MASARYKOVA UNIVERZITA

FM MU
VLA 2025

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Homeostasis. Stress and general adaption sydrom

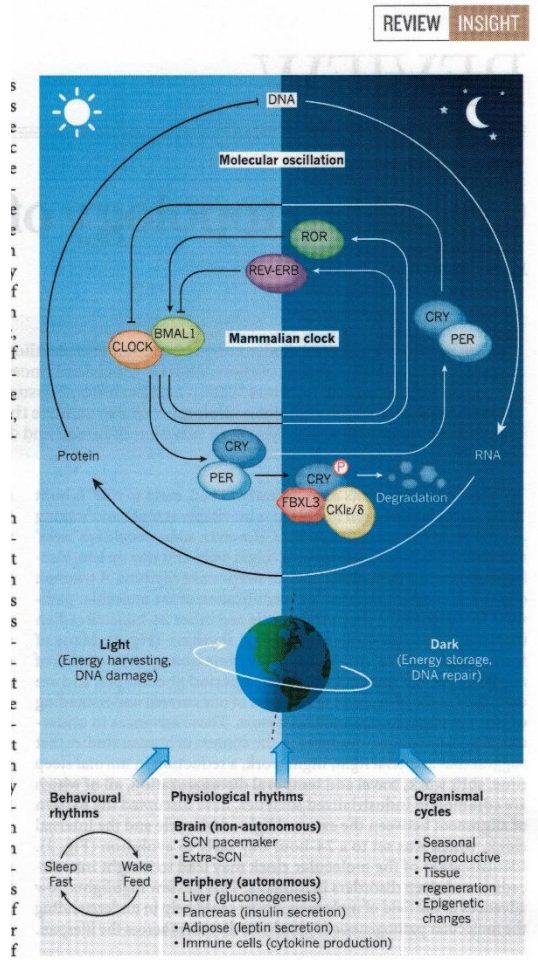
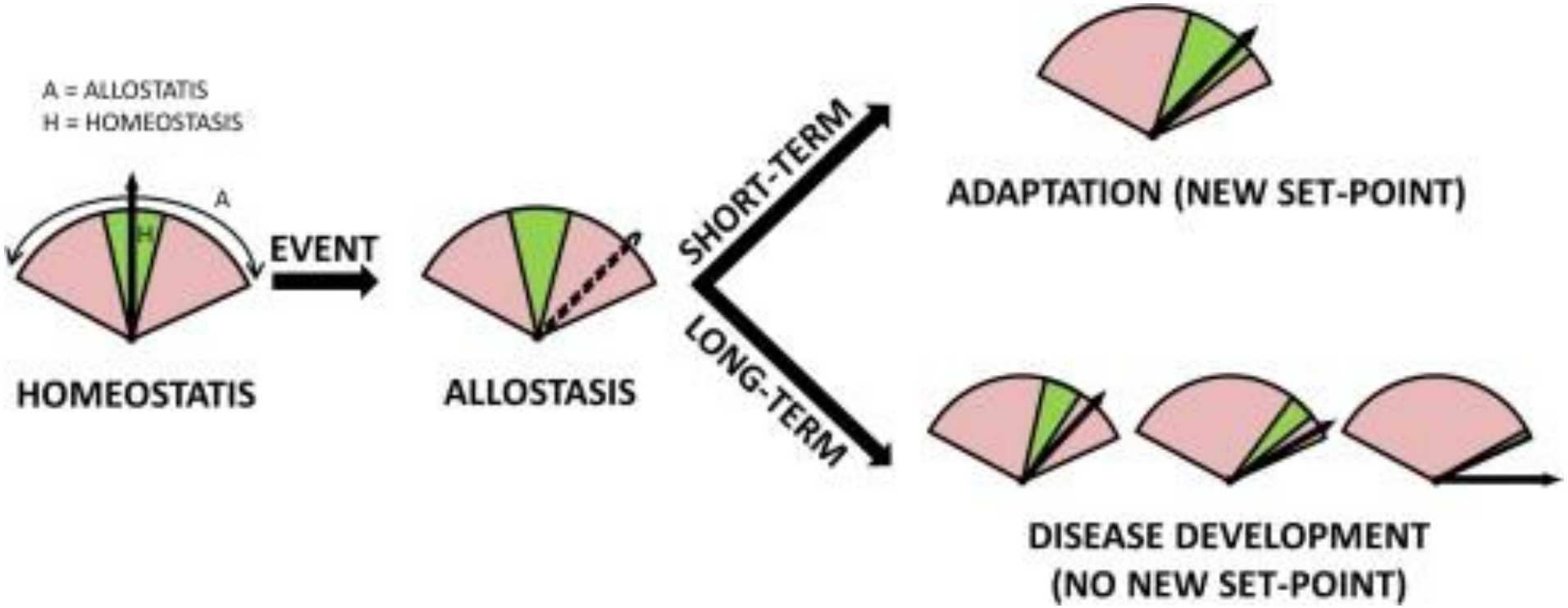
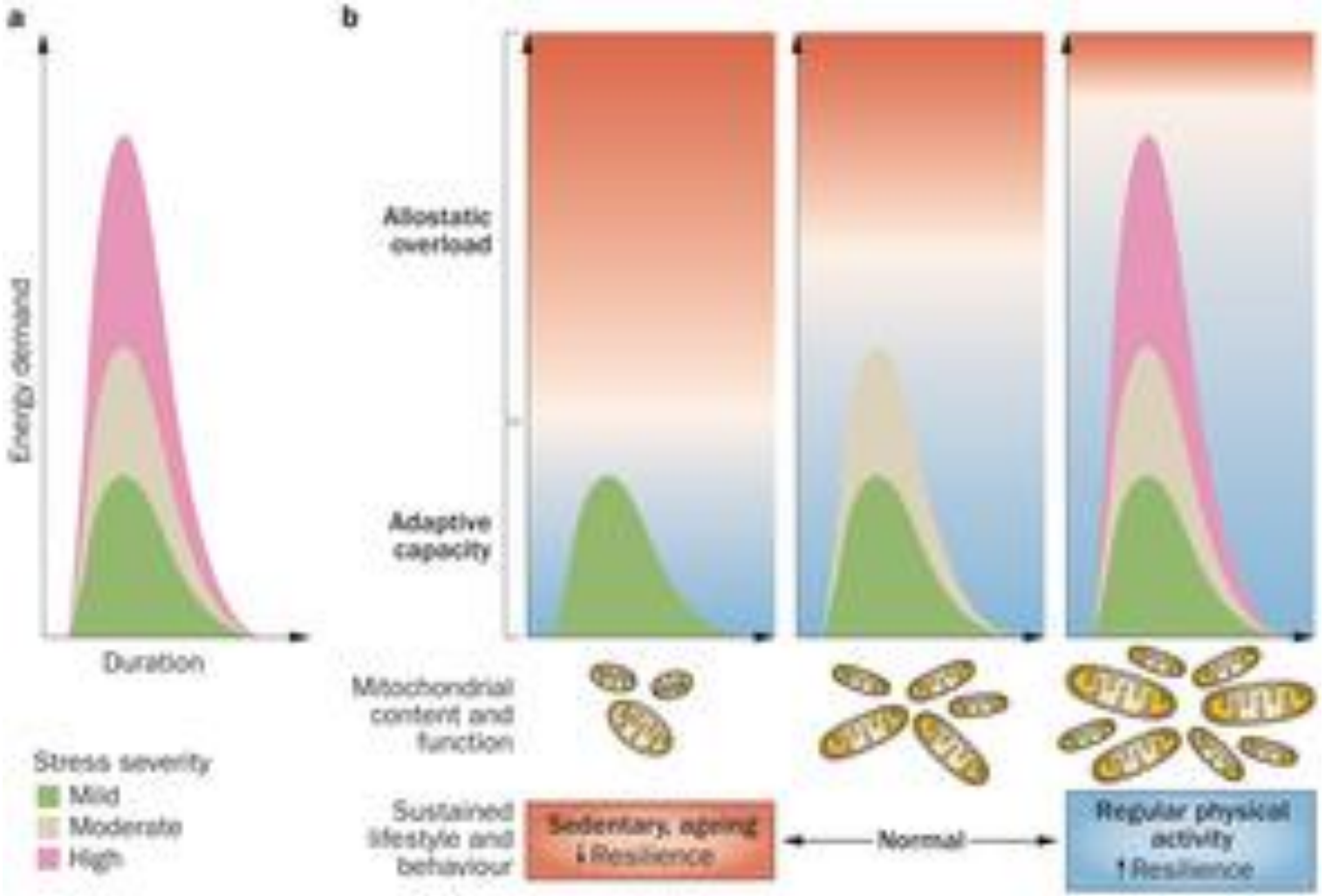


Figure 1 | Circadian adaptation as a unifying model that integrates behaviour and physiology. The circadian clock allows light-sensitive organisms to synchronize their daily molecular oscillations, behavioural rhythms, physiological rhythms and organismal cycles with the rotation of Earth on its axis. Core molecular pathways dictate behavioural and physiological cycles. This core molecular clock in mammals, expressed both in brain and peripheral metabolic tissues, comprises a series of transcription–translation feedback loops that include opposing transcriptional activators (CLOCK–BMAL1) and repressors (PER–CRY)[1]. The non-phosphorylated PER–CRY complex represses CLOCK–BMAL1; phosphorylation, in turn, results in the degradation of PER–CRY and the turnover of these repressors. In addition, CLOCK–BMAL1 induces transcription of REV-ERB and of ROR, which regulate BMAL1 expression. During the night, PER–CRY is degraded through the ubiquitylation of CRY by FBXL3. The circadian clock coordinates anabolic and catabolic processes in peripheral tissues with the daily behavioural cycles of sleep–wake and fasting–feeding. SCN, suprachiasmatic nucleus.



Med Hypotheses. 2014 Mar;82(3):271-4. doi: 10.1016/j.mehy.2013.12.008. Epub 2013 Dec 19.
"Stress entropic load" as a transgenerational epigenetic response trigger.
Bienertová-Vašků J[1], Nečesánek I[2], Novák J[2], Vinklárek J[2], Zlámal F[2].



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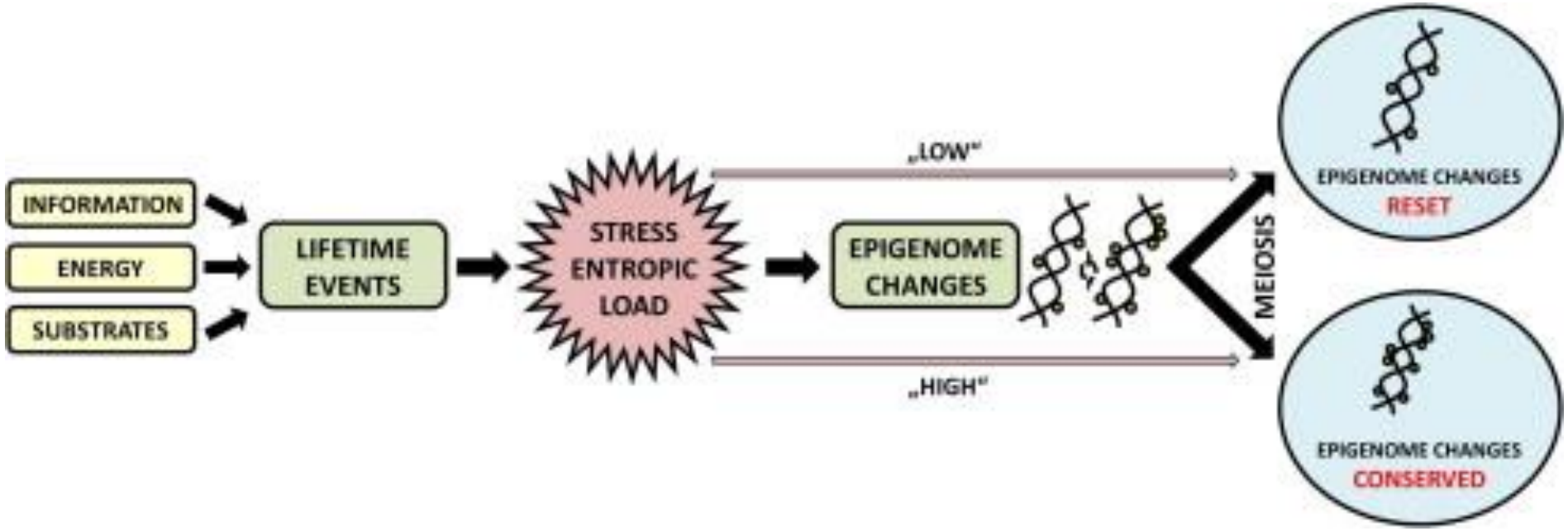

Relationship between lifetime events, stress entropic load (SEL) and epigenome changes. Lifetime events represent those events that influence the flow of energy, substrates and information within the body. Generally, the organism has to cope with these changes, whereas we consider SEL to be the universal parameter reflecting the "severity" of the influencing events. SEL therefore leads to epigenome changes that are according to SEL "severity" either conserved or reset during meosis and thus passed transgenerationally or not.

Med Hypotheses. 2014 Mar;82(3):271-4.
"Stress entropic load" as a transgenerational epigenetic response trigger.
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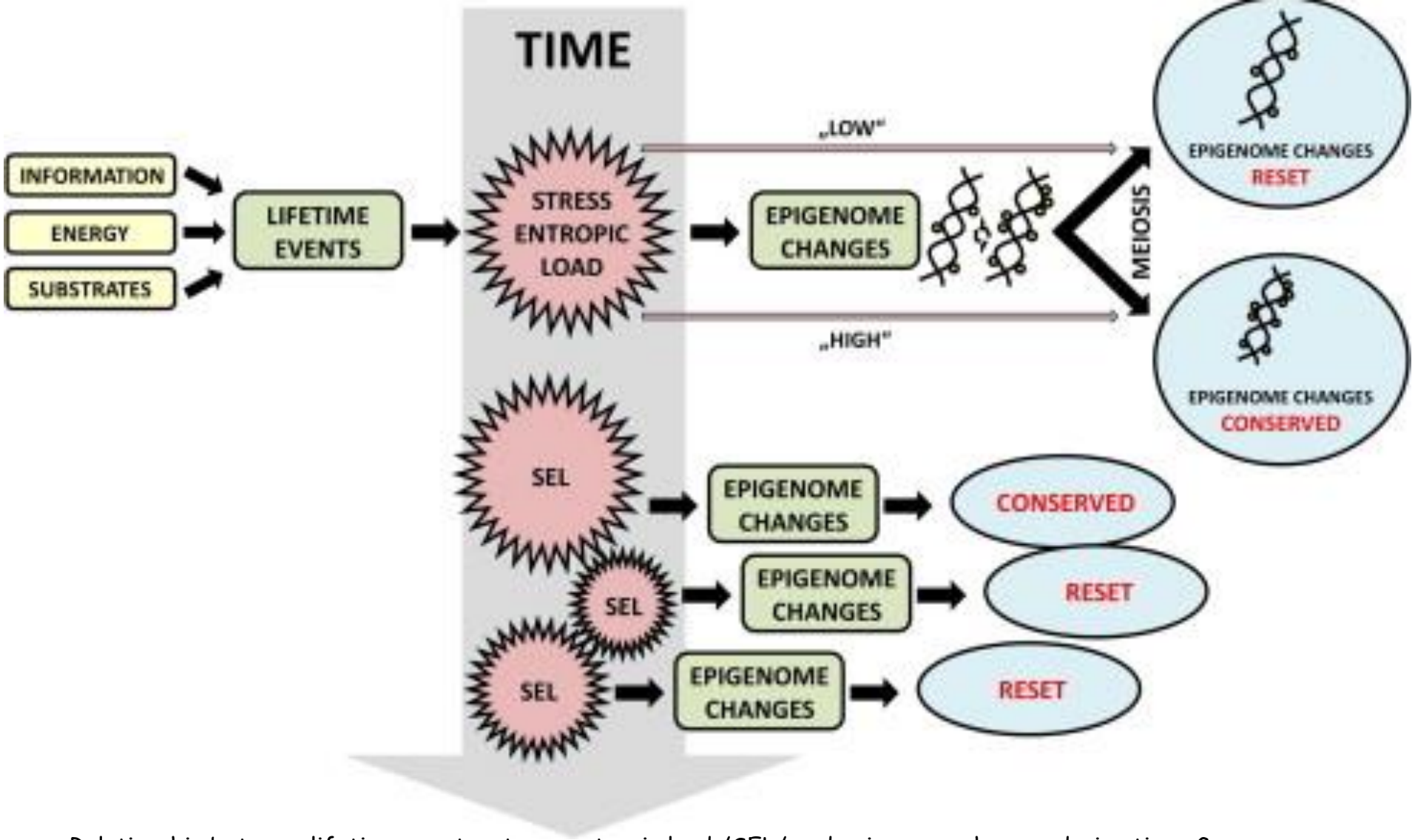
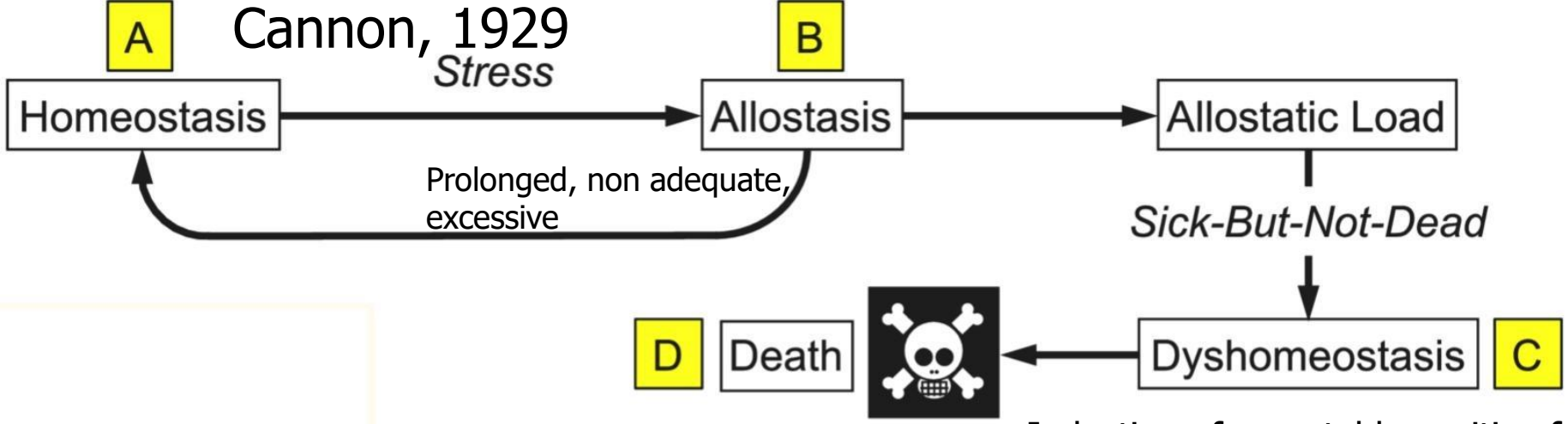


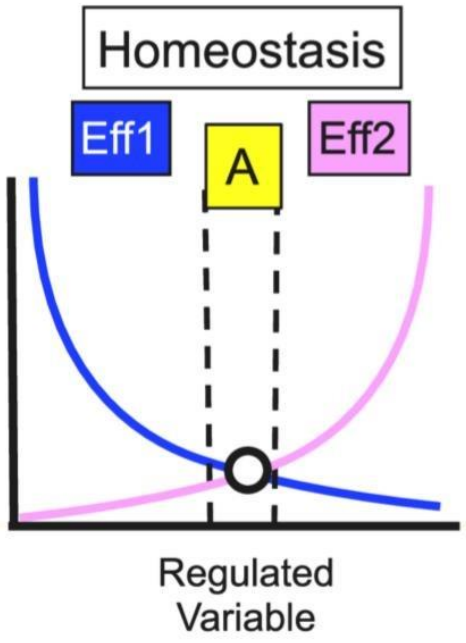
Relationship between lifetime events, stress entropic load /SEL/ and epigenome changes during time. Grey arrow represents the time flow and it should suggest that as time passes, different events are evaluated differently and their associated SEL level may consecutively increase or decrease and thus affect whether the epigenomic changes are passed to other generation or not.

Med Hypotheses. 2014 Mar;82(3):271-4. "Stress entropic load" as a transgenerational epigenetic response trigger.
Bienertová-Vašků J[1], Nečesánek I[2], Novák J[2], Vinklárek J[2], Zlámal F[2].

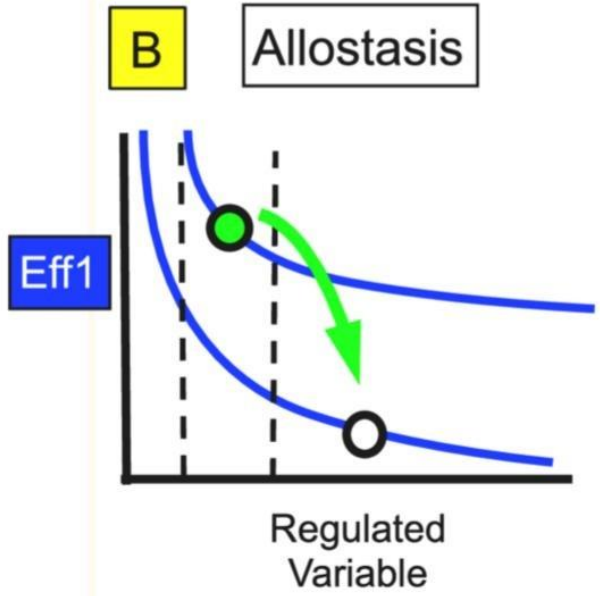


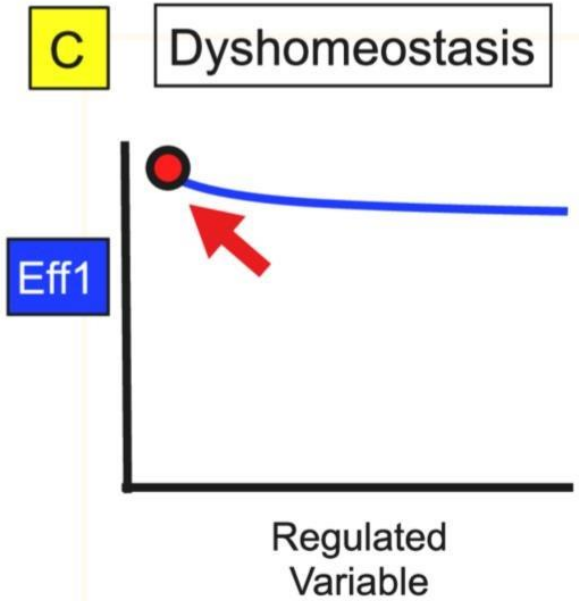
Goldstein DS. Stress and the "extended" autonomic system. Auton Neurosci. 2021 Oct 2;236:102889.

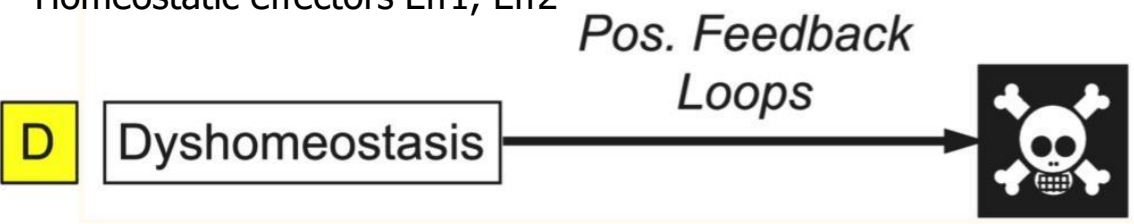
Induction of non-stable positive feedbacks by decreasing of treshold



Homeostatic effectors Eff1, Eff2







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Hans Selye

- ***A syndrome produced by diverse nocous agents, Nature 138, 32, 1936***

- General adaptation syndrome-stress reaction of organism:
- Experiments with animals showed that different toxic substances applied into the organisms led to stereotyped response explicable by suprarenal gland activation.

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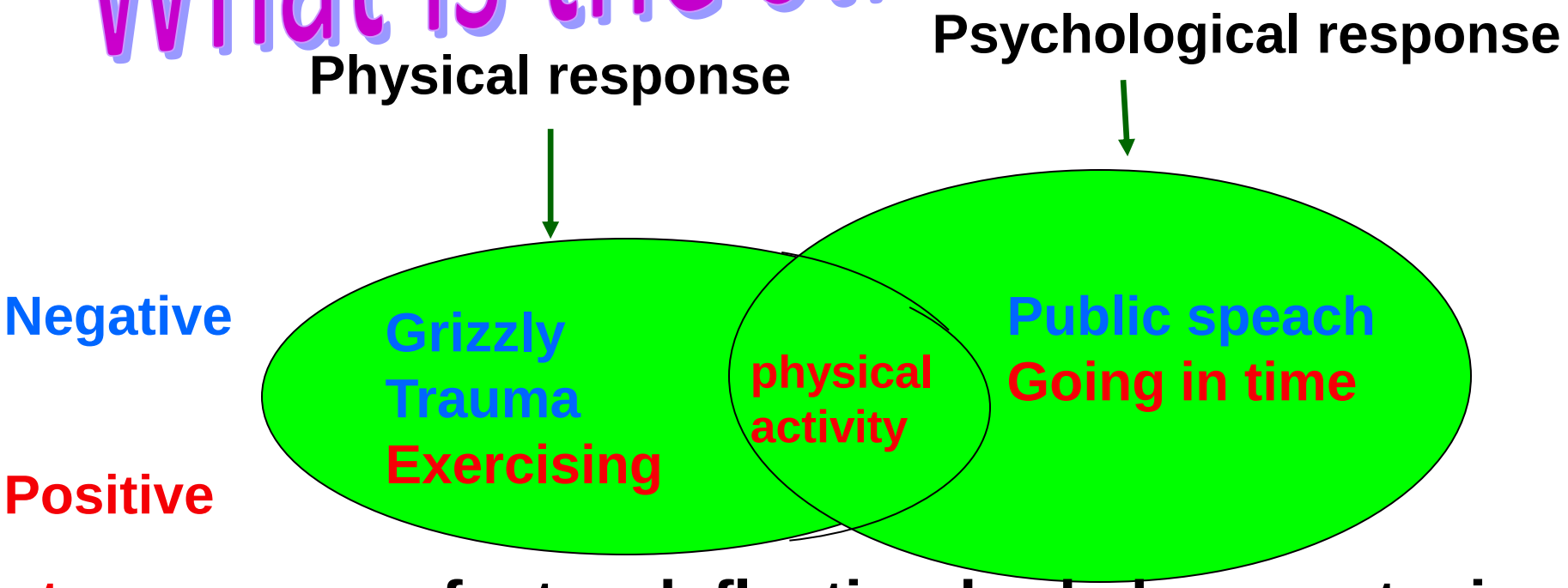
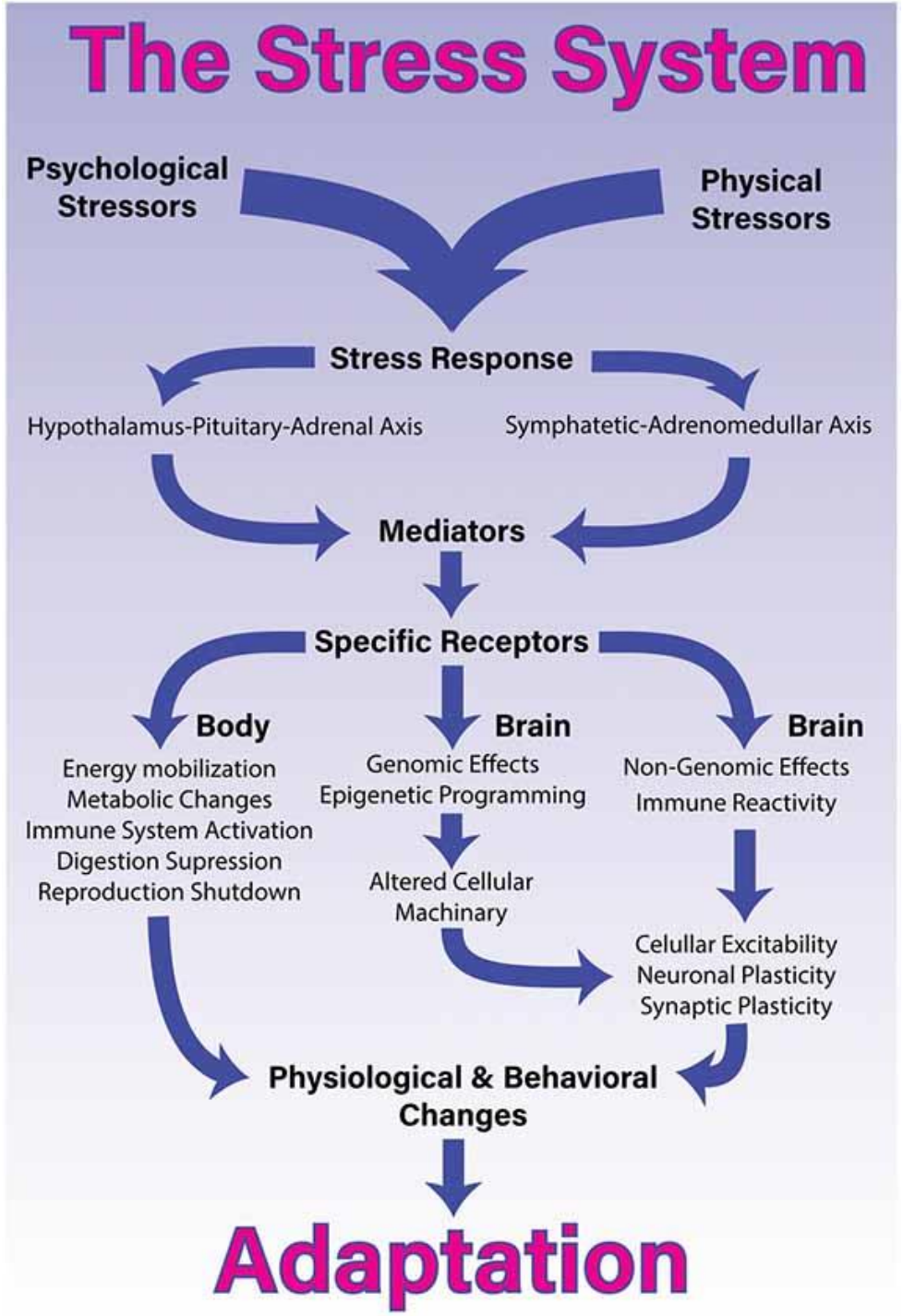
What is the stress?



stressor=any factor deflecting body homeostasis

stress response= body adaptation to homeostasis restoring

stress= the complexity of factors provoking stress response


The Stress System
Psychological Stressors
Physical Stressors
Stress Response
Hypothalamus-Pituitary-Adrenal Axis
Symphatetic-Adrenomedullar Axis
Mediators
Specific Receptors
Body
Energy mobilization
Metabolic Changes
Immune System Activation
Digestion Supression
Reproduction Shutdown
Brain
Genomic Effects
Epigenetic Programming
Altered Cellular Machinary
Brain
Non-Genomic Effects
Immune Reactivity
Celullar Excitability
Neuronal Plasticity
Synaptic Plasticity
Physiological & Behavioral Changes
Adaptation

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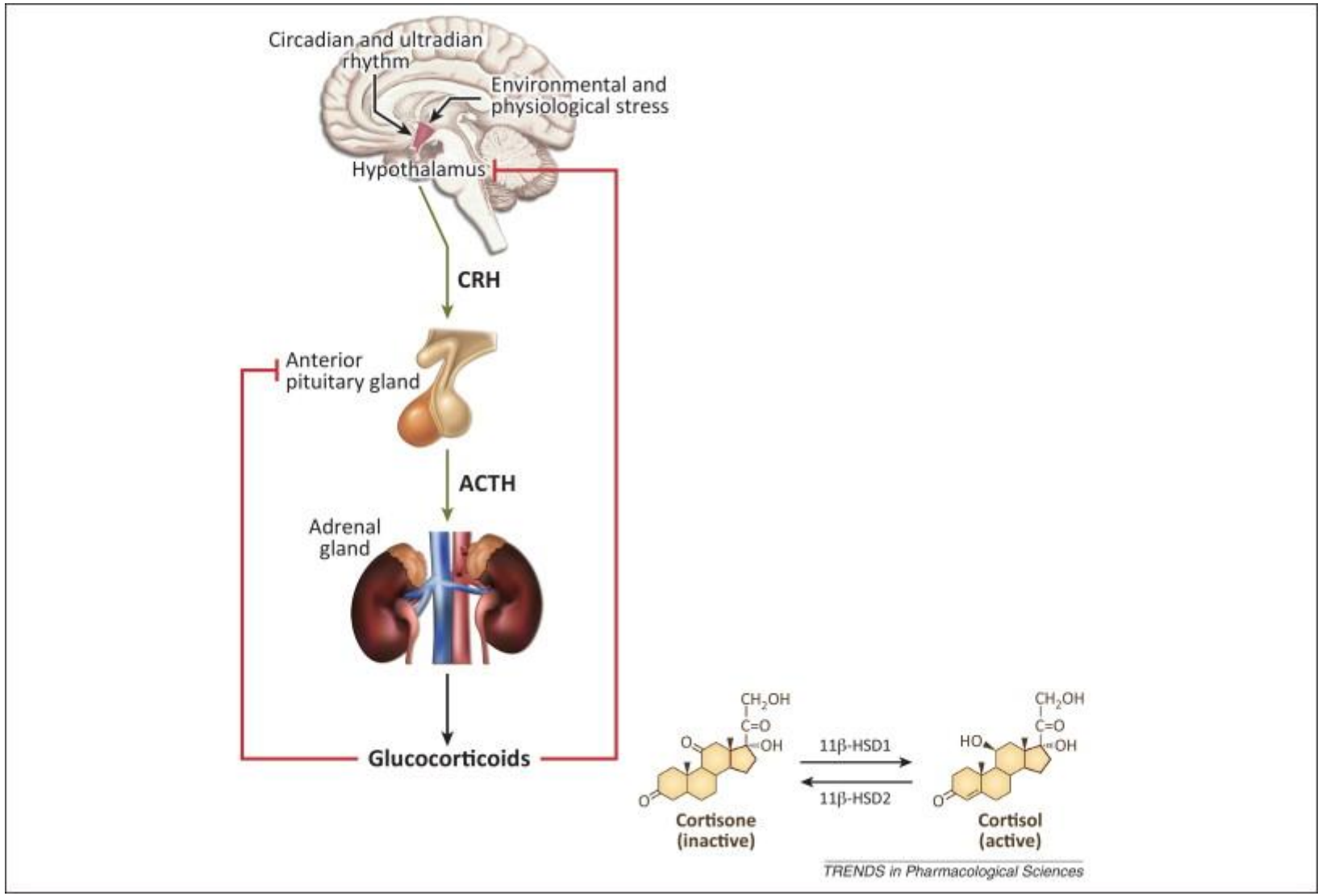
Circadian and ultradian rhythm
Environmental and physiological stress
Hypothalamus
CRH
Anterior pituitary gland
ACTH
Adrenal gland
Glucocorticoids
CH2OH
C=O
OH
O
11β-HSD1
11β-HSD2
HO
Cortisone (inactive)
Cortisol (active)
TRENDS in Pharmacological Sciences

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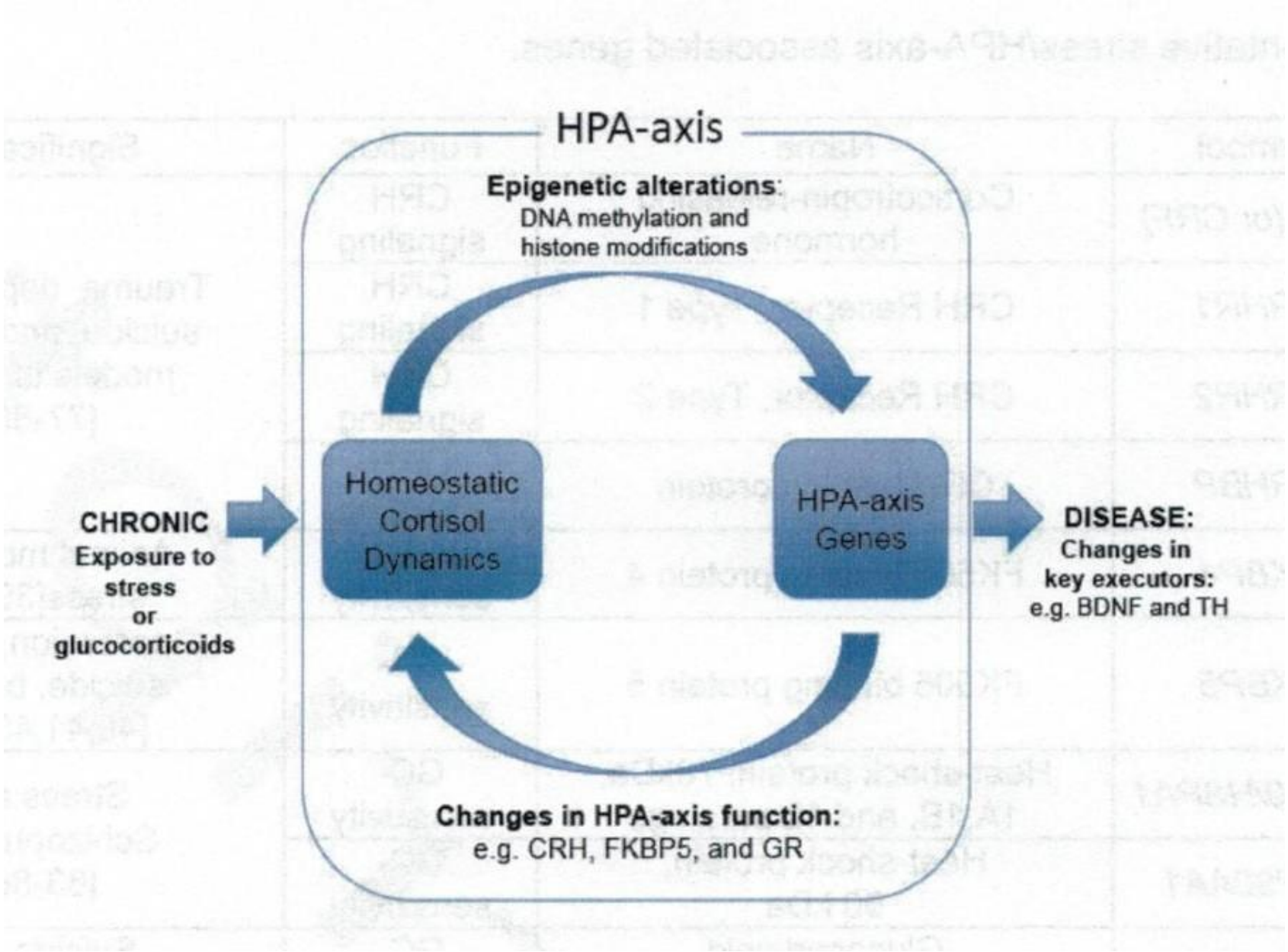
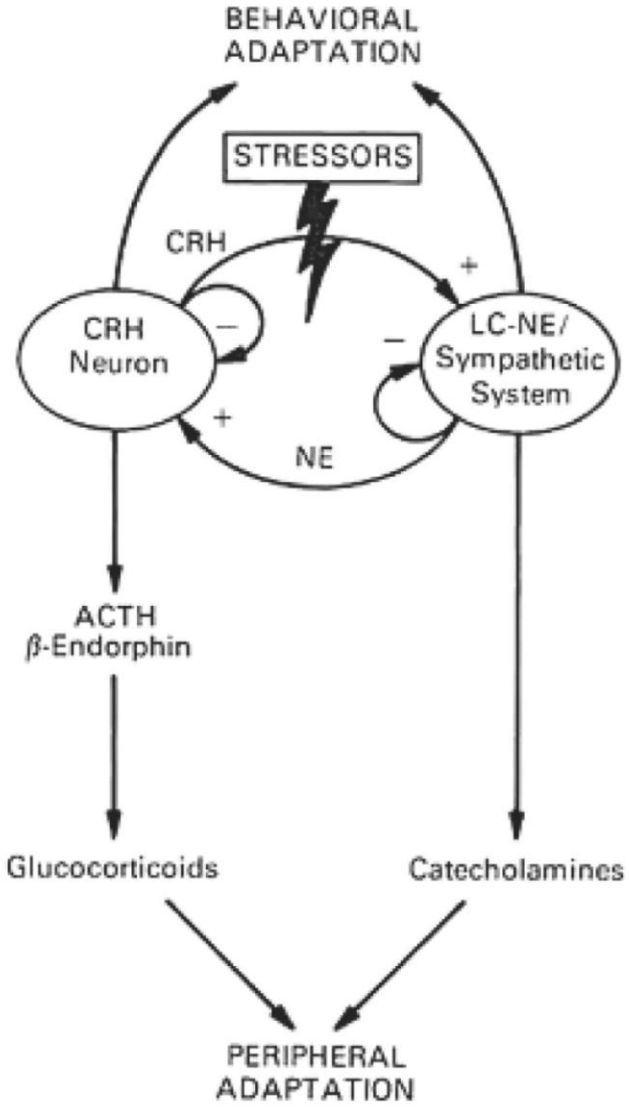
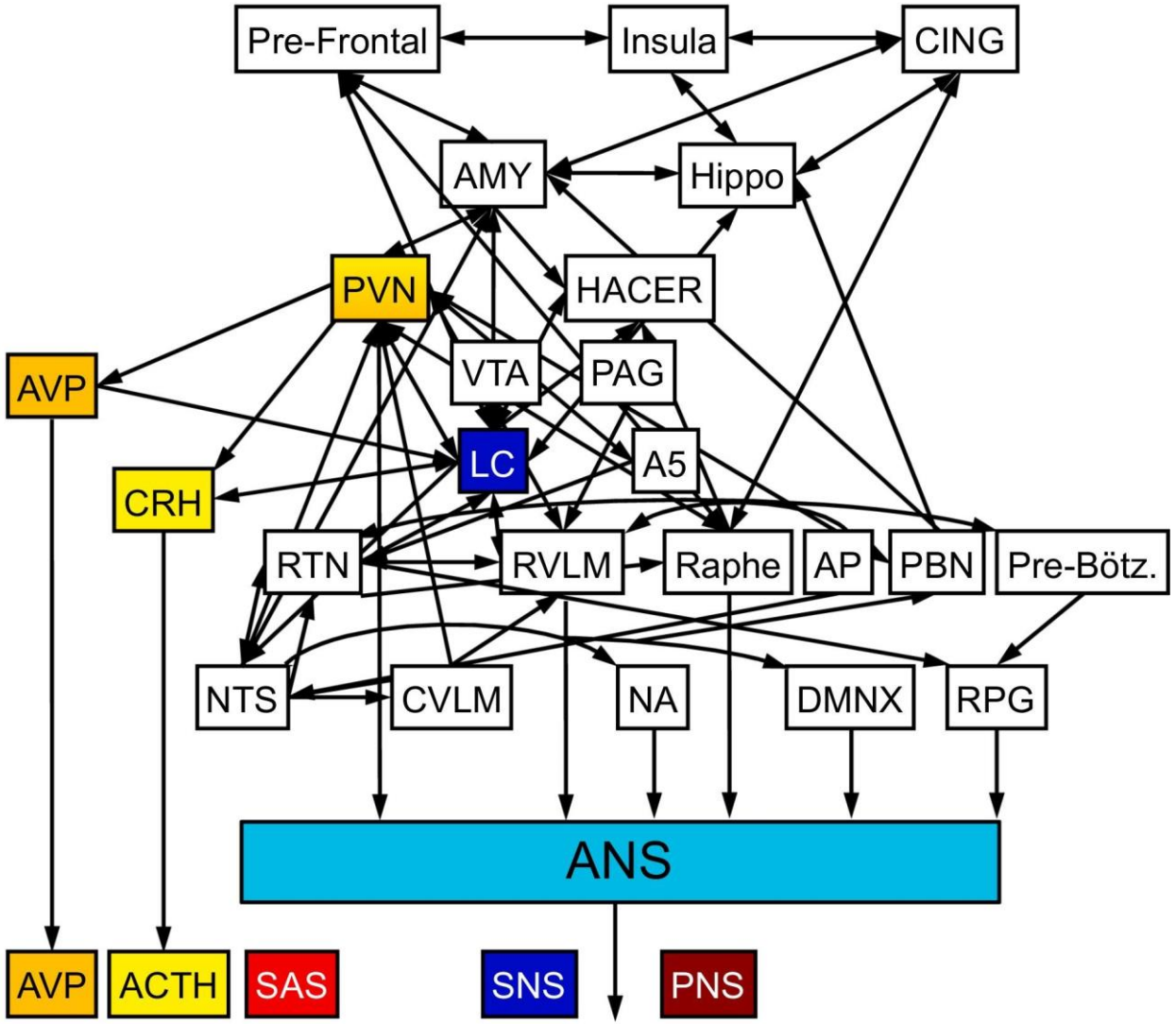

HPA-axis
Epigenetic alterations:
DNA methylation and
histone modifications
CHRONIC
Exposure to
stress
or
glucocorticoids
Homeostatic
Cortisol
Dynamics
HPA-axis
Genes
DISEASE:
Changes in
key executors:
e.g. BDNF and TH
Changes in HPA-axis function:
e.g. CRH, FKBP5, and GR





Goldstein DS. Stress and the "extended" autonomic system. Auton Neurosci. 2021 Oct 2;236:102889.

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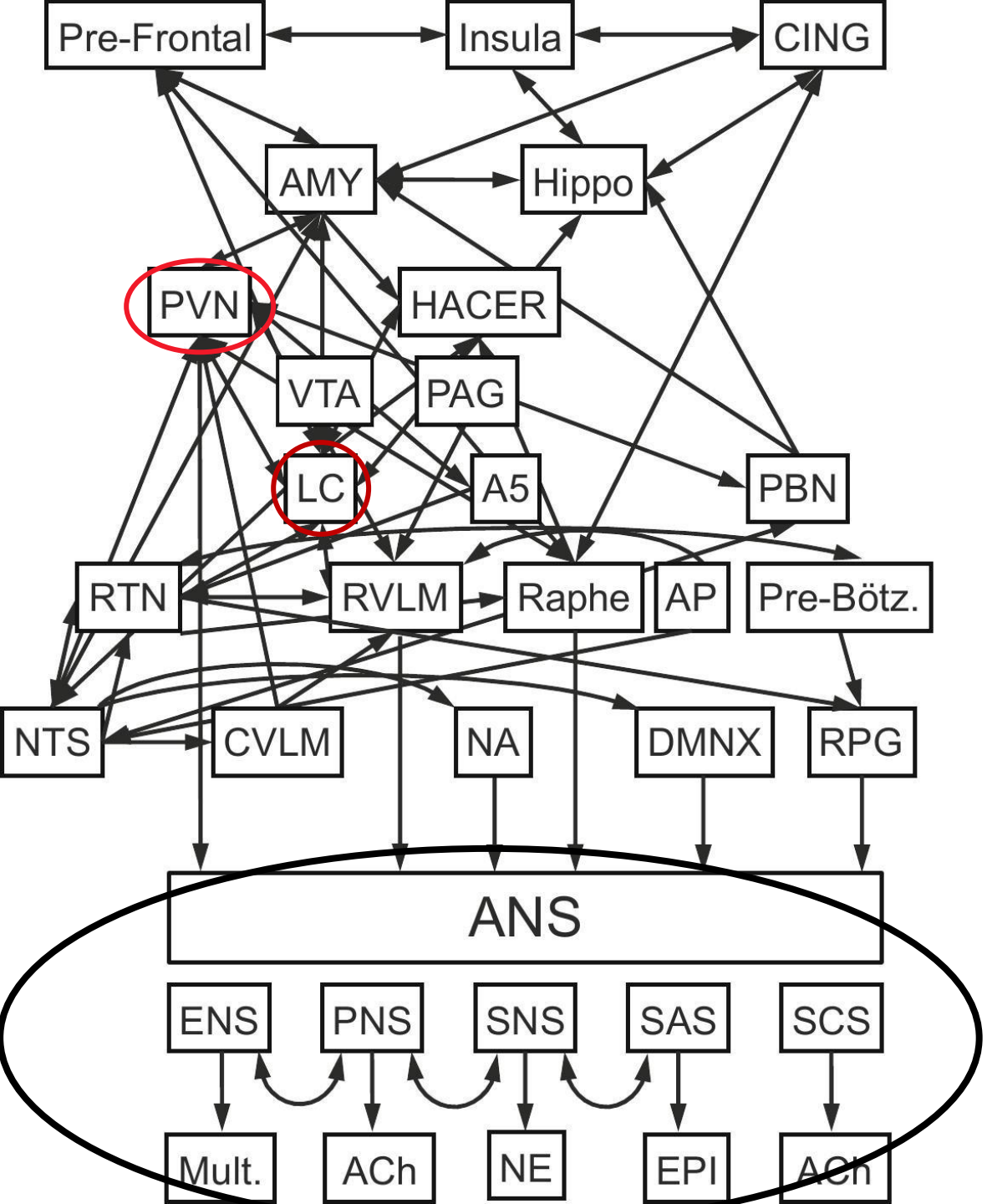

Cortex

Limbic sys.

Hypothalamus

Midbrain

Pons

Medulla

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CAN = central autonomic network
HACER=hypothalamic area controlling emotional responses
SCS= sympathetic cholinergic systém

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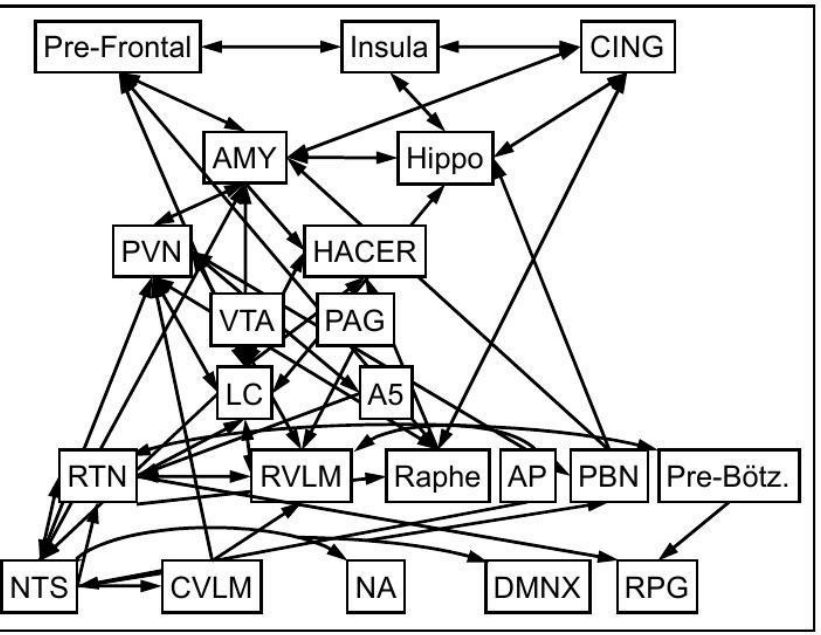
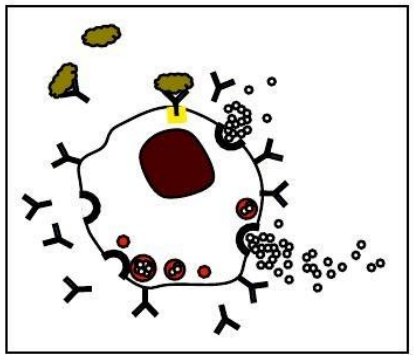


SNS PNS ENS

AVP HPA SAS RAS



Central Autonomic Network

Langley's ANS

Neuroendocrine Systems

Immune/Inflammatory Systems

Extended Autonomic System

Goldstein DS. Stress and the "extended" autonomic system. Auton Neurosci. 2021 Oct 2;236:102889.

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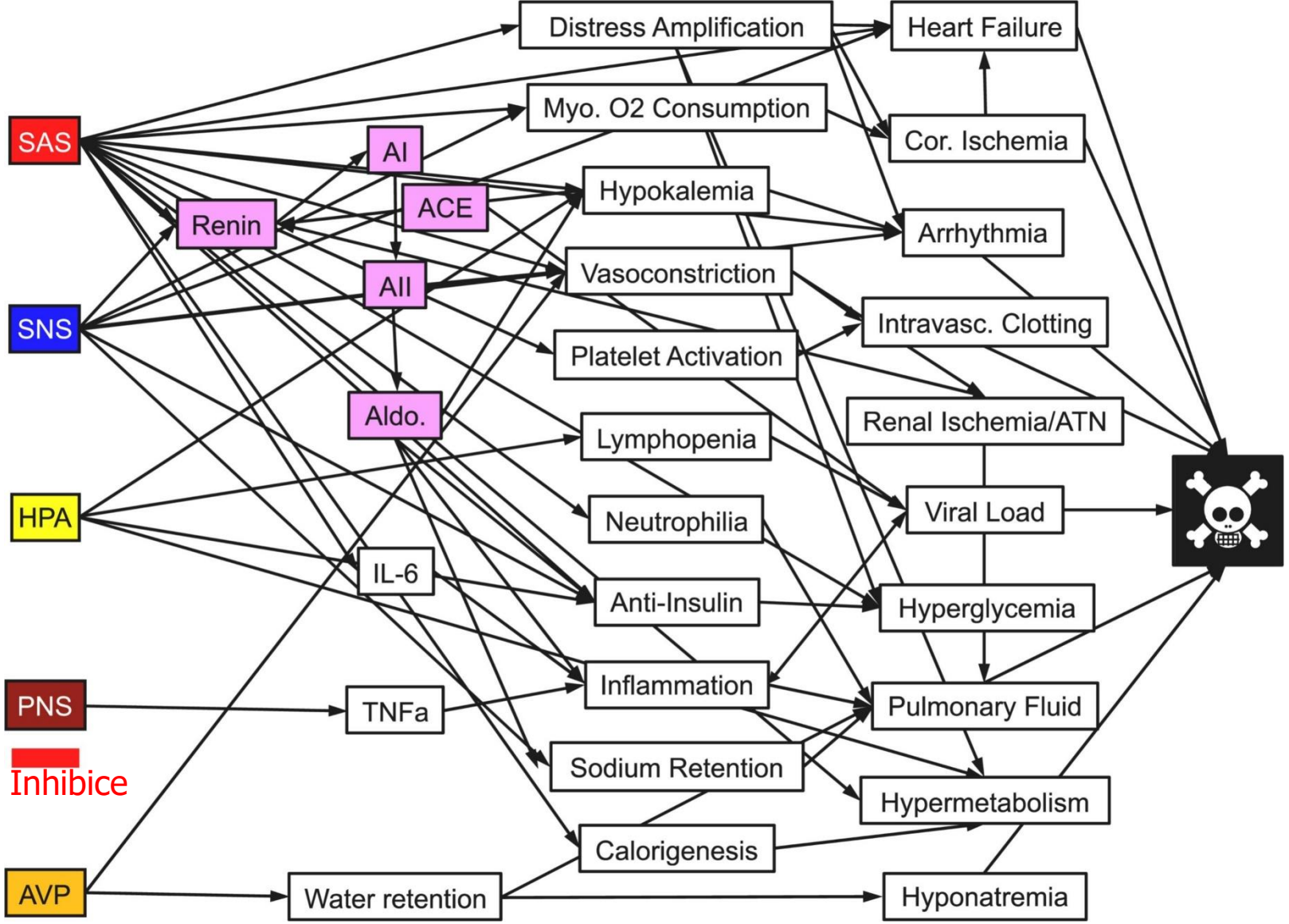
Overview of extended autonomic system (EAS)

- The EAS is conceptualized to consist of the central autonomic network (CAN);Langley's autonomic nervous system (ANS), with its three component sub-systems the sympathetic nervous system (SNS), parasympathetic nervous sys-tem (PNS), and enteric nervous system (ENS); neuroendocrine systems including the arginine vasopressin (AVP) system, hypothalamic-pituitary-adrenocortical (HPA) system, sympathetic adrenergic system (SAS), and renin-angiotensin-aldosterone system (RAS); and immune/inflammatory systems, represented by a stylized mast cell. Langley's SNS involves three chemical messengers, norepinephrine (sympathetic noradrenergic system, abbreviated as SNS in this review), acetylcholine (sympathetic cholinergic system), and epinephrine (SAS).

Goldstein DS. Stress and the "extended" autonomic system. Auton Neurosci. 2021 Oct 2;236:102889

Od aktivace stresového systému k dyshomeostáze a smrti



Efektory CNS

Intervenující proměnné

Faktory přispívající ke chronickému onemocnění nebo smrti

Goldstein DS. Stress and the "extended" autonomic system. Auton Neurosci. 2021 Oct 2;236:102889.

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Stages of stress

- **alarm reaction (fight and flight-Cannon´s emergent reaction): shock, contra-shock**
- **stage of resistence**
- **stage of exhaustion**

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- Eustress- increases possibilities of the organism, healthy and life motivation
- Distress- decreases possibilities, facilitates diseases development
- Stressors= stress causes (frustrations, conflicts)
- Factors influencing stress severity
- stressor characteristics
- subjective stress responsibility
- Reactions to acute and chronic stress: physical and psychological

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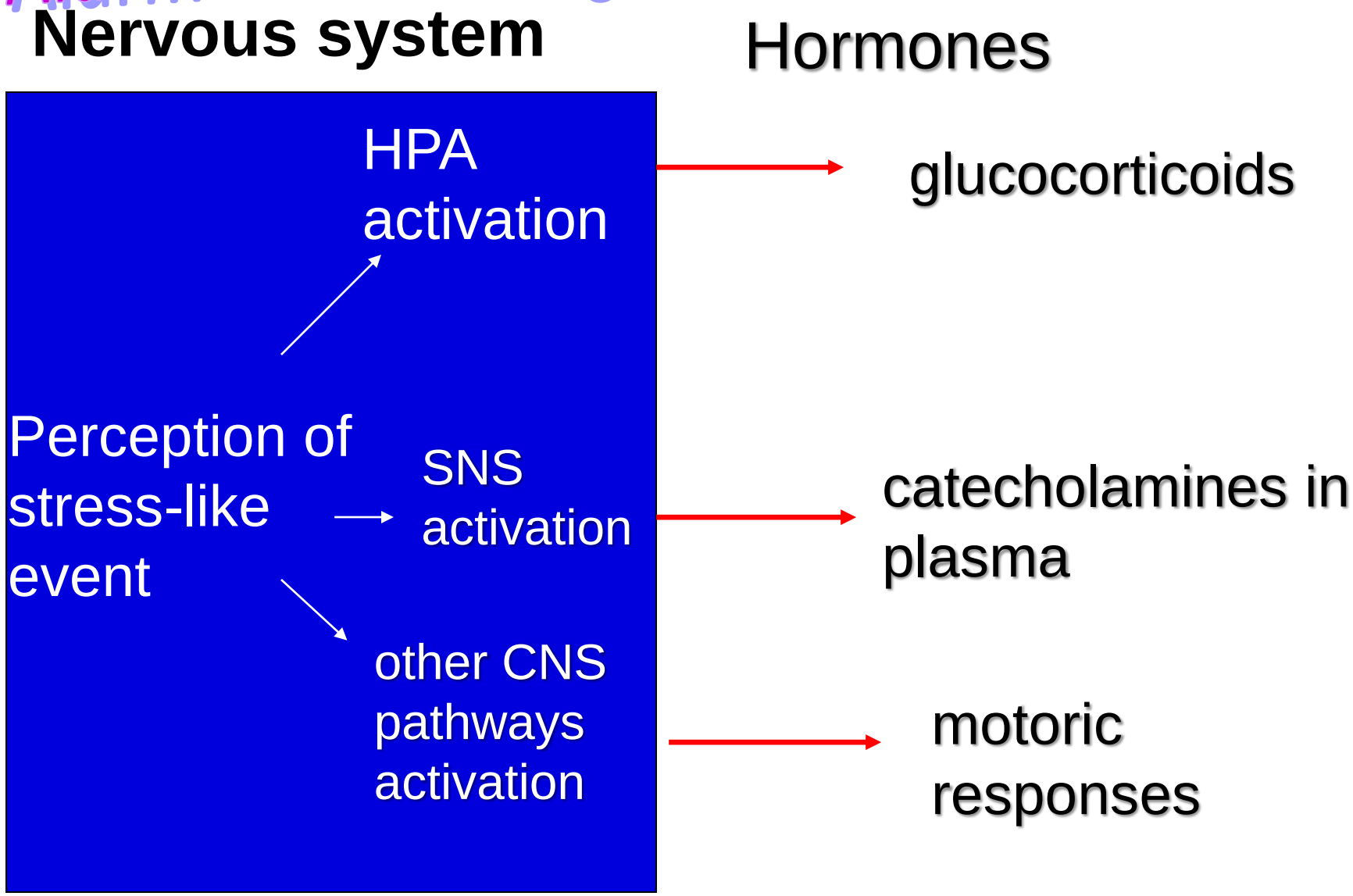
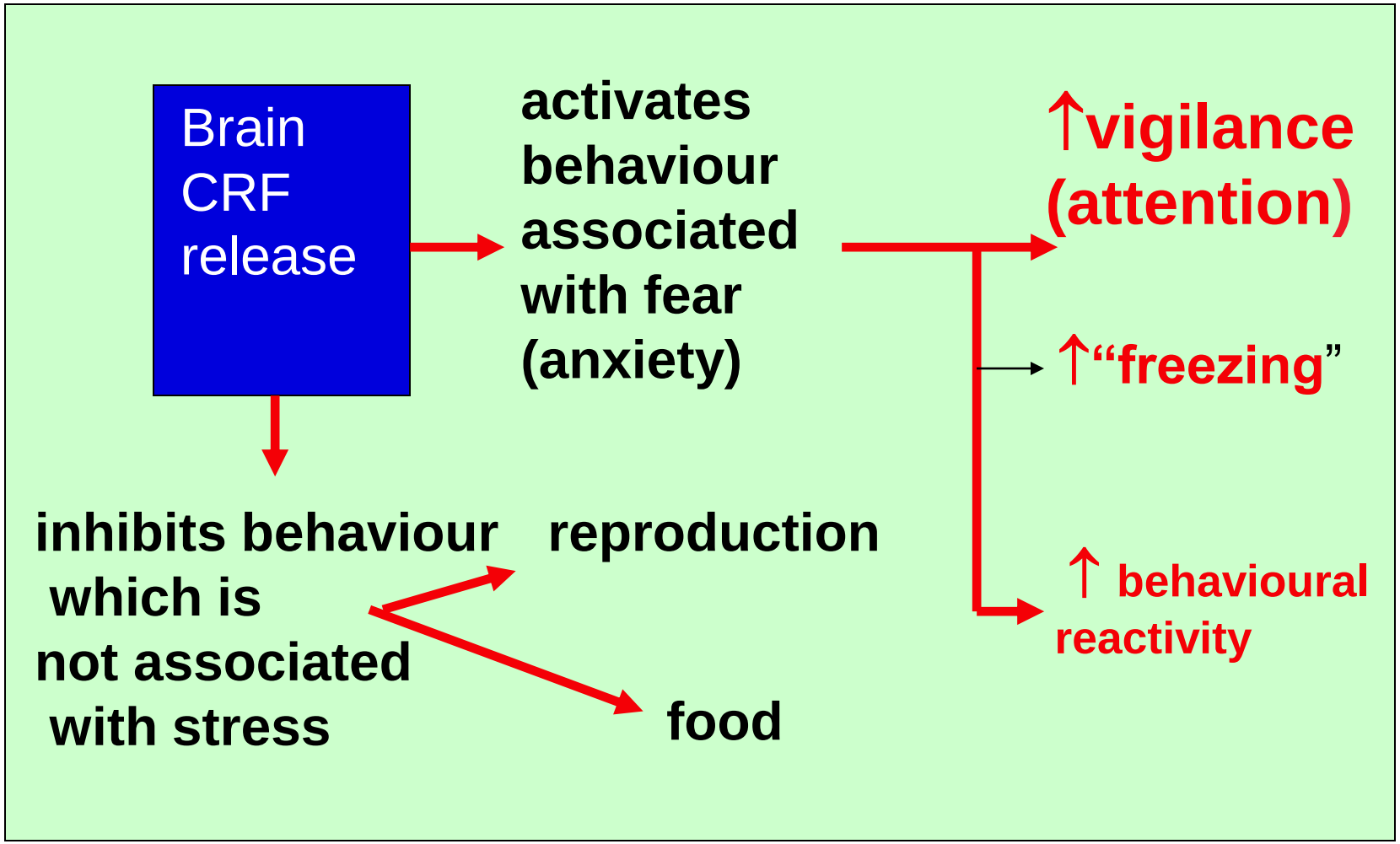
Alarm reaction "fight or flight"



Acute stress response: behavioral alterations caused by CRF release



Autonomic nervous system

Parasympathetic nervous system

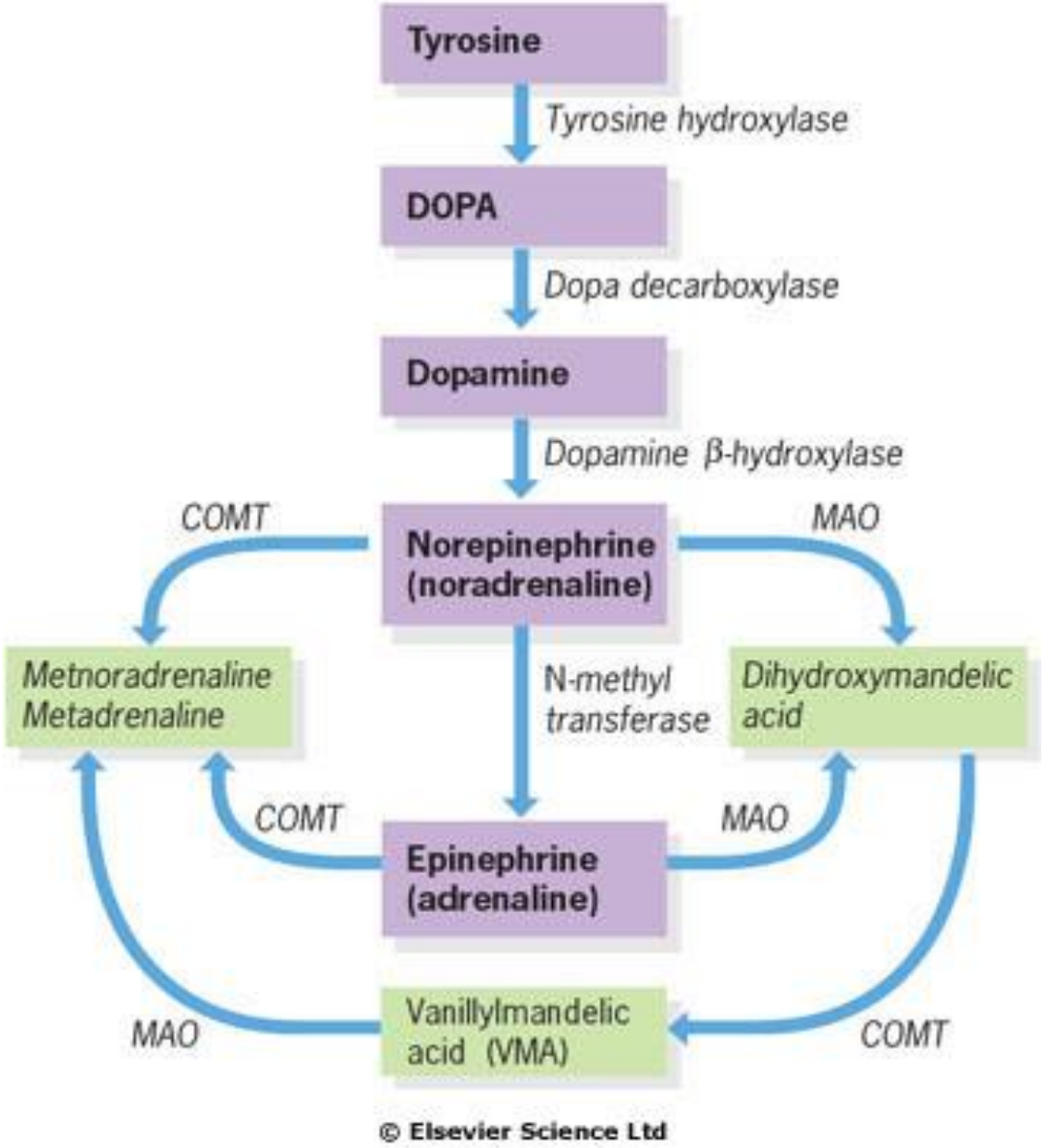
↑ digestion
↑ salivation
↓ heart rate
↑ intestine perfusion

rest state

Sympathetic nervous system

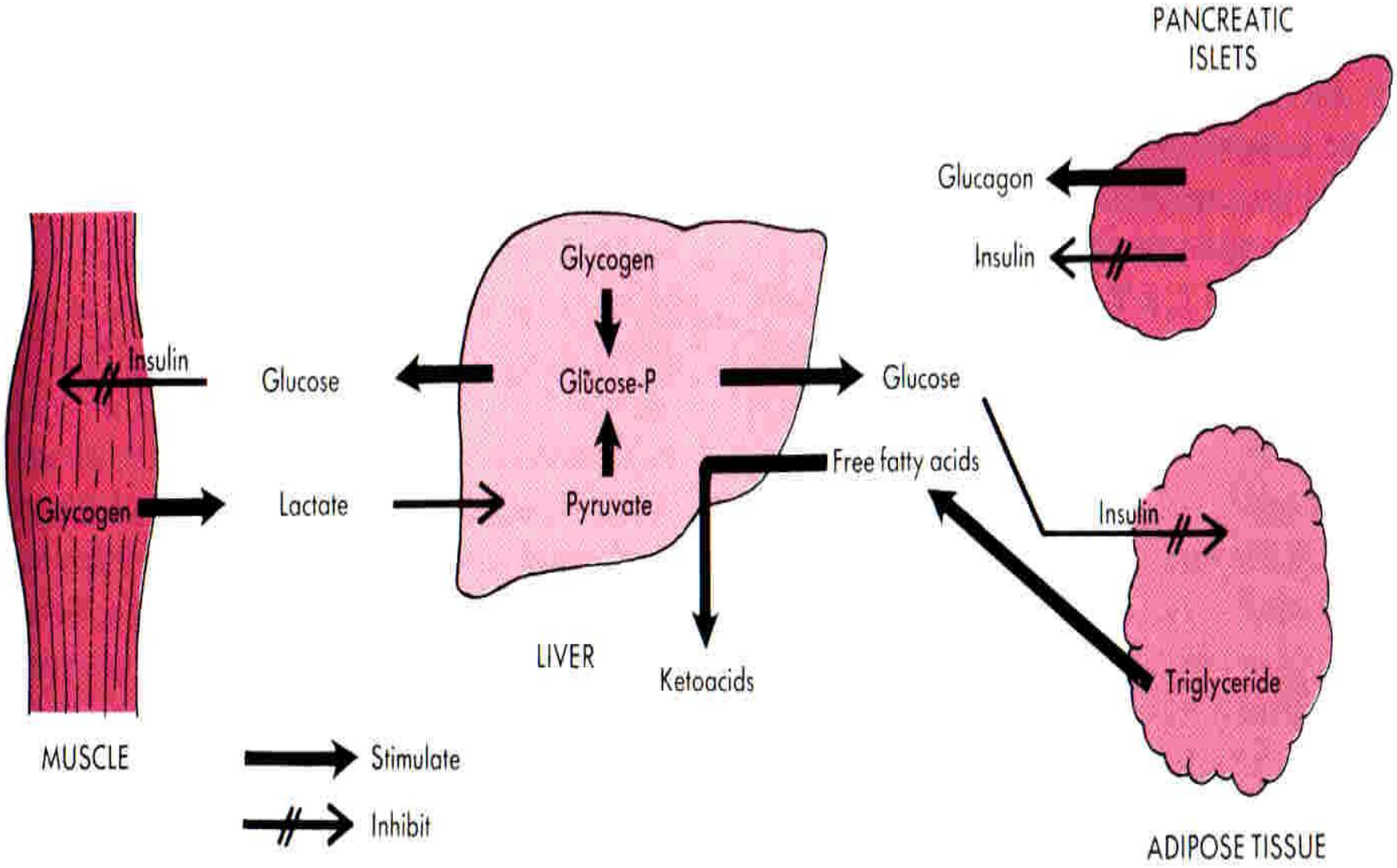
"F& F" response

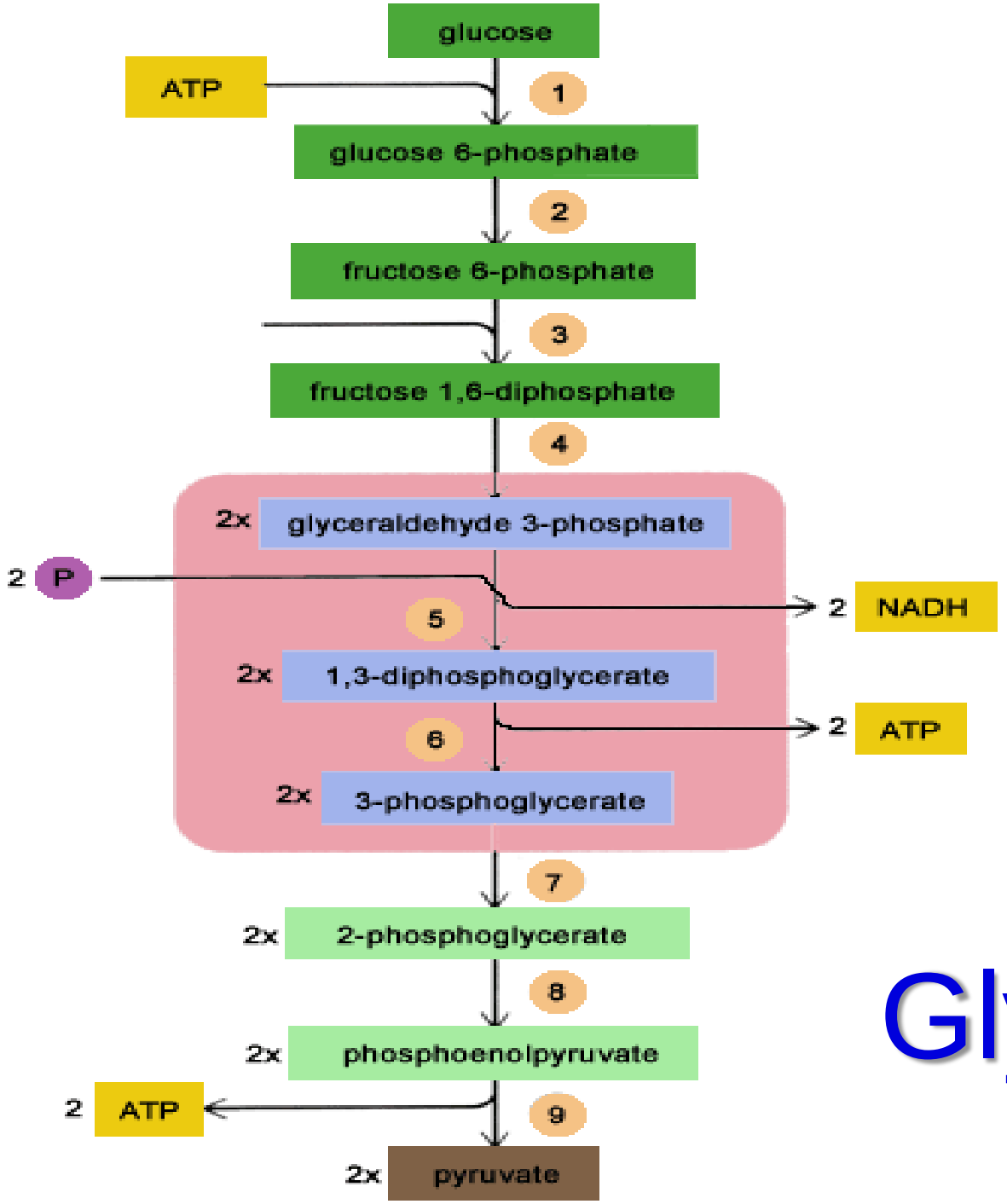
↓digestion
↓ salivation
↑ heart rate
↑ respiration
✓blood redistribution from intestine to muscles, brain and heart
✓ increased activity and vigilance



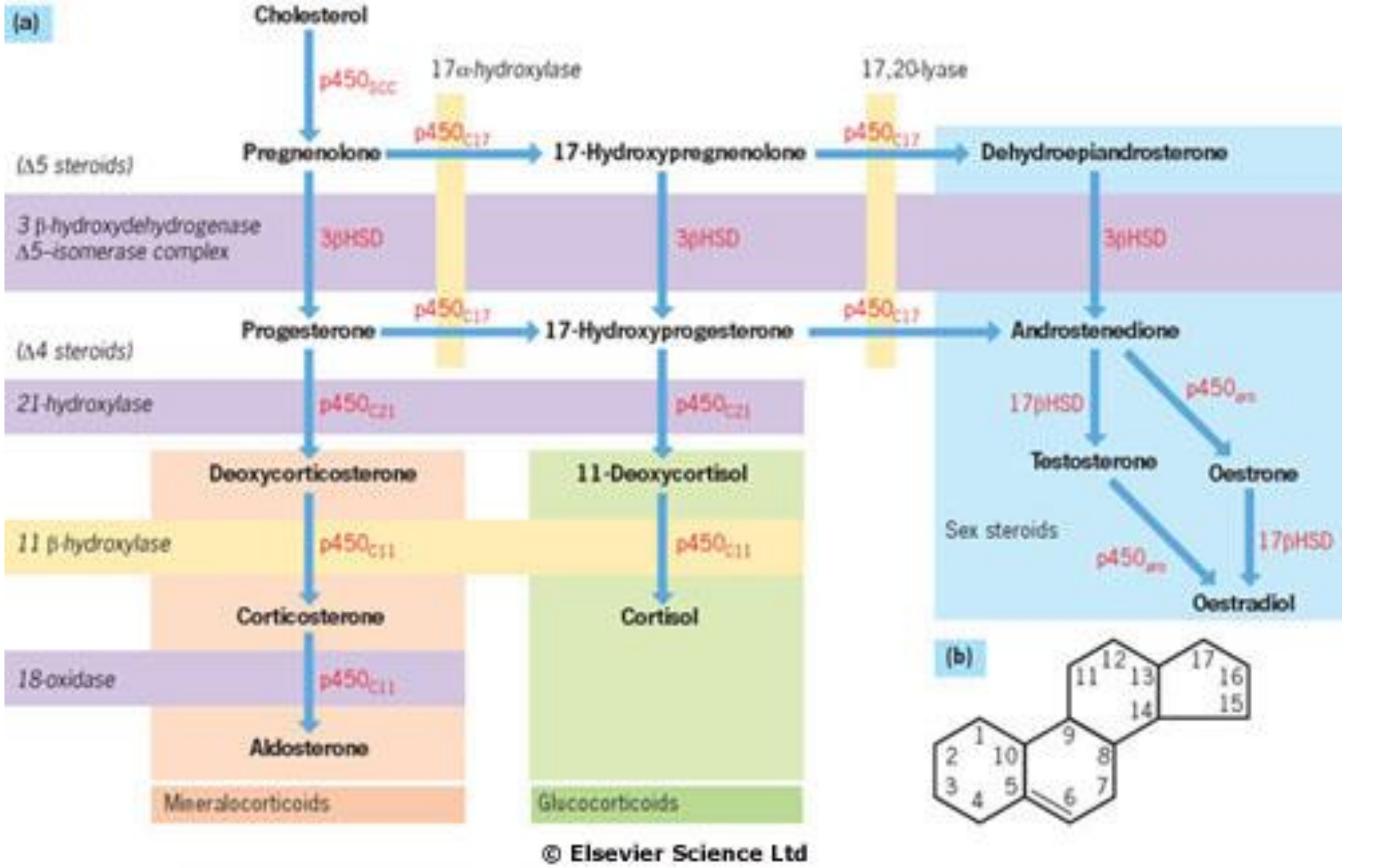
Catecholamines synthesis and metabolism

Metabolic effects of epinephrine




glucose
ATP
1
glucose 6-phosphate
2
fructose 6-phosphate
3
fructose 1,6-diphosphate
4
2x
glyceraldehyde 3-phosphate
2
P
2
NADH
5
2x
1,3-diphosphoglycerate
2
ATP
6
2x
3-phosphoglycerate
7
2x
2-phosphoglycerate
8
2x
phosphoenolpyruvate
2
ATP
9
2x
pyruvate

Glycolysis



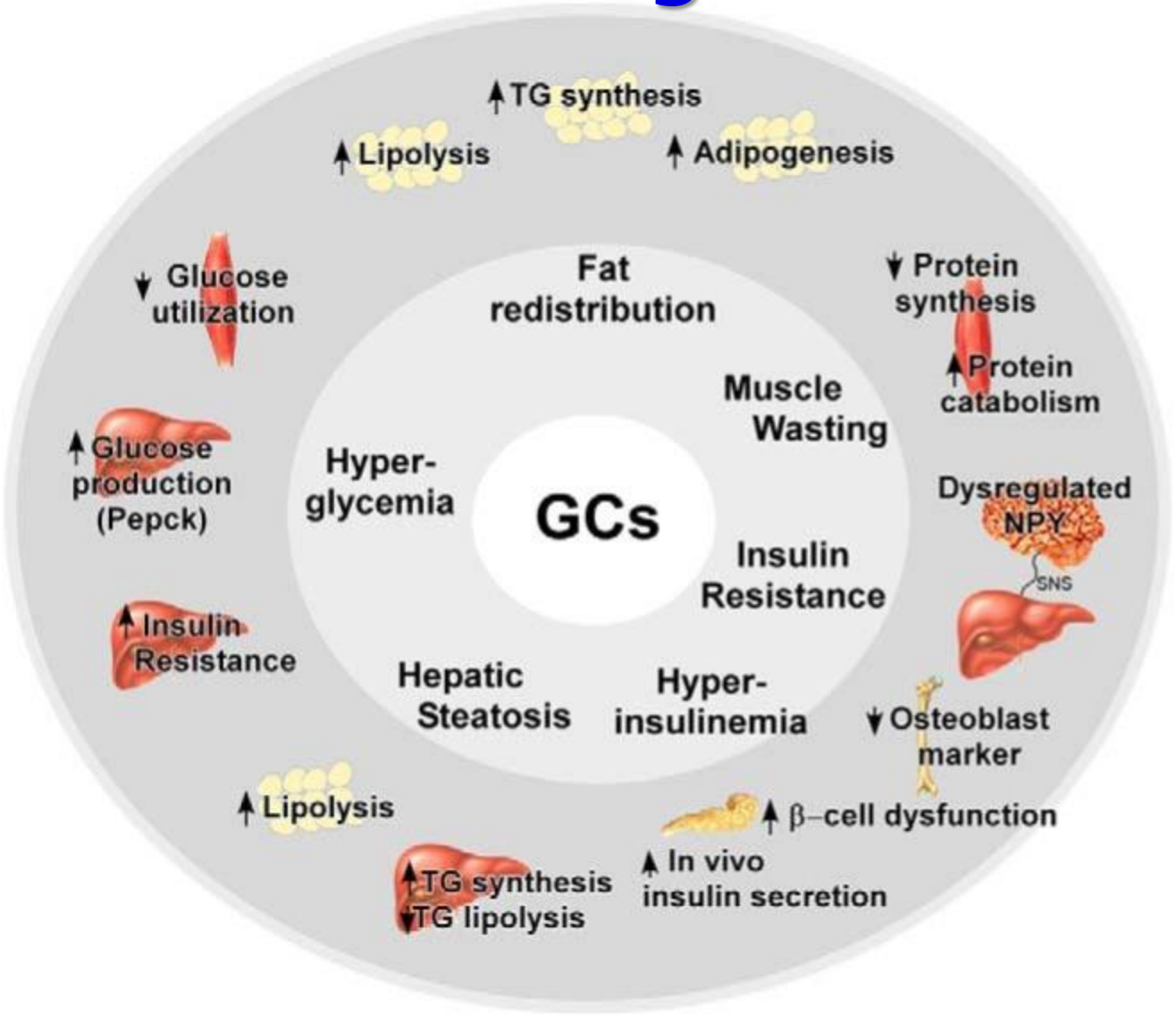
(a) The major steroid biosynthetic pathways. Enzymes catalysing reactions are in red: p450 enzymes are in mitochondria and each catalyses several reaction steps; 3βHSD (hydroxysteroid dehydrogenase) is in cytoplasm, bound to endoplasmic reticulum; 17βHSD and $p450_{aro}$ are found mainly in gonads. **(b) The steroid molecule.**

Table 18.27

The major actions of glucocorticoids

Increased or stimulated	Decreased or inhibited
Gluconeogenesis	Protein synthesis
Glycogen deposition	Host response to infection
Protein catabolism	Lymphocyte transformation
Fat deposition	Delayed hypersensitivity
Sodium retention	Circulating lymphocytes
Potassium loss	Circulating eosinophils
Free water clearance	
Uric acid production	
Circulating neutrophils	

Metabolic effects of glucocorticoids



Patel R et al., Mol Endocrinol. 2014 Jul; 28(7): 999–1011.

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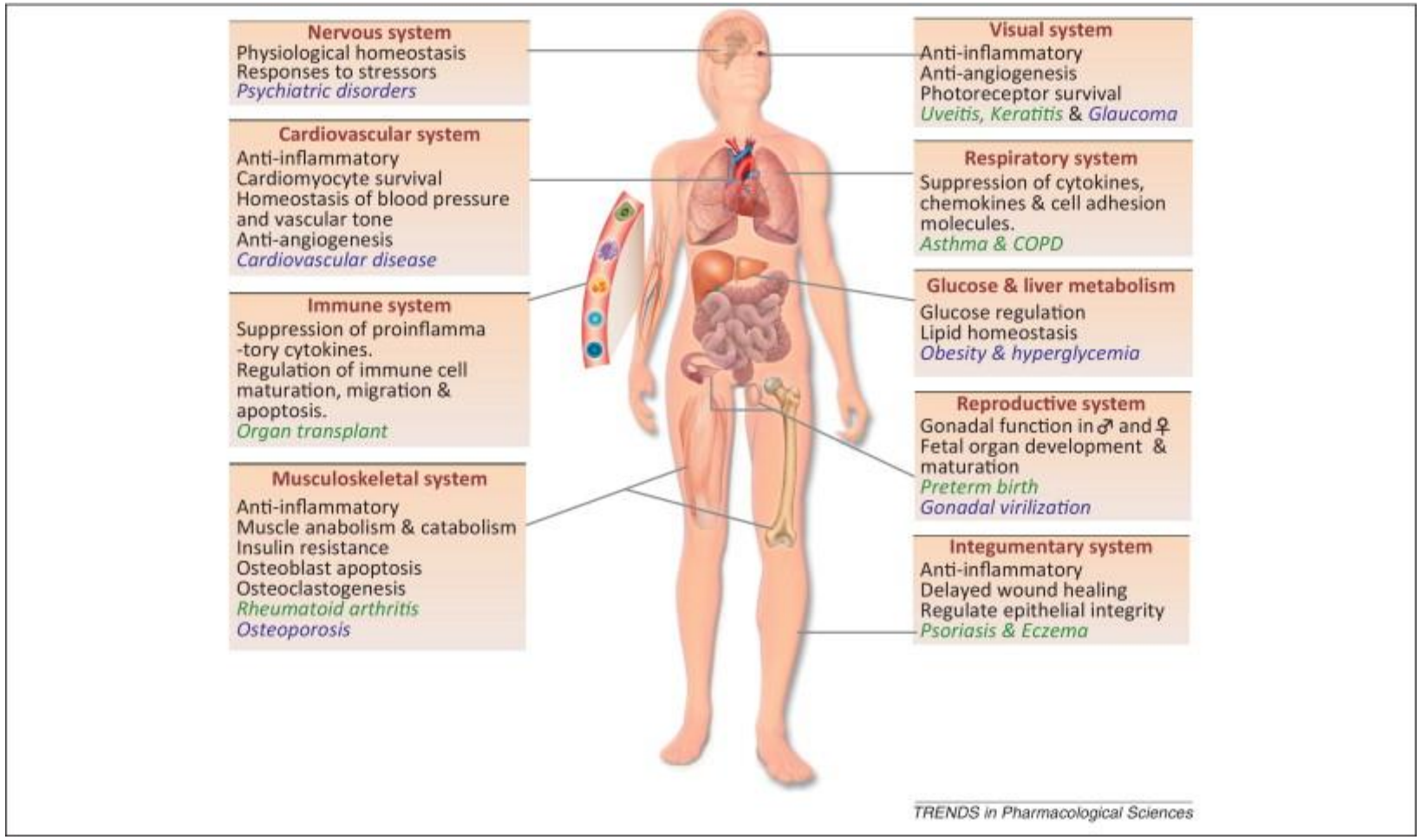
Glucocorticoid effects on body systems



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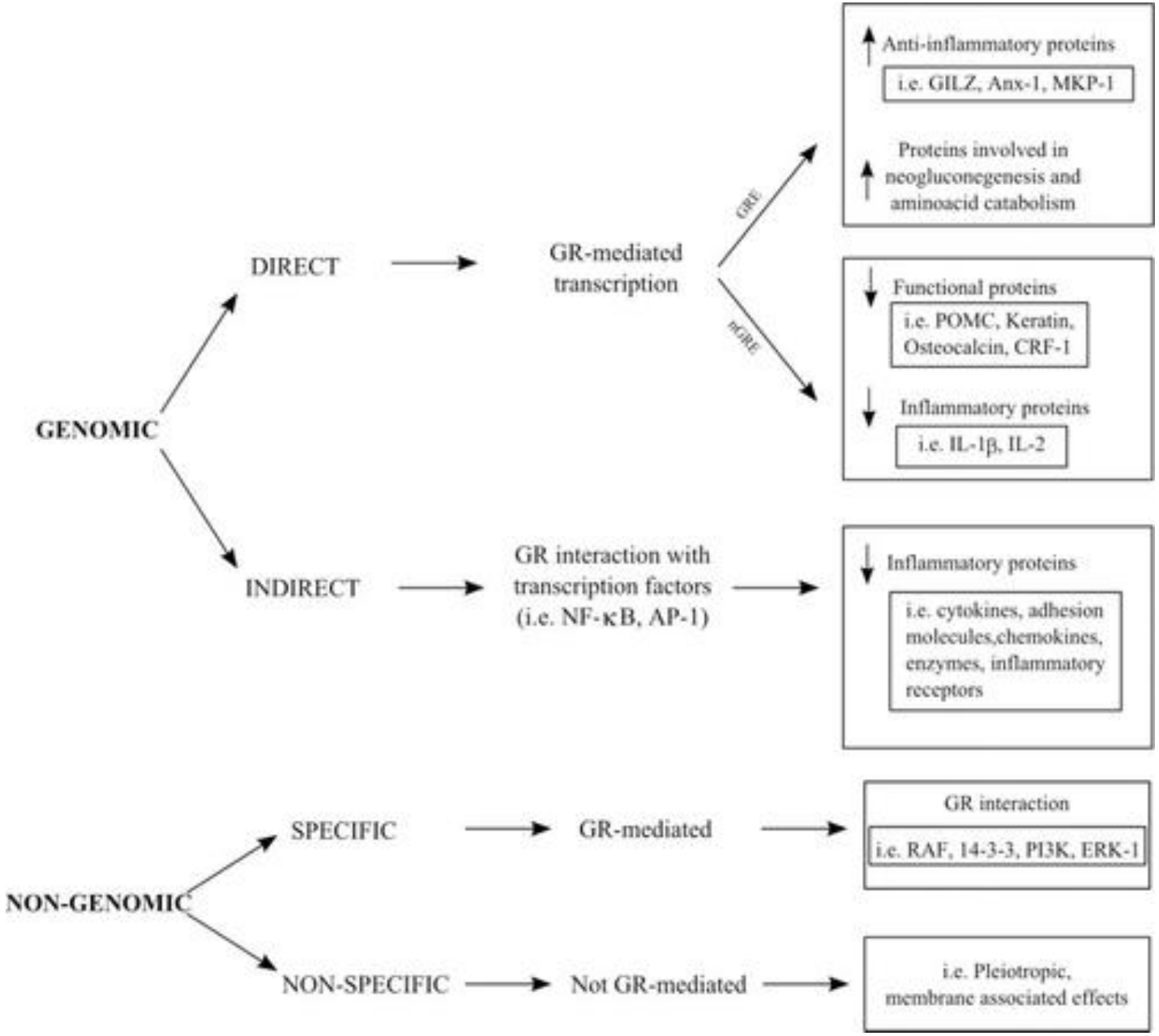
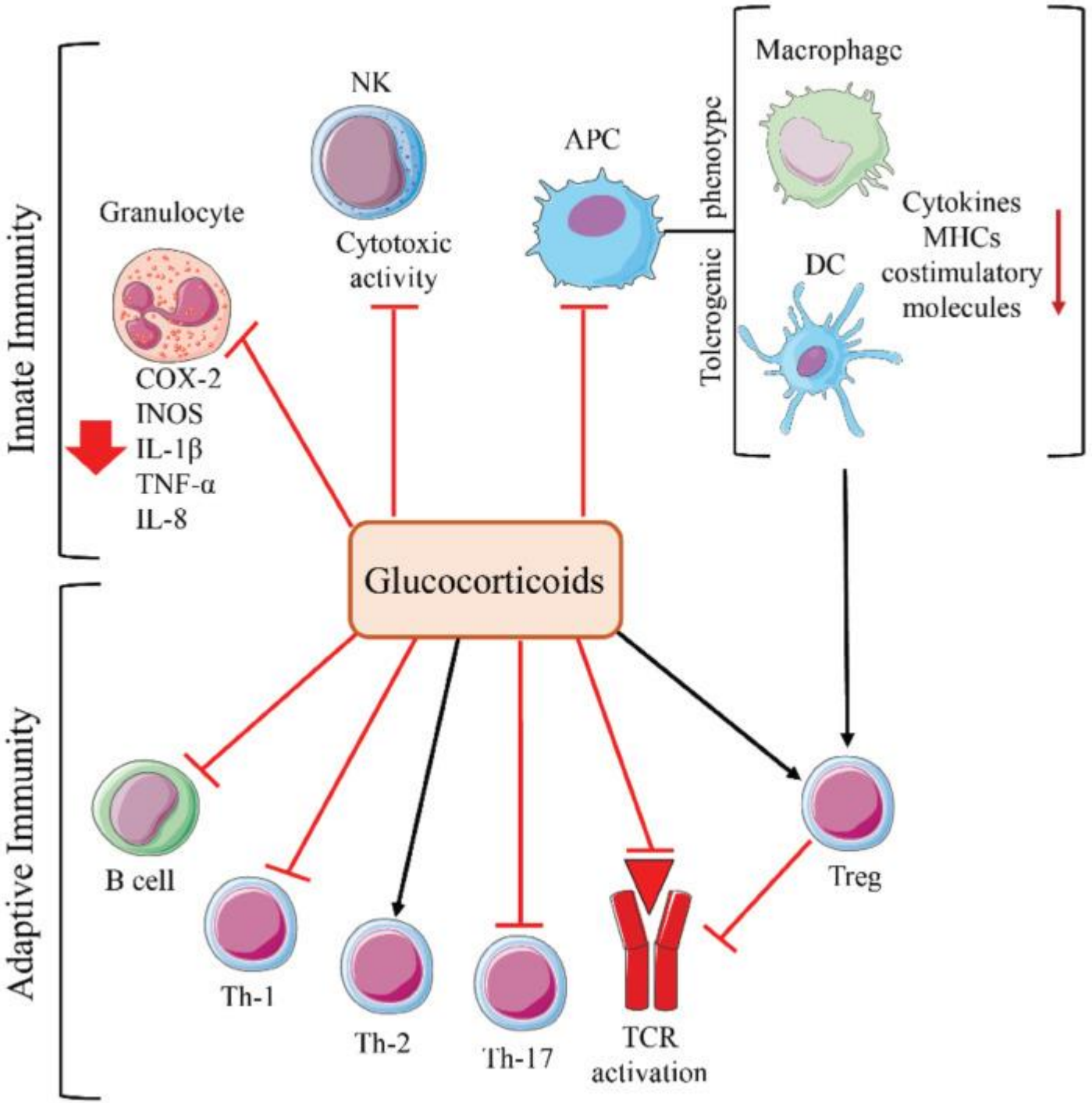


Genomic and non genomic effects of glucocorticoids

Patel R et al., Mol Endocrinol. 2014 Jul; 28(7): 999–1011



Adorisio S. Cells. 2021 Sep; 10(9): 2333.

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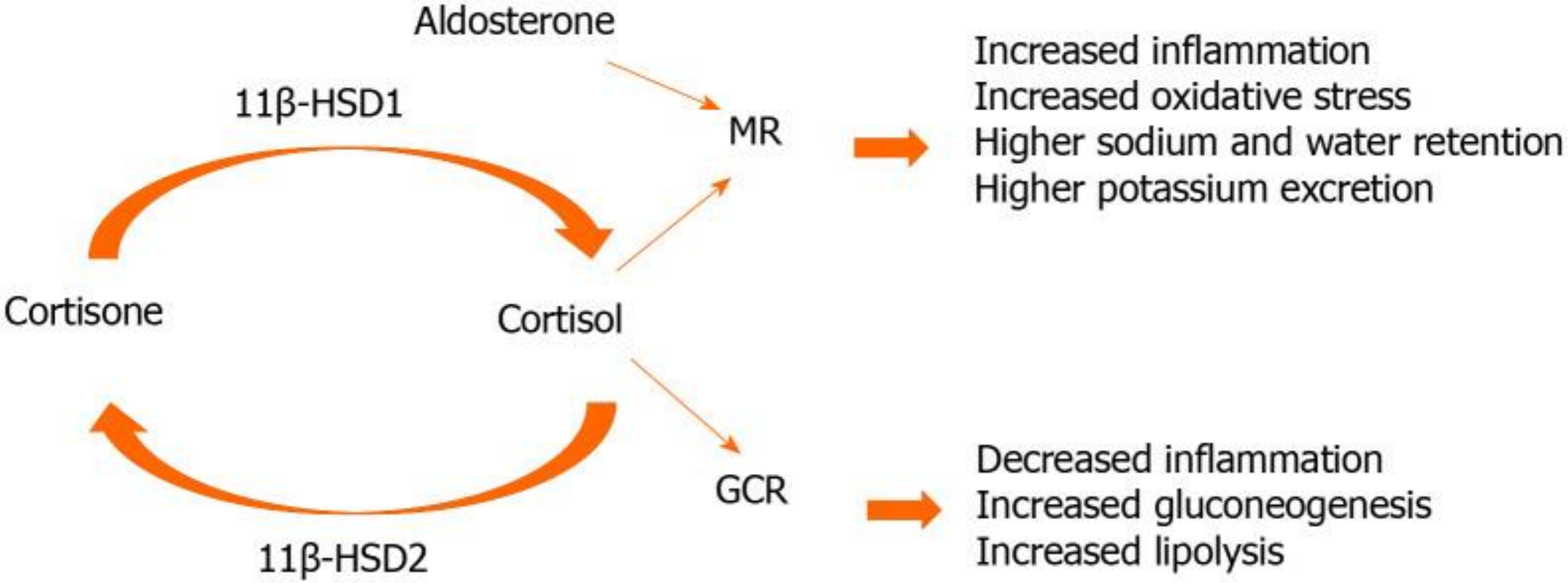

Vassiliou AG et al., *World J Crit Care Med* 2021; 10(4): 102-111

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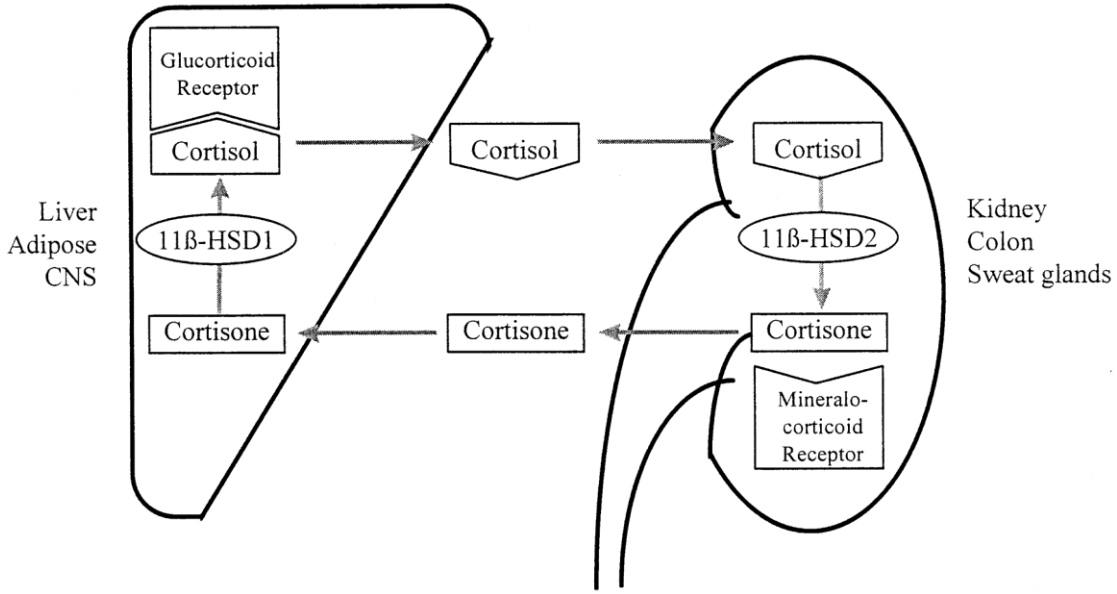
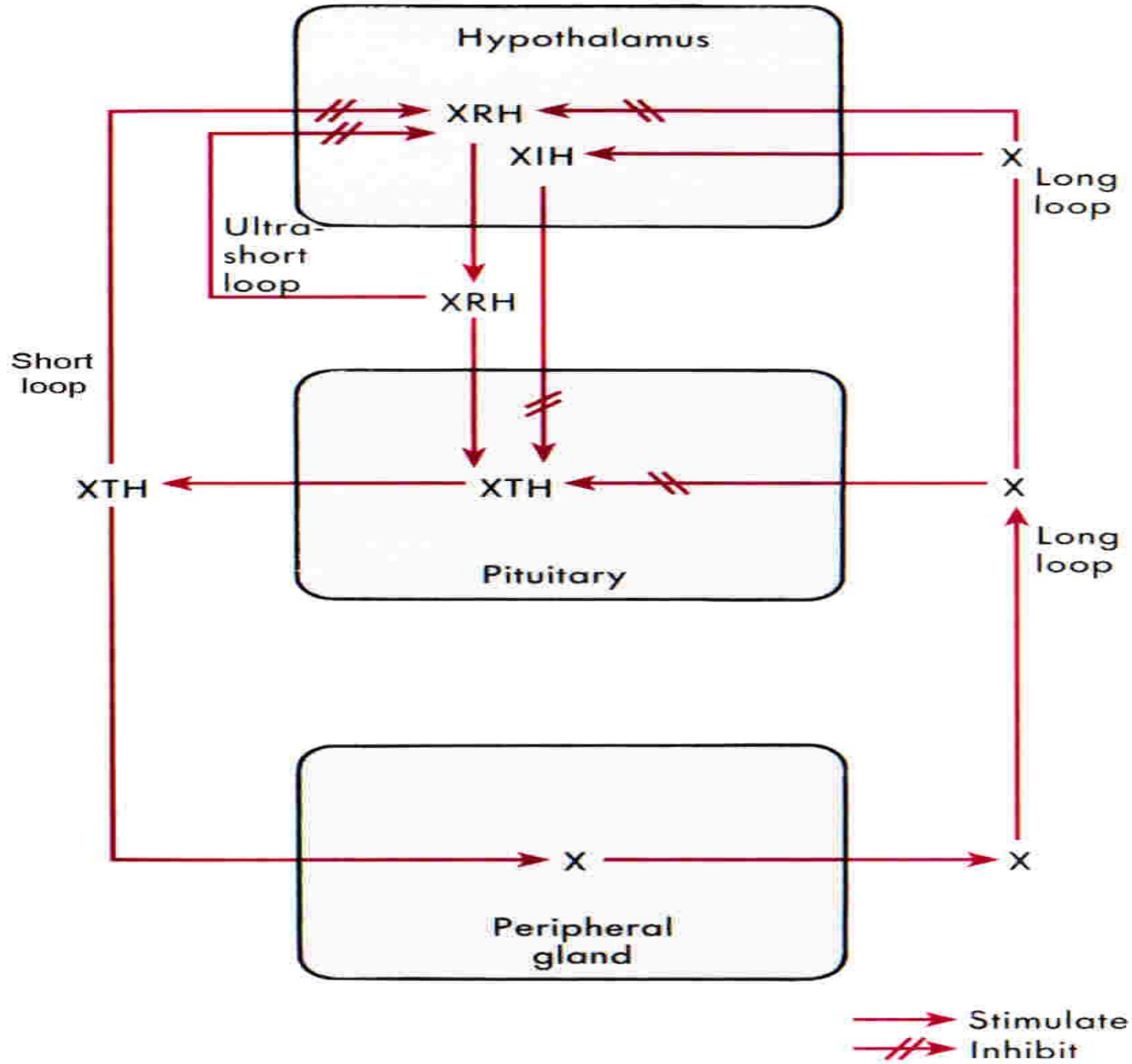
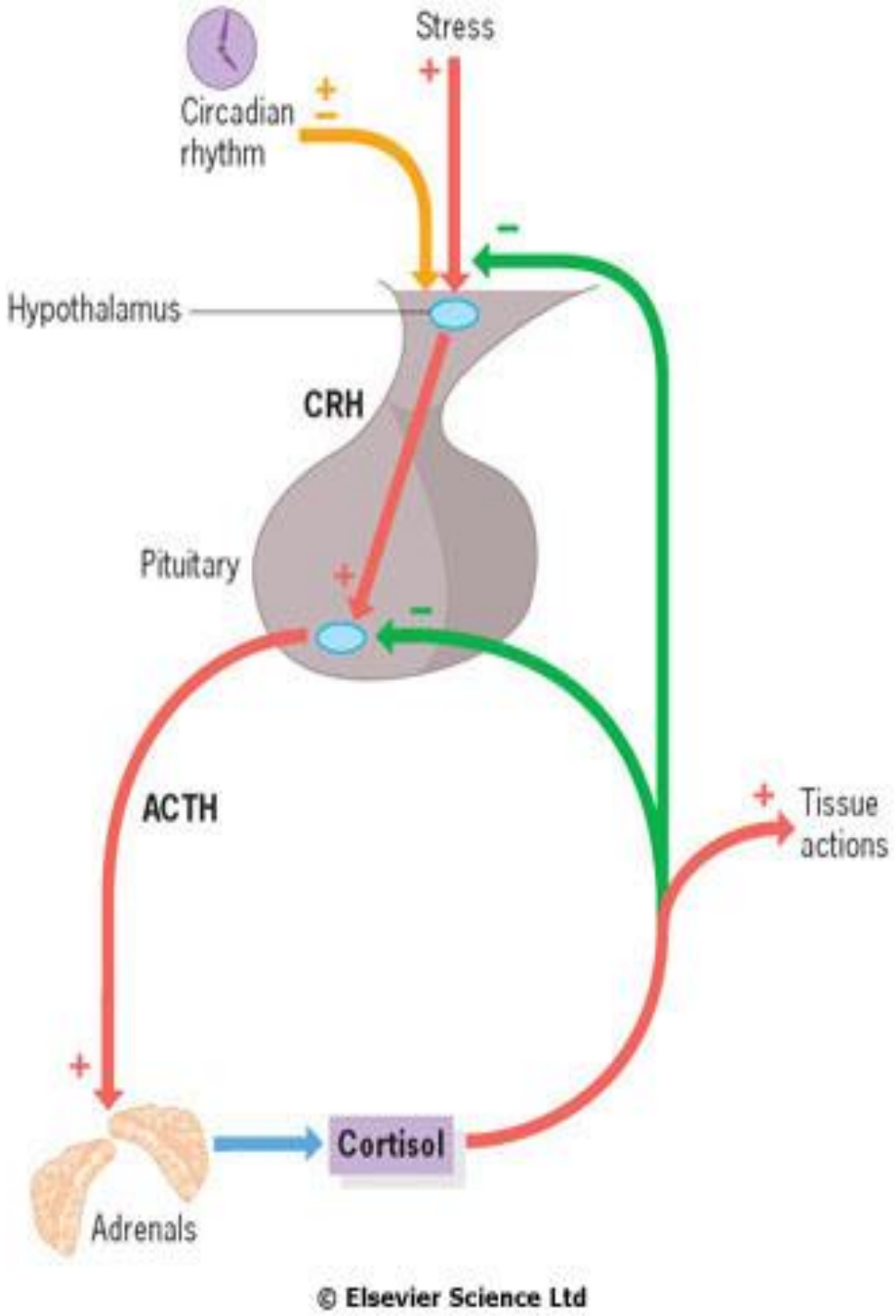
Figure 1. Contrasting functions of the isozymes of 11ß-HSD. 11ß-HSD2 is an exclusive 11ß-dehydrogenase that acts in ...

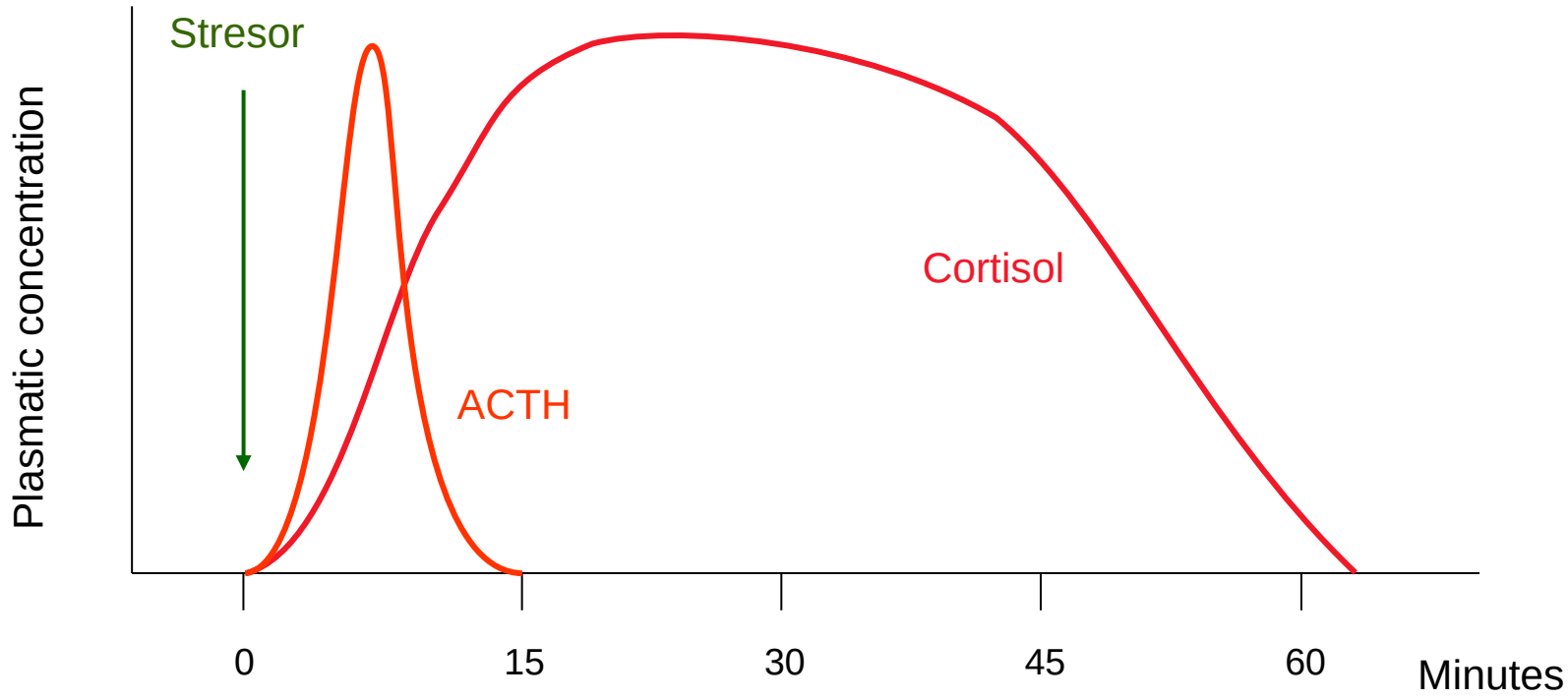


Endocrinology, Volume 142, Issue 4, 1 April 2001, Pages 1371–1376, https://doi.org/10.1210/endo.142.4.8114


Hypothalamus
XRH
XIH
X
Long loop
Ultra-short loop
XRH
Short loop
XTH
XTH
X
Pituitary
Long loop
X
X
Peripheral gland
Stimulate
Inhibit

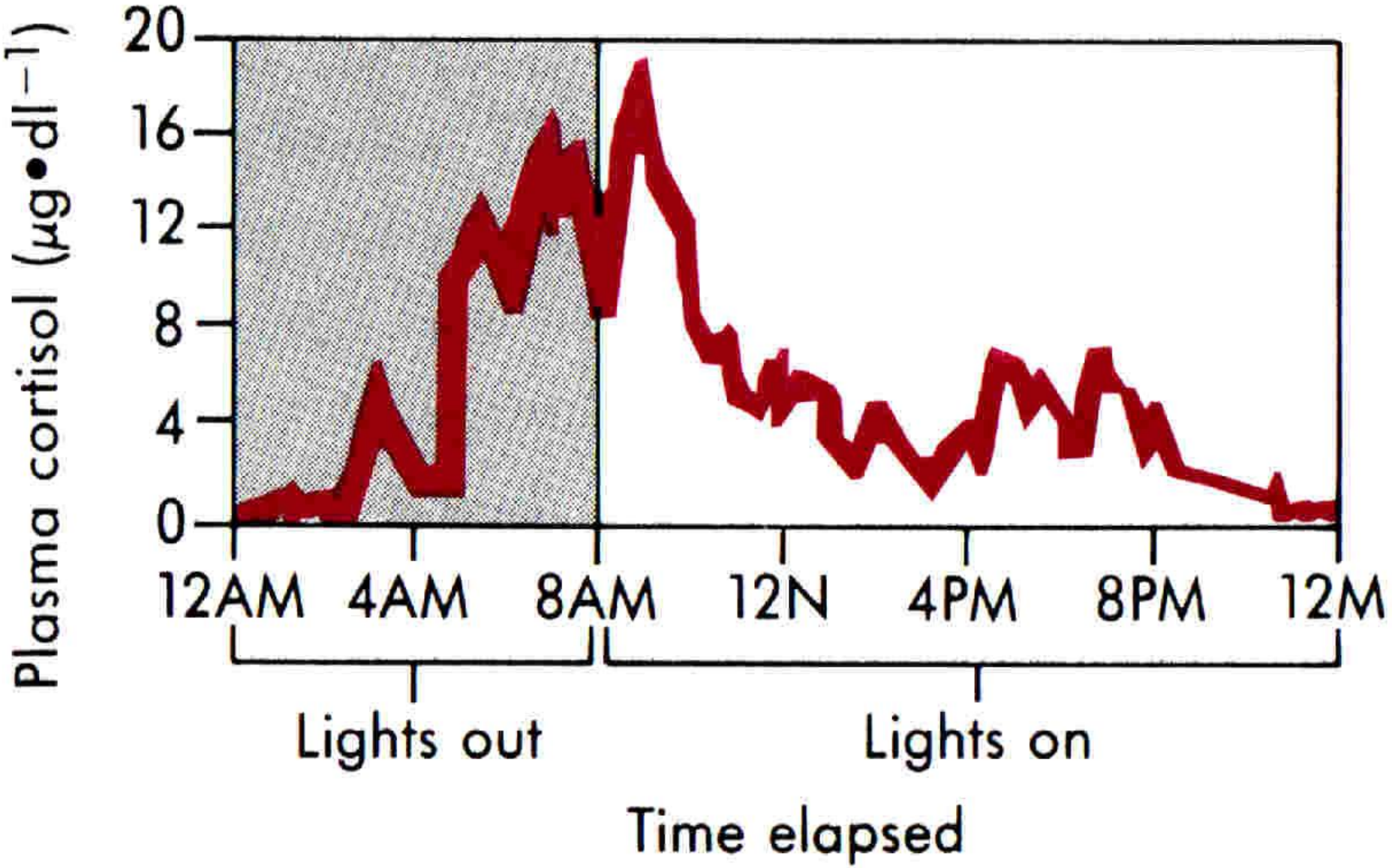


Control of the hypothalamic-pituitary adrenal axis. CRH, corticotropin-releasing hormone.

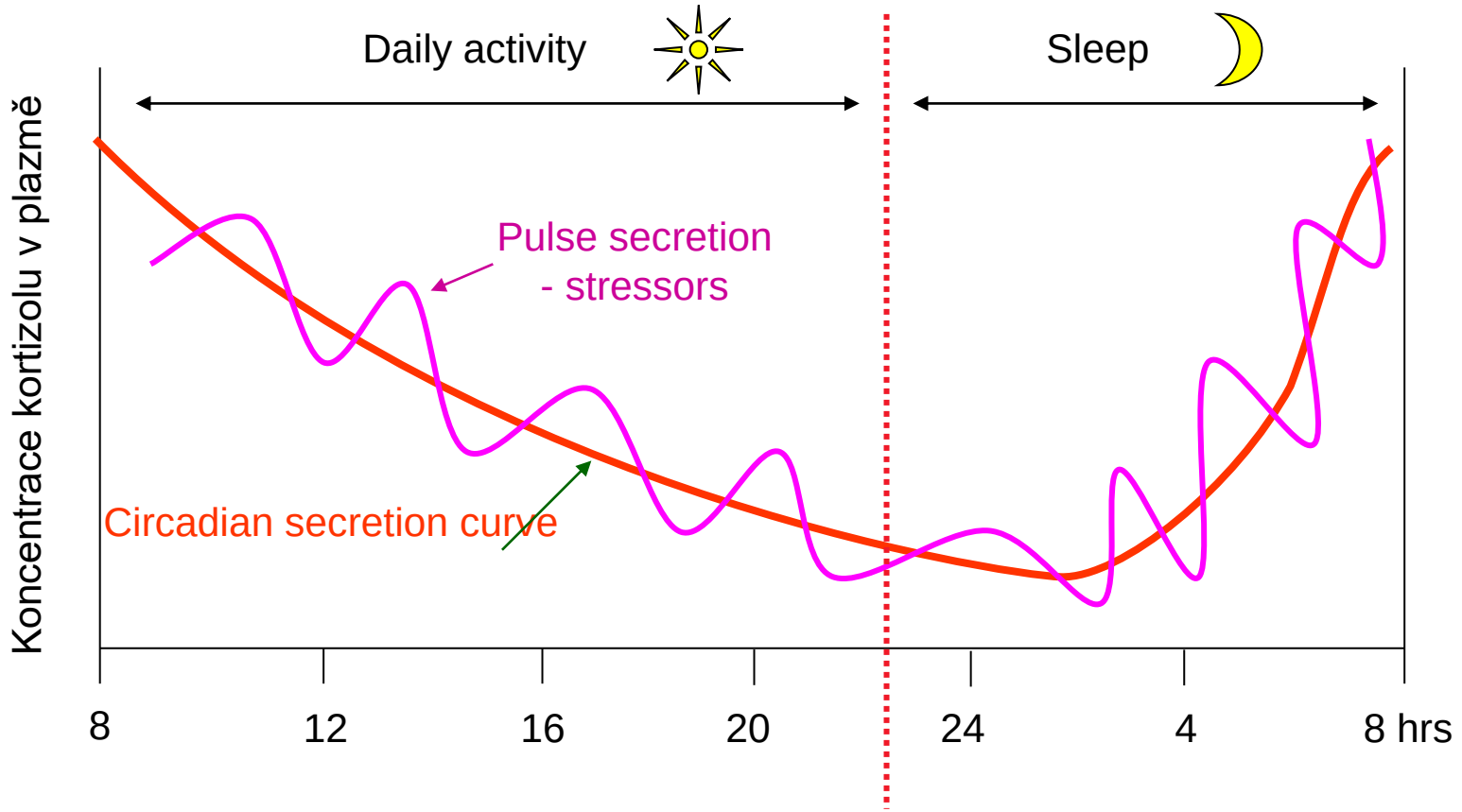


(Podle Felker B and Hubbard JR: In Handbook of Stress Medicine, CRC Press, Boca Raton, FL, 1998)

Pulsatile and diurnal character of glucocorticoid secretion



Pulse and diurnal secretion of glucocorticoids



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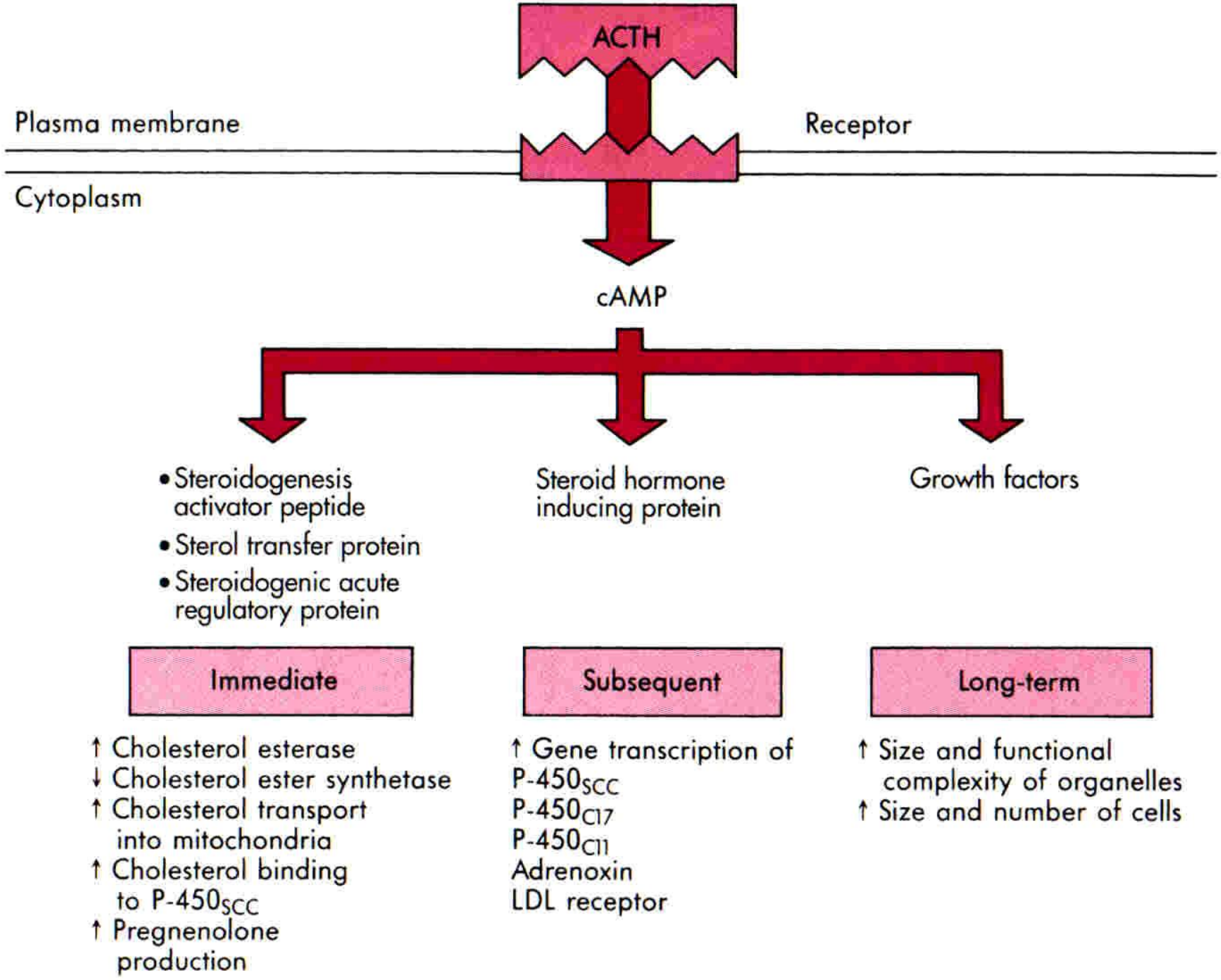
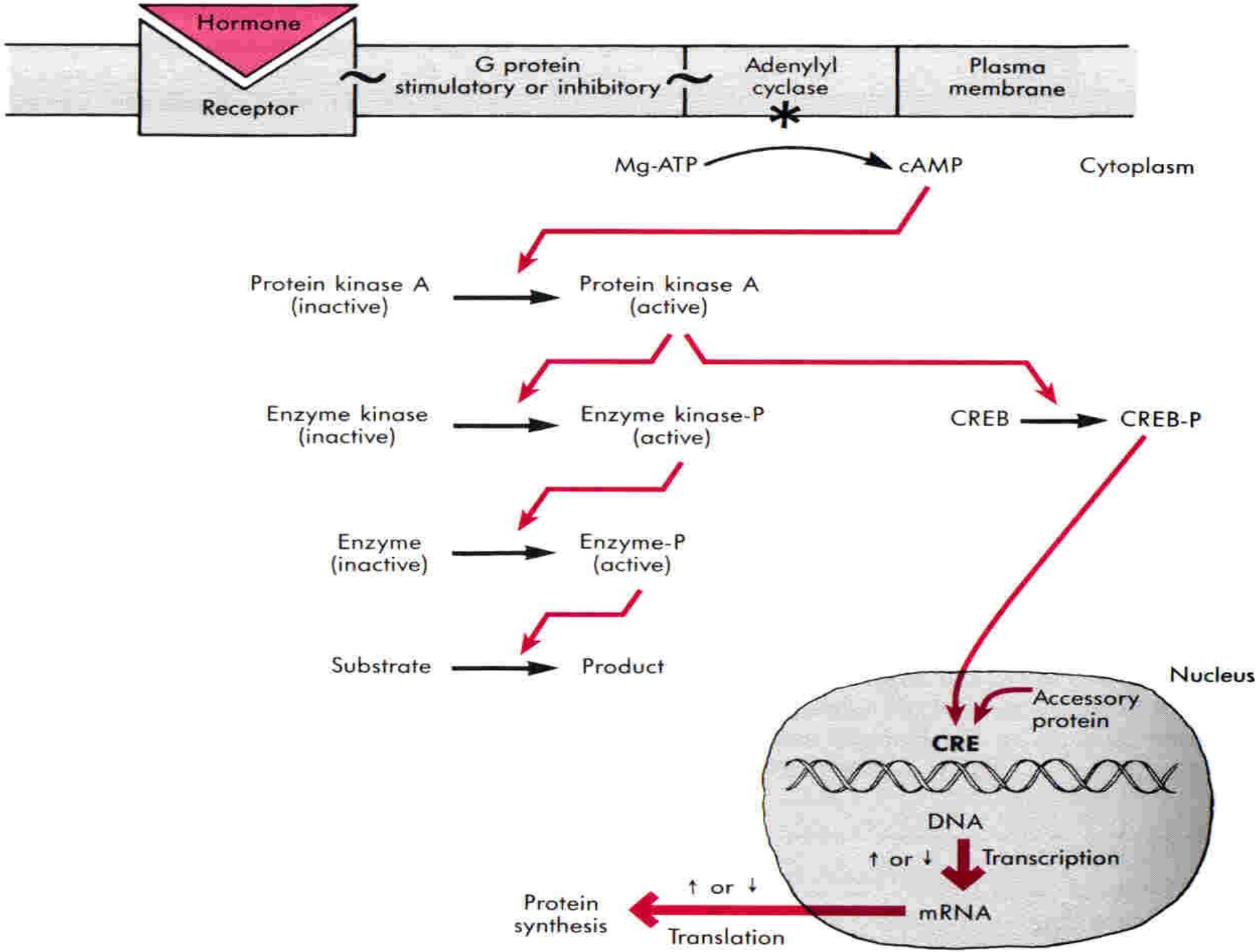
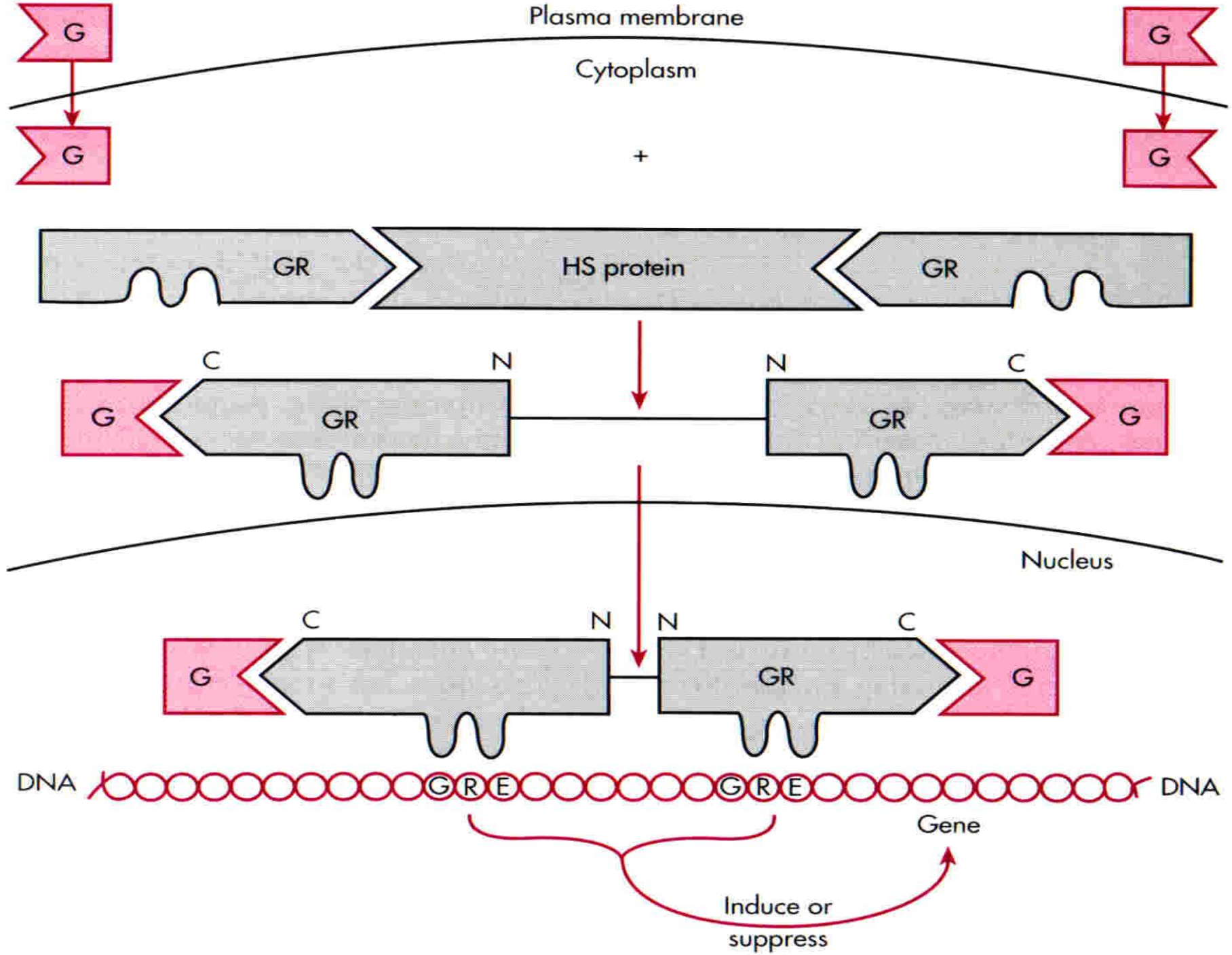
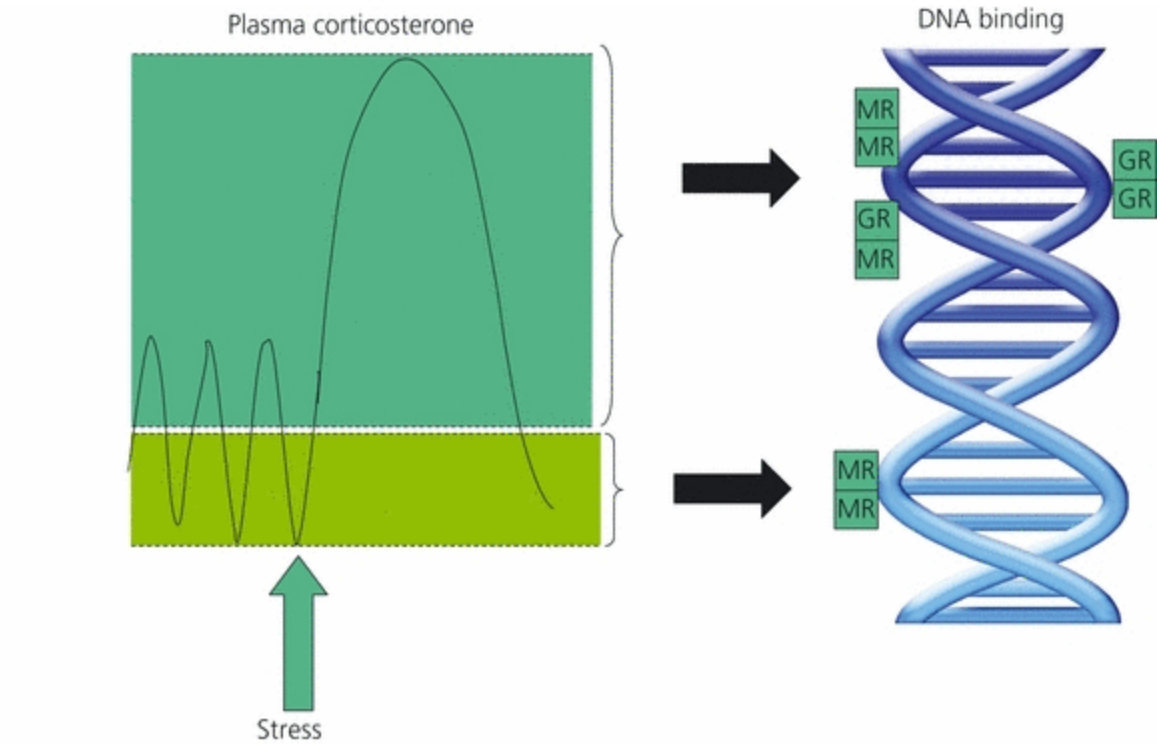

ACTH
Plasma membrane
Receptor
Cytoplasm
cAMP
• Steroidogenesis activator peptide
• Sterol transfer protein
• Steroidogenic acute regulatory protein
Steroid hormone inducing protein
Growth factors
Immediate
Subsequent
Long-term
↑ Cholesterol esterase
↓ Cholesterol ester synthetase
↑ Cholesterol transport into mitochondria
↑ Cholesterol binding to P-450SCC
↑ Pregnenolone production
↑ Gene transcription of
P-450SCC
P-450C17
P-450C11
Adrenoxin
LDL receptor
↑ Size and functional complexity of organelles
↑ Size and number of cells

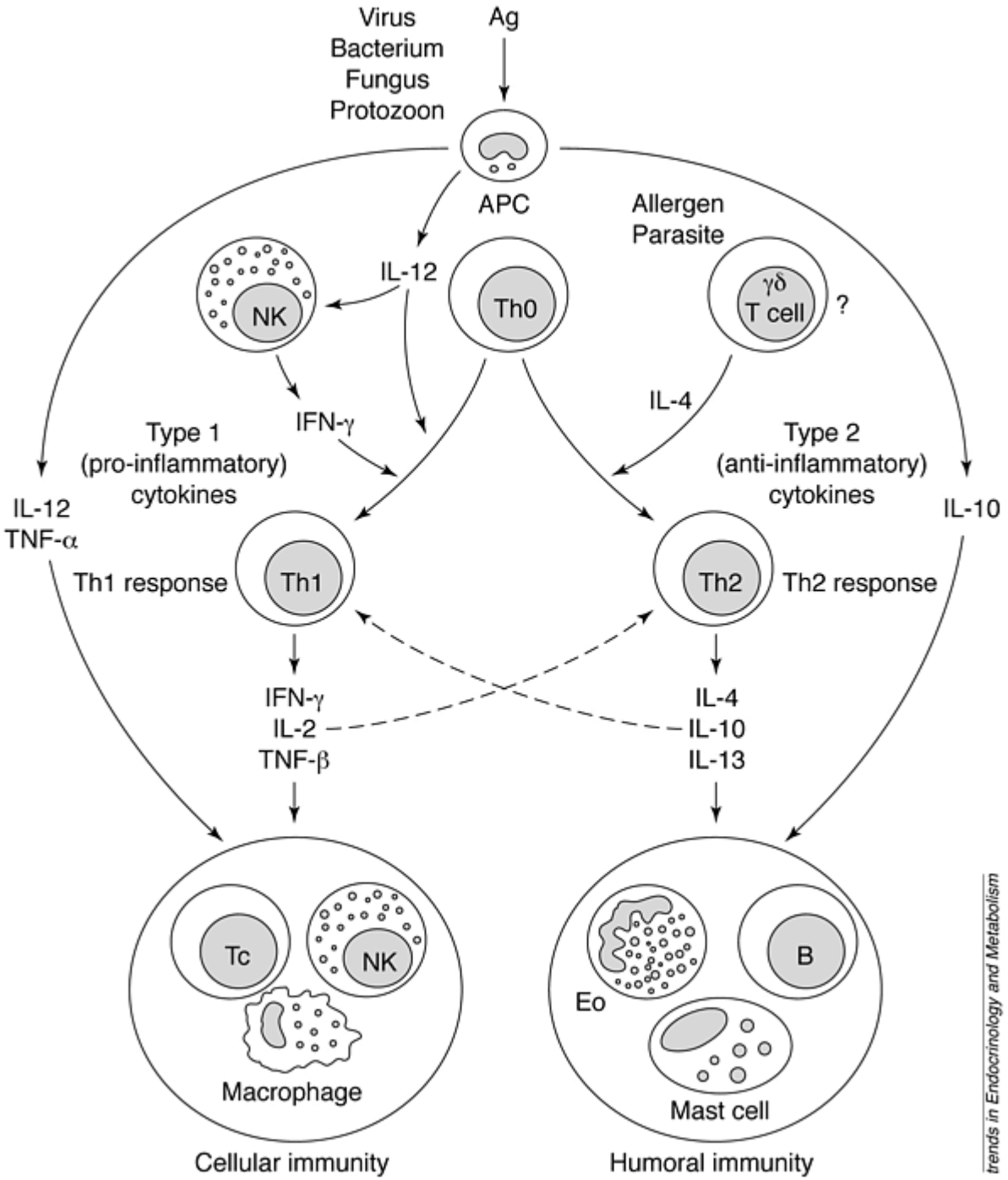

Hormone
Receptor
G protein
stimulatory or inhibitory
Adenylyl
cyclase
Plasma
membrane
Mg-ATP
cAMP
Cytoplasm
Protein kinase A
(inactive)
Protein kinase A
(active)
Enzyme kinase
(inactive)
Enzyme kinase-P
(active)
CREB
CREB-P
Enzyme
(inactive)
Enzyme-P
(active)
Substrate
Product
Nucleus
Accessory
protein
CRE
DNA
↑ or ↓
Transcription
mRNA
↑ or ↓
Protein
synthesis
Translation


Plasma membrane
Cytoplasm
G
G
+
G
G
GR
HS protein
GR
C
N
N
C
G
GR
GR
G
Nucleus
C
N
N
C
G
GR
G
DNA
G R E
G R E
DNA
Gene
Induce or
suppress

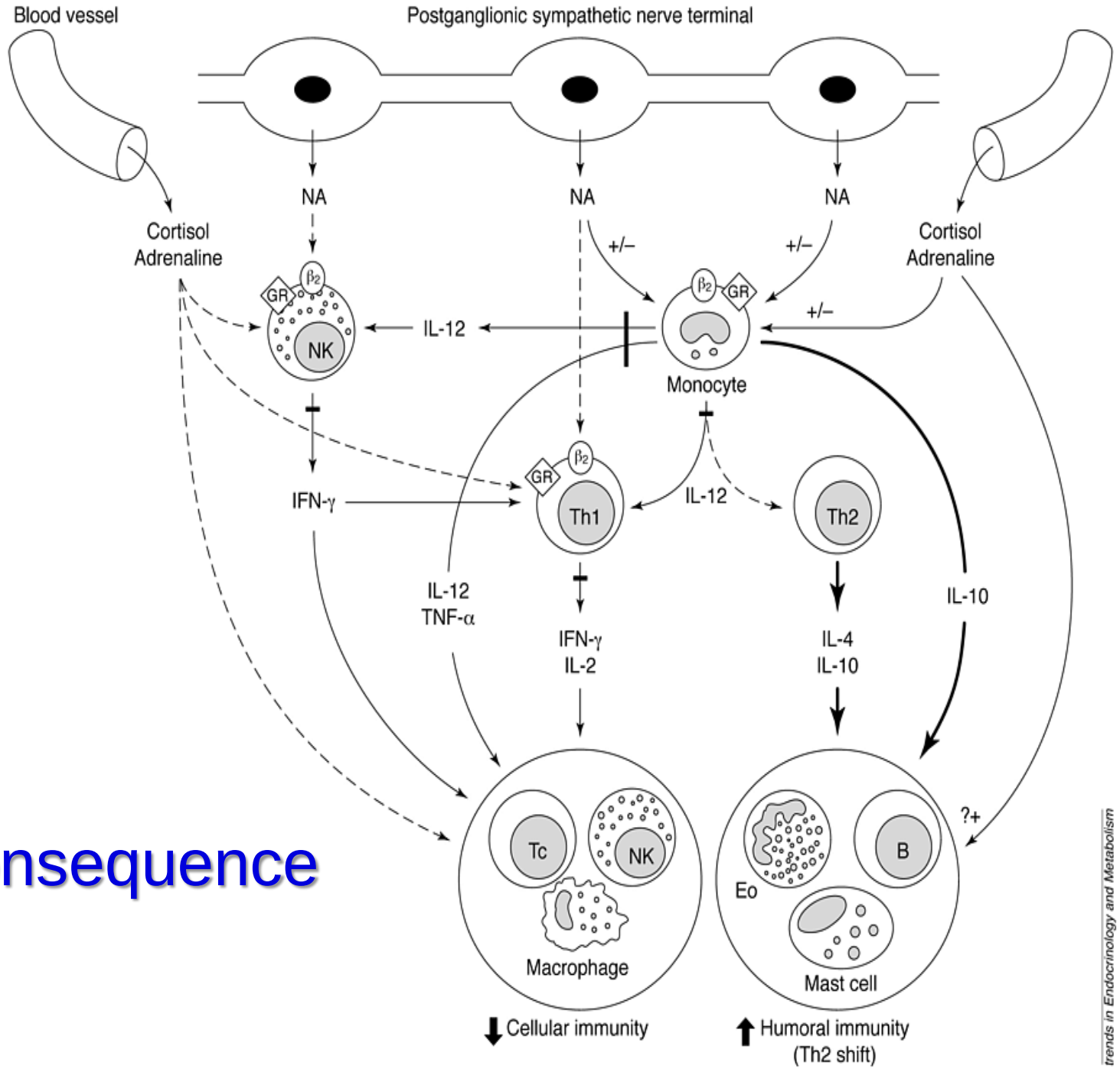


The effect of glucocorticoid pulses and an acute stressor on glucocorticoid responsive genes. Note that, at nadir levels of corticosterone, there is only mineralocorticoid receptor (MR) binding to DNA but that, at peak and stress levels, there is both glucocorticoid receptor and MR binding.

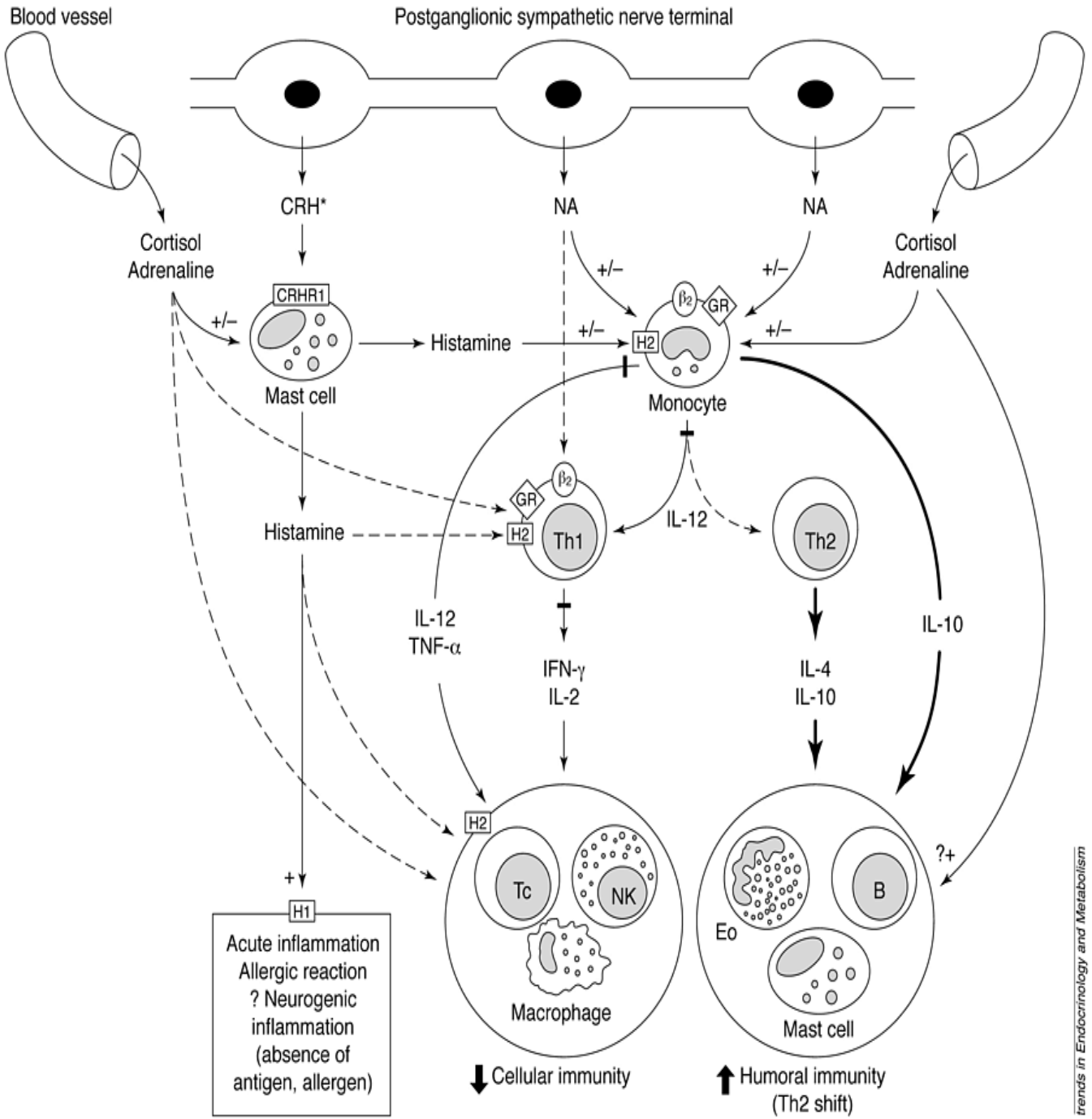
Balance of Th1/Th2 immune resposes



Th2 shift as a consequence of stress



Th2 shift
as a consequence of stress and acute inflammation



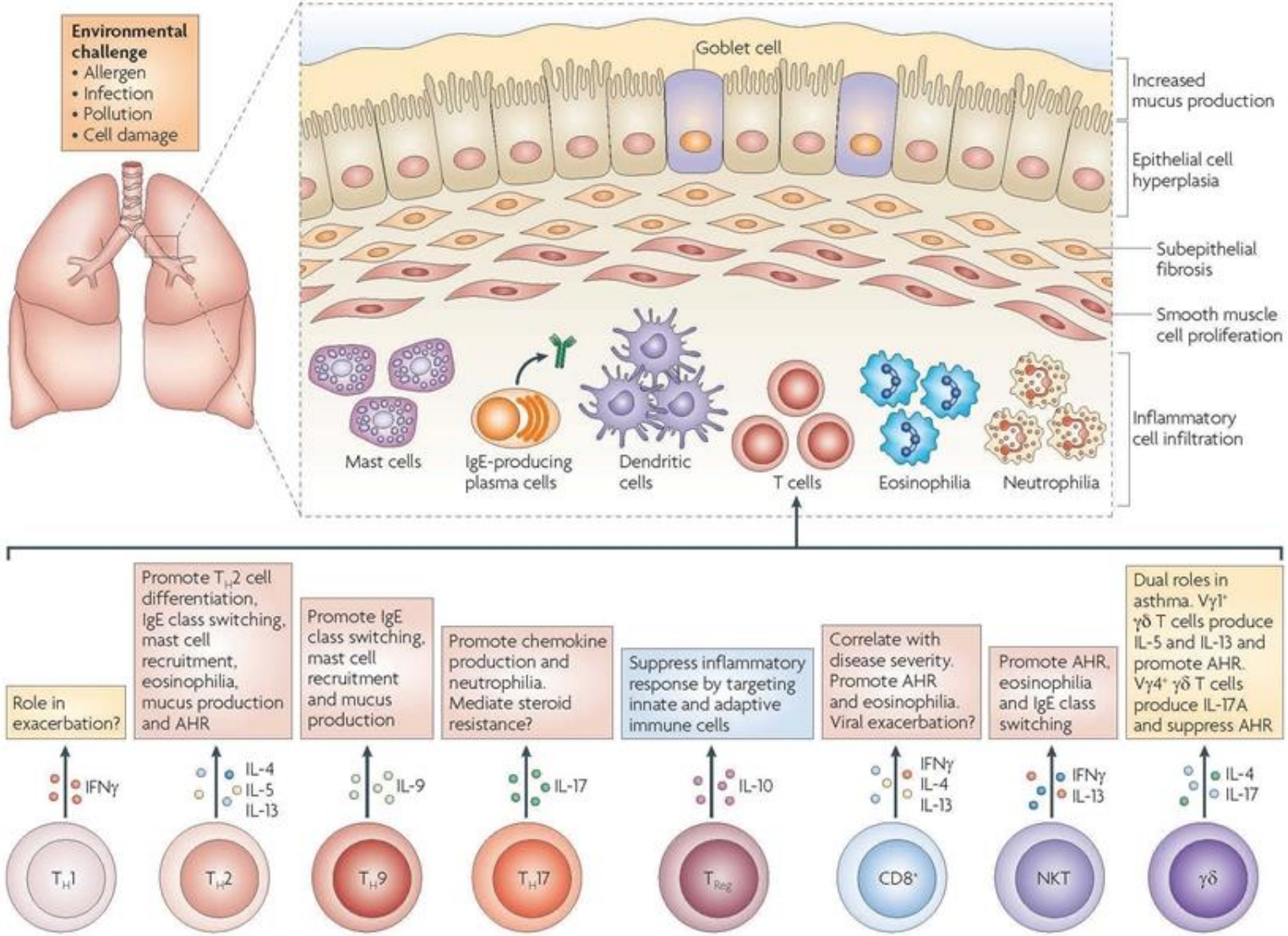


Figure 1 | **T cells involved in the induction of the allergic phenotype.** Asthma is a heterogeneous disease that is characterized by airway hyperresponsiveness (AHR), recruitment of inflammatory leukocytes to the lung and tissue remodelling, including mucus production and airway smooth muscle changes. A number of different T cell subsets are thought to influence the nature and magnitude of the allergic immune response by the cytokines that they secrete. T helper 2 (T_H2) cells are thought to promote eosinophil recruitment, in conjunction with nature killer T (NKT) cells and $CD8^+$ T cells. By contrast, T_H1 cells and T_H17 cells are thought to be associated with severe, steroid-resistant asthma, which is often marked by neutrophilic infiltrates. Regulatory T (T_{Reg}) cells and subtypes of γδ T cells are able to downregulate pulmonary immune responses and are thought to be important for maintenance of immune homeostasis in the lungs. The nature and magnitude of allergic inflammation in the lung is influenced by external environmental stimuli, such as exposure to allergens and pollution as well as infection with pathogens. IFNγ, interferon-γ; IL, interleukin.

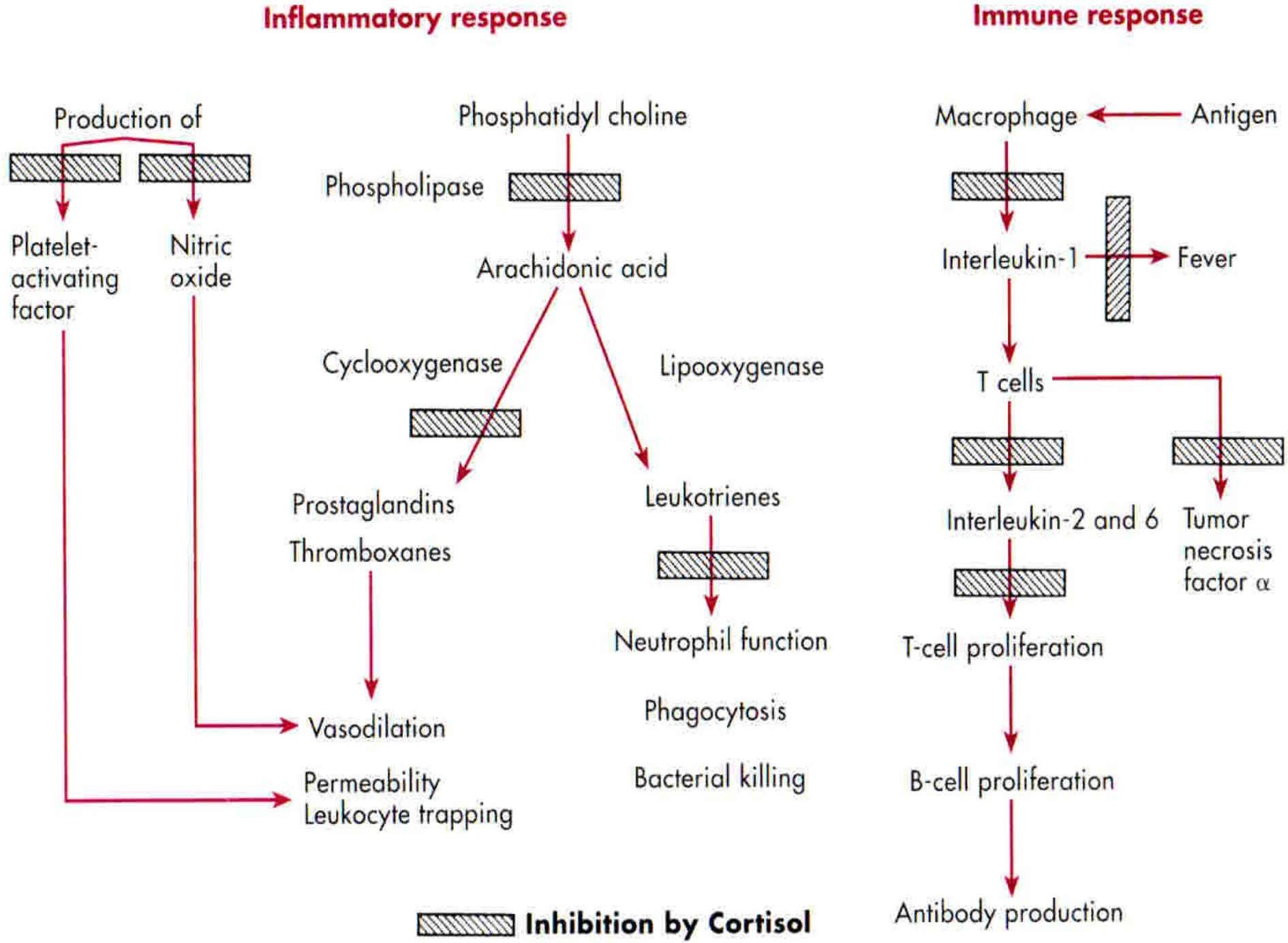

Inflammatory response
Immune response
Production of
Platelet-activating factor
Nitric oxide
Vasodilation
Permeability
Leukocyte trapping
Phosphatidyl choline
Phospholipase
Arachidonic acid
Cyclooxygenase
Lipooxygenase
Prostaglandins
Thromboxanes
Leukotrienes
Neutrophil function
Phagocytosis
Bacterial killing
Macrophage
Antigen
Interleukin-1
Fever
T cells
Interleukin-2 and 6
Tumor necrosis factor α
T-cell proliferation
B-cell proliferation
Antibody production
Inhibition by Cortisol

Table 18.32
Causes of Cushing's syndrome

ACTH-dependent disease
Pituitary-dependent (Cushing's disease)
Ectopic ACTH-producing tumours
ACTH administration

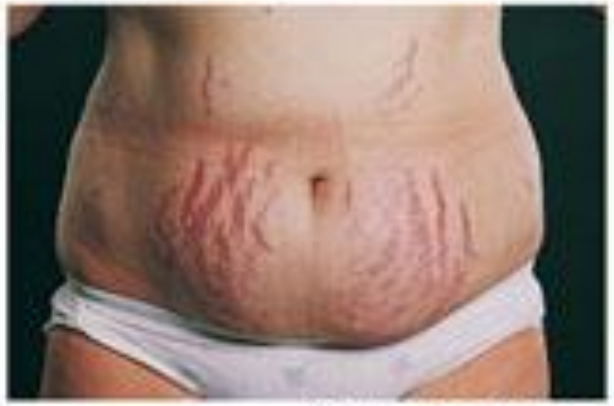
Non-ACTH-dependent causes
Adrenal adenomas
Adrenal carcinomas
Glucocorticoid administration

Others
Alcohol-induced pseudo-Cushing's syndrome

Symptoms

Weight gain (central)
Change of appearance
Depression
Insomnia
Amenorrhoea/
oligomenorrhoea
Poor libido
Thin skin/easy bruising
Hair growth/acne
Muscular weakness
Growth arrest in children
Back pain
Polyuria/polydipsia
Psychosis

Old photographs may
be useful

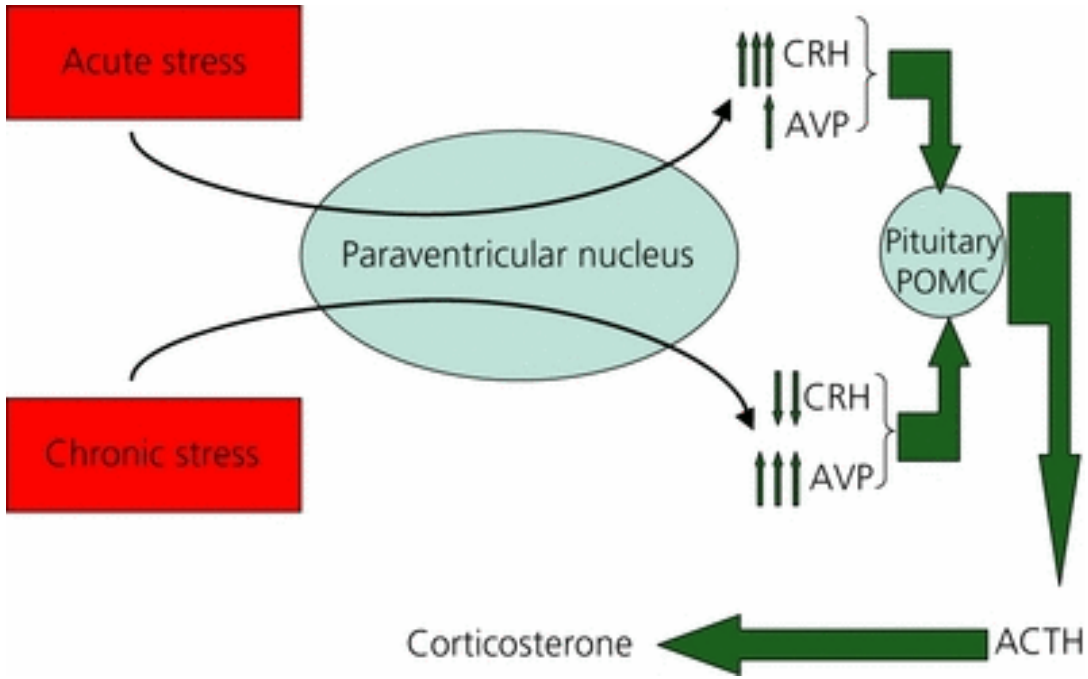


Signs

Moon face
Plethora
Depression/psychosis
Acne
Hirsutism
Frontal balding (female)
Thin skin
Bruising
Poor wound healing
Pigmentation
Skin infections
Hypertension
Osteoporosis
Pathological fractures
(especially vertebrae and ribs)
Kyphosis
'Buffalo hump'
(dorsal fat pad)
Central obesity
Striae (purple or red)
Rib fractures

Oedema
Proximal myopathy
Proximal muscle
wasting
Glycosuria

The symptoms and signs of Cushing's syndrome.
Bold type indicates signs of most value in discriminating Cushing's syndrome from simple obesity and hirsutism.



The hypothalamic-pituitary-adrenal axis response to acute and chronic stressors.
ACTH, adrenocortocotrophin; AVP, arginine vasopressin;
CRH, corticotrophin-releasing hormone; POMC, pro-opiomelanocortin.

Acute stress response

- adaptive, enabling surveillance
- although different reactions are used, the aim is always the same: = surveillance
- *metabolic:* ↑glycemia
- *cardiovaskular/respiratory*- glucose traffic to muscles, heart and brain
- *analgesia*
- *inhibition of processes decreasing surveillance chance* (reproduction, food).

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Acute stress reaction-metabolic effects

☺Purpose: to increase glycemia using catecholamines and glucocorticoids

☺Glucose uptake is inhibited; proteins, fatty acids and glycogen synthesis is stopped. Lysis og lipids and proteins (immune systém is „sacrificed“)

☺Glycogenolysis by catecholamines (short-time effects on glycemia), gluconeogenesis (glucocorticoids with long-time effects on glycemia).

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Acute stress response-cardiovascular/ respiratory effects

☺Purpose: to increase cardiovascular tonus for a quick transport of mobilized glucose to the tissues with the highest oxygen consumption.

☺Vasopressin release from axon neurohypophysal terminals leading to reabsorbtion of water in the kidney Purpose: to increase cardiovascular circulating volume

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Acute stress response-analgesia

☺Purpose: to decrease pain perception

☺Two forms of stress-induced analgesia can be distinguished (SIA)

☺-opiates-dependent SIA (enkephalins and β-endorphine)

☺-opiates independent SIA (glutamate)

Both SIA can combine one to another.

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Chronic stress response

☹maladaptive = imparing effects

☹chronic stress can contribute to development of diseases as peptic ulcer, visceral obesity, lower growth, higher risk of CAD

☹chronic stress influences behaviour:

☹inhibition of reproduction

☹ depression, schizophrenia etc.

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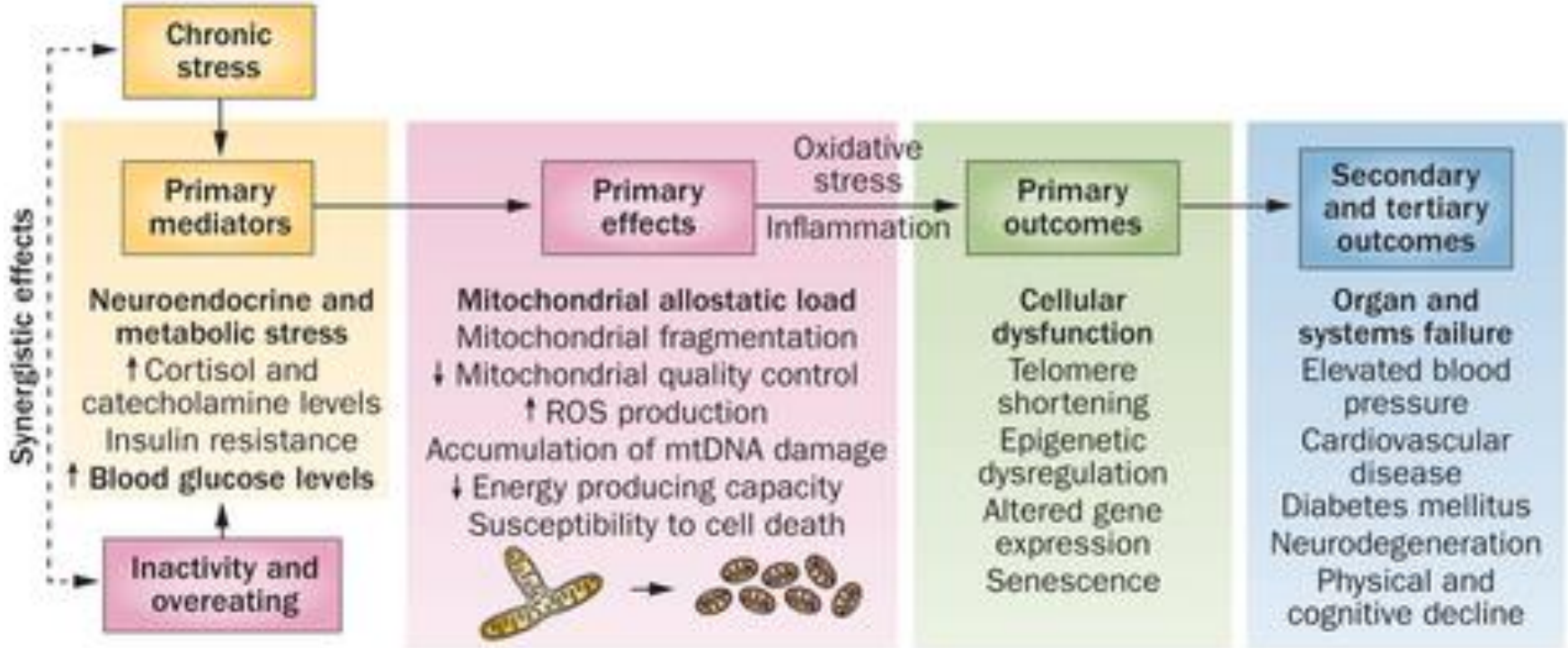
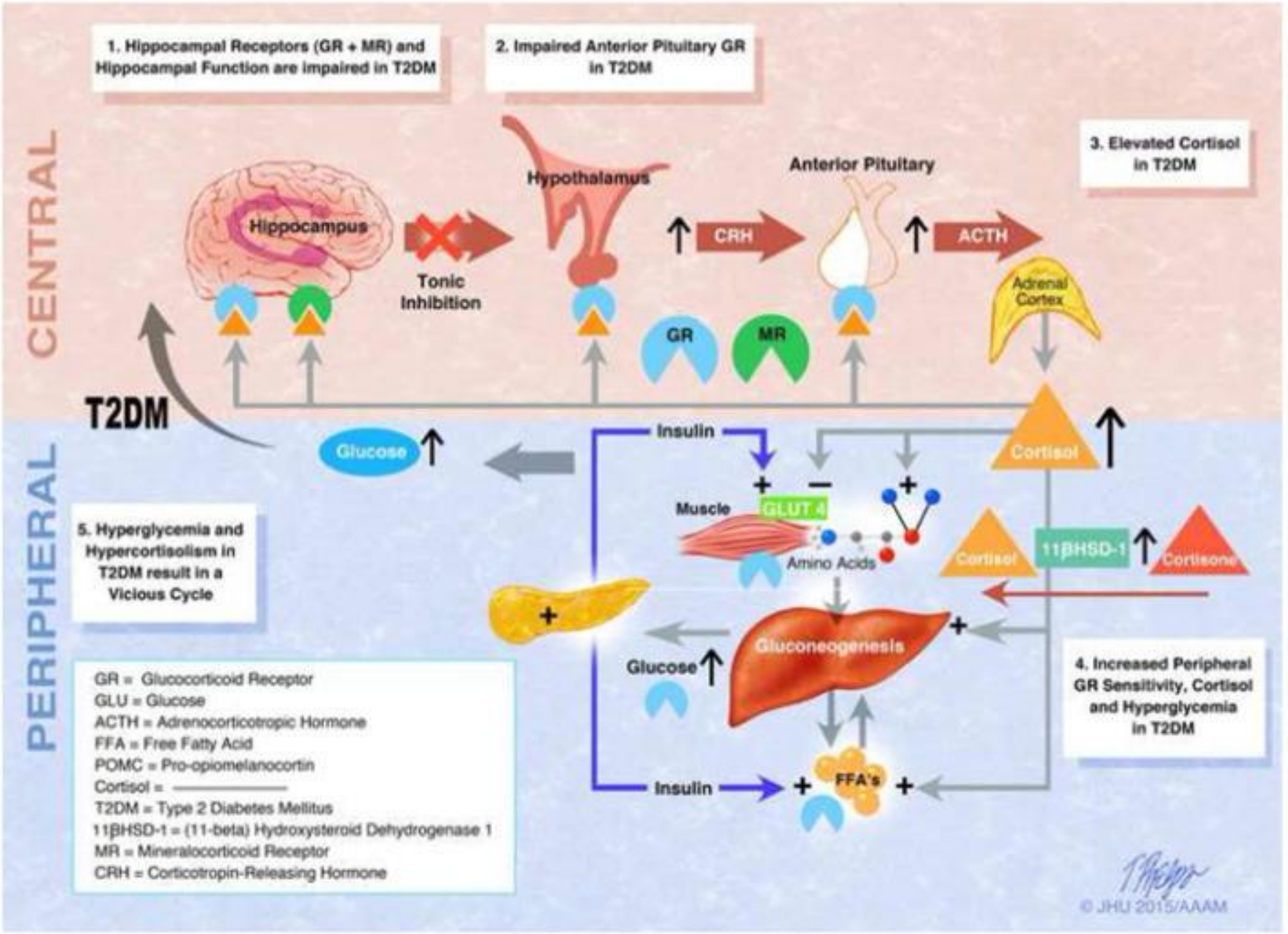

Chronic stress
Primary mediators
Primary effects
Oxidative stress
Inflammation
Primary outcomes
Secondary and tertiary outcomes
Synergistic effects
Neuroendocrine and metabolic stress
↑ Cortisol and catecholamine levels
Insulin resistance
↑ Blood glucose levels
Inactivity and overeating
Mitochondrial allostatic load
Mitochondrial fragmentation
↓ Mitochondrial quality control
↑ ROS production
Accumulation of mtDNA damage
↓ Energy producing capacity
Susceptibility to cell death
Cellular dysfunction
Telomere shortening
Epigenetic dysregulation
Altered gene expression
Senescence
Organ and systems failure
Elevated blood pressure
Cardiovascular disease
Diabetes mellitus
Neurodegeneration
Physical and cognitive decline



Joseph J.J. et al., Psychoneuroendocrinology. 2015 Dec; 62: 327–335.

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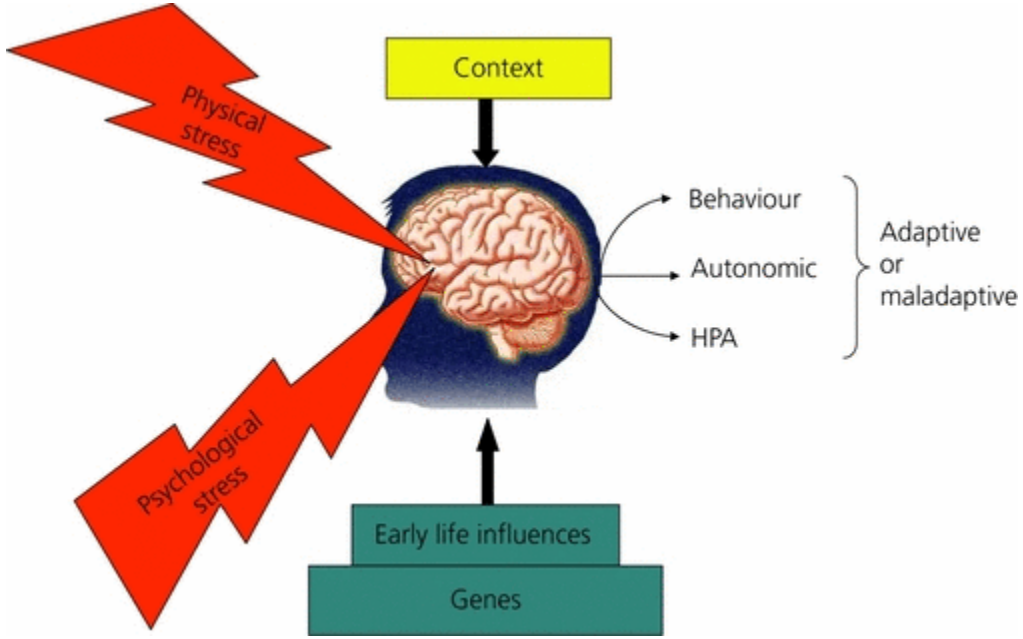

Physiological and pathological responses to stress. The resilience or vulnerability
of any one individual to stressful situations in adulthood seems to depend upon that person's genetic inherence and early life experiences.

Stress and multiplex factors role

- Dominant and subdominant primates (males):
- In stable conditions (no teritorial emergency), dominant males have lower glucocorticoids levels than subdominant ones.
- But, in unstable conditions, these levels in dominant males increase and they are the same or higher thain in subdominat males.
- “Personal power” of dominant male correlates with low GCs levels during rest conditions.

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Stress and multiplex factors role

☺„Good state of mind” is necessary !

☺Social supporting groups forming- f.e. non sexually based friendship between men and women in the team

☺Training of ability to anticipate stressful event and undertake the control.

☺Transformation of agresivity (sports)

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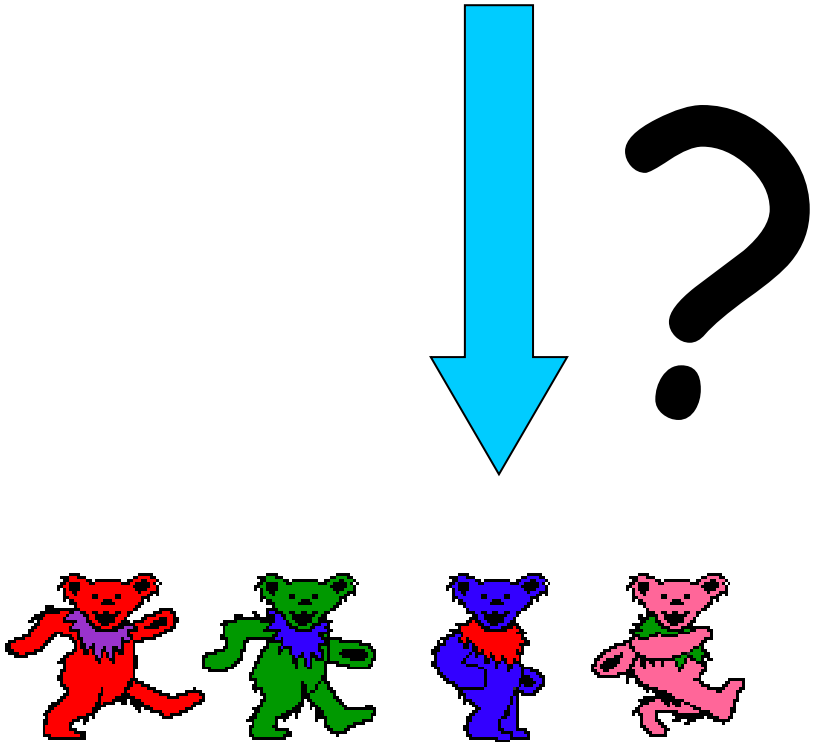

Thank you for your attention

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Děkuji vám za pozornost