General adaptation syndrome (GAS)

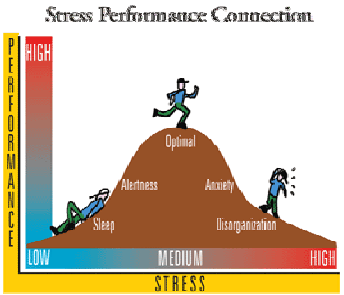
Definition of stress and GAS

Phases of stress reaction

Consequences of GAS

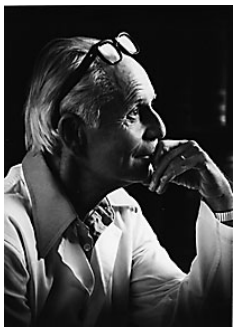
Definition of stress and GAS

- GAS is a term describing body's short-and long-term reactions and adaptations to stress in order to **restore homeostasis**, which, regardless on the nature of the stress, have quite **uniform pattern**
- stress
  - a sum of biological reactions to stimul or events that we perceive as challenging or threatening (= stressors) that tends to disturb the homeostasis
    - "positive" stress (eustress) – limited duration, helps to overcome daily challenges and accomplish demanding tasks → stimulates **performance** and leads to **reward** afterwards
      - ☛ lack of ability to react to stress due to diseases affecting the relevant pathways (e.g. Addison disease) is life-threatening
    - "negative" stress (disstress) - should the compensating reactions be inadequate or inappropriate or stressor acts far too long, they may lead to **disorders**



- stressor
  - any factor disturbing body homeostasis
    - type: physical, mental, emotional
    - source: external or internal

GAS was introduced by Hans Selye



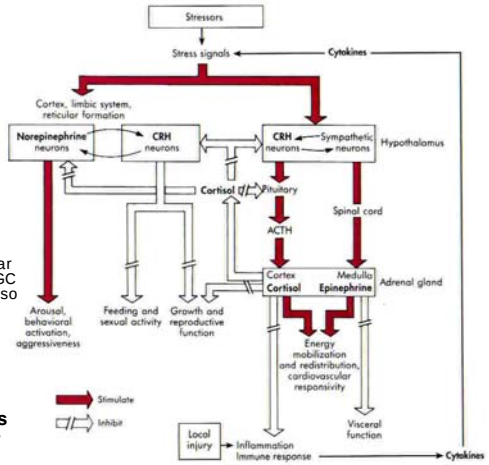
- Austrian-born physician (1907-1982) who emigrated to Canada in 1939
  - born in Hungary, studied in Prague
  - he searched for a new hormone (by injecting rats with ovary extracts, which produced enlargement of adrenal cortex, involution of immune tissue and hemorrhagic gastric ulcers; however, he found out that numerous substances produce the same effect → he described a stereo-typical reaction to all sorts of substances as a stress response or GAS
    - therefore, old-fashioned, non-scientific methods such as bloodletting could have exercised some effects in fact, because it relieved the body from common final consequences of various initiating stressors
  - wrote > 30 books and > 1,500 articles on stress and related problems, incl. *Stress without Distress* (1974) and *The Stress of Life* (1956)
- Nature 138, 32, 1936: **GAS represents a three-stage reaction or ways of coping with stress**
  - (1) general - because it is produced only by agents which have a general effect upon large portions of the body
  - (2) adaptive - because it stimulates defence
  - (3) a syndrome - because its individual manifestations are coordinated and largely dependent upon each other
- GAS involves 2 major regulatory systems of the body
  - autonomic nervous system (ANS), mainly sympathetic
  - endocrine system – hypothalamo-pituitary-adrenal axis
- 3 distinctive stages in the syndrome's evolution
  - **alarm reaction** (already described by Walter B. Cannon in 1914 and 1935)
  - **stage of resistance**
  - **stage of exhaustion**
- the novelty of his work was recognition of GAS as uniform predetermined reaction to deviation from homeostasis
  - Claude Bernard (**specific regulatory mechanisms** to maintain individual homeostatic components stable) vs. Hans Selye (powerful stereotypic **unspecific reaction** to maintain crucial homeostatic parameters within the range compatible with life)

Stages of stress & their purpose

- **(1) alarm reaction (AR)**
  - fright → fight or flight (F&F or Cannon´s emergent reaction)
  - the body's **resistance** to physical damage **drops** for a short-time so that organism can rearrange its priorities to cope with the stressor
    - use of available body sources for energy (glycogen), redistribution of blood to maintain higher blood pressure by increase of the peripheral resistance, increased oxygenation by bronchodilation, increased muscle, coronary and brain perfusion in order to act
  - if the stressor no longer exists the body returns to its normal level of resistance
- **(2) stage of resistance (SR)**
  - if the stressor persists ("we can't fight or flee from it or, rather, we are unable to apply counteracting psychosocial resources"), level of **resistance increases** beyond normal, relaxed levels → quite energy-consuming state
    - increased energy demands covered by adipo- and proteo-catabolism, blood pressure maintained by Na retention, …
  - this stage is an example of **allostasis** (= achieving stability through change, active process)
- **(3) stage of exhaustion (SE)**
  - if the exposure to stressor continues (**allostatic overload**) for a long time (weeks – years) body resistance collapses due to the inability to meet energy demands and due to side effects of extreme or exaggerated stress reactions → **diseases of adaptation**
    - extreme catabolism, immunodeficiency, cardiovascular consequences of metabolic derangements, …

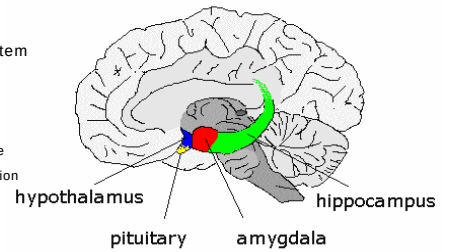
(1) Alarm reaction (AR)

- adaptive, enabling surveillance by alteration of metabolism, cardiovascular & respiratory functions, decreasing pain perception (analgesia) and, at the same time, inhibition of processes decreasing surveillance chance such as reproductive functions and food intake and processing
  - **metabolic alterations** → increase of glycemia using catecholamines (CAT) and glucocorticoids (GC)
    - ↓ insulin-stimulated glucose uptake
    - ↓ protein, fatty acid and glycogen synthesis
    - ↑ lipolysis and proteolysis (incl. part of the immune systems which is "sacrificed" in order to to gain AA)
    - ↑ glycogenolysis by CAT (short-term effects on glycemia)
    - ↑ gluconeogenesis by GC (long-term effects on glycemia)
  - **cardiovascular and respiratory alterations** → glucose and oxygen traffic to muscles, heart and brain using CAT, GC and ADH
    - apart from CAT effects on cardiovascular and respiratory functions and effect of GC on Na retention in the kidney there is also release of ADH to help ↑ circ. volume
  - **stress-induced analgesia** (SIA) → decrease of pain perception by 2 ways
    - opiates-dependent SIA: enkephalins and β-endorphines
    - opiates independent SIA: glutamate
  - **cognitive and emotional alterations**
    - ↑ motivation, arousal, vigilance, anxiety by ↑ delivery of NE to CNS structures

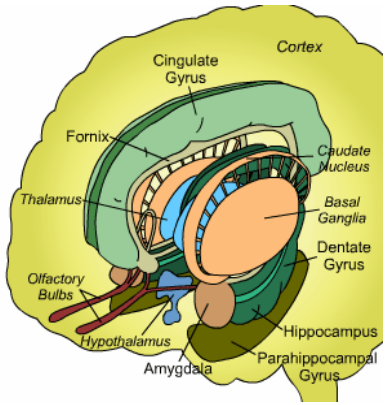


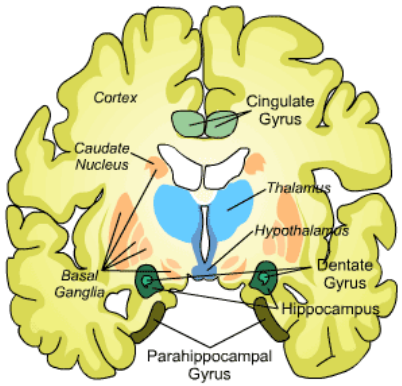
Analysis of the situation by CNS

- (1) analysis of the potentially threatening situation
  - higher cognitive areas – **prefrontal cortex**
    - major connections to amygdala and LC, however, gives us a voluntarily option to modify automatic responses (conscious control over anxiety)!
      - process of extinction = stimulus that triggers a conditioned fear gradually loses this effect
      - involved in the final phase of confronting a danger, = after the initial automatic, emotional reaction, the action that is best for us is chosen (people whose frontal cortex is damaged - "frontal syndrome" can't plan the simplest task)
- (2) respective autonomic and neuroendocrine reactions
  - limbic system
    - **hippocampus**
      - memory (storage and retrieving), connections to amygdala → origin of strong emotions triggered by particular memories
      - processing of the context of a situation
      - connections to hypothalamus
    - **amygdala**
      - essential for decoding emotions, and in particular stimuli that are threatening to the organism
      - many inputs converge in the amygdala directly from the sensory thalamus or from various sensory cortexes
  - **thalamus**
    - sensory information to amygdala
  - **hypothalamus**
    - activated by the structures of the limbic system
    - controls activity of pituitary and ANS (LC)
  - **brain stem**
    - pons
      - **locus coeruleus** (LC) – afferentation from hypothalamus, controls activity of the SNS and other CNS parts by NE release → increase of cognitive functions (prefrontal cortex), motivation, HPA activity (↑ CRH), SNS activation
    - medulla oblongata – n. tractus solitarii



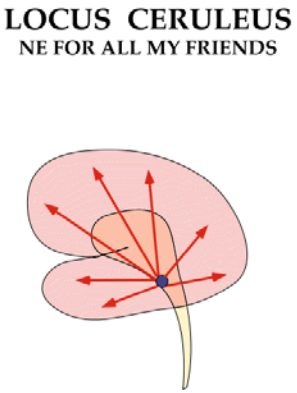
Limbic system



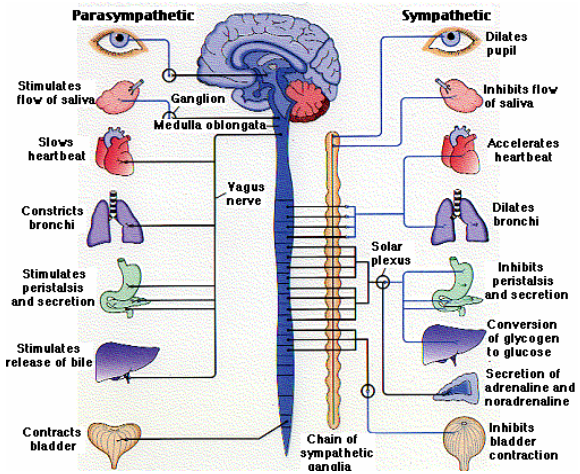


Various nature of the stressors vs. uniform reaction

- stress response can be elicited by various stressors:
  - real
    - external (sensed)
      - from sensory cortex via prefrontal cortex
    - internal (detected/quantified)
      - from various hypothalamic centers, somatic and autonomous afferent nerves perceived
    - emotional (amygdala)
    - memory (hippocampus)
- no matter what was the initial stressor, reaction is carried by uniform pathways involving limbic system →
  - LC - SNS – adrenal medulla – CAT
  - hypothalamus – HPA – cortisol
  - higher CNS functions (motoric, cognitive, behavioral reactions)

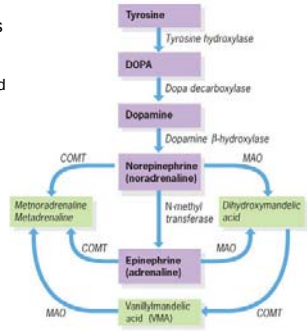


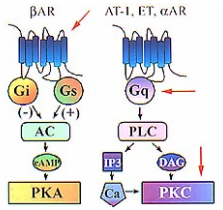
(1a) AR – nervous response - ANS



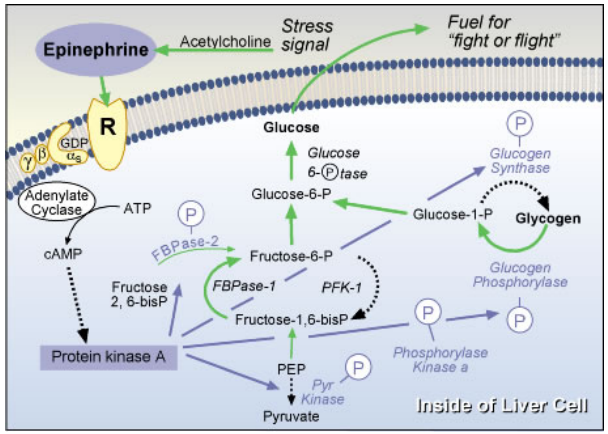
SNS → adrenal medulla → CAT

- adrenal medulla = stress-responsive CAT reservoir whose activity is modulated by limbic system, LC and hypothalamus (CRH), pituitary (ACTH) and cortisol
- produces
  - 80% of E (thus majority of response during F&F reaction is carried predominantly by E from adrenal medulla)
  - 20 % of NE
- CAT circulate bound to albumin, rapid degradation in liver → quite short-acting and thus flexible regulators
- CAT synthesis and metabolism (see Fig.)
  - rate-limiting enzyme: tyrosin hydroxylase
  - inherited defects of synthesis (enzyme defects)
  - overproduction in pheochromocytoma cells
- effects
  - ↓ GIT secretion, motility, digestion
  - ↓ salivation
  - ↑ heart rate, conduction & contractility
  - ↑ respiration & bronchodilation
  - blood redistribution from splanchnic circulation and skin to muscles, brain and heart
  - ↑ activity and vigilance
  - metabolic effects (↑ Glc and FFA)
- effects mediated by post-synaptic adrenergic receptors and respective signaling cascades
  - G-protein coupled receptor superfamily
    - α (1 and 2) – PLC/IP3/DAG pathway
    - β (1 to 3) - cAMP/PKA pathway

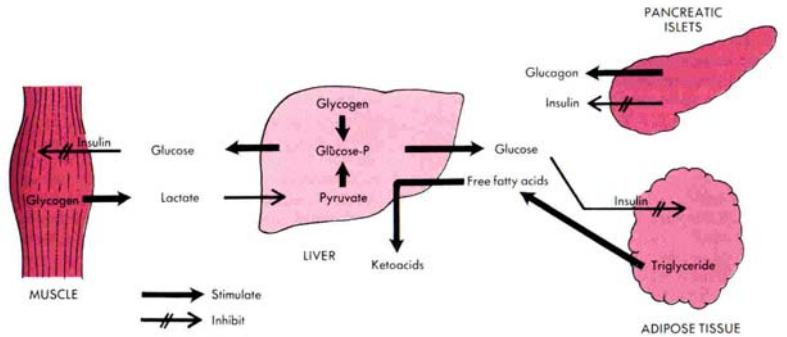




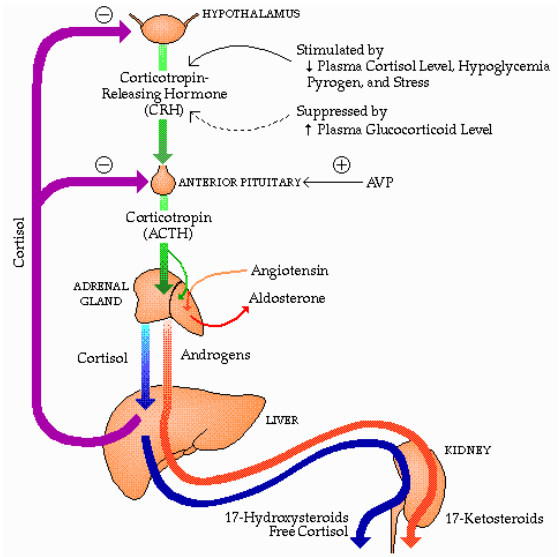
Metabolic effects of E - glycemia



Overall metabolic effects of E

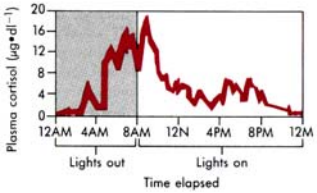


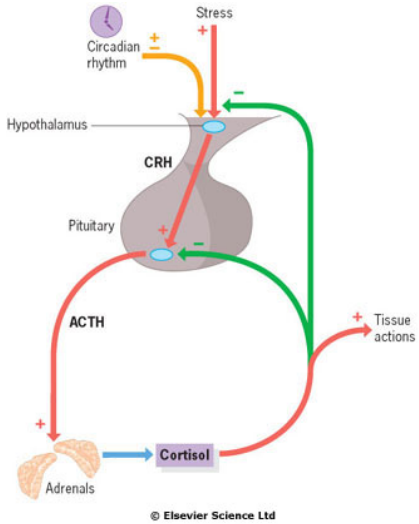
(1b) AR – humoral response – HPA



- CRH produced in n. paraventricularis (PVN) → reaches pituitary via hypothalamo-hypophyseal portal system → stimulates release of ACTH
  - from the precursor proopiomelanocrtin (POMC)
  - ACTH binds to G-prot. receptor → cAMP
- effects of CRH
  - HPA-mediated
    - metabolic action of cortisol
  - non-HPA mediated
  - in immune system
- cortisol half-life in circulation ~90min
  - majority bound to cortisol-binding globulin (CBG, ~75%) and albumin (~15%)
- peripheral tissue-specific modulation of cortisol availability by enzymes
  - 11β hydroxysteroid dehydrogenase type 1 (11βHSD1)
  - 11β hydroxysteroid dehydrogenase type 2 (11βHSD2)
- pathological stress response
  - hypocorticalism (Addison disease)
  - panhypopituitarism (Sheehan sy)

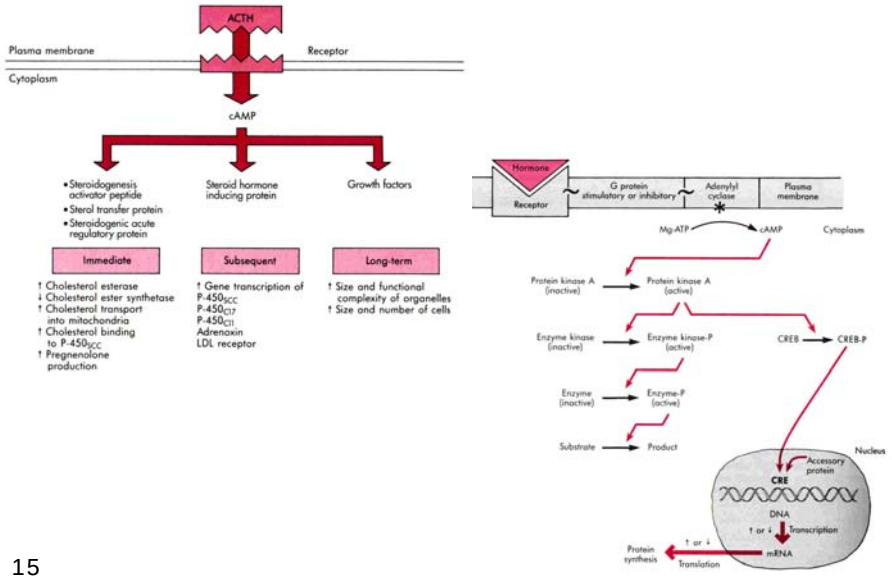
Regulation of cortisol production



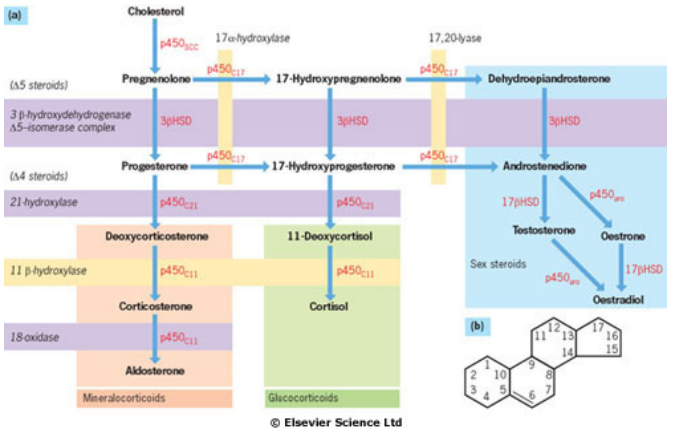


- several factors influence cortisol production
  - (1) diurnal rhythm
  - (2) negative feedback
    - cortisol → ACTH and CRH
    - substrates (Glc) → insulin → HPA
  - **(3) stress**
- GC participate in all 3 stages of GAS
  - alarm reaction is associated with short-term activation of HPA
  - sustained activation represents the stage of resistance
  - upon further prolongation of stress GC overproduction induces stage of exhaustion

ACTH action



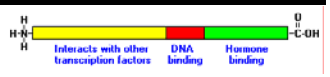
Major steroid biosynthetic pathways

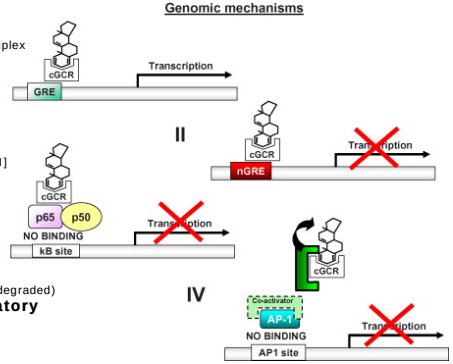


- p450 enzymes are in mitochondria, each catalyses several reaction steps
- 3βHSD (hydroxysteroid dehydrogenase) is in cytoplasm, bound to endoplasmic reticulum
- 17βHSD and p450aro are found mainly in gonads

GC action – genomic effects

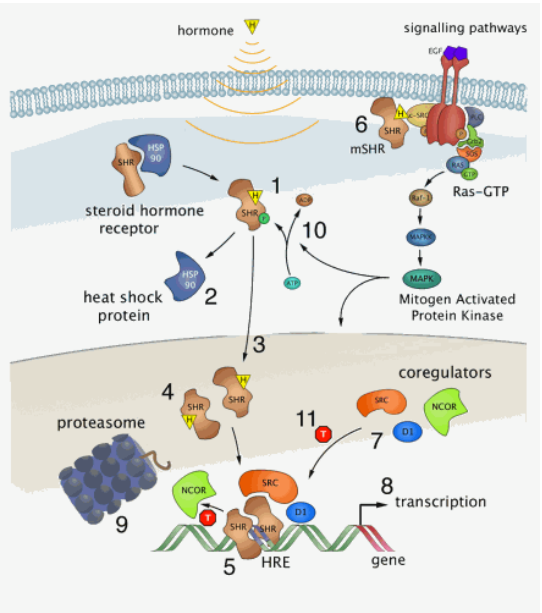
- GCs have receptor (GR) existing in two isoforms
  - cytoplasmic (cGR)
  - membrane bound (mGR)
- therefore, GCs have several modes of action
  - **genomic** – mediated by cytosolic receptors (cGR) upon binding to GC responsive elements (GREs)
  - **non-genomic** – mediated by cGR, mGR and non-specific effects by interaction with other proteins and cell membranes
- **(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!!
  - 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
  - receptor activation
    - upon binding of GC in cytoplasm → conformational changes and release from inhibitory complexes with Hsp → translocation to nucleus and homodimerisation
  - 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]

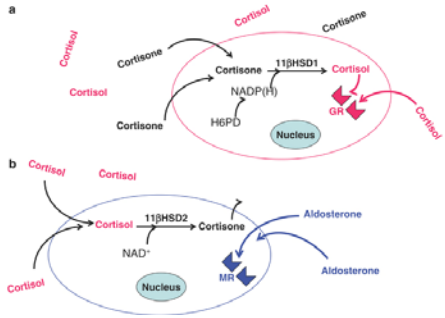


Metabolic effects of GC – increased turnover of free and stored substrates

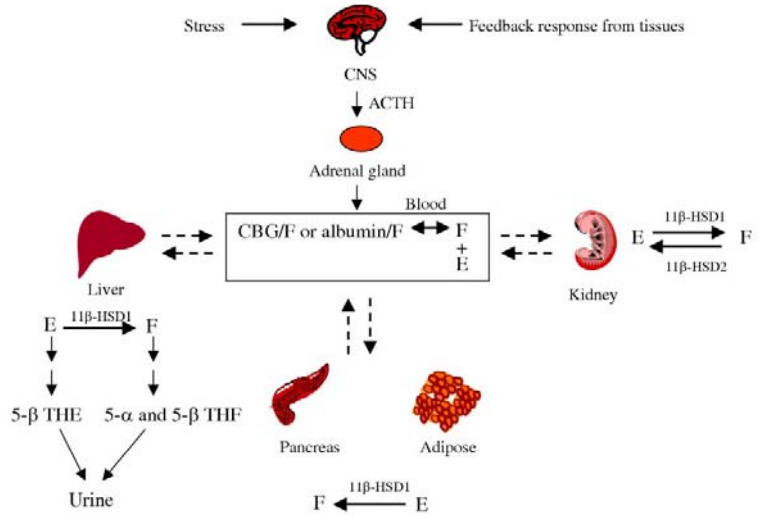
Tissue / organ	Physiologic effects	Effects of overproduction
Liver	↑**hepatic gluconeogenesis (↑ Glc)** (stimulation of key enzymes – pyruvate carboxylase, PEPCK, G6Pase)	impaired glucose tolerabce/diabetes mellitus
	hepatic lipogenesis (↑ FA and VLDL) (stimulation of key enzymes acetyl-CoA-carboxylase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



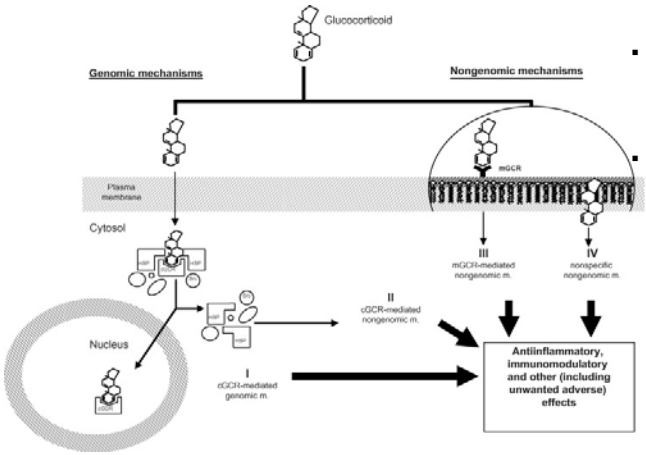
(2) Stage of resistance

- if the stress does not cease shortly (after completing F&F reaction) increased energetic demands must be met by metabolism increasing availability of Glc and FFA
  - mainly via regulation of hepatic gluconeogenesis and adipose tissue lipolysis
- also, optimalisation of the survival following trauma or infection is achieved by alterations of **immune function**
  - suppression of adaptive immunity
  - activation of certain parts of innate immunity, while suppressing the others
- there are many **non-metabolic, non-immune effects** of GC (see Tab.) which are desirable in short-term prospect but become adverse in long-term

Tissue / organ	Physiologic effects	Effects of overproduction
Bone and connective tissue	↓ osteoblast action and bone formation vs. ↑ osteoclast action and bone resorption	osteoporosis
	↓ collagen synthesis and proteolysis	osteoporosis, poor wound healing, easy bruising, thin skin
GIT	↓ calcium absorption	osteoporosis
	↑ gastric juice secretion, ↓ mucus secretion	stress-induced peptic ulcers
Kidney	↑ Na retention (glucocorticoid-activated kinase, increased Na channel and angiotensinogen expression (liver))	hypertension, hypokalemia
Bone marrow	↑ erythrocyte and PMN maturation	polyglobulia, granulocytosis
Reproductive system	supression of production of estradiol and testosterone	oligomenorhea, infertility
Behaviour	Expression of GR in hippocampus → genomic and non-genomic action (↑ glutamate, Ca, serotonin, opiates, ...), NE from LC	post-traumatic stress disorder, "burn-out", depression, anxiety
Fetal and neonatal development	surfactant and fetal lung maturity; fetal hepatic and gastrointestinal enzyme systems	fetal lung immaturity

GC action on immunity

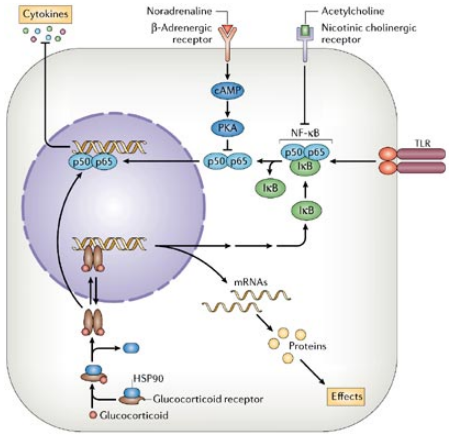
- suggested to be mediated via:
  - genomic effects [I]
    - transactivation and transrepression of many immunoproteins
  - non-genomic effects
    - cGR by sequestering proteins [II]
      - e.g. kinases (MAPK) → blockade of action
    - mGR [III] - multi-protein complexes with other membrane receptors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



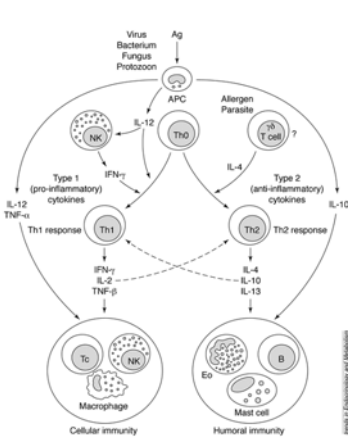
GCs and immune system

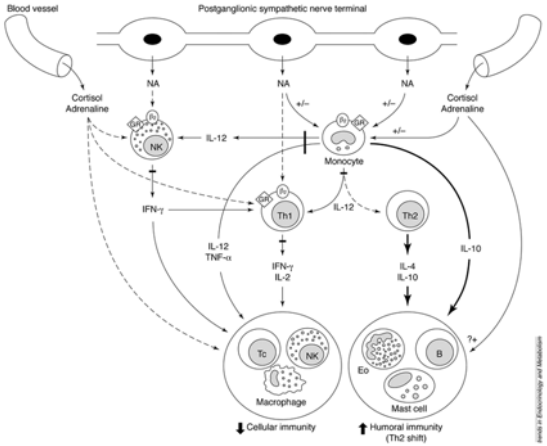
Glucocorticoid effects on primary and secondary immune cells	
Monocytes / macrophages	↓ Number of circulating cells (↓ myelopoiesis, ↓ release)
	↓ Expression of MHC class II molecules and Fc receptors
	↓ Synthesis of pro-inflammatory cytokines (e.g. IL-1, -2, -6, TNFα) and prostaglandins
T cells	↓ Number 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

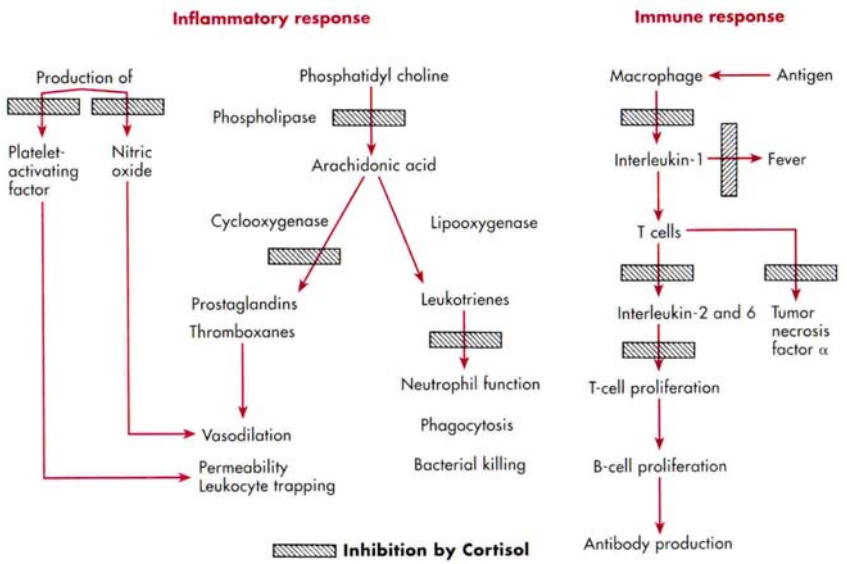


Balance of Th1/Th2 immune responses - Th2 shift as a consequence of stress





Summary – effects of GC on immunity



(3) Stage of exhaustion (wear and tear)

- examples of clinically significant consequences:
  - one of the non-heritable components of metabolic syndrome (→ cardiovascular events)
  - high incidence of death in the first years of retirement for those not prepared for it (sudden end of years in a stressful, demanding job without much relaxation)
  - weekend headache
  - high incidence of illness during holidays
  - anxiety or depressive disorders

Subjective stress responsibility

- flourish or perish
- there are enormous interindividual differences in the response to stress due to
  - prenatal stress
    - fetal programming
  - early-life experiences
    - postnatal handling and mother care, mother separation, …
      - ☛ e.g. animal (rodent) models – maternal care (licking and grooming) produces exploratory, open-to-novelty and less emotionally active animals = **neophilic** (↓ HPA activity) with ↑ longevity and less mortality later in the life, while poor maternal care or separation produces less explorative, emotional, anxious animals scared of novelty = **neophobic** with shortened life-span
        - » interestingly, apart of stressoric effect, abuse of the young (rough handling by the mother) leads to attachment rather than avoidance → increases the chance of survival by continuing to obtain food until weaning (much longer and complex in humans though!)
  - adult-life experiences
    - school, work, family, relationships, sleep deprivation, …
      - ☛ e.g. someone who has been treated badly in the job and/or has been fired will approach a new job quite differently than someone with altogether positive employment history
  - sex differences
  - genetics - sensitivity to stress/reward mediators
    - many genes/common alleles !! e.g. serotonin transporter, brain-derived neurotrophic factor, glucocorticoid receptor, …

Common indications for therapeutic use of GCs and major adverse effects

- respiratory diseases
  - allergies, asthma, sarcoidosis , prevention/treatment of ARDS
- renal diseases
  - some types of nephrotic syndromes and glomerulonephritides
- gastrointestinal disease
  - ulcerative colitis, Crohn's disease, autoimmune hepatitis
- rheumatological diseases
  - systemic lupus erythematosus, polymyalgia rheumatica, temporal arteritis, juvenile idiopathic arthritis, vasculitides, rheumatoid arthritis
- emergency situations
  - cerebral oedema
- skin diseases
  - allergies, pemphigus, eczema
- tumours
  - Hodgkin's lymphoma, other lymphomas
- transplantation immunosuppression
- side-effects
  - physiological
    - adrenal and/or pituitary suppression
  - pathological
    - increased blood pressure, peptic ulceration (or exacerbation), pancreatitis, polyuria, nocturia, depression/uuphoria, psychosis, insomnia, weight gain, impaired glucose tolerance/diabetes, impaired growth, qmenorrhoea, osteoporosis, proximal myopathy and wasting, aseptic necrosis of the hip, pathological fractures, skin thinning, easy bruising, cataracts (including inhaled drug), increased susceptibility to infection, septicaemia, reactivation of TB, fungal infections

Phylogenetic differences in stress response

- stress response plays different roles in different species according to the characteristic patterns of social behaviors, environment etc.
  - example: dominant and subdominant primates (males)
    - in stable conditions (no territorial emergency), dominant males have lower GC levels than subdominant ones
    - in unstable conditions, however, GC levels in dominant males increase and they are the same or higher than in subdominant males
  - i.e. “personal power” of dominant male correlates with low GCs levels during rest conditions
- human beings compared to other species are used and ready to adapt to the long-term stress situations by elevated activity of certain systems (survival advantage)
  - nowadays the outcome of such selection contributes to the common pathologic conditions such as metabolic syndrome