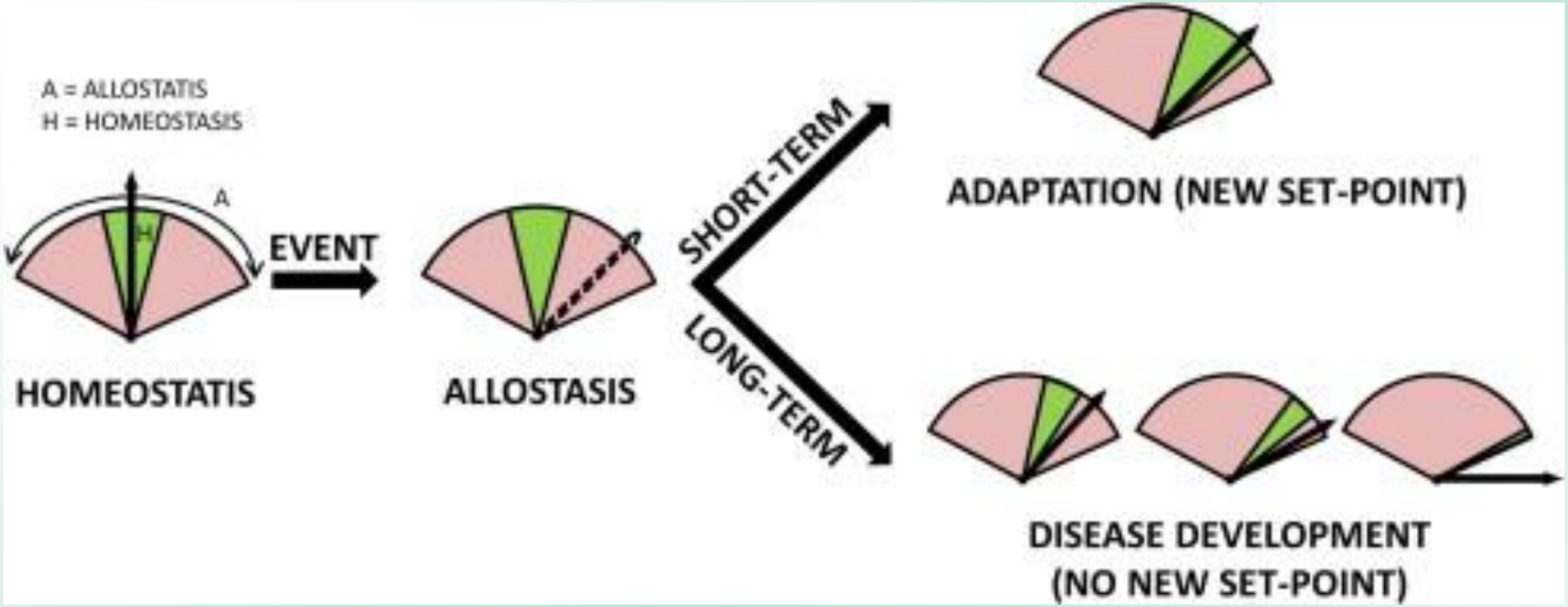
General adaptation syndrom

November 13, 2018



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.
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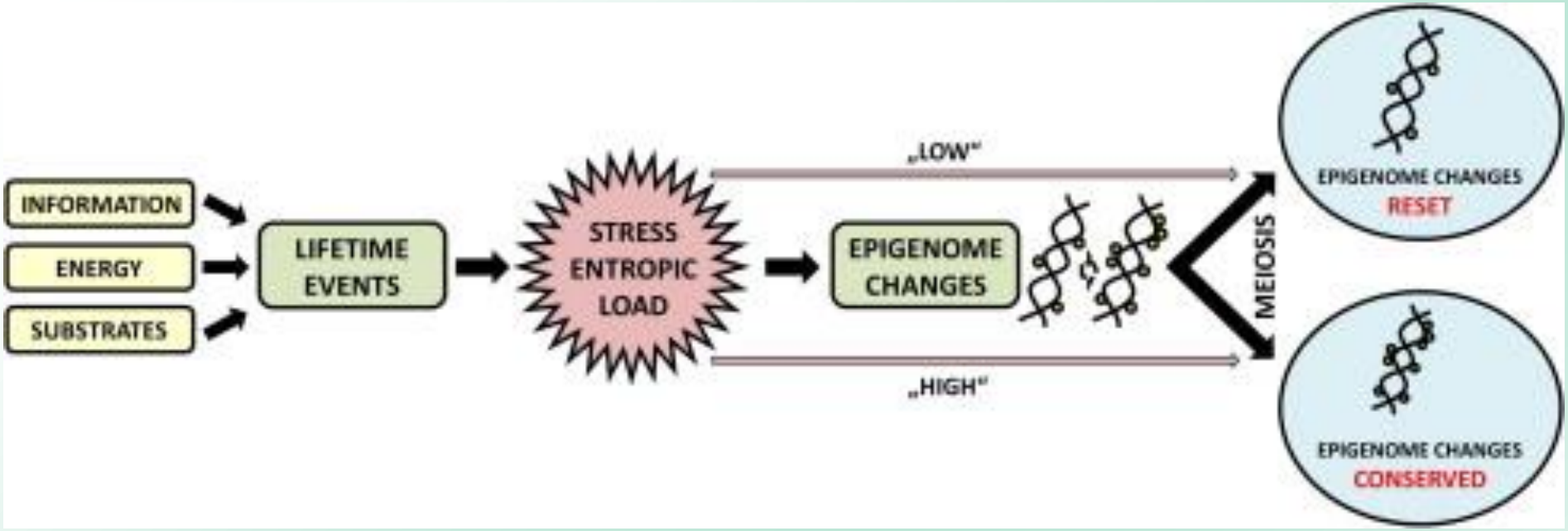

Relationship between lifetime events, stress entropic load (SEL) and epigenome changes. Lifetime events represent those events that influence the flow of energy, substrates and information within the body. Generally, the organism has to cope with these changes, whereas we consider SEL to be the universal 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.

