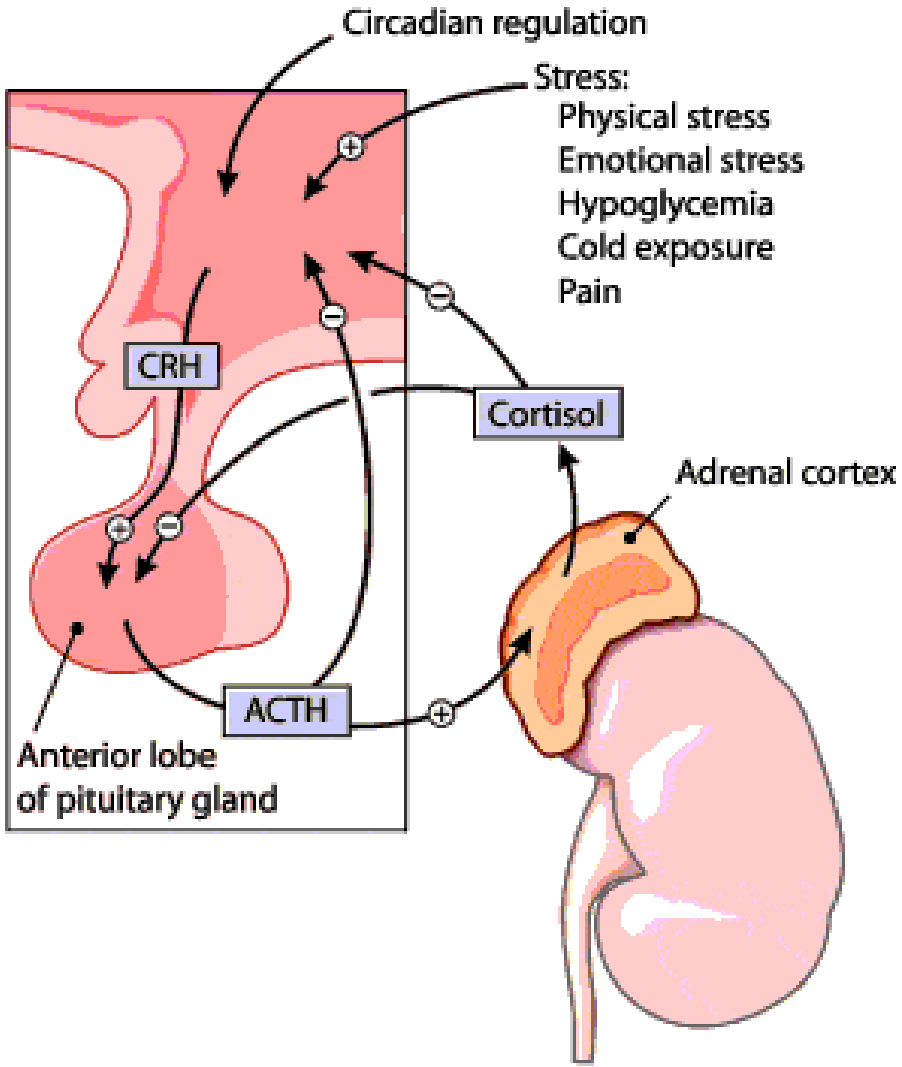
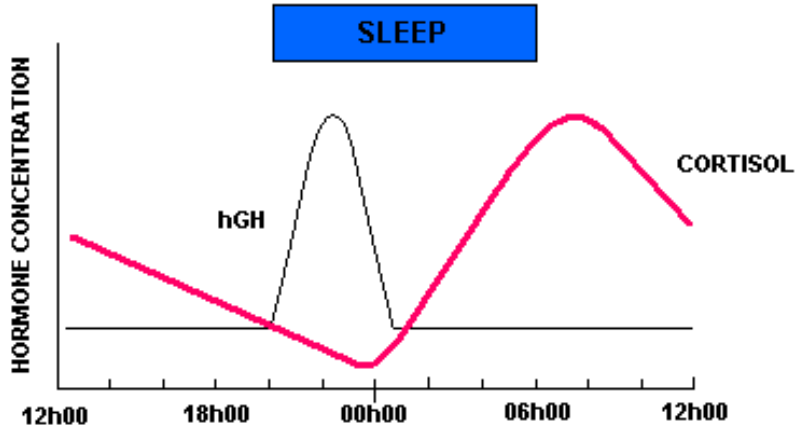
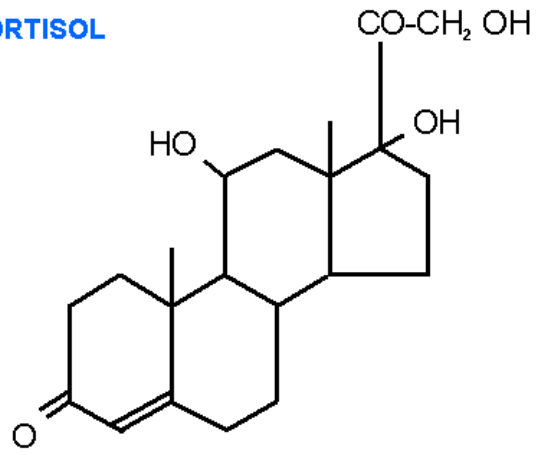
Cortisol profile & regulation





CORTISOL



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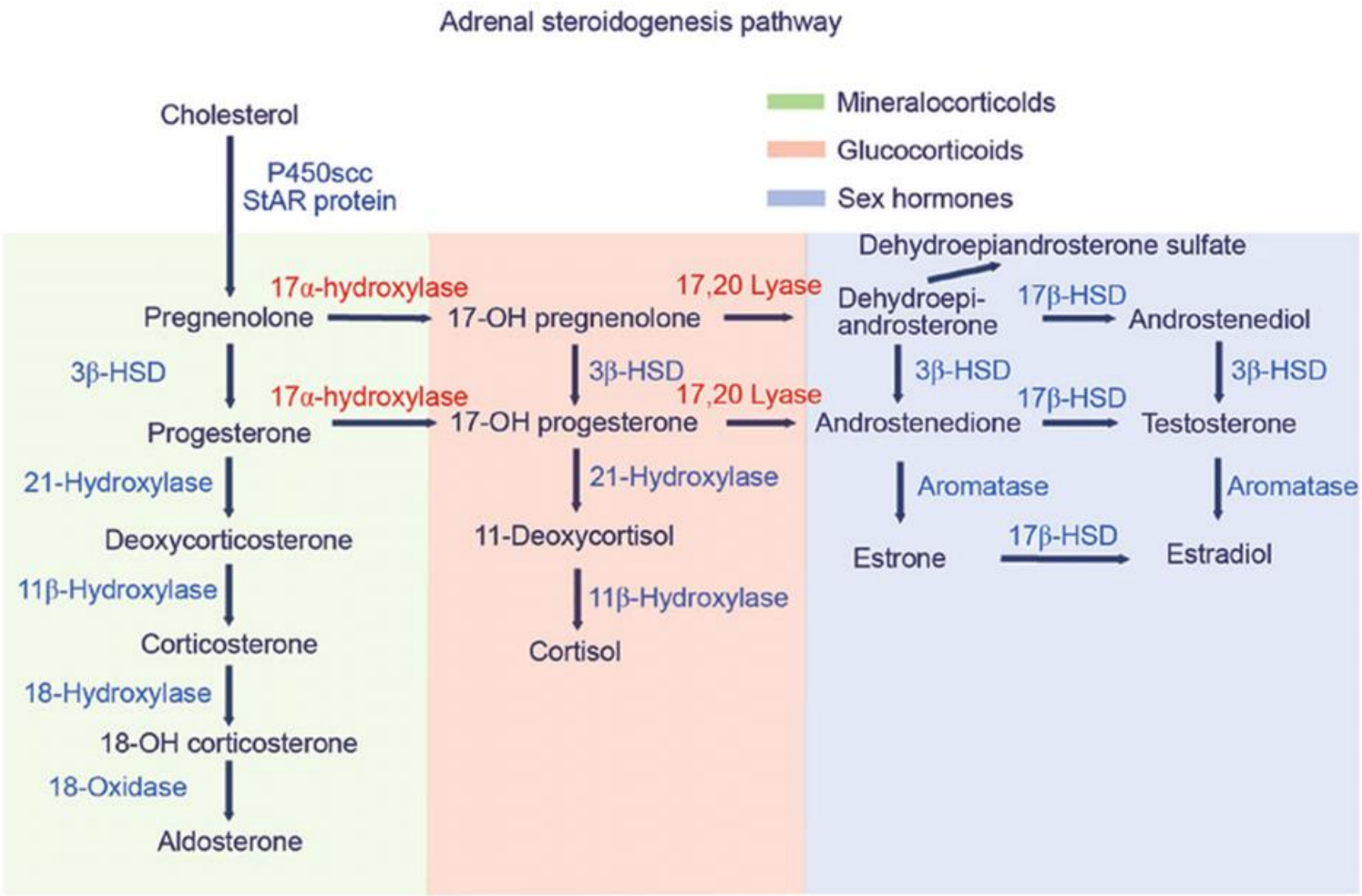
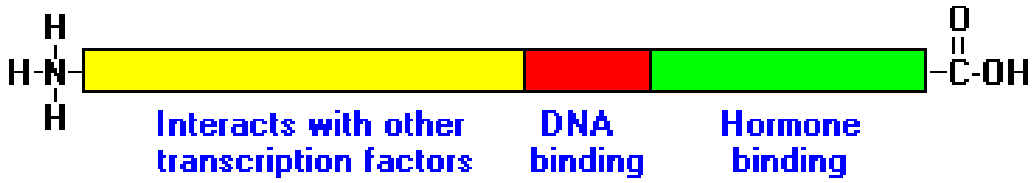
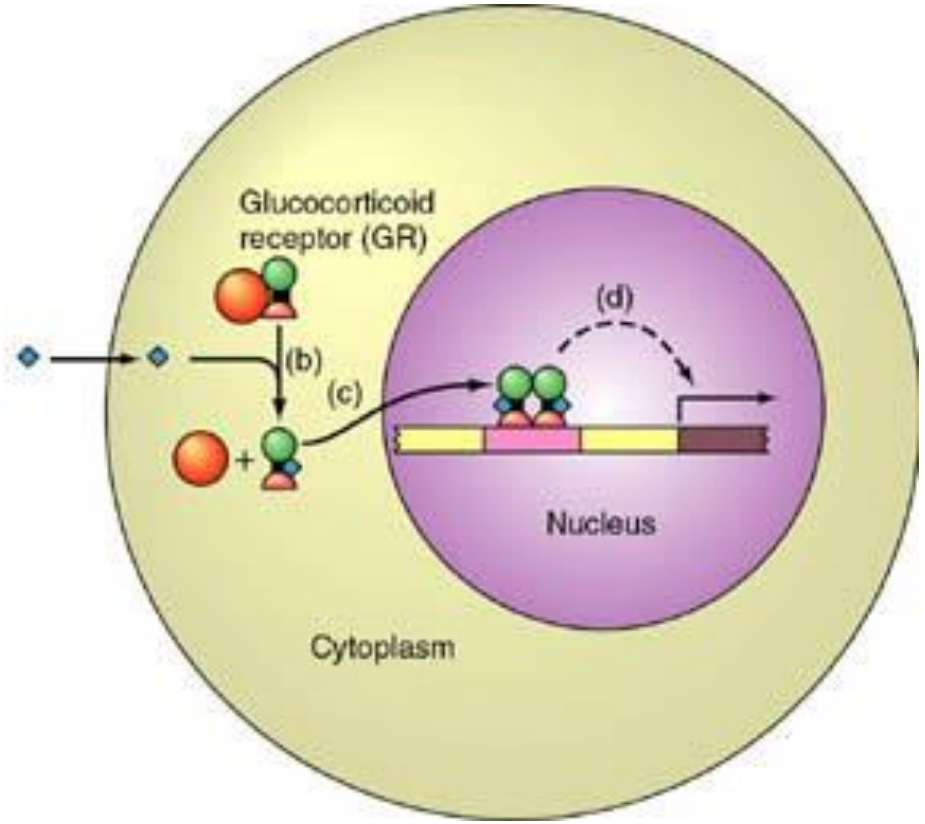
Major steroid biosynthetic pathways



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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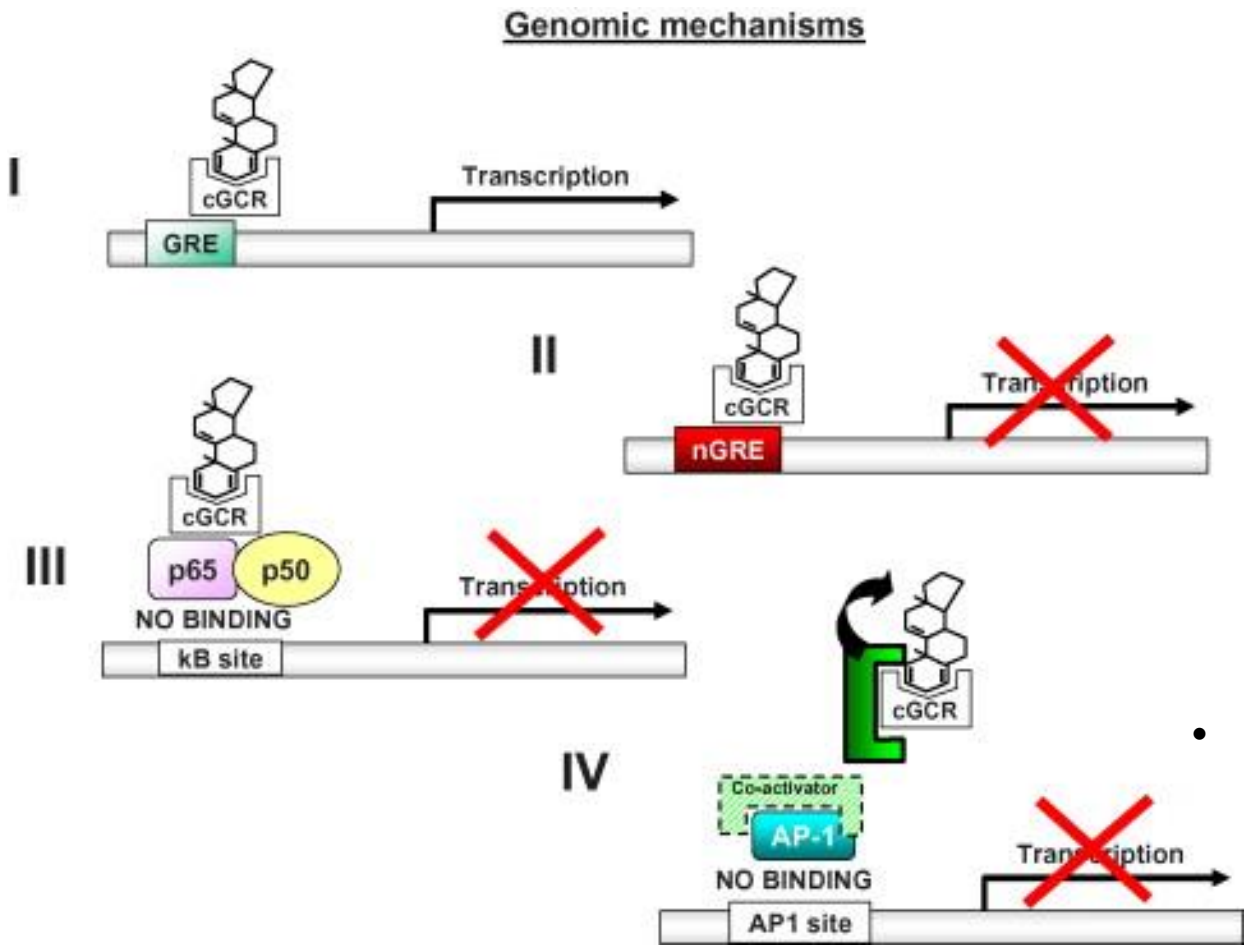
GC action – genomic effects



- (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) trans-repression = binding to negative GRE (nGRE) [II] or interaction with other TF [III] or their coactivators [IV]
      - repression of transcription or blocking the action of other TF on gene transcription (such as AP-1, NFkB, ...)
  - the whole sequence of events following the binding of GCs to cGRs takes at least 20-30min – late effects compared to the action of peptide hormones or to the non-genomic action of GCs
  - affinity of steroid receptors (for GC, aldosterone, estradiol) is not specific!!
    - e.g. GCs bind avidly to MR in the brain, not in the kidney though (degraded, see further)
- (B) non-genomic effects - **evident in many of anti-inflammatory and immunosuppressive effects**
  - nonspecific interactions with the cell membrane
  - specific interactions with cytosolic GRs (cGRs)
  - or membrane-bound GRs (mGRs)

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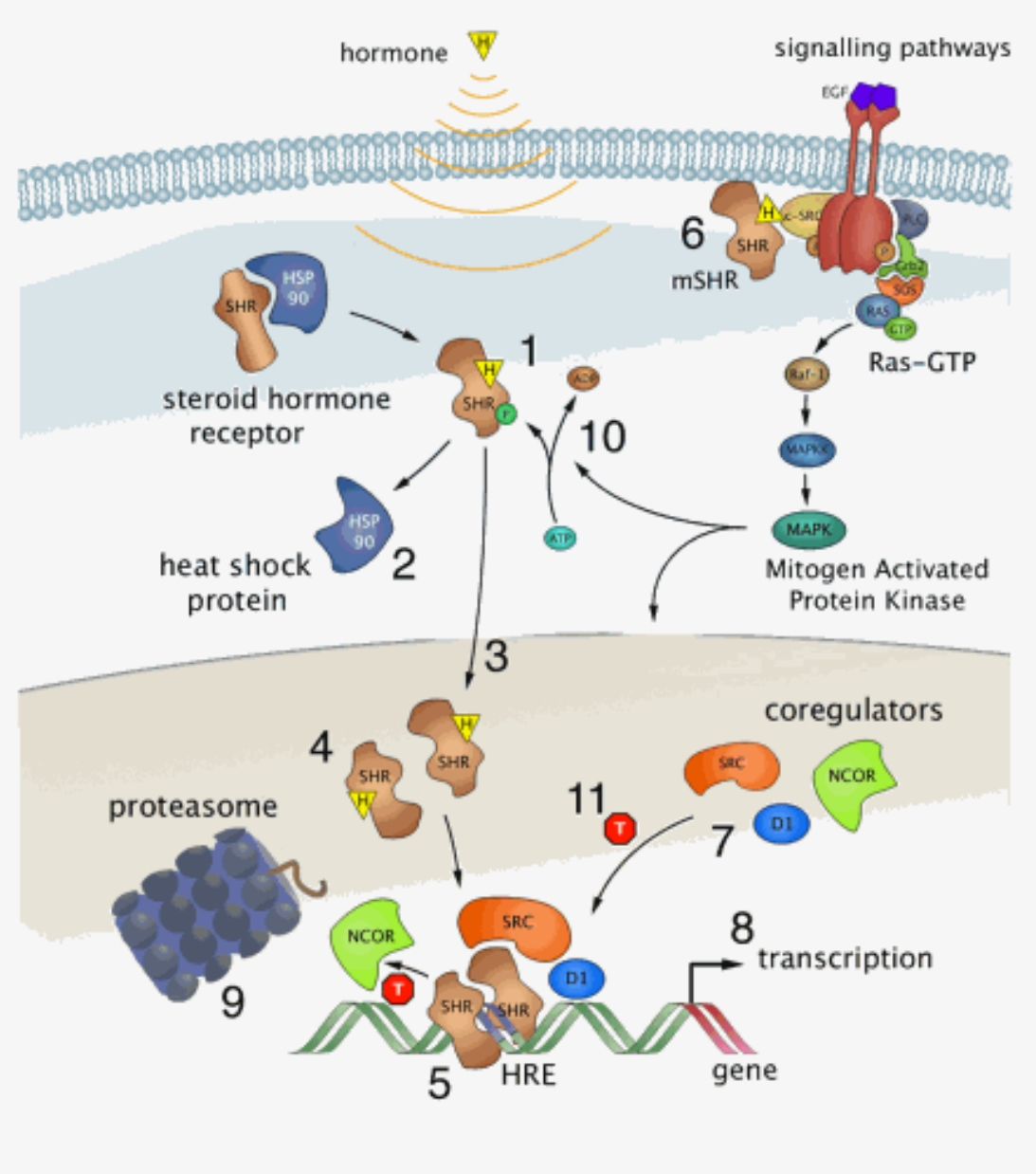
Steroid hormone receptor signalling



- 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 subcutaneous 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 synthase)	muscle atrophy, weakness, steroid myopathy
Pancreas (β cells)	↓ **insulin secretion** (suppression of GLUT2 and K^+ channel, apoptosis)	impaired glucose tolerance/diabetes mellitus

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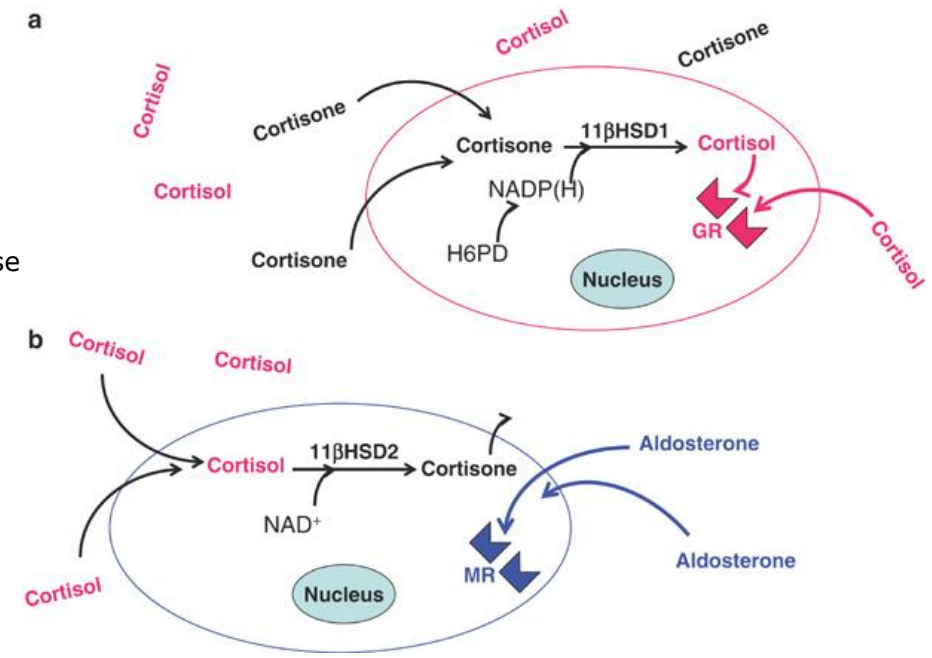
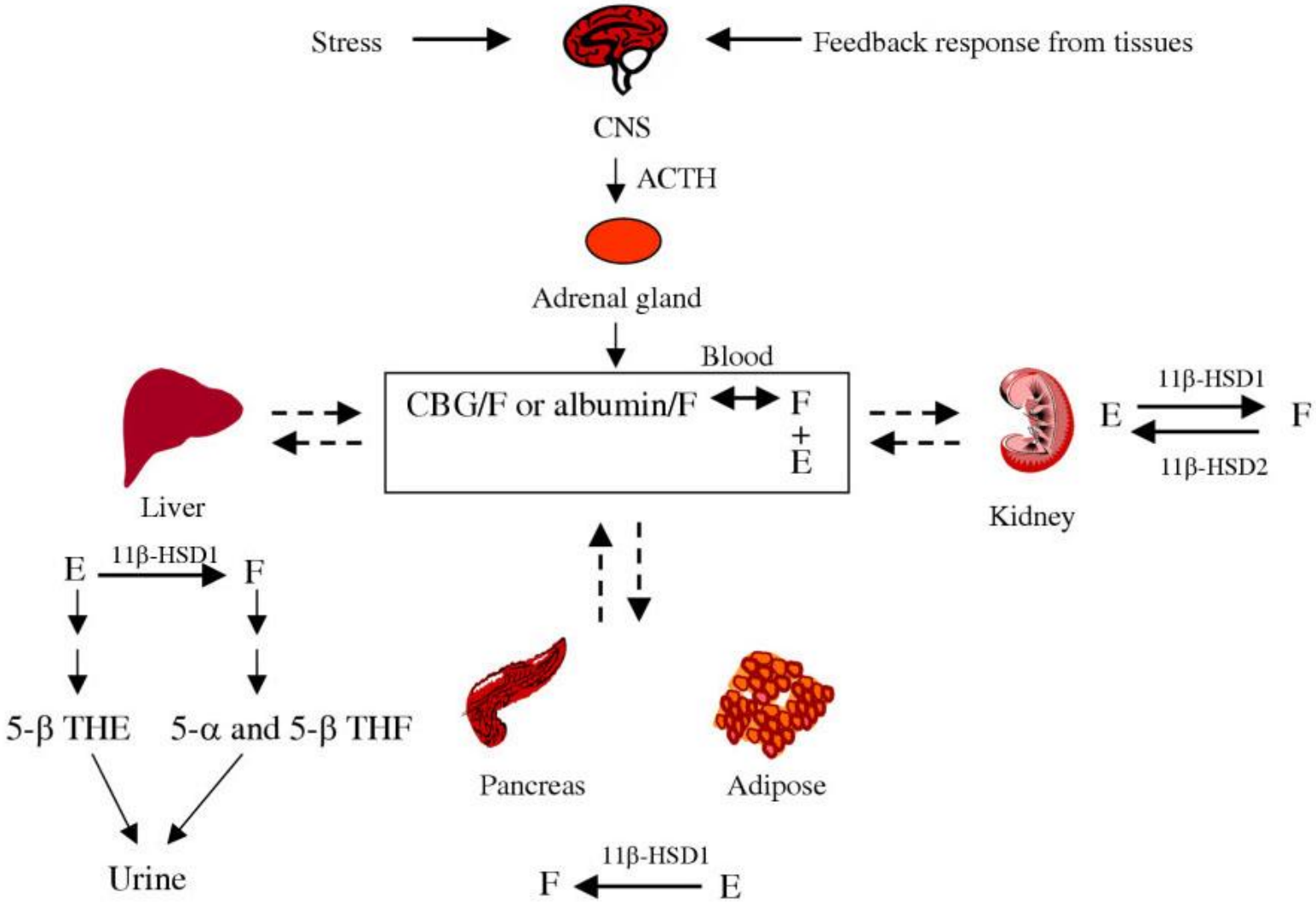
Peripheral modulation of GC availability

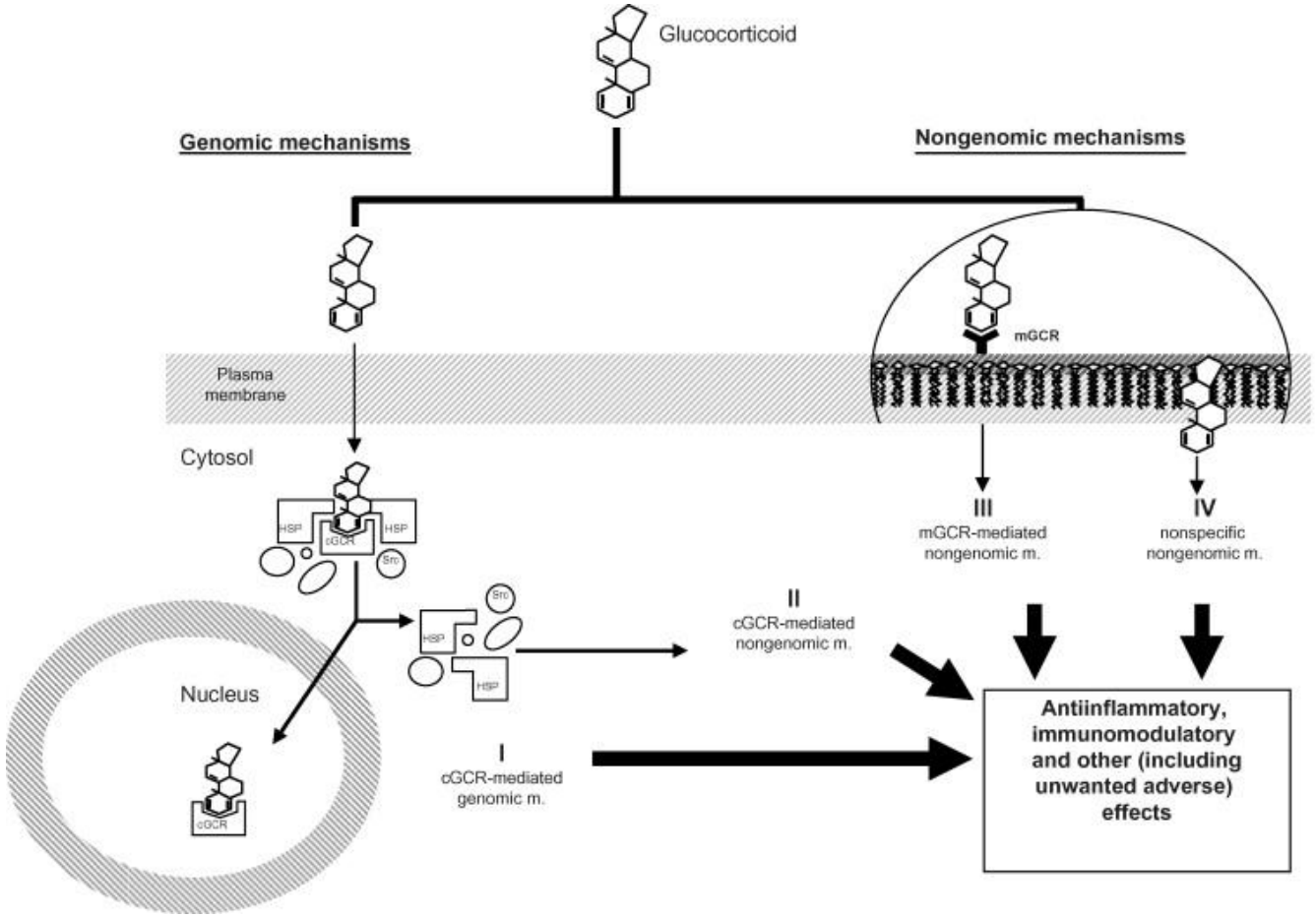
- peripheral tissue-specific modulation of cortisol availability by enzymes catalysing interconversions of active and inactive forms of GCs
- **(a) 11β hydroxysteroid dehydrogenase type 1 (11βHSD1)**
  - act as a reductase regenerating cortisol from cortisone → ↑ intracellular cortisol concentration
    - **mainly in the 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 the first source of substrate, but higher suppression with GC, while enhanced GC action leads to lipolysis in adipose tissue, the fat cumulates in visceral
    - congenital deficiency of 11βHSD1 (apparent cortisone reductase deficiency) → compensatory over-activation of HPA axis → adrenal androgen excess, oligomenorrhea, 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 the concentration of plasma cortisol >>> aldosterone
  - pathology associated with 11βHSD2
    - congenital deficiency of 11βHSD2 (apparent mineralocorticoid excess) → monogenic form of hypertension
    - 11βHSD2 is expressed in the 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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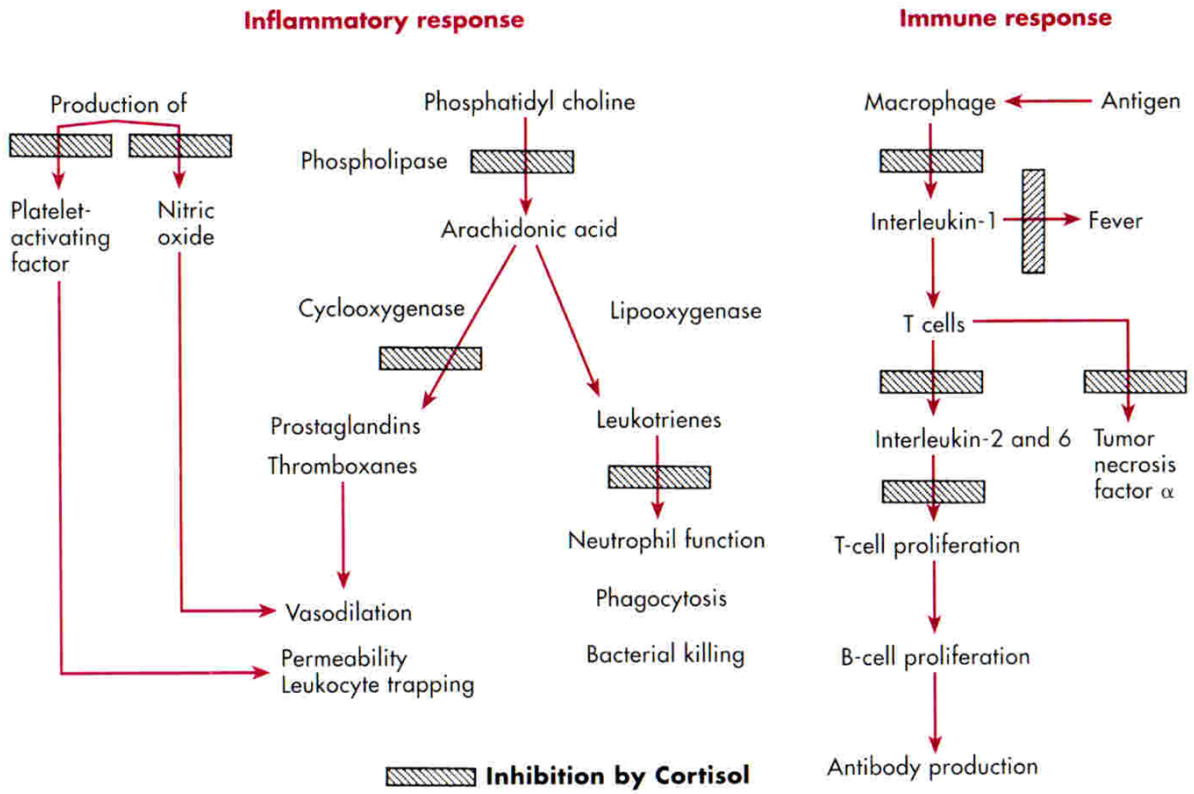
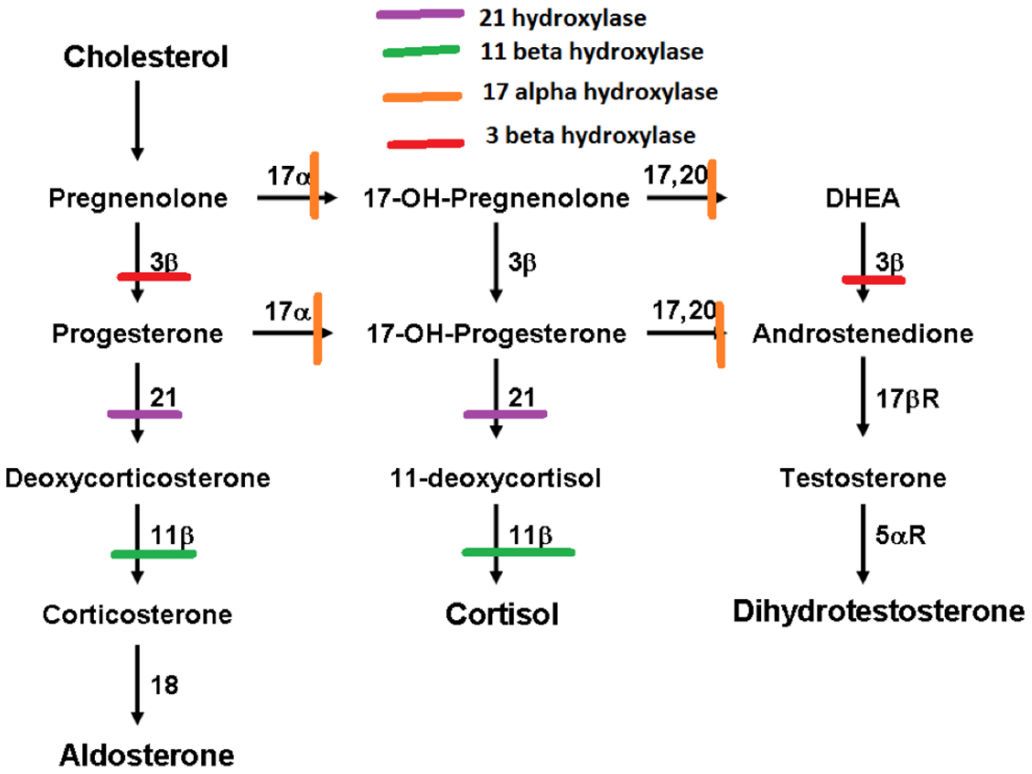
GCs and immune system

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



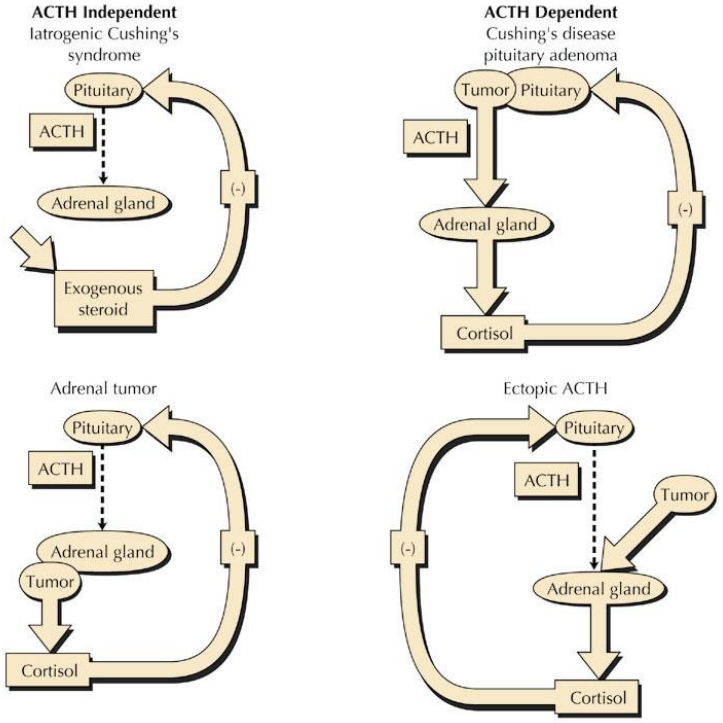
Disorders of adrenal gland

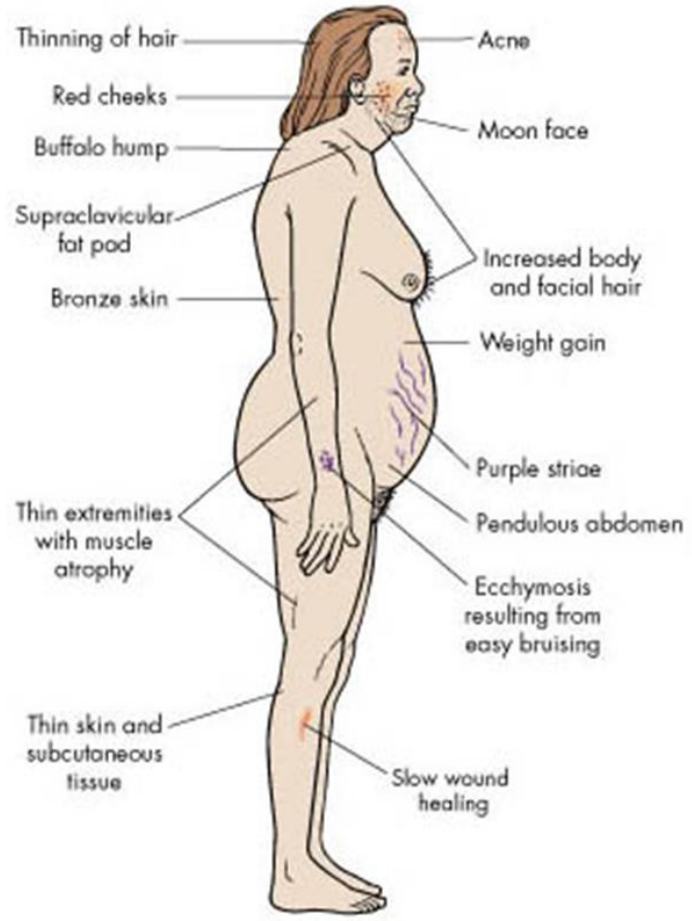
- hyper-corticalism
  - usually selective
  - primary vs. secondary
  - Cushing syndrome
  - Conn syndrome
  - adrenal hyperandrogenism
    - DHEA producing adrenal adenoma
- hypo-corticalism
  - usually generalised
  - Addison syndrome
- dissociation of adrenal function
  - abnormality of steroid biosynthesis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



Glucocorticoid excess: Cushing's syndrome

- Etiology
  - primary
    - GC overproduction by adrenal tumor (adenoma or carcinoma)
    - adrenal hyperplasia
    - 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 or CRH production
      - typically mediastinum (i.e. small cell lung carcinoma)
    - low CBG
  - iatrogenic





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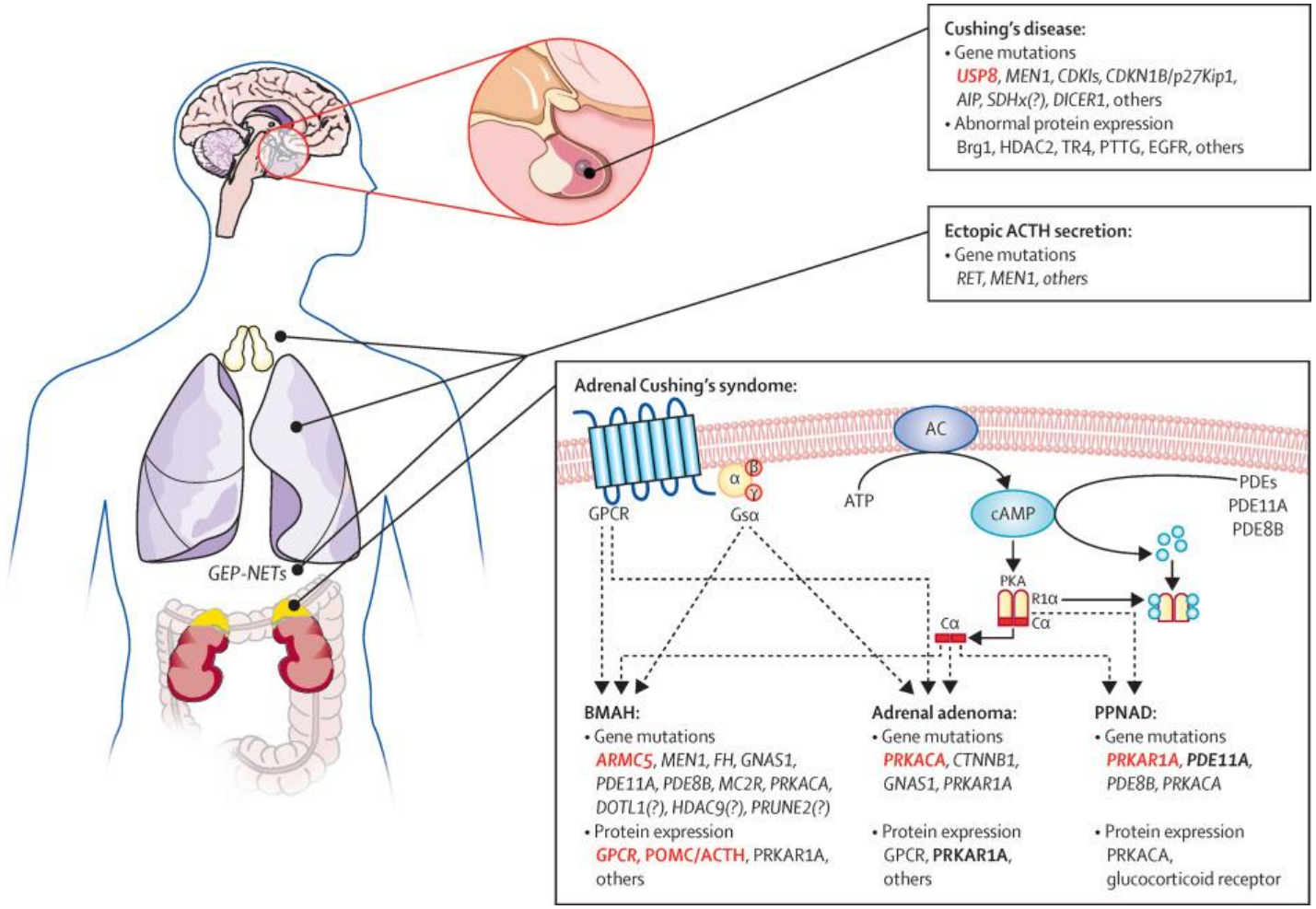
Genetic and molecular mechanisms implicated in Cushing's syndrome



Dexamethasone suppression test – CS dg.

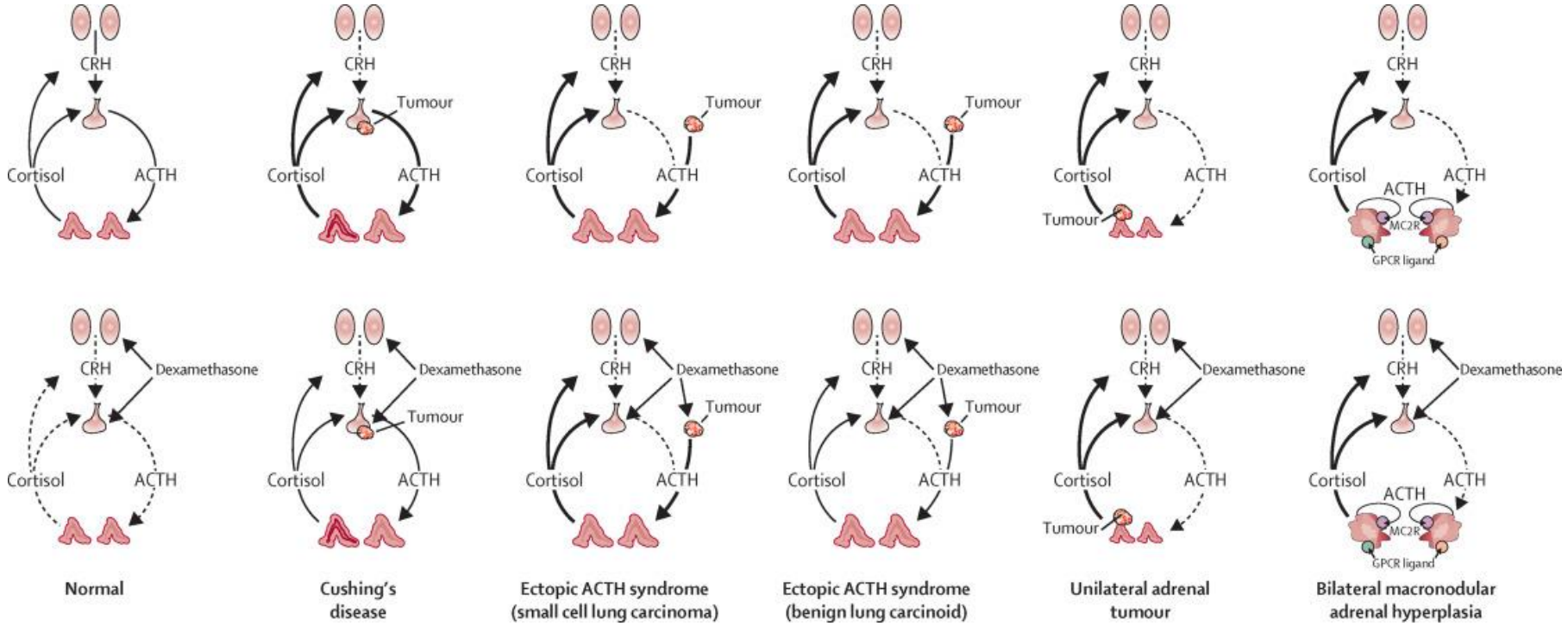


Table 1. Aetiology of Cushing's syndrome.

Cause of Cushing's syndrome	%	F:M
ACTH-dependent		
Cushing's disease	70%	3.5:1
Ectopic ACTH syndrome	10%	1:1
Unknown source of ACTH*	5%	5:1
ACTH-independent		
Adrenal adenoma	10%	4:1
Adrenal carcinoma	5%	1:1
Macronodular hyperplasia (AIMAH)	< 2%	
Primary pigmented nodular adrenal disease (PPNAD)	< 2%	
McCune Albright syndrome	< 2%	

* Patients may ultimately prove to have Cushing's disease.

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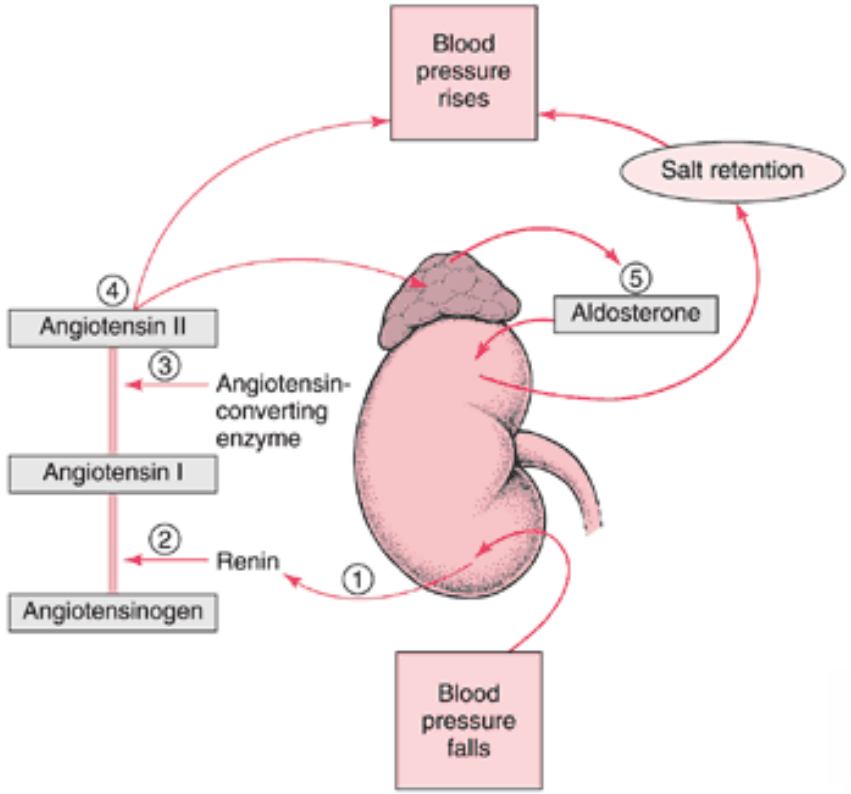
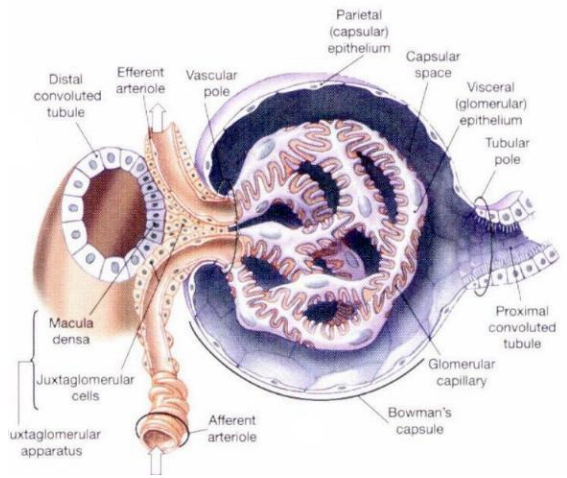
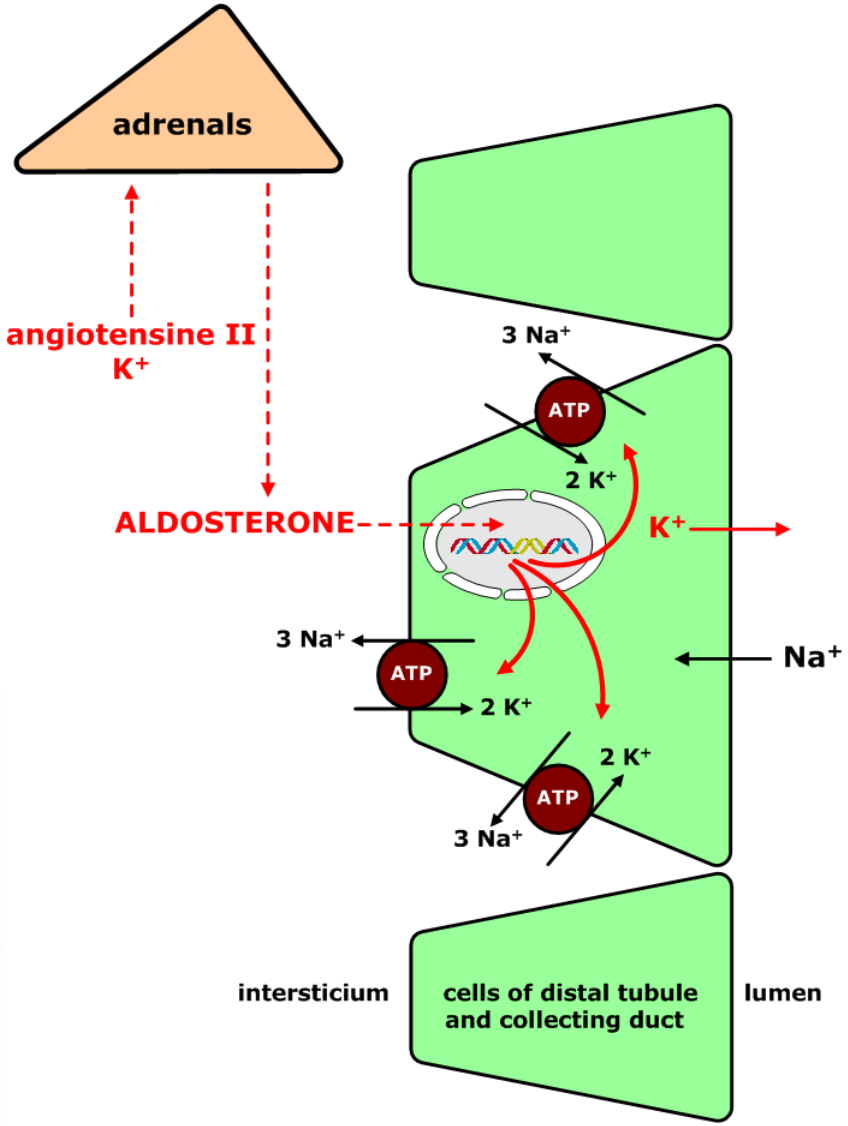
Mineralocorticoid regulation

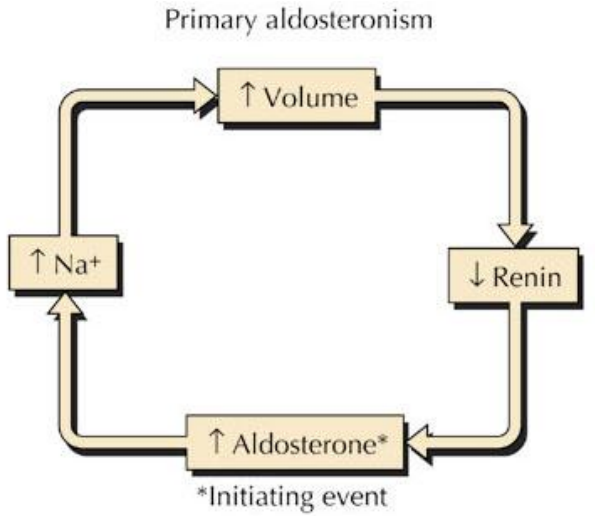


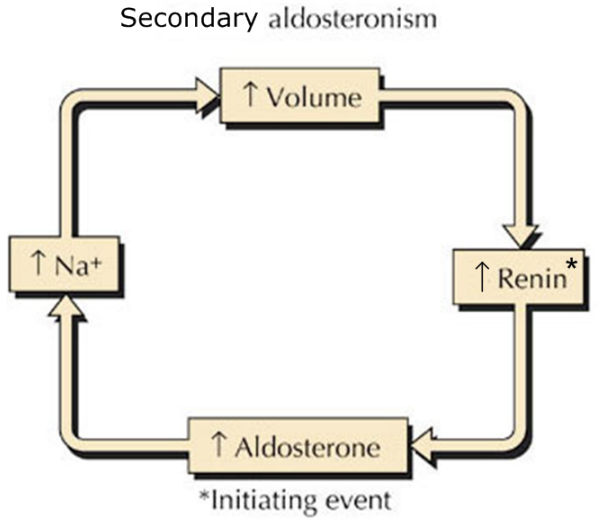




Hyperaldosteronism

- 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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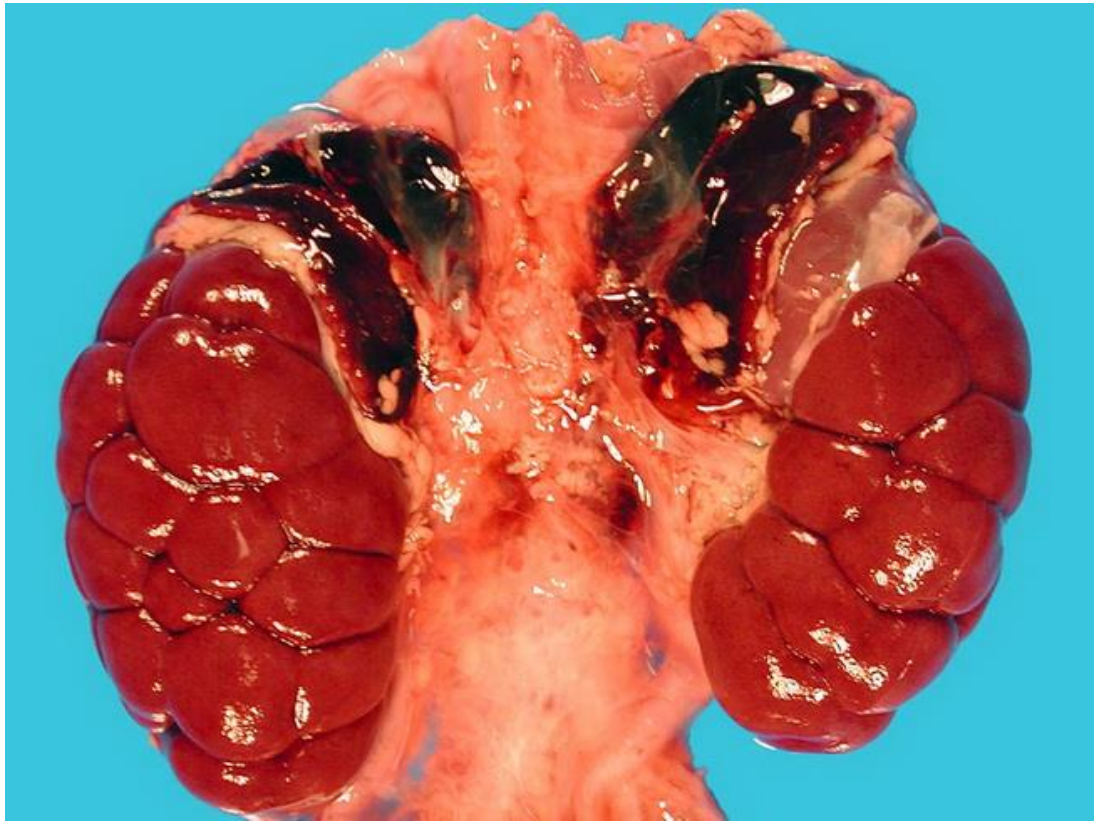
Adrenocortical insufficiency - etiology

- 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 hemorrhage into the adrenal gland, more often bilateral, caused by meningococcal 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, diarrhoea or constipation (↑Ca)
  - vomiting (hypoglycemia)
  - abdominal pain (lymphocytosis)
  - weight loss
  - hyperpigmentation (POMC → MSH → melanocytes)



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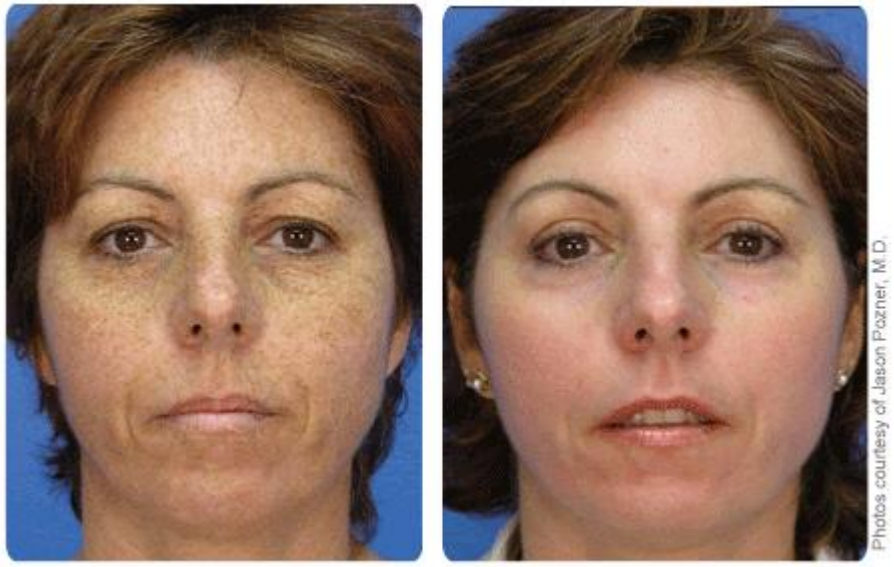
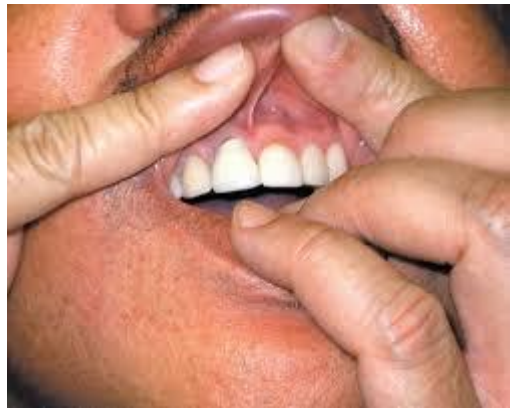
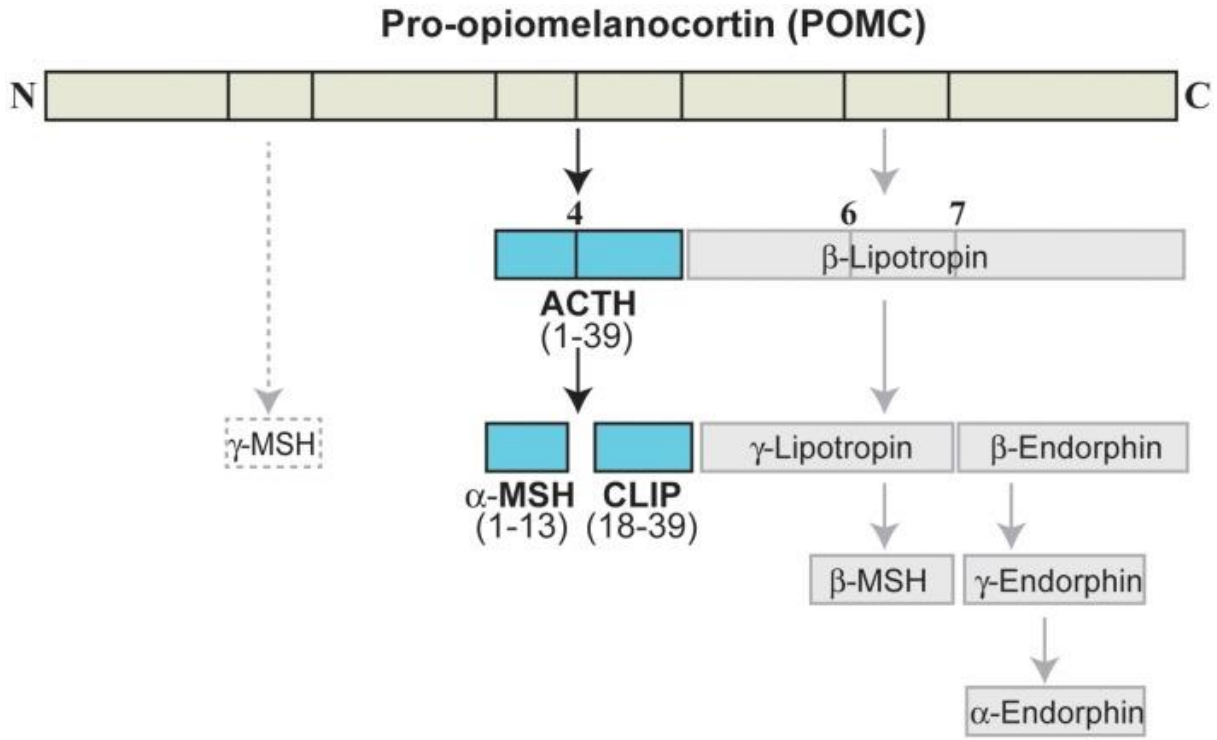
Addison's disease







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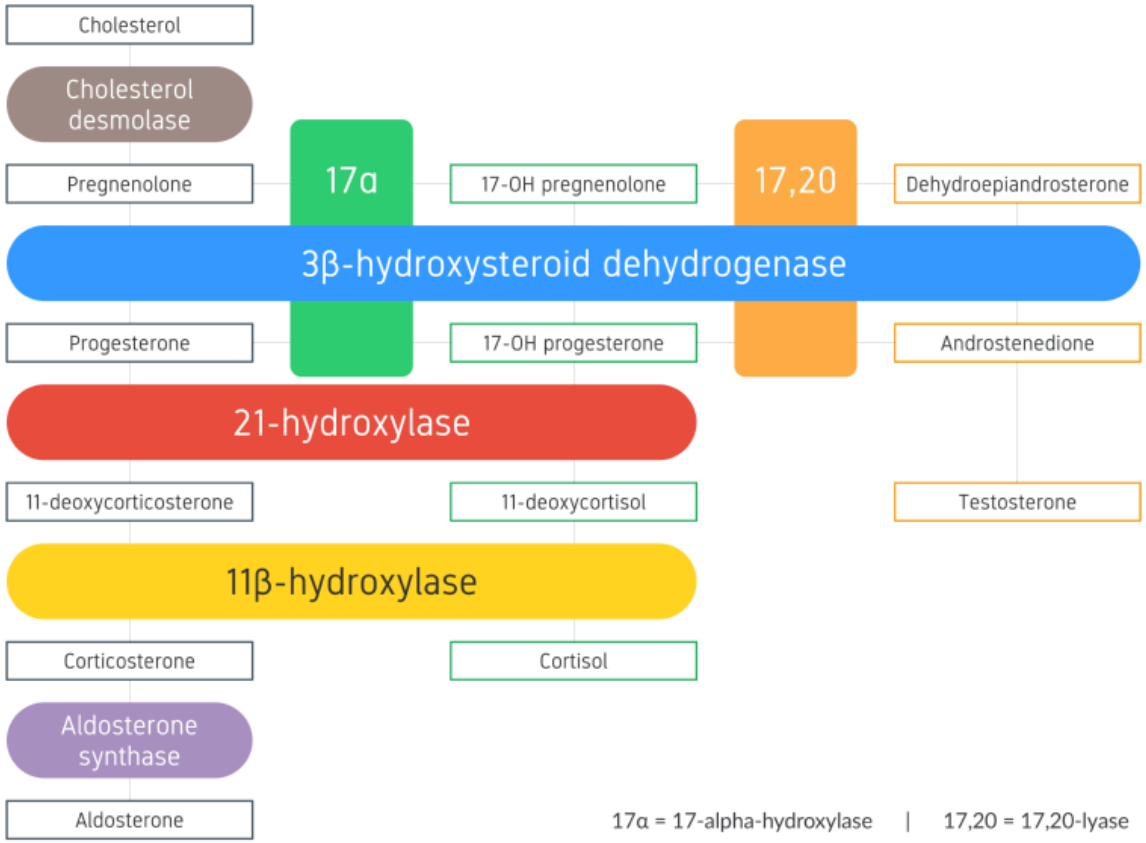
Congenital adrenal hyperplasia (CAH)



- 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 virilisation), 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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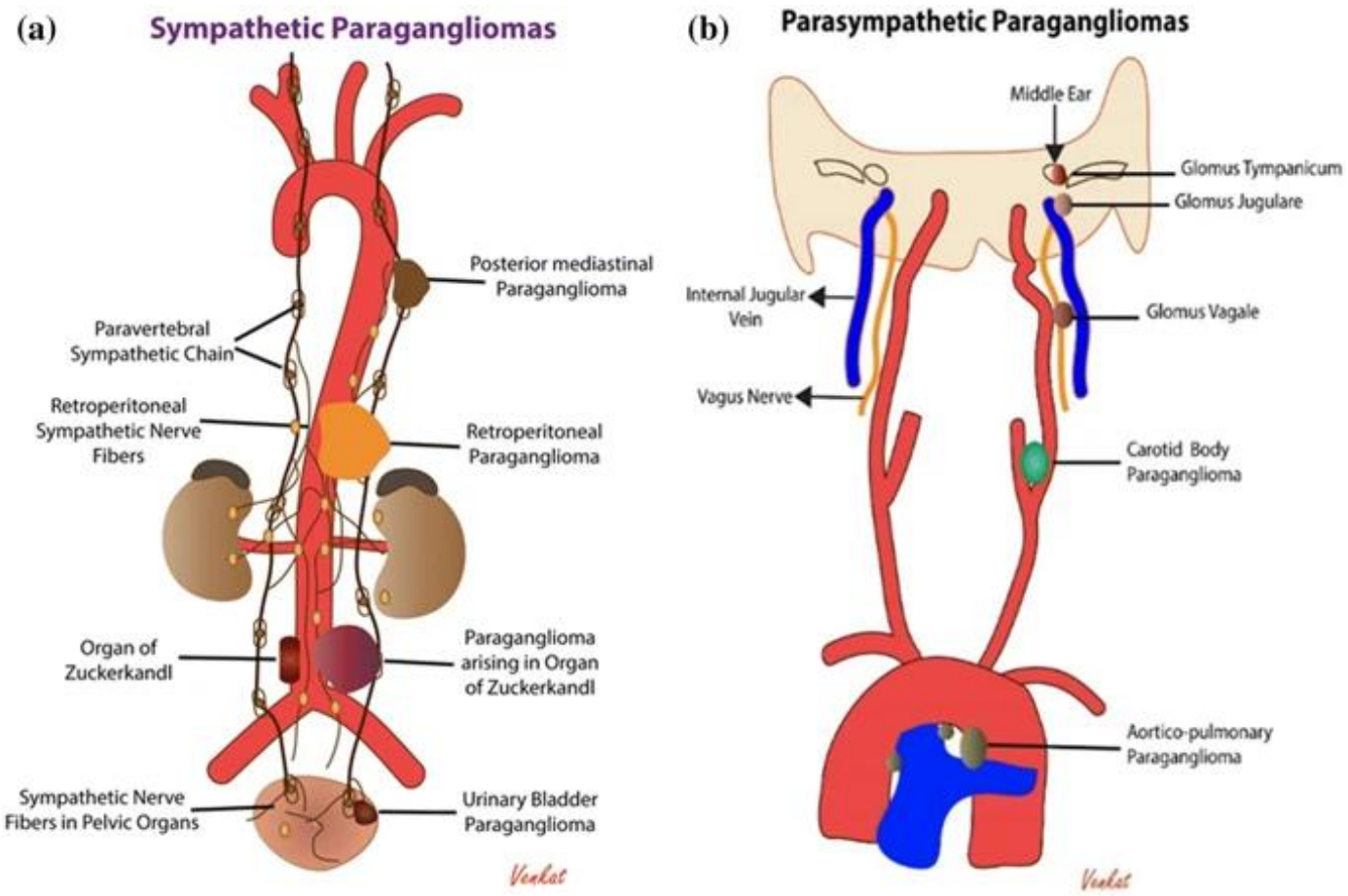
Adrenal medulla



- 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 pheochromocytomas
- paragangliomas may be benign or malignant cancer

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THE THYROID

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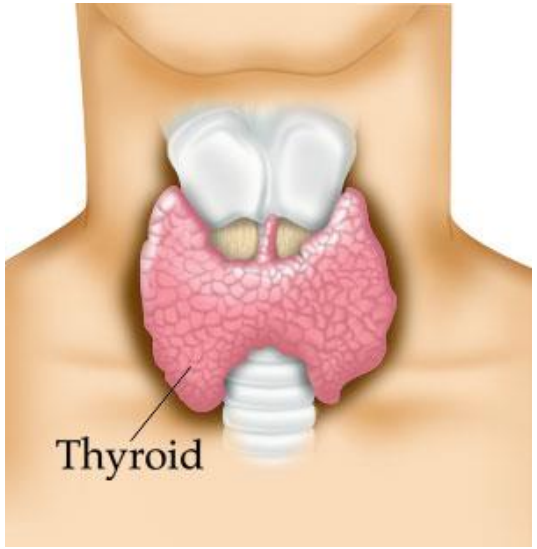
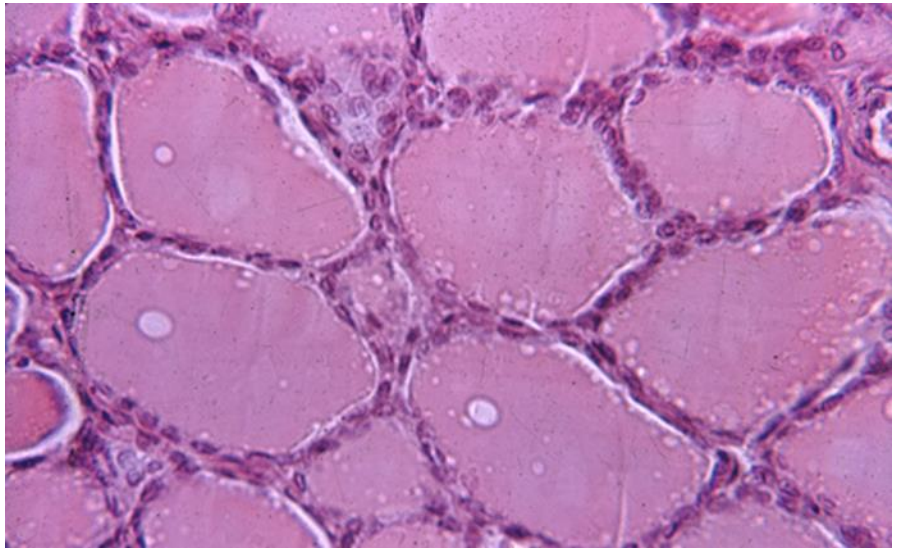
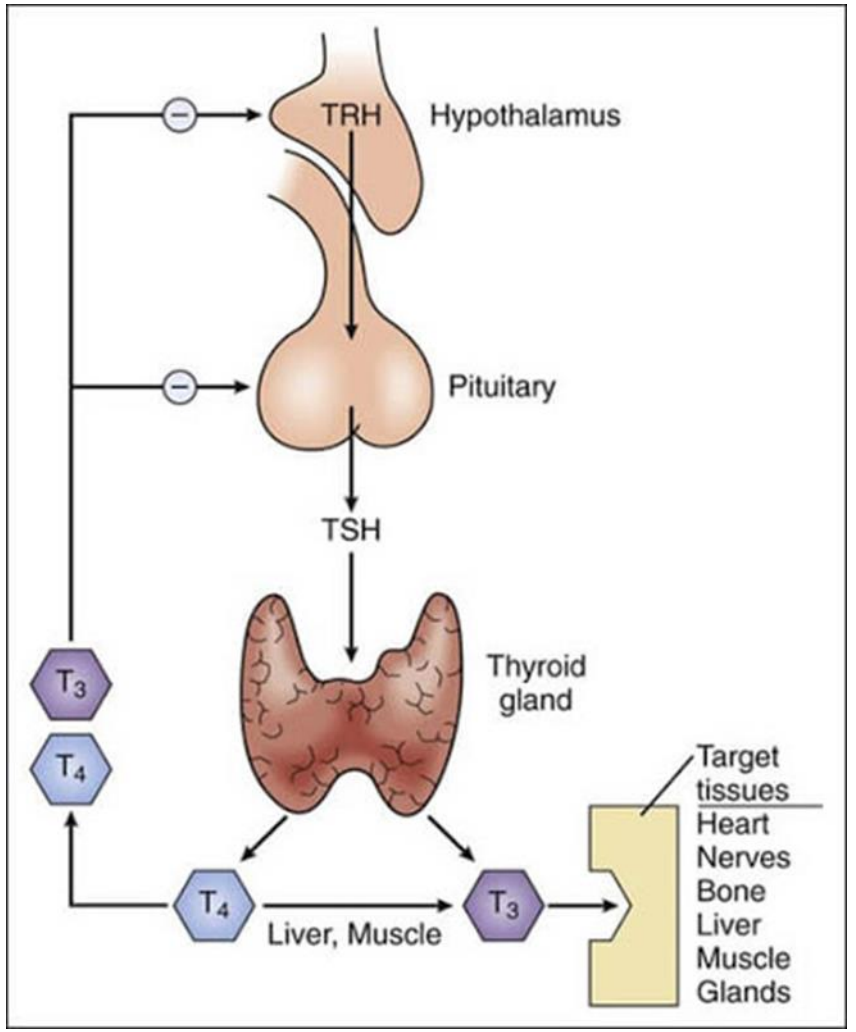
Anatomy and histology of the thyroid, HPT axis







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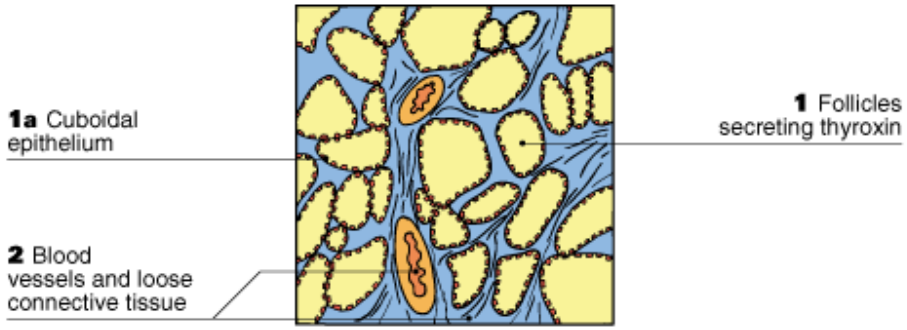
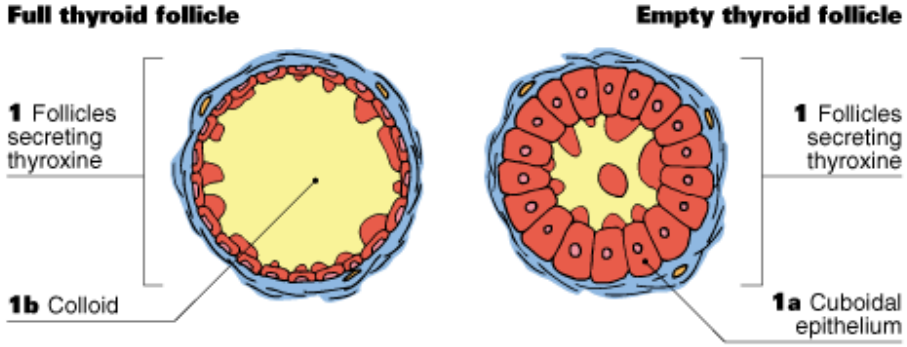
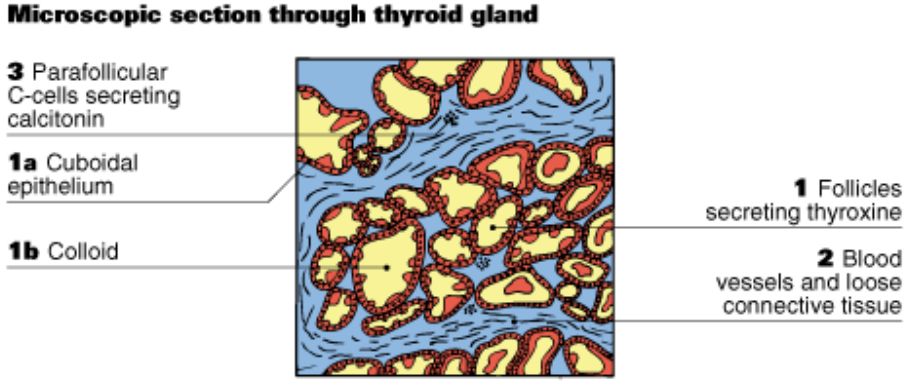
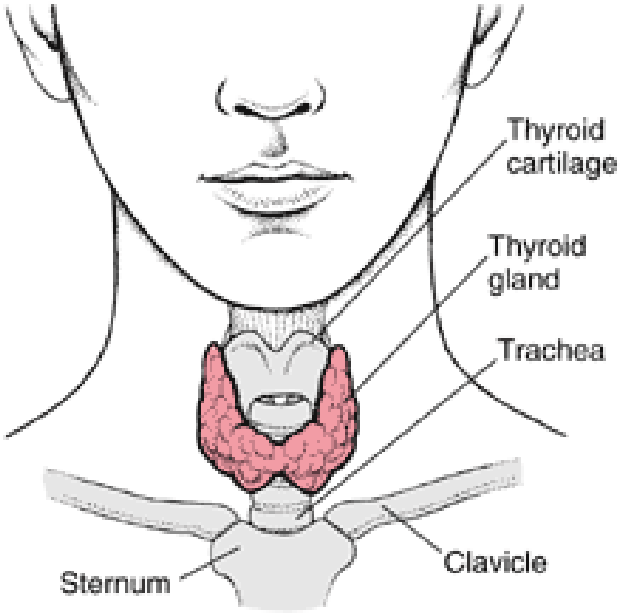
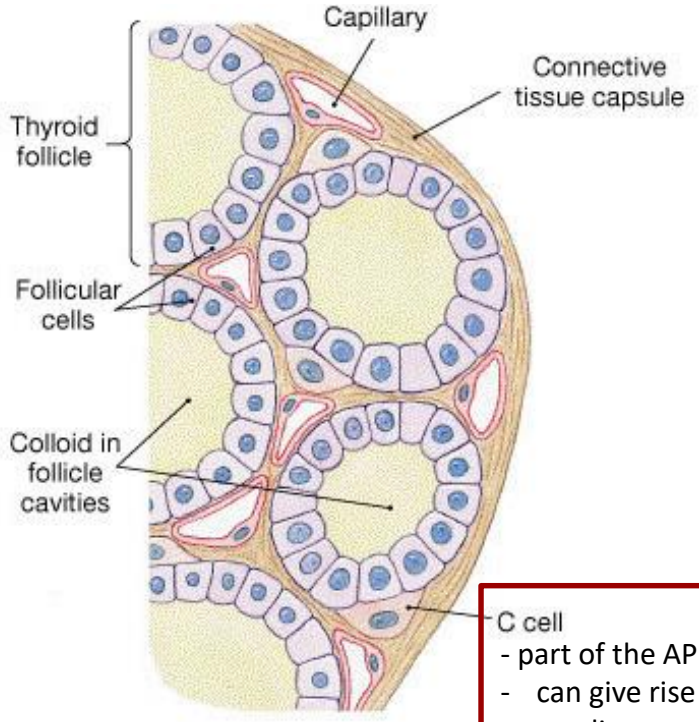
hysiology of thyroid gland











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

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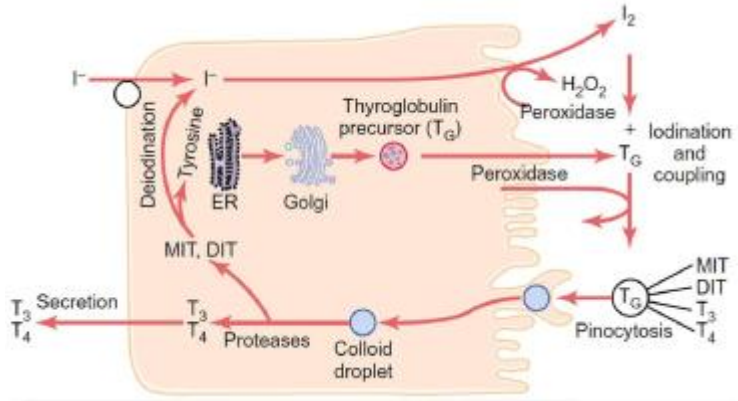
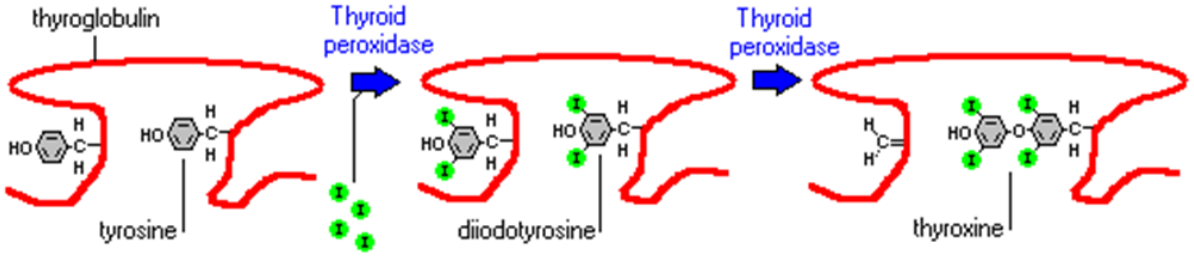
Hormone synthesis by follicular cell





- upon nutritional iodide intake in 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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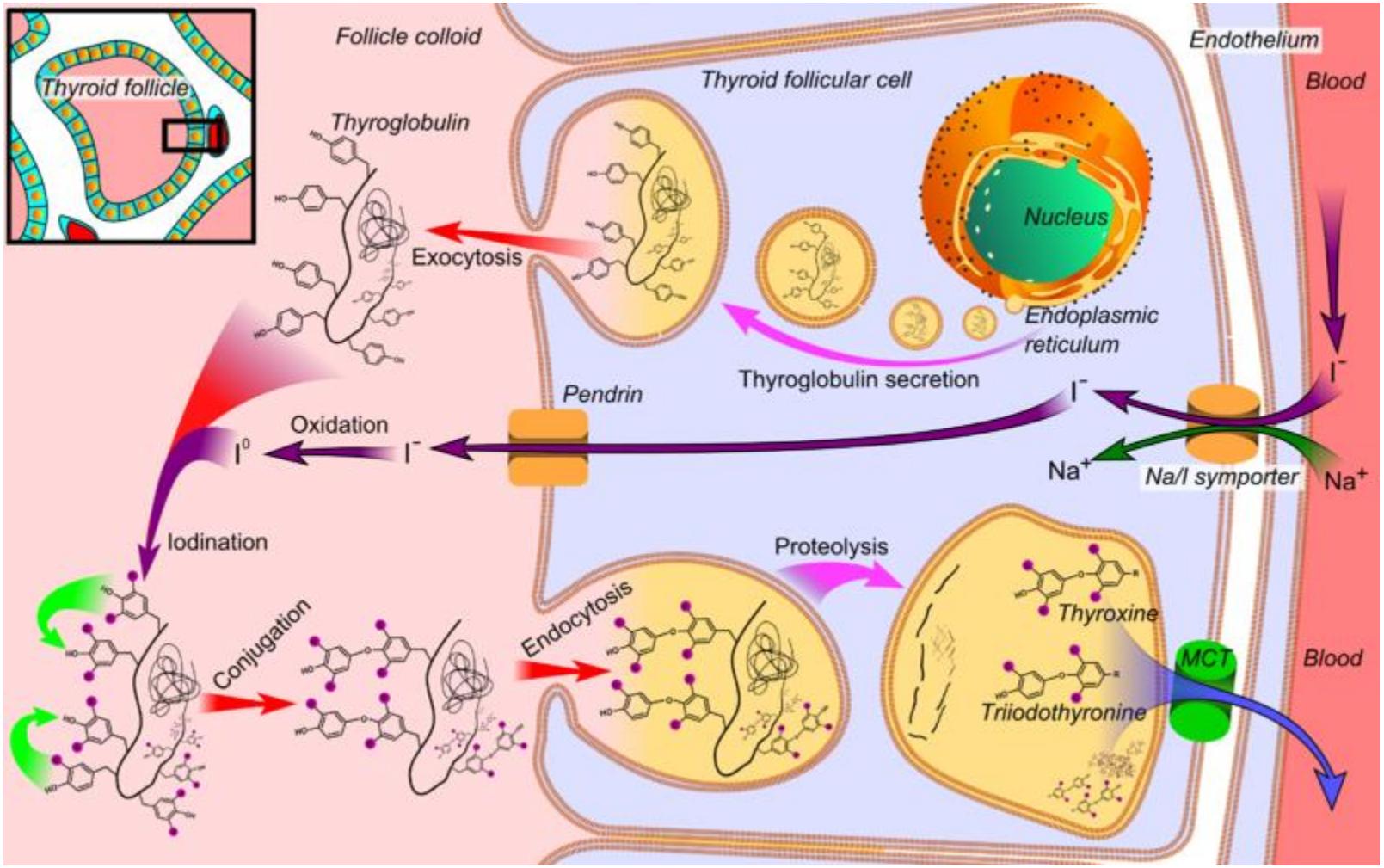
Hormone synthesis by follicular cell - detail



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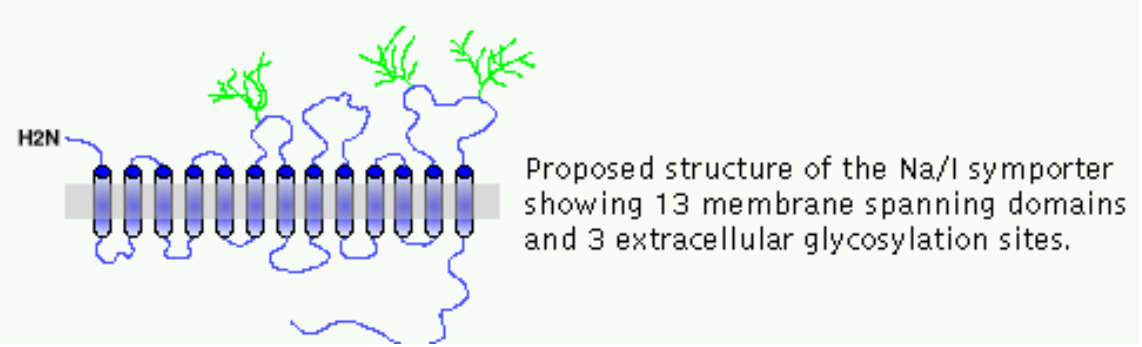
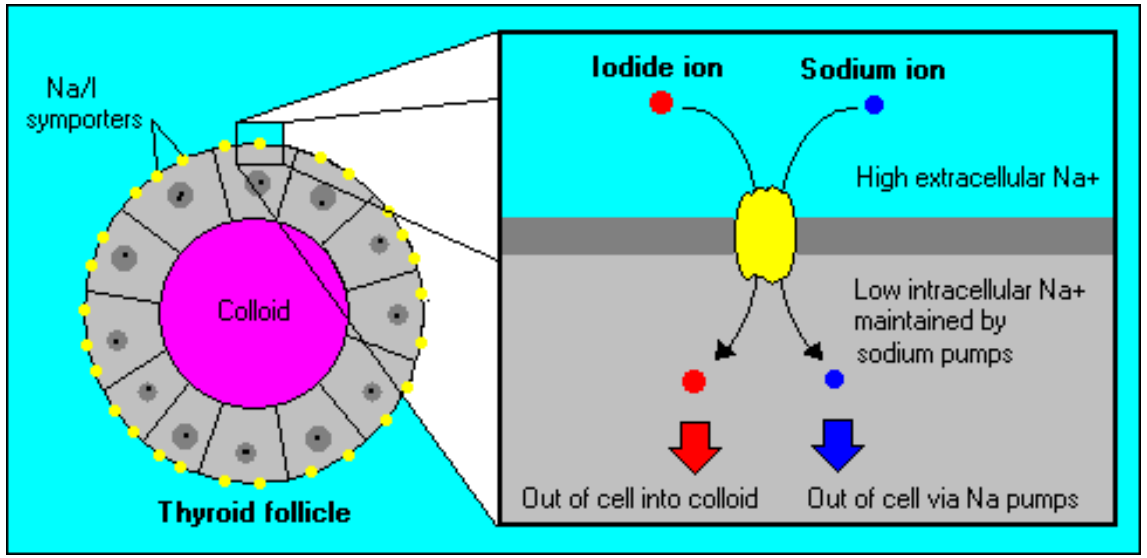
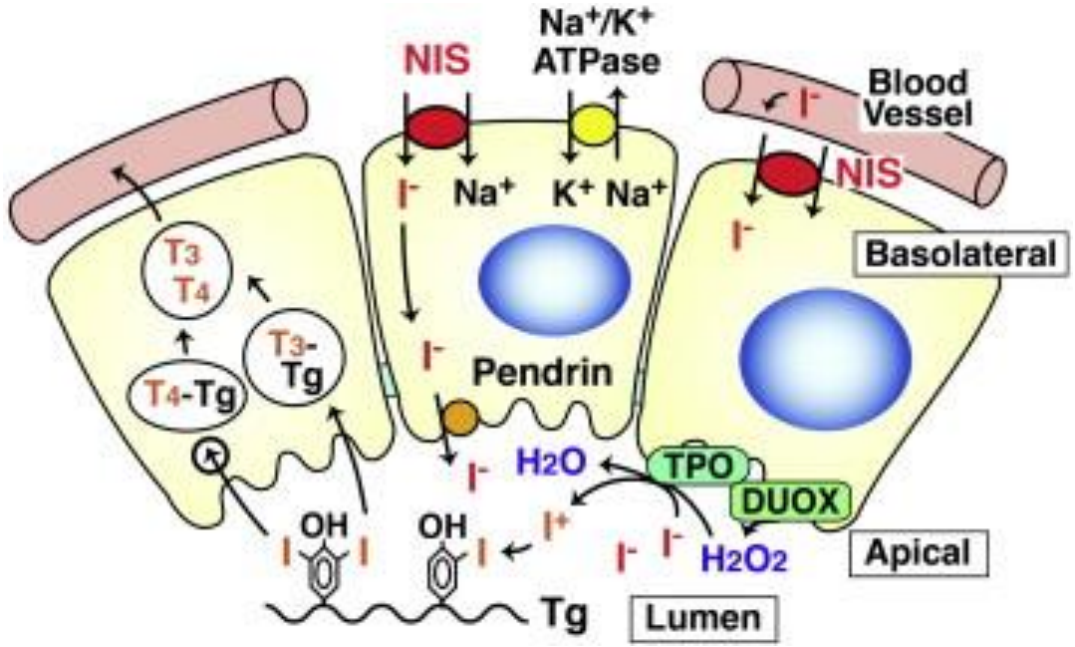
The sodium-iodide symporter



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





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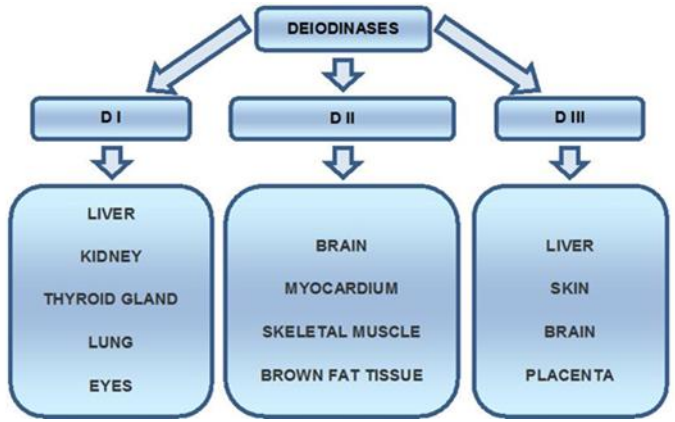
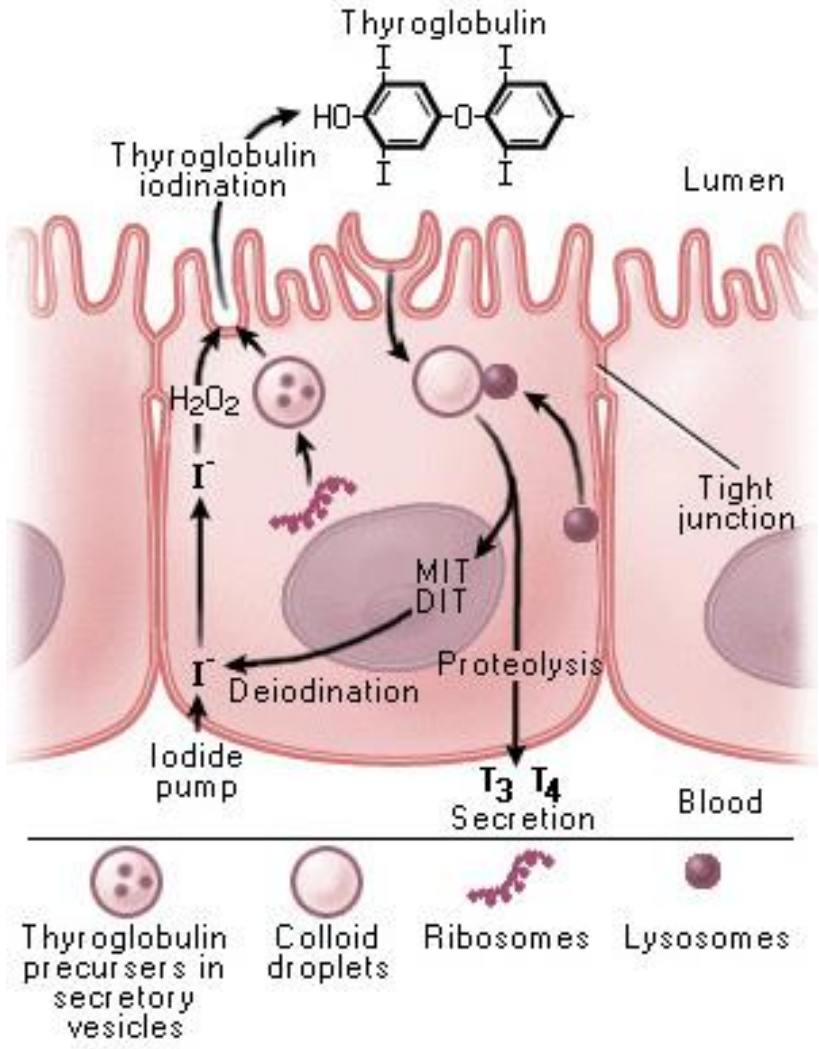
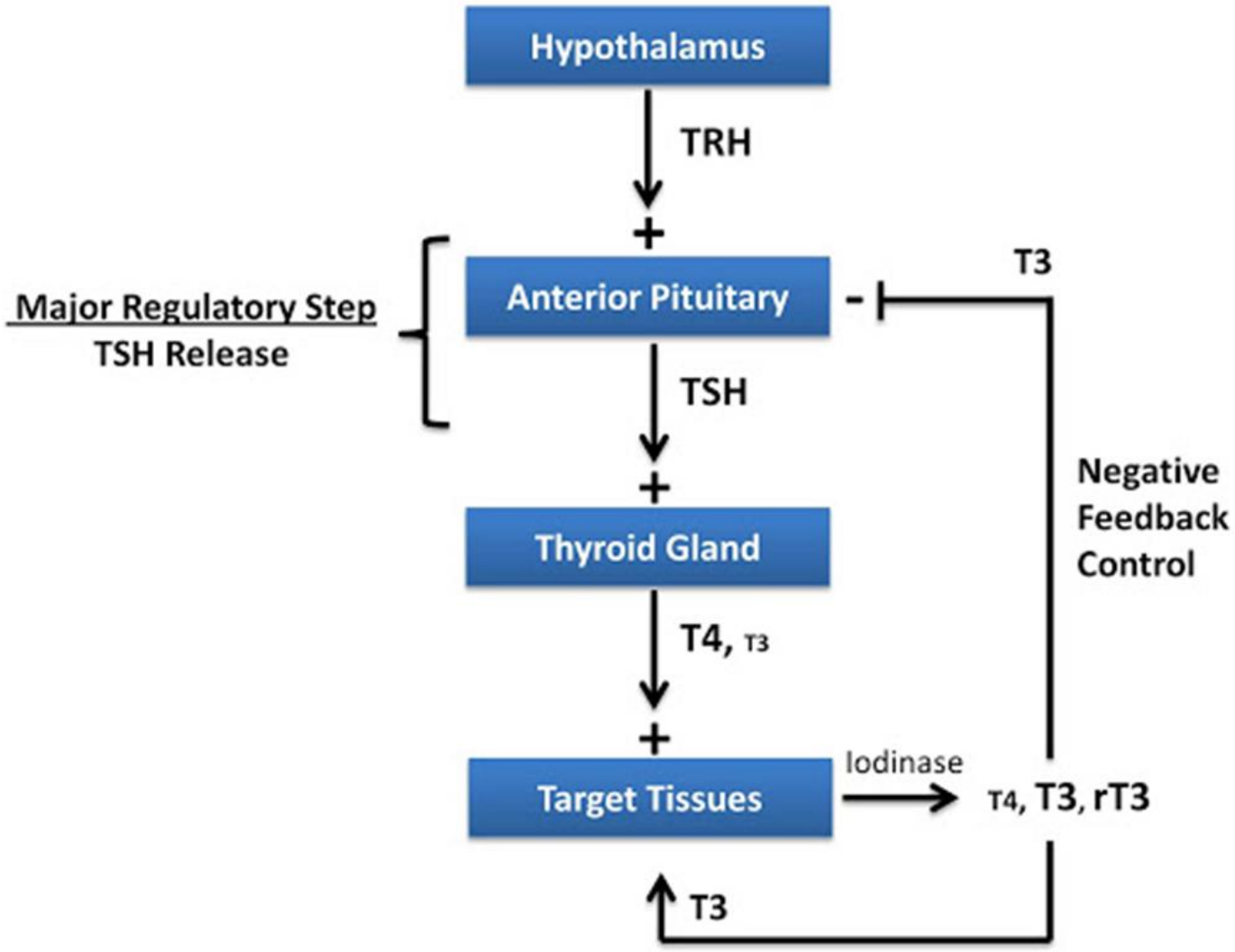
Secretion of thyroid hormones

- 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, …)

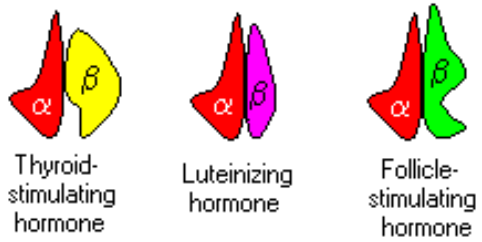




Control of the T3/T4 production – HPT axis



- 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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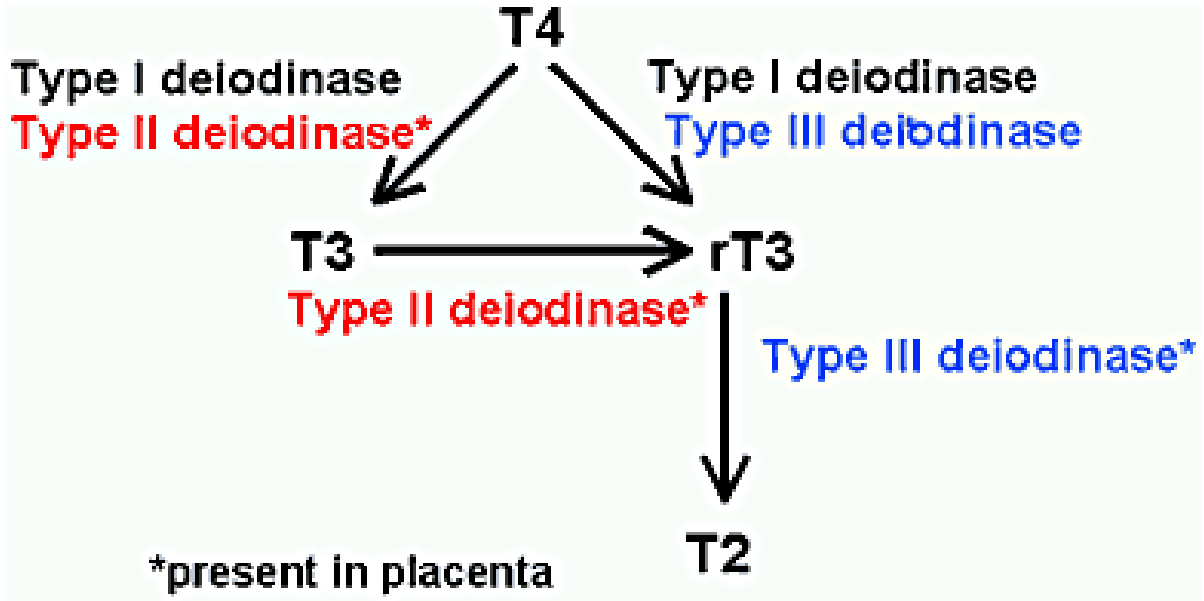
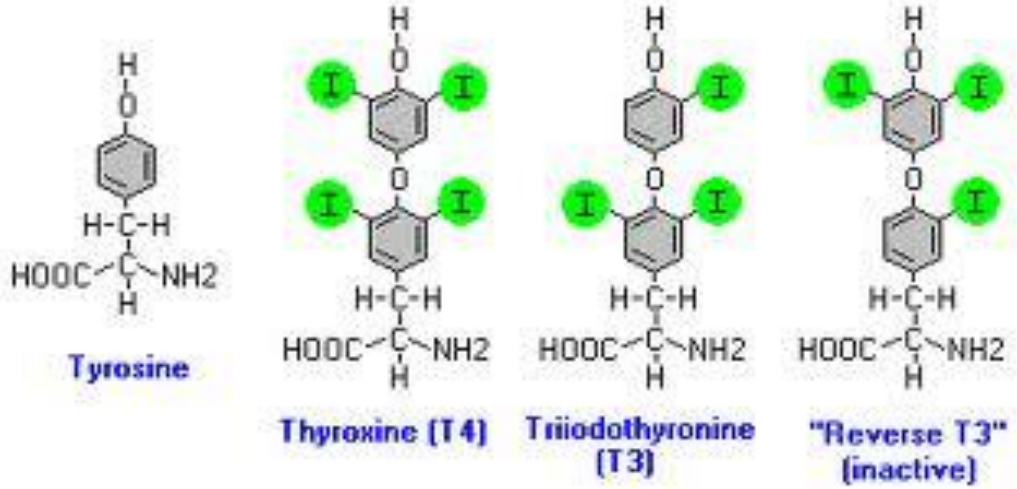
Peripheral modulation of T4 and T3 levels

- 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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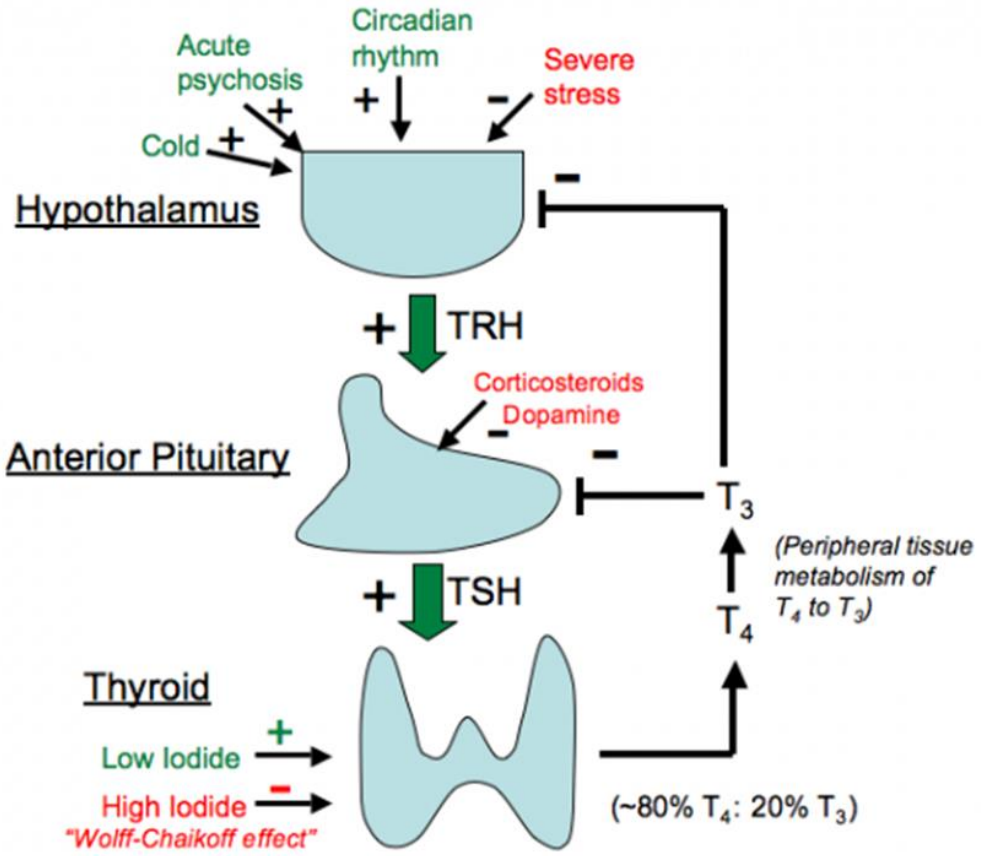
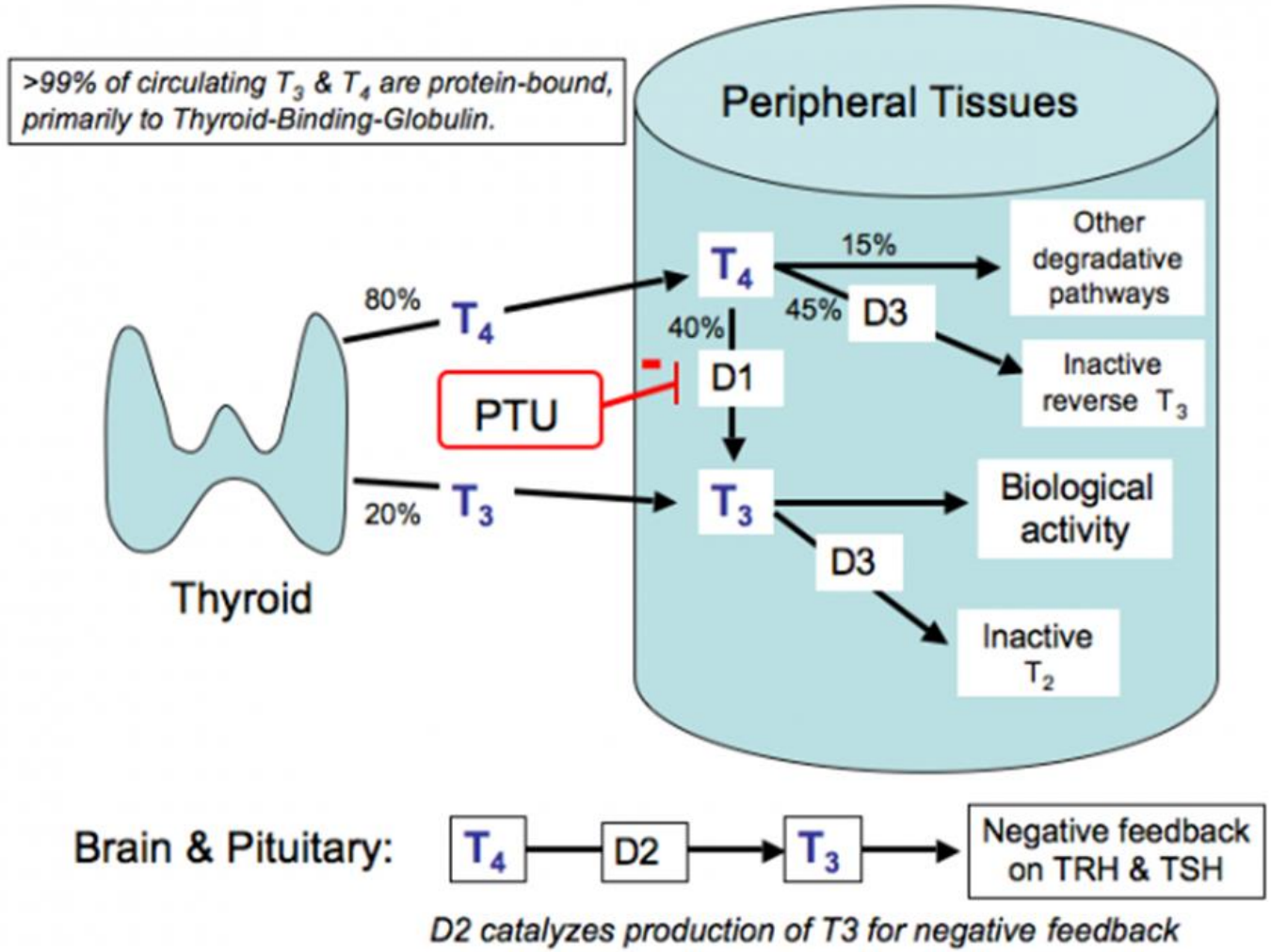
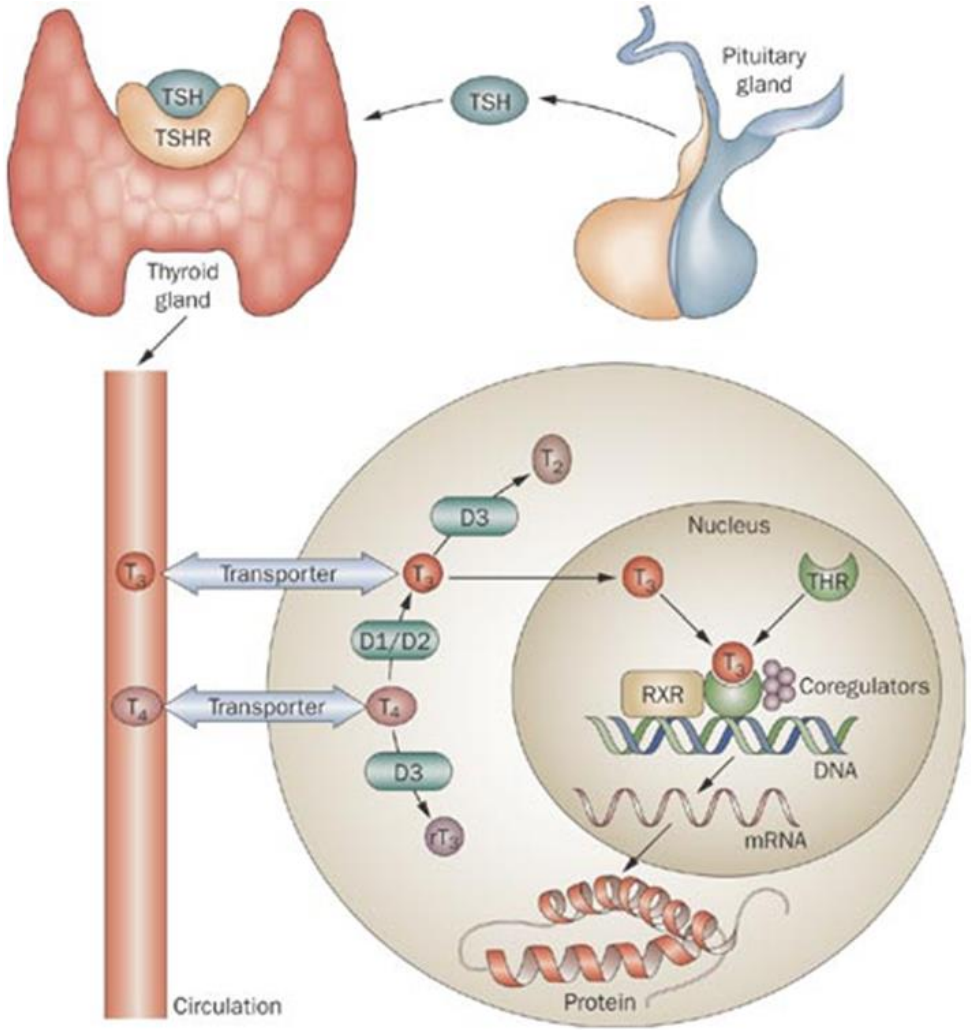
Quantitatively





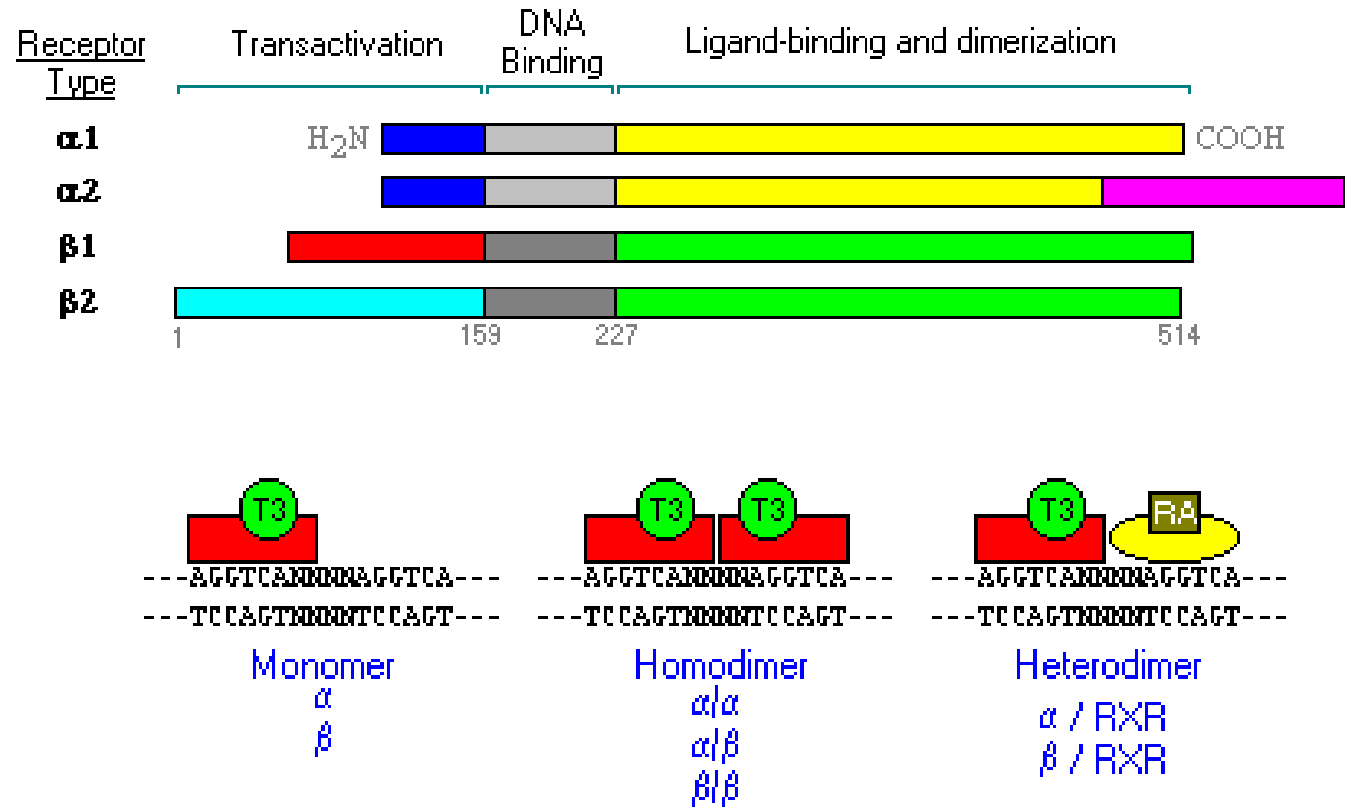
Molecular basis of T3/T4 action

- (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

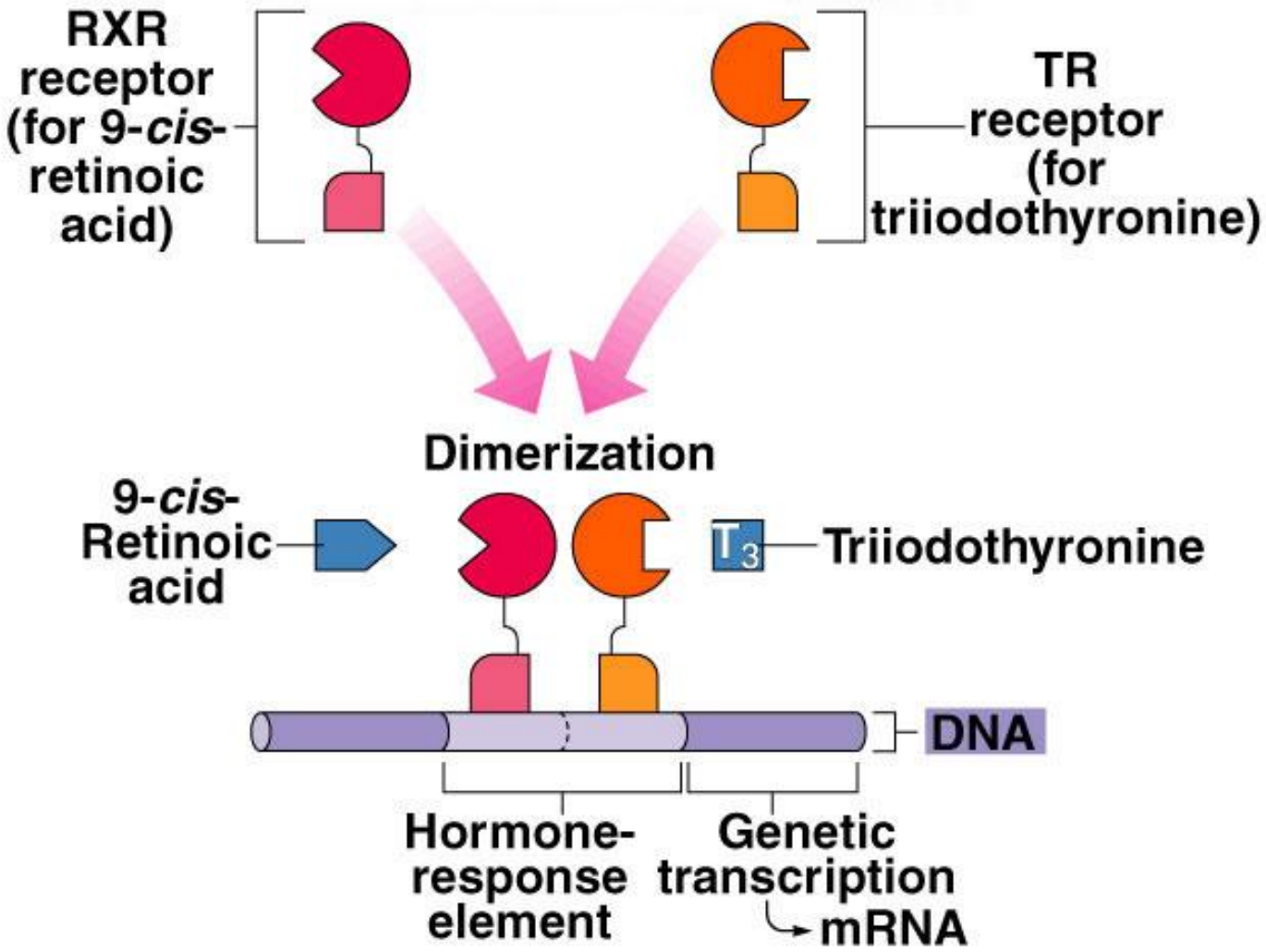


Thyroid hormone receptors

- 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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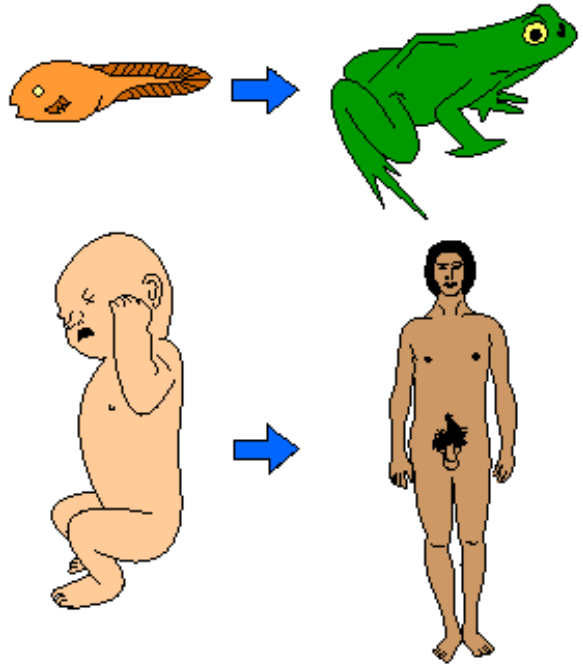
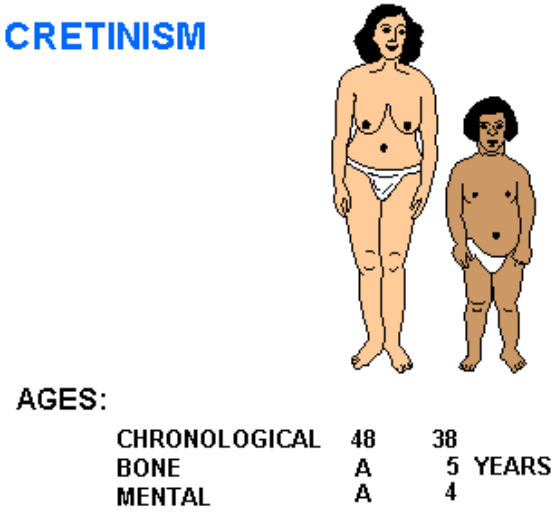
Physiologic effects of T3/T4

- (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
- (3) reproduction





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Mexican axolotl (*Ambystoma mexicanum*) – T3 effects and regeneration

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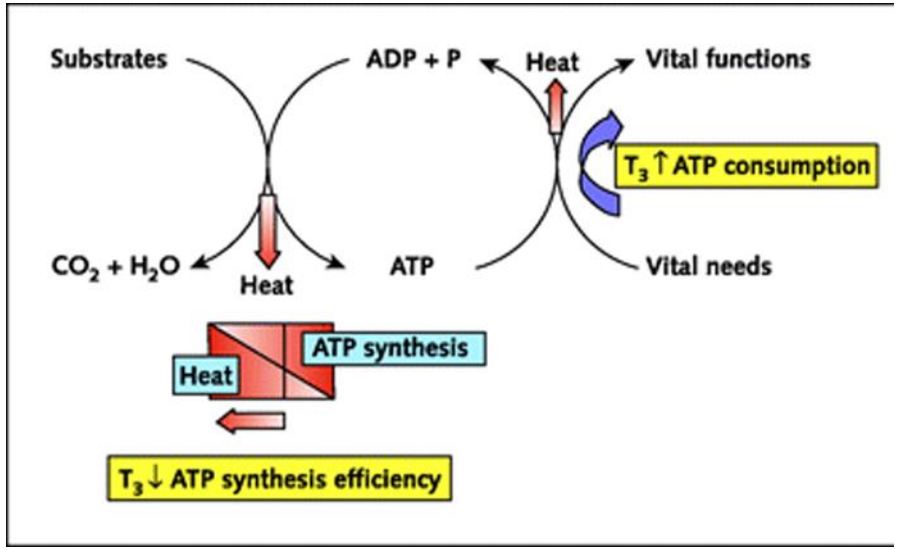
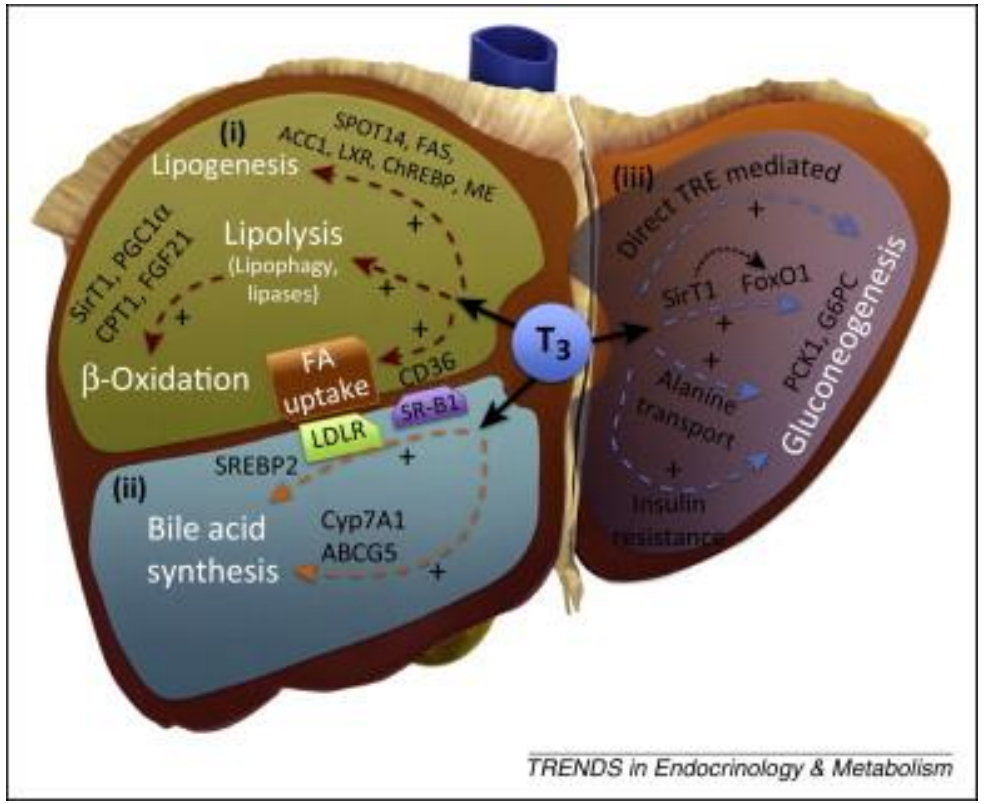
Physiologic effects of T3/T4

- (4) 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
      - **hypothyroidism – combined dyslipidaemia (hypertriglyceridemia, hypercholesterolemia), NAFLD**
  - 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
      - **hyperthyroidism – worsening of DM compensation or T2DM**
  - protein metabolism
- (5) other effects
  - cardiovascular, CNS, immune systém, …





DISEASES OF THE THYROID GLAND

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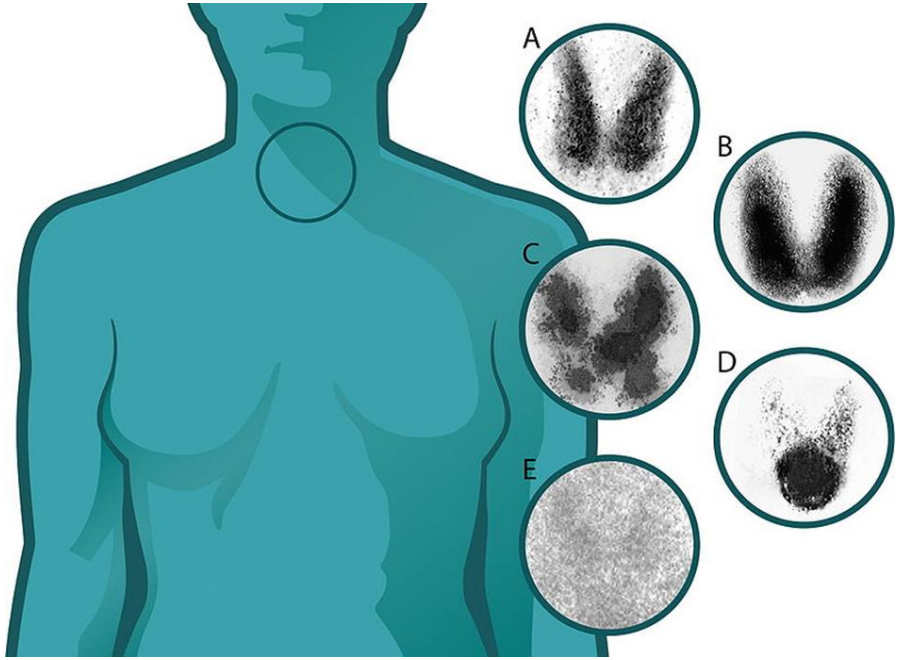
Thyroid function assessment

- morning urine - ioduria
- 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



- 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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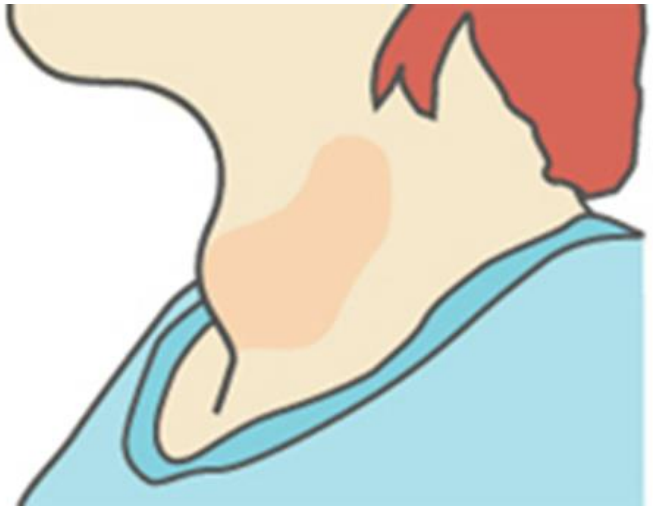
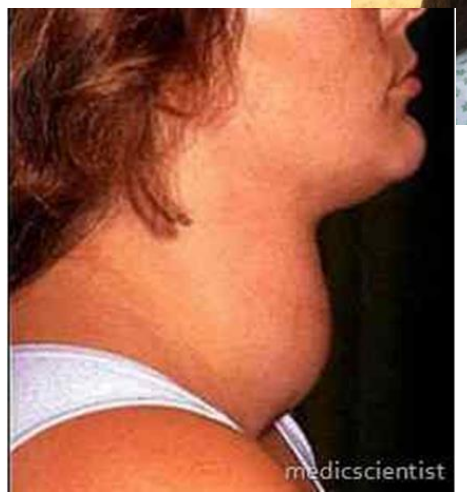
Goiter

- 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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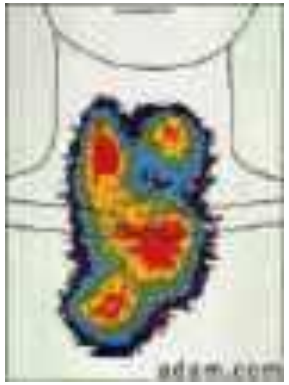
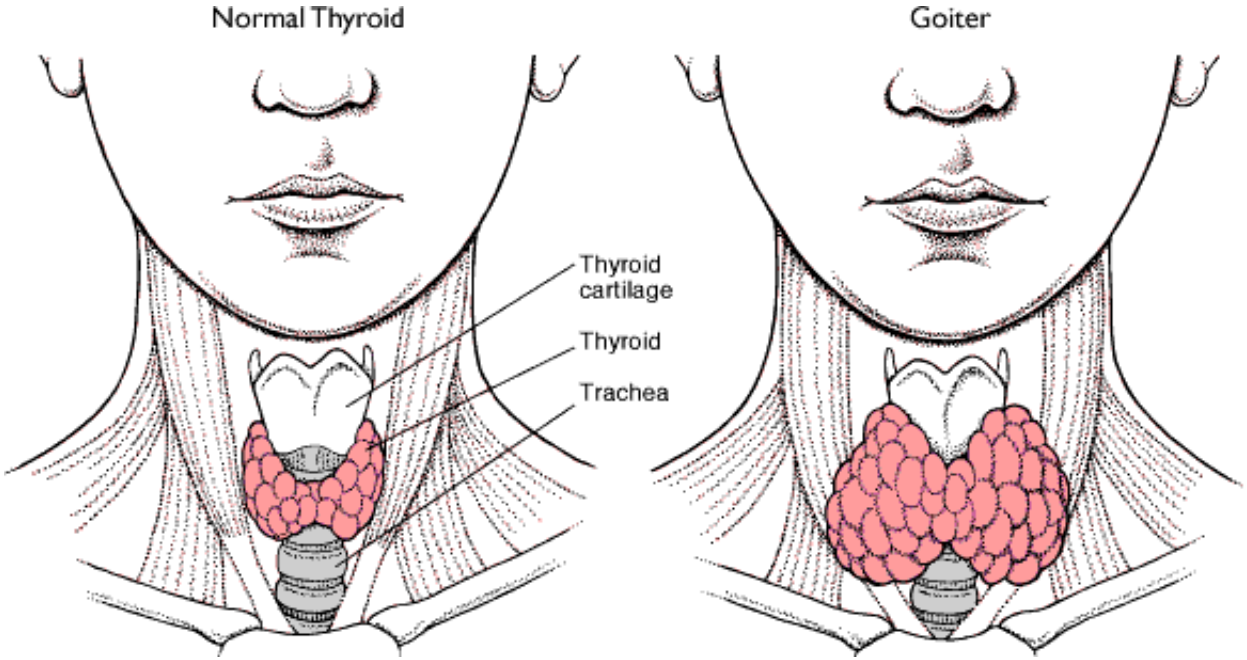
Types of goiter





- 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

- remote, inland, mountain regions 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
    - South America – Andes
    - Central Africa
- iodine prophylaxis !!!

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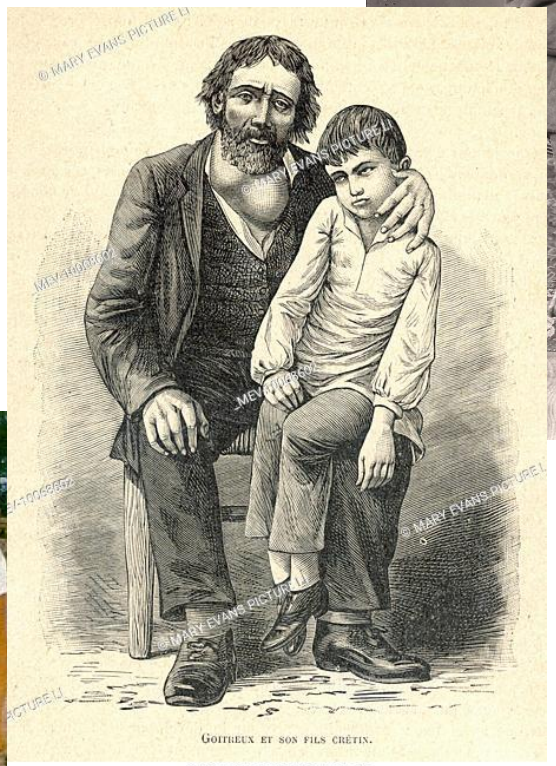
Cretinism

- develops due to pre- and/or postnatal iodine and thus T3/T4 deficiency
  - (A) neurological form
    - mental retardation, deafness, spastic palsy
      - prenatal deficiency of T3 (critical esp. between 12th – 18th week of gestation)
  - (B) myxoedema form
    - grave growth retardation, face malformation, myxoedema, hypogonadisms, sterility
      - postnatal deficiency of T3
      - other etiological factors considered incl. toxins



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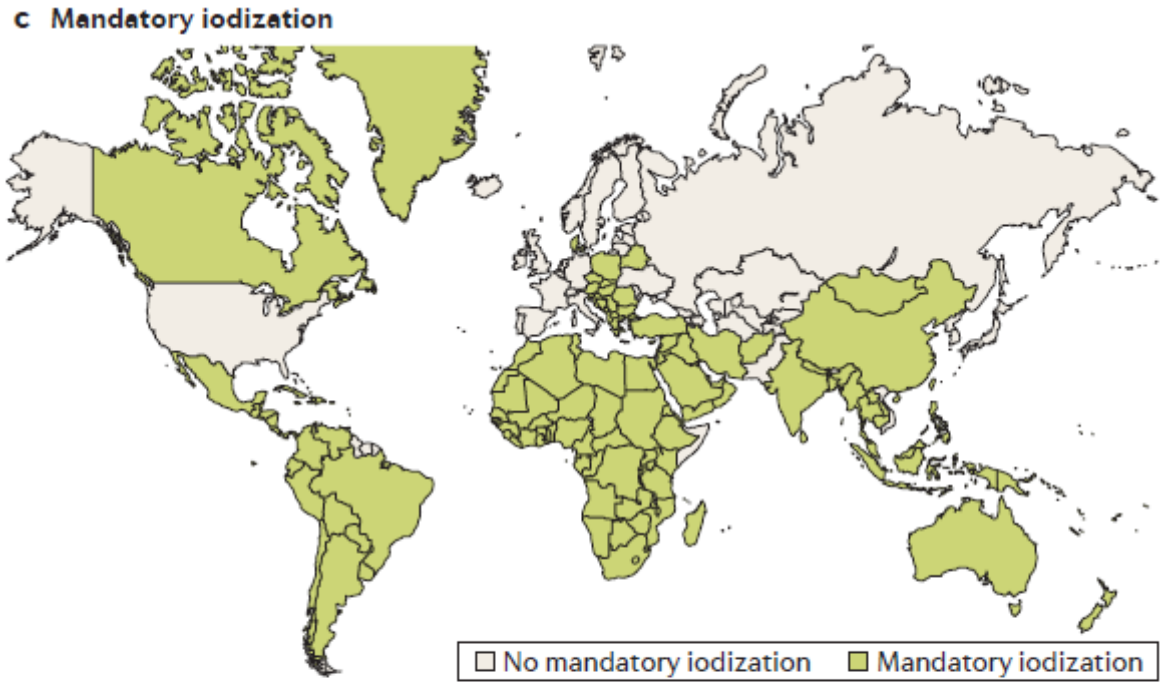
Global data on iodine status



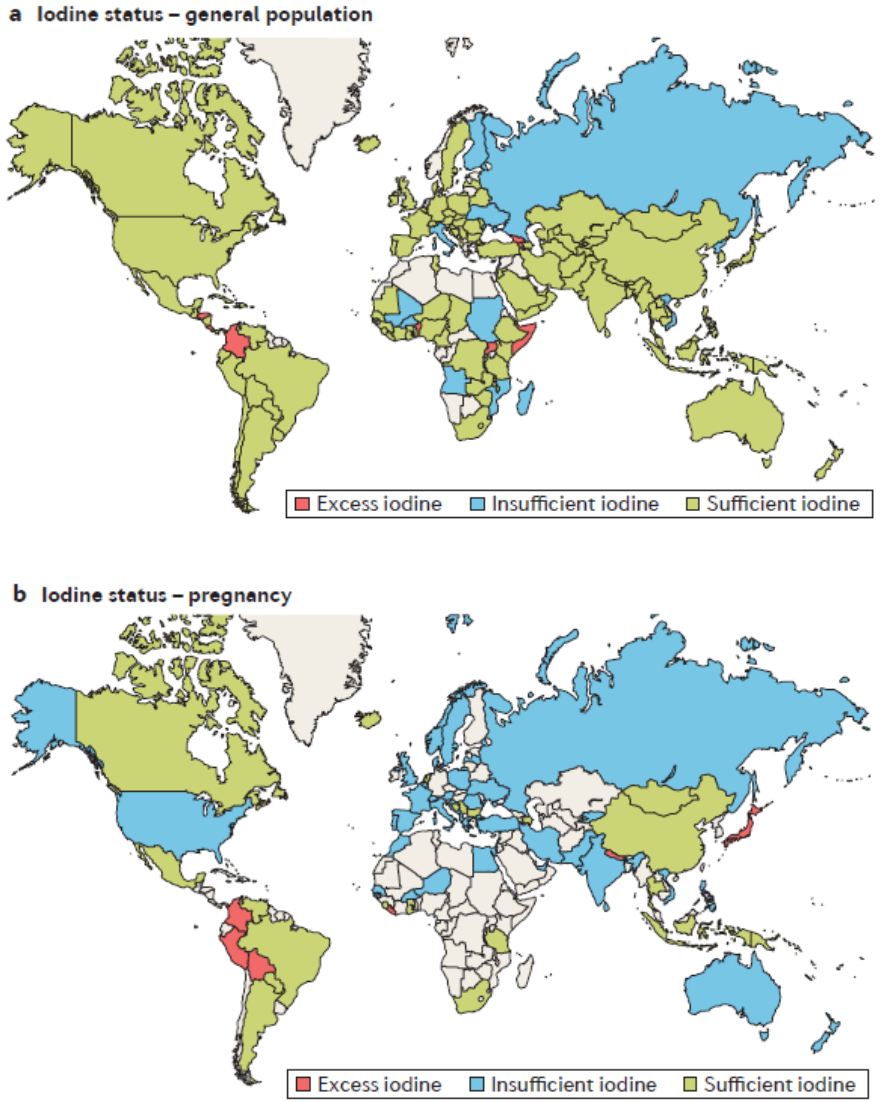


Fig. 3 | **Global iodine status and mandatory salt iodization. a** | World map showing global iodine status from general population studies based on the latest data (2017) from the Iodine Global Network[169]. Iodine status is defined as insufficient, sufficient or excessive. Countries in white represent no data available. **b** | World map showing global iodine status of pregnant women from studies based on the latest data (2017) from the Iodine Global Network[169]. **c** | World map showing countries that have mandatory salt iodization. This figure was created using Tableau software version 10.3.

*Taylor, P., Albrecht, D., Scholz, A. et al. Global epidemiology of hyperthyroidism and hypothyroidism. Nat Rev Endocrinol **14,** 301–316 (2018)*

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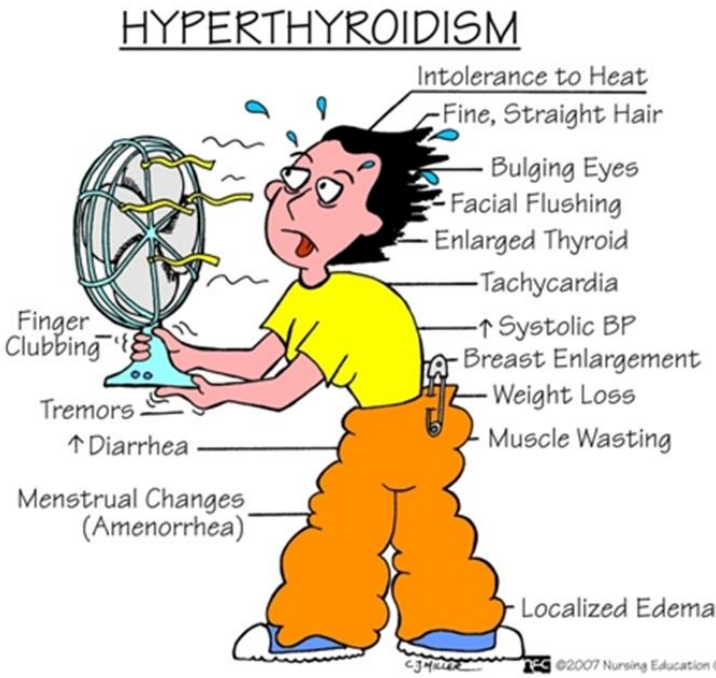
Thyroid endocrinopathies – functional aspects

- Hyperthyroidism (thyrotoxicosis)
  - common in iodine-replete populations
    - Graves' disease (toxic diffuse goitre)
      - younger adults
    - autoimmune
  - common in iodine-deplete populations
    - toxic multi-nodular goitre (Plummer's disease)
      - older adults
    - toxic adenoma
  - rare
    - thyroiditis
      - de Quervaine – acute (following respiratory infection, painful, self-limiting course of hyperthyroidism
      - post-partum
    - primary and/or metastatic follicular carcinoma
    - TSH-producing tumour of the pituitary
    - drug-induced
      - amiodarone, lithium, INF-γ, anti-viral

- Hypothyroidism
  - autoimmune thyroiditis (Hashimoto)
    - for both autoimmune – Graves and Hashimoto - predominance of women, middle age
  - hypothalamic or pituitary - rare
  - drug-induced
    - amiodarone, lithium, INF-γ, anti-viral



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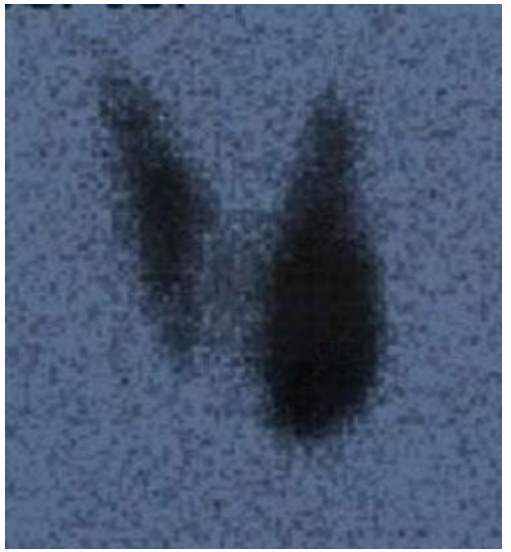
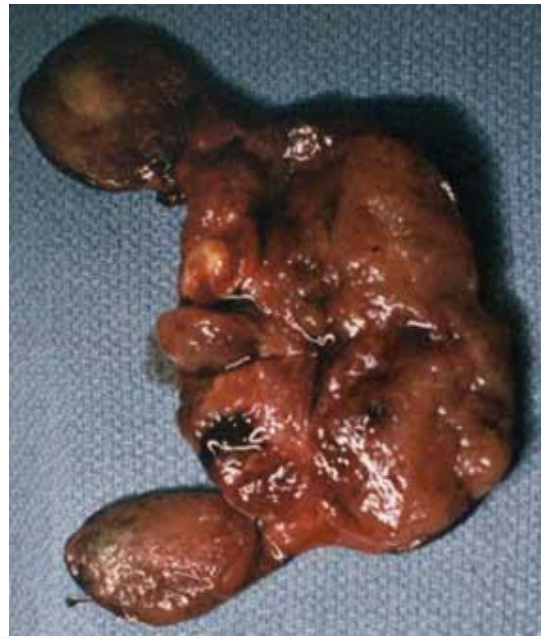
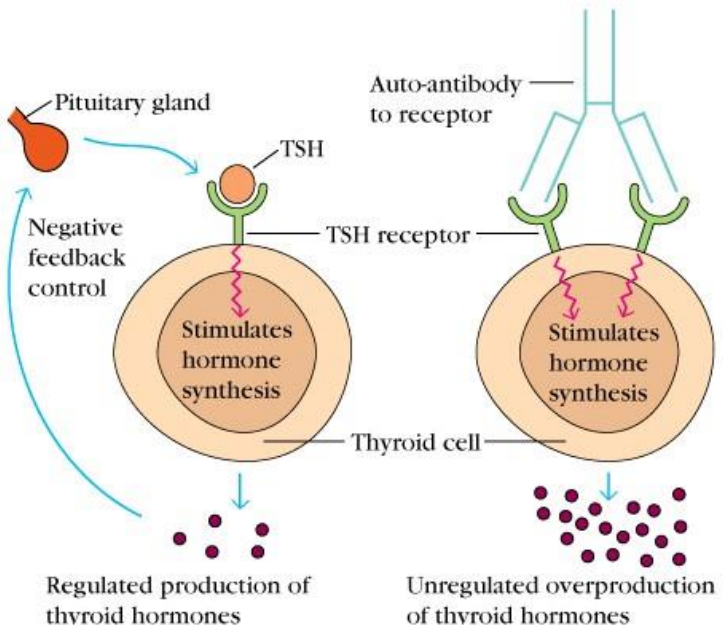
Toxic goiter

- 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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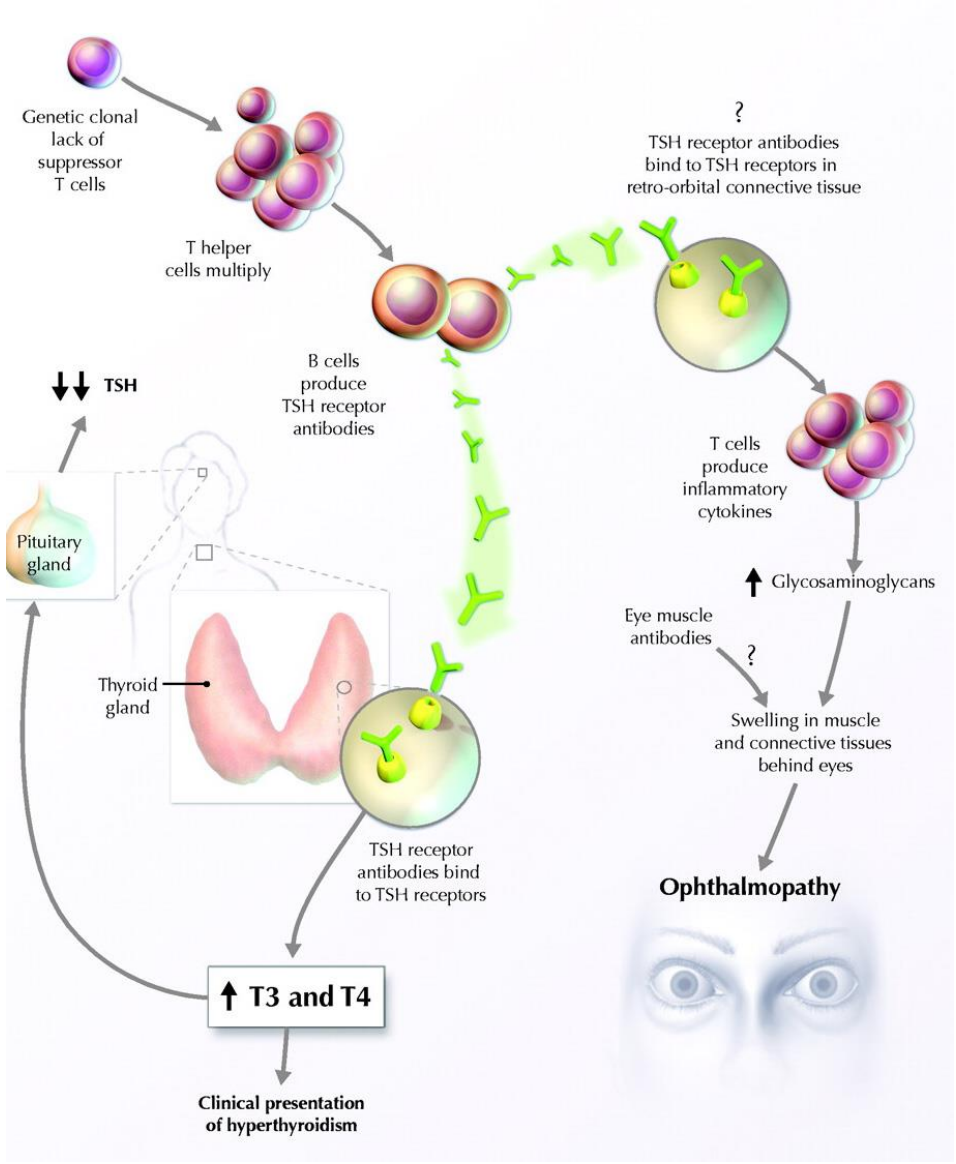
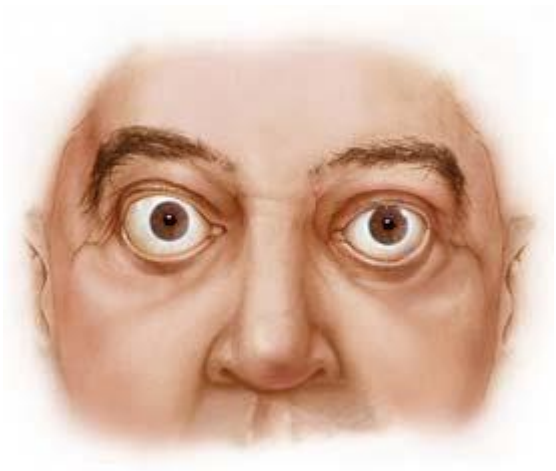
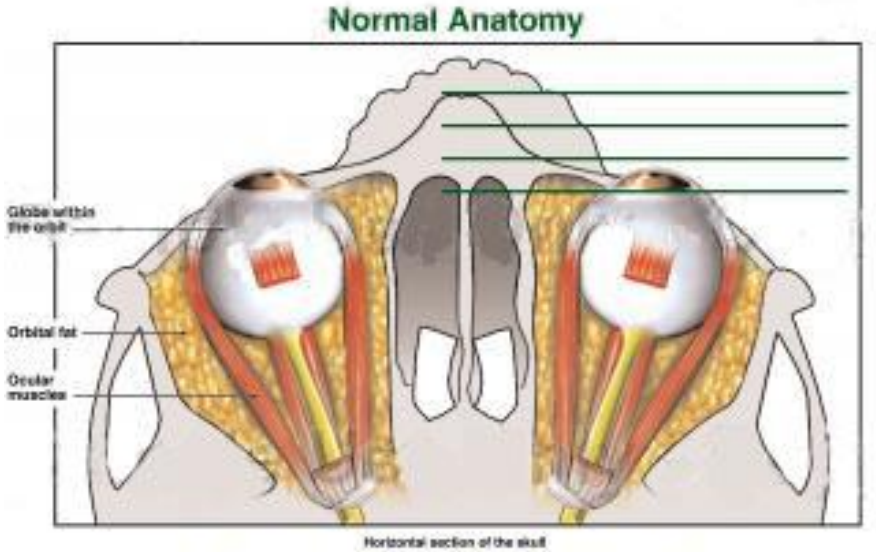
Grave's disease

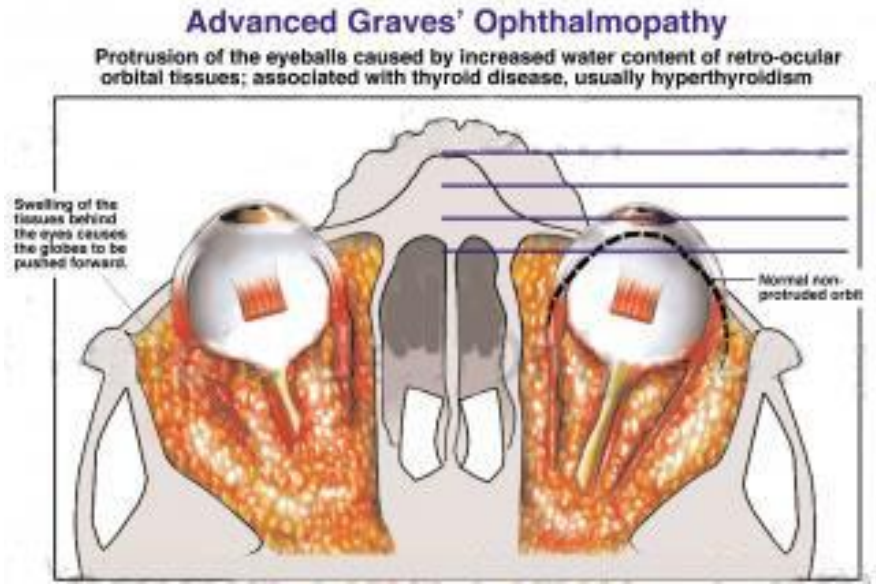
- hyperthyroidism +
- infiltrative ophthalmopathy
  - ~1/2 od the cases, independent on hyperthyroidism
  - involves periorbital connective tissue, ocular muscles and fat
- infiltrative dermopathy
  - ~1/5 of cases
  - pretibial myxedema



Ophthalmopathy







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Hypothyroidism

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

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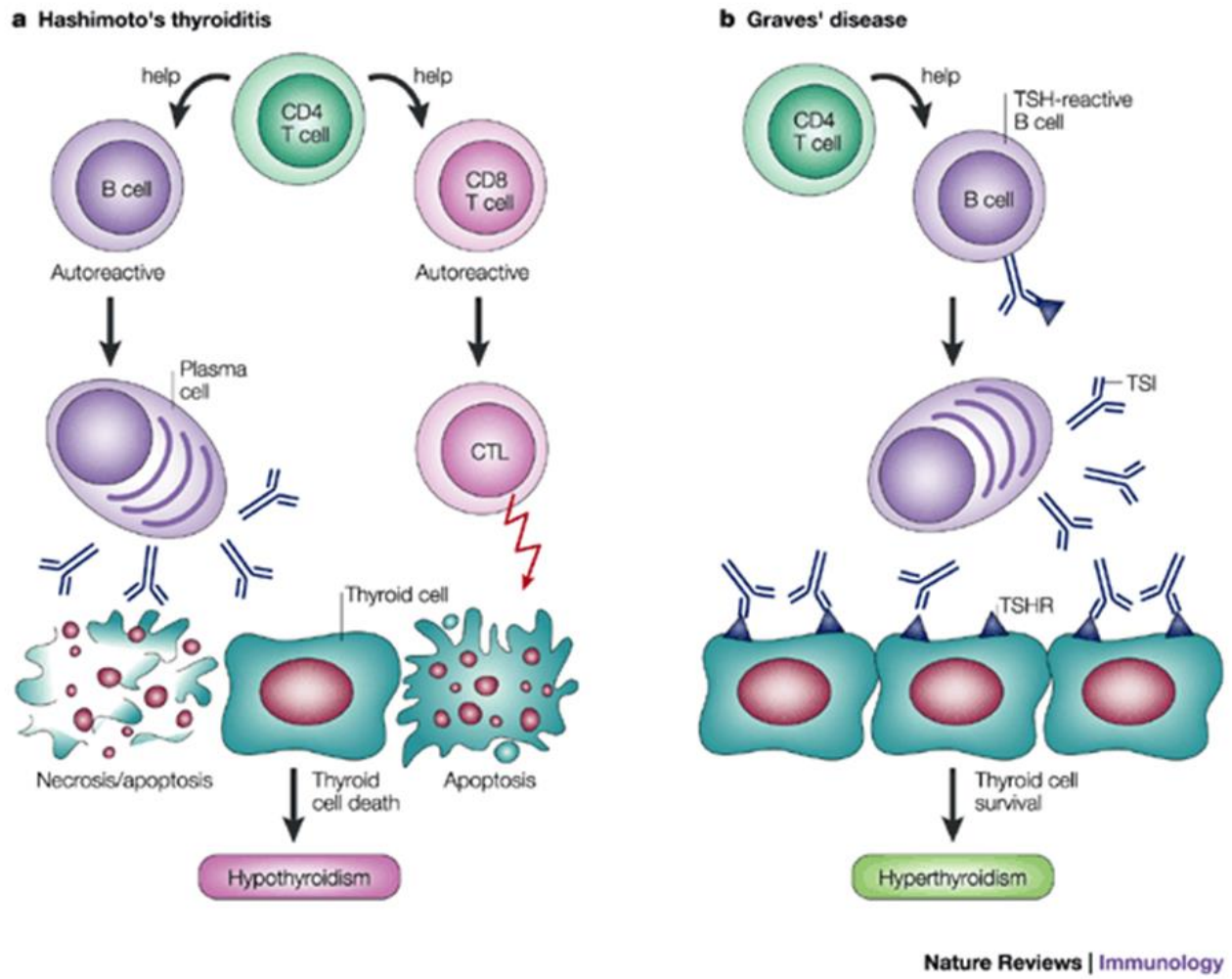

A. During Hashimoto's thyroiditis, self-reactive $CD4^+$ T lymphocytes recruit B cells and $CD8^+$ T cells into the thyroid. Disease progression leads to the death of thyroid cells and hypothyroidism. Both autoantibodies and thyroid-specific cytotoxic T lymphocytes (CTLs) have been proposed to be responsible for autoimmune thyrocyte depletion.

B. In Graves' disease, activated $CD4^+$ T cells induce B cells to secrete thyroid-stimulating immunoglobulins (TSI) against the thyroid-stimulating hormone receptor (TSHR), resulting in unrestrained thyroid hormone production and hyperthyroidism.

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