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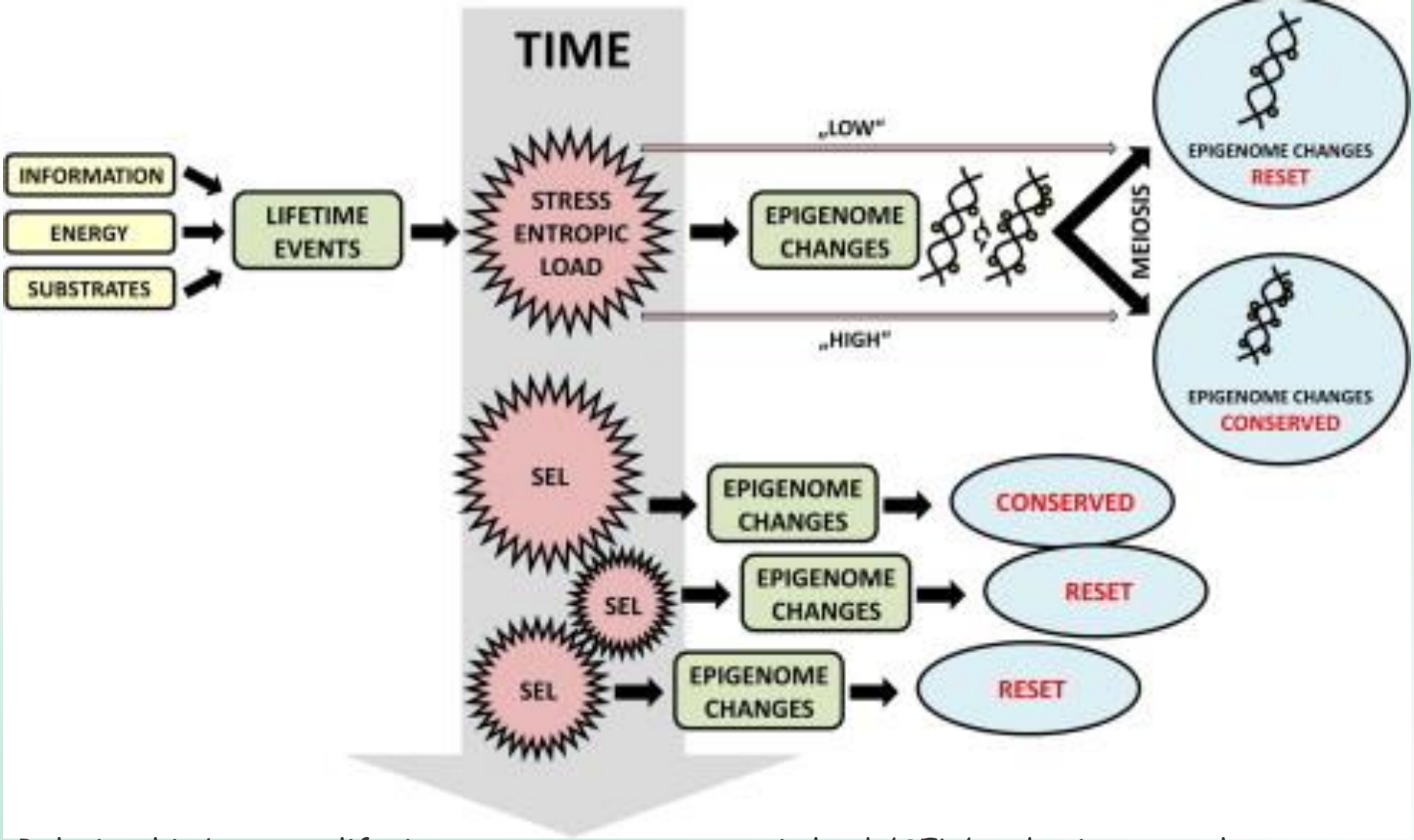

Relationship between lifetime events, stress entropic load /SEL/ and epigenome changes during time. Grey arrow represents the time flow and it should suggest that as time passes, different events are evaluated differently and their associated SEL level may consecutively increase or decrease and thus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

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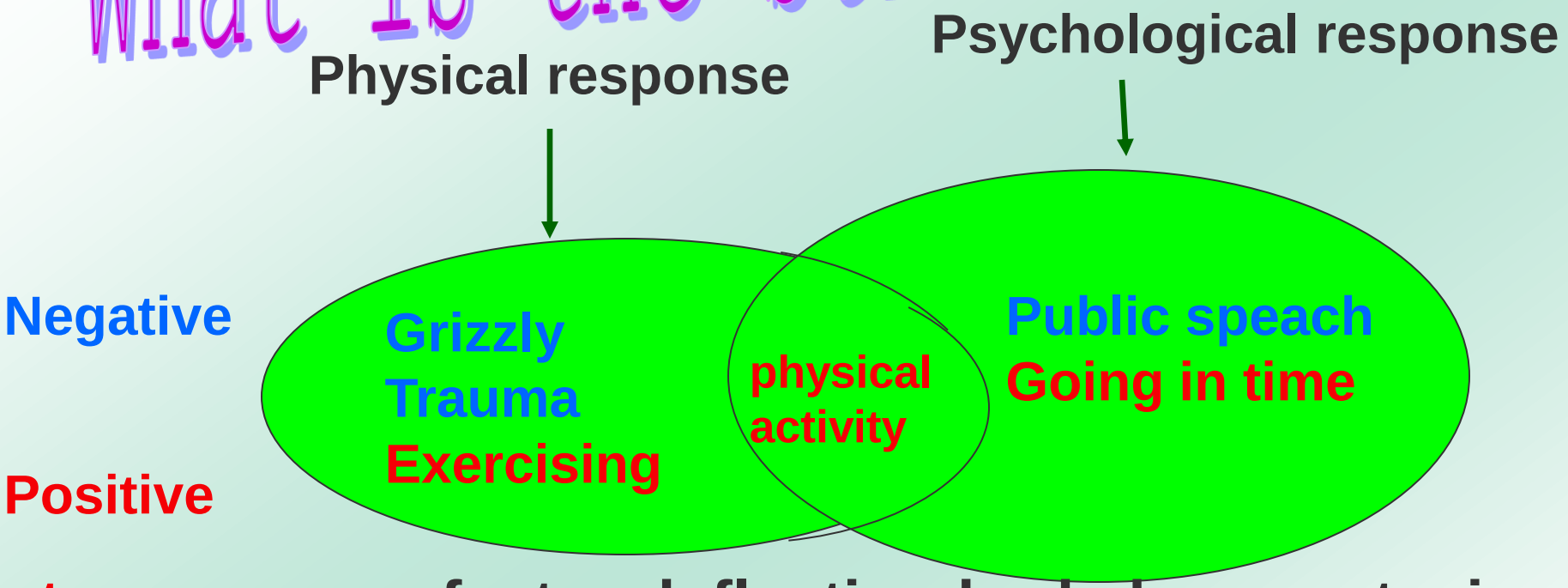
What is the stress?



stressor=any factor deflecting body homeostasis

stress response= body adaptation to homeostasis restoring

stress= the complexity of factors provoking stress response

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.

Stages of stress

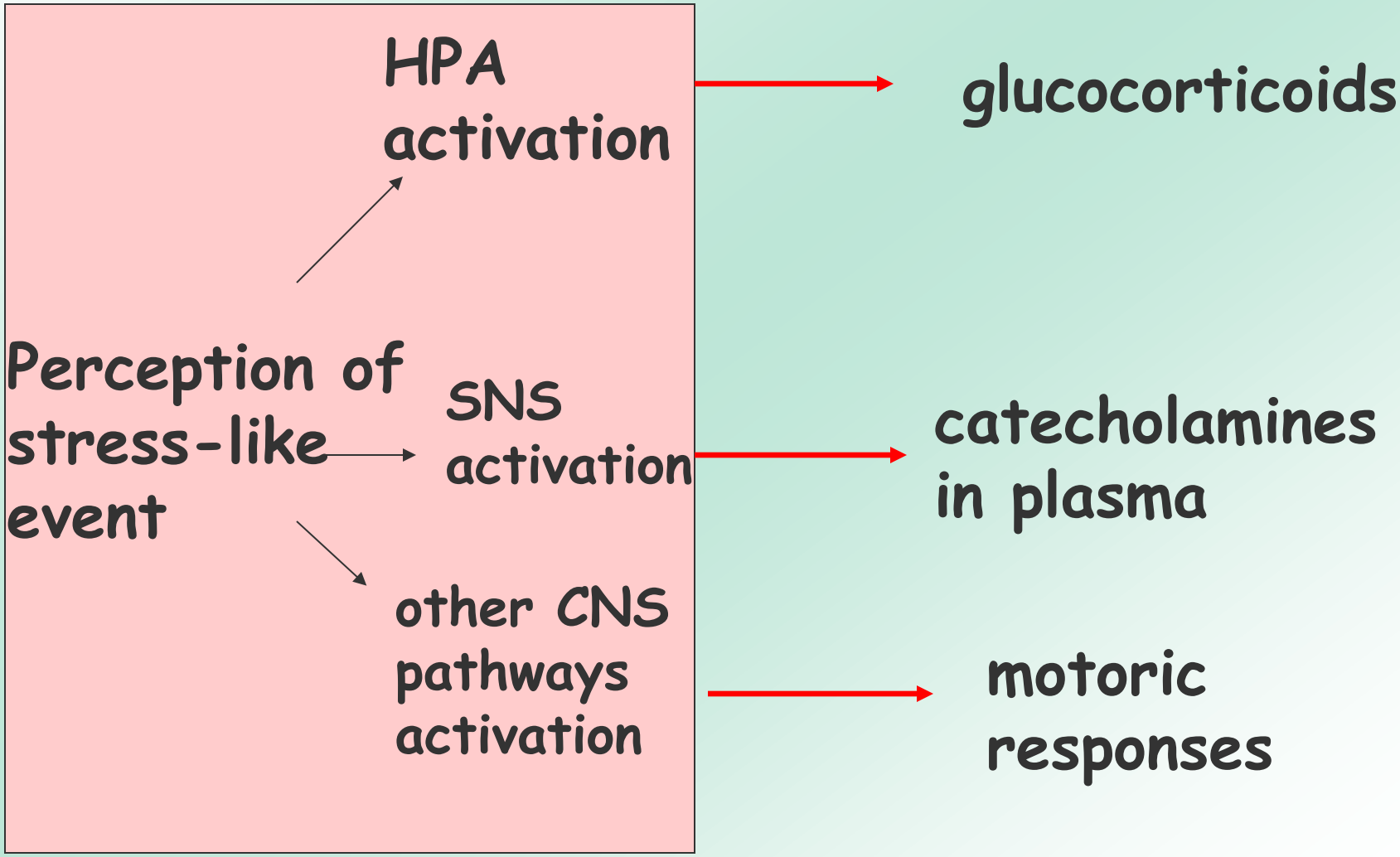
- **alarm reaction** (fight and flight- Cannon´s emergent reaction): shock, contra-shock
- **stage of resistence**
- **stage of exhaustion**

- **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**

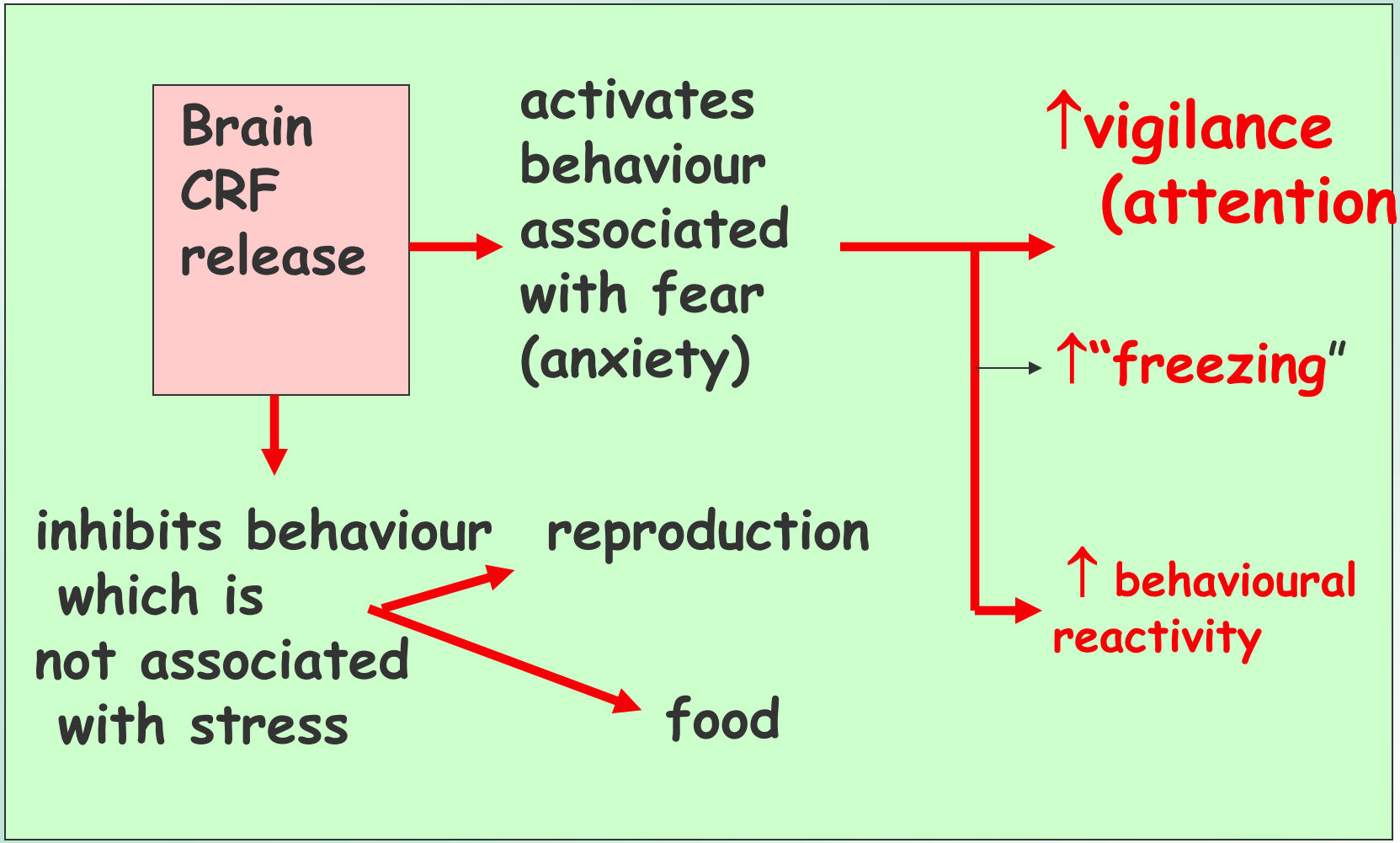
  stressor characteristics

  subjective stress responsibility
- **Reactions to acute and chronic stress**: physical and psychological

Alarm reaction "fight or flight"



Acute stress response: behavioral alterations caused by CRF release



Autonomic nervous system

Parasympathetic nervous system

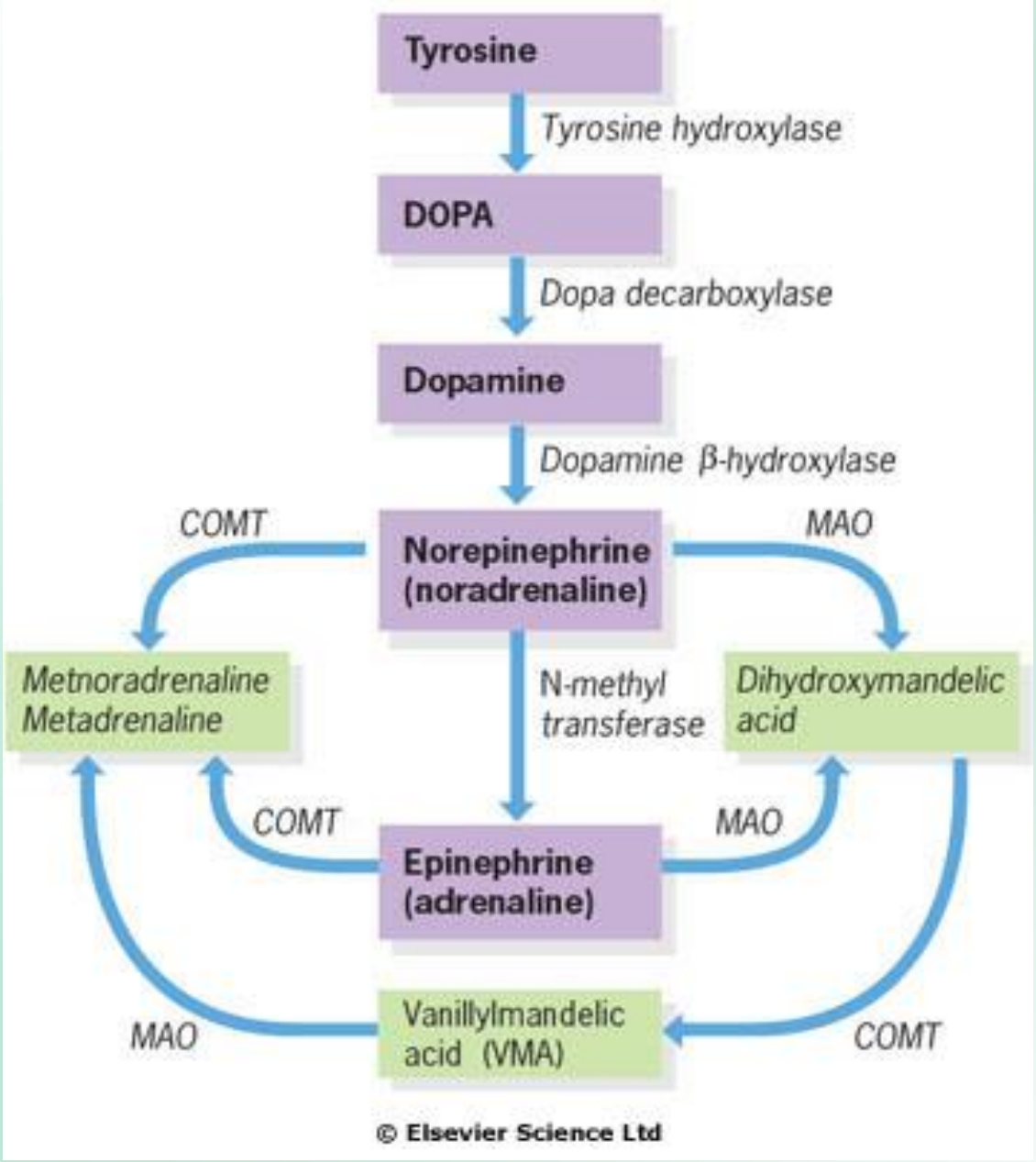
↑ digestion
↑ salivation
↓ heart rate
↑ intestine perfusion

rest state

Sympathetic nervous system

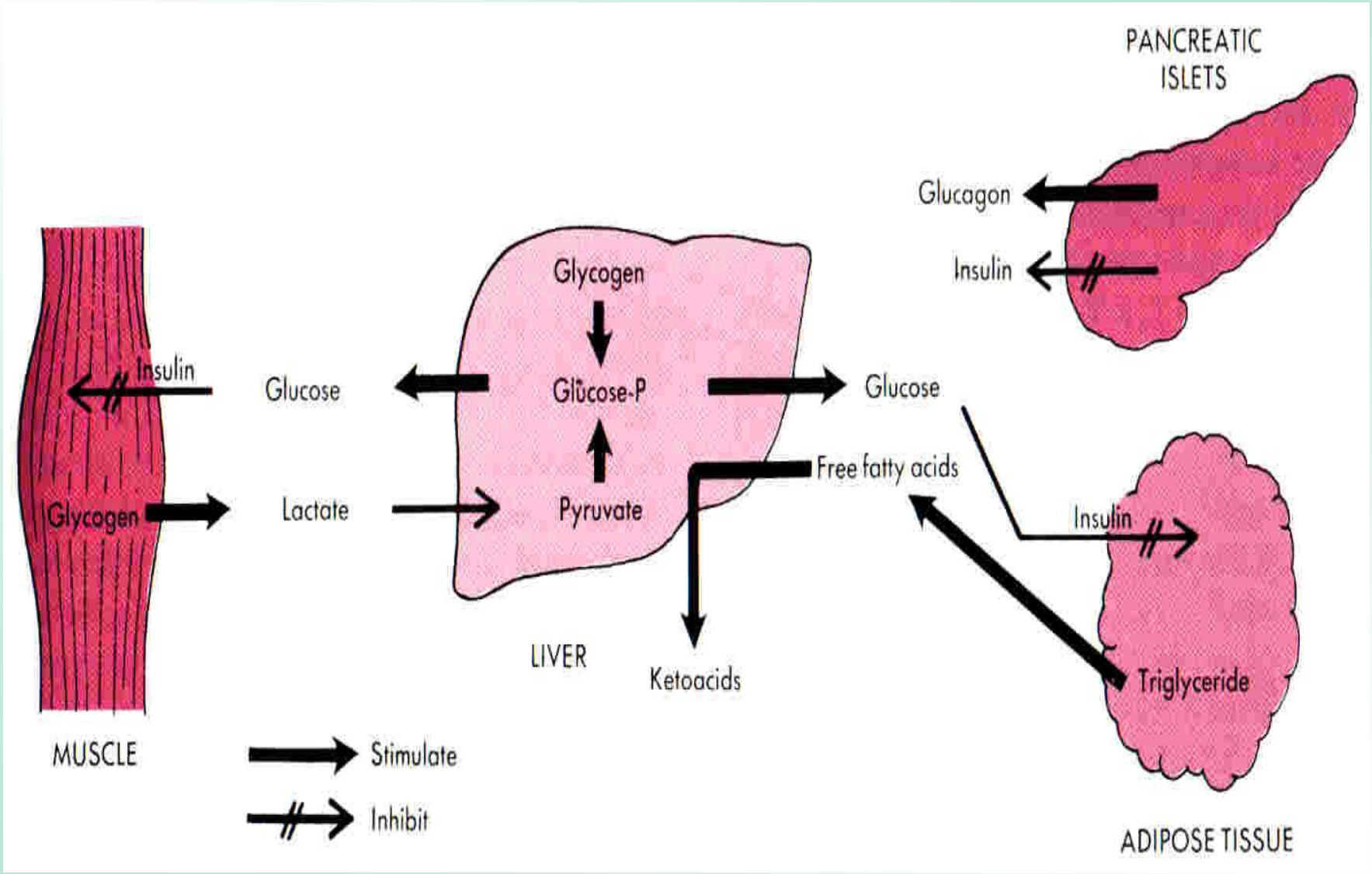
"F& F" response

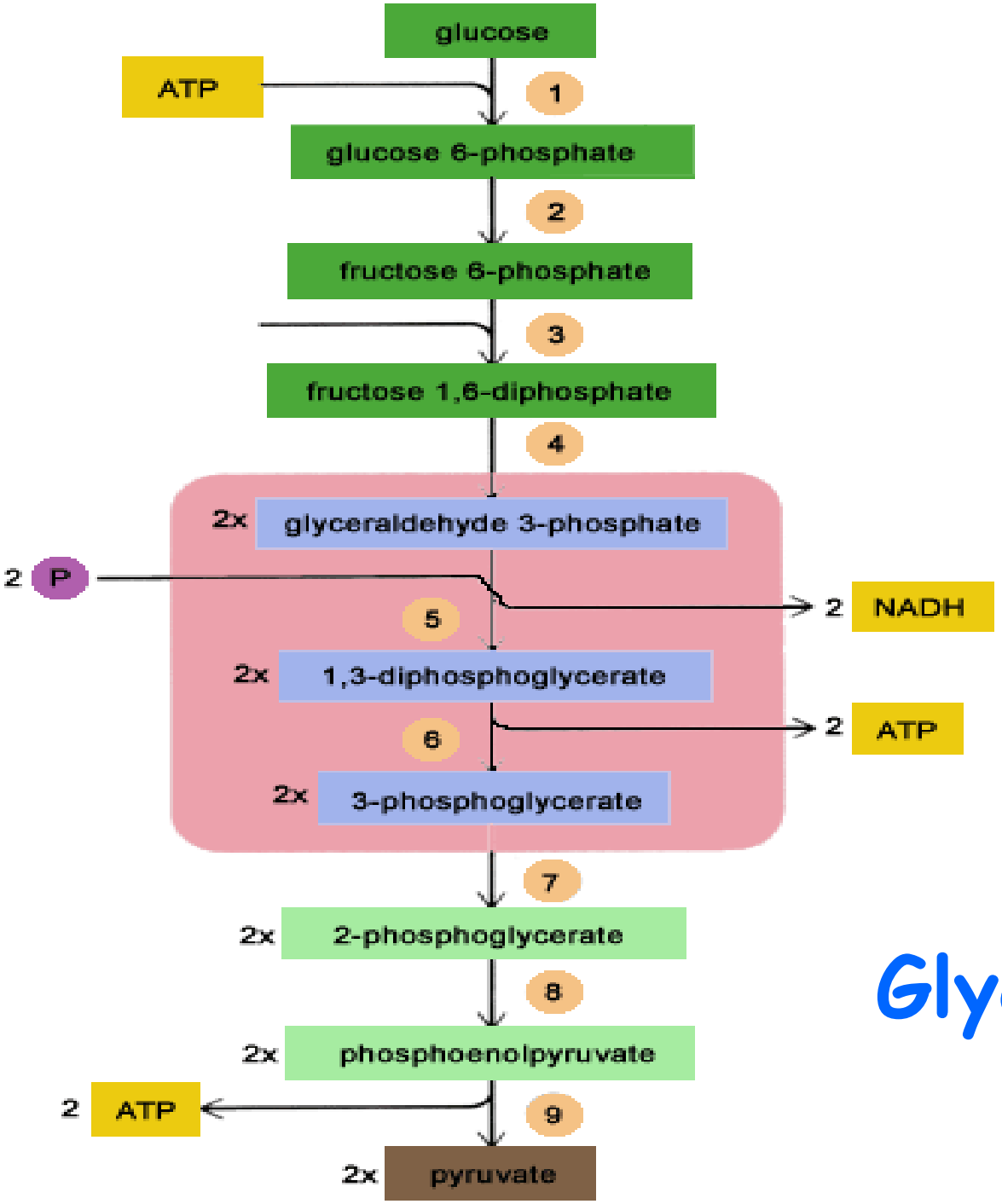
↓digestion
↓ salivation
↑ heart rate
↑ respiration
✓blood redistribution from intestine to muscles, brain and heart
✓ increased activity and vigilance



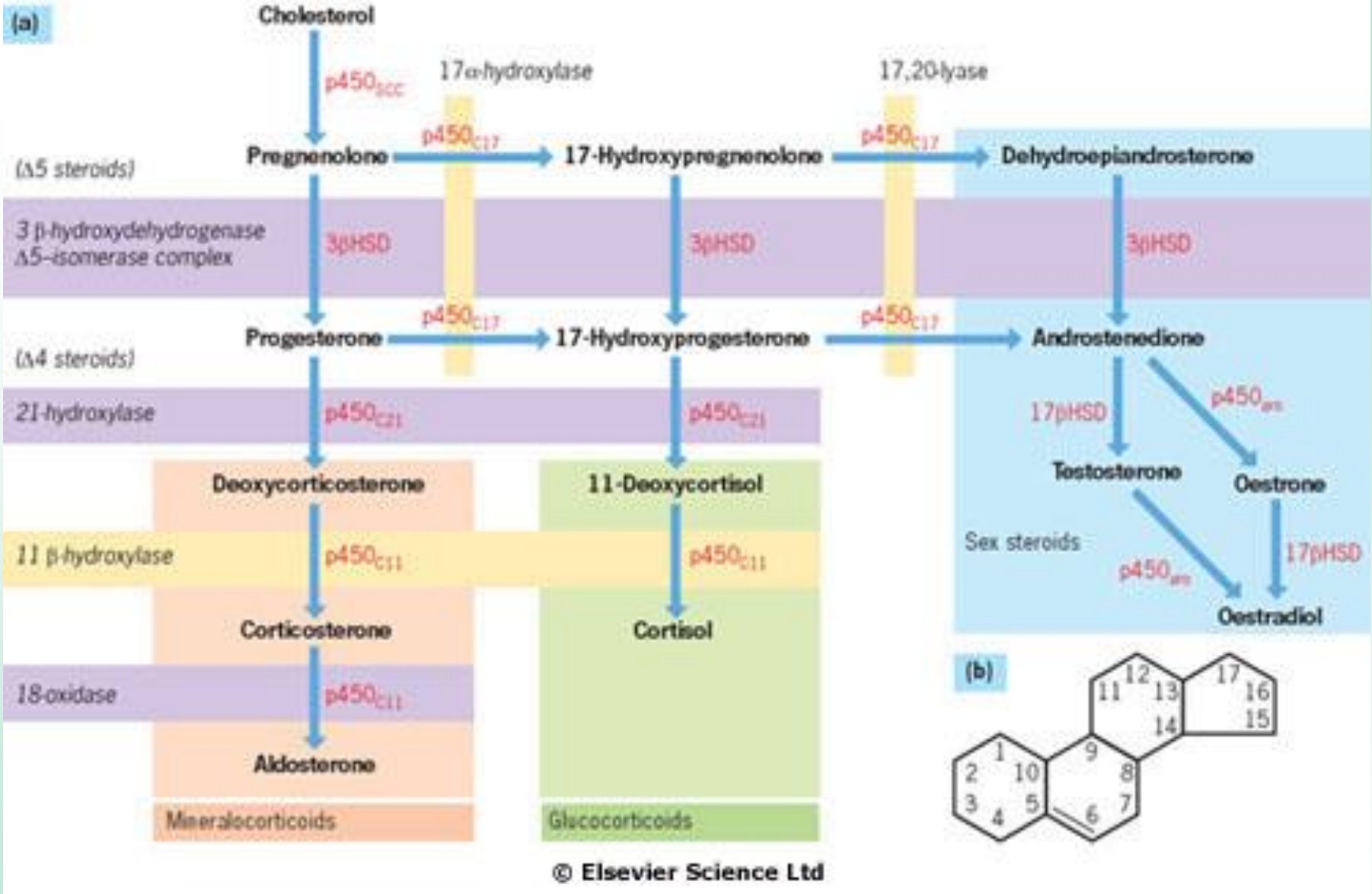
Catecholamines synthesis and metabolism

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



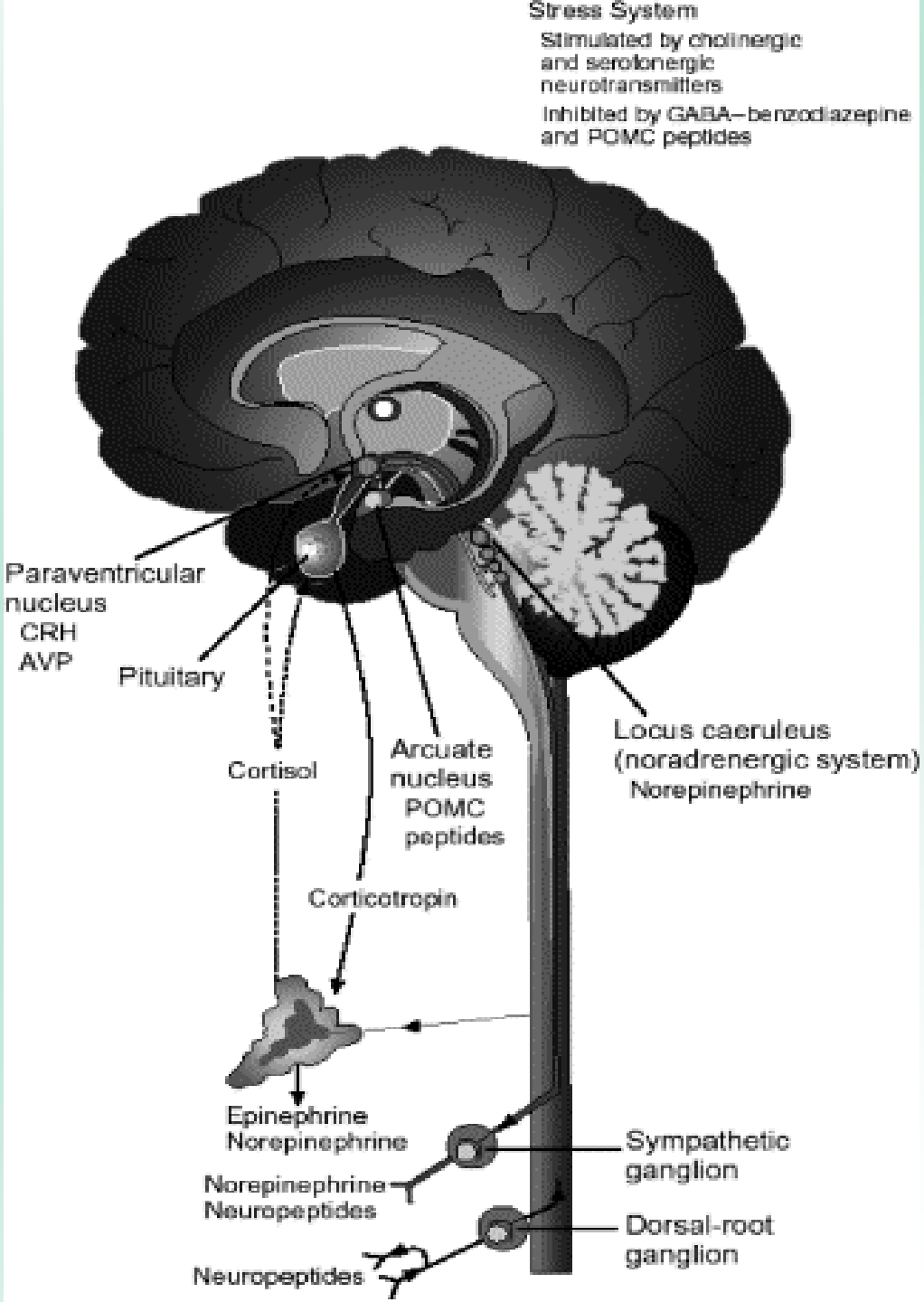
(a) The major steroid biosynthetic pathways. Enzymes catalysing reactions are in red: p450 enzymes are in mitochondria and each catalyses several reaction steps; 3βHSD (hydroxysteroid dehydrogenase) is in cytoplasm, bound to endoplasmic reticulum; 17βHSD and $p450_{aro}$ are found mainly in gonads. **(b)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

Classic stress components of the CNS systems.

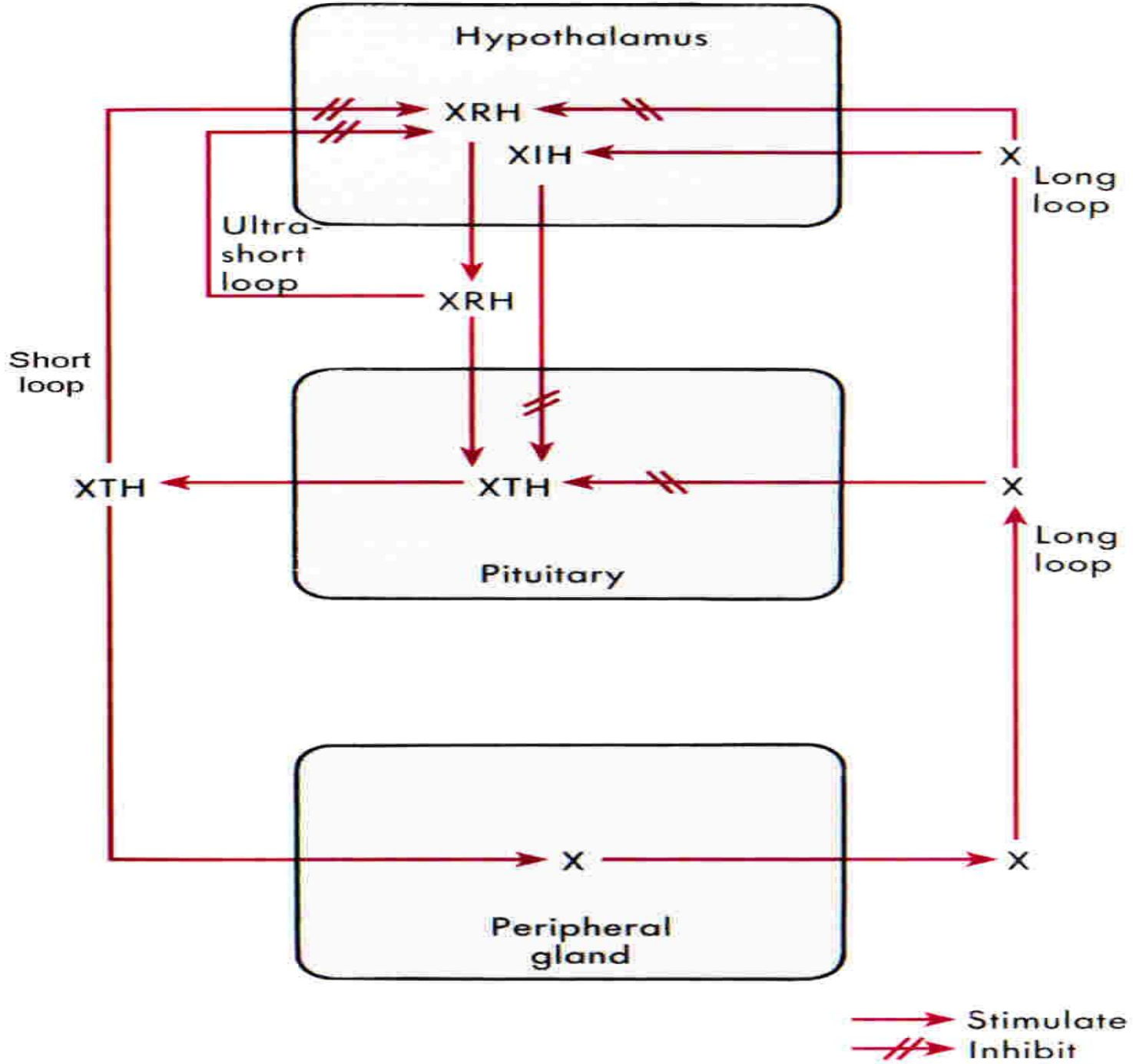


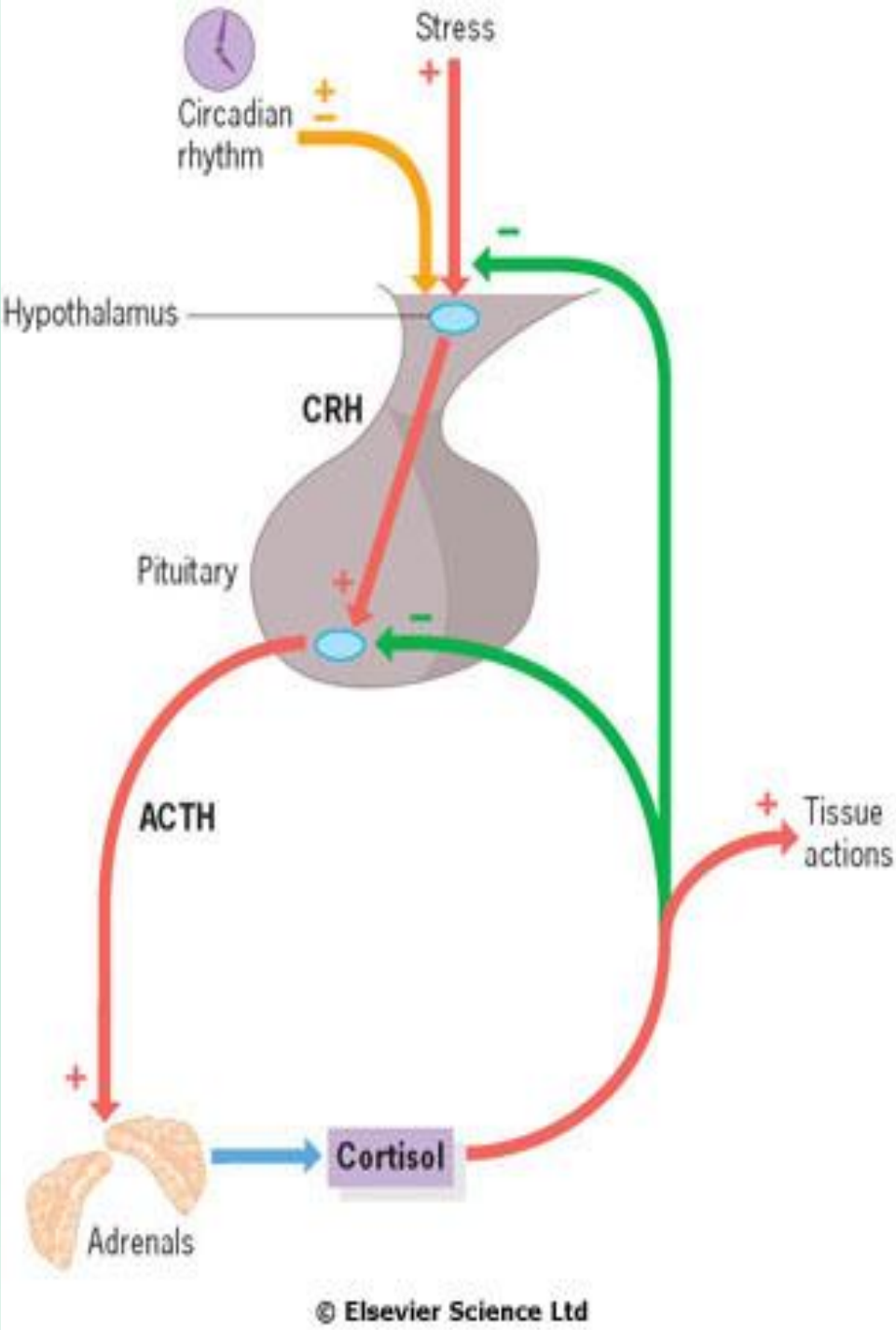
To the previous picture: The HPA doctrine

- (A) Classic components of the HPA–CNS–immune systems.
- (B) Neurons of the hypothalamus that synthesize CRF and vasopressin (VP) are found in the paraventricular nucleus (PVN). These cell bodies send axons to the median eminence; here, peptides are released from the nerve terminals and are transported through vessels of the portal system. When they reach the anterior pituitary, these peptides act on their respective receptors, thereby stimulating ACTH secretion.
- (C) Following its release into the general circulation, ACTH acts on the cortex of the adrenal glands, which manufacture and secrete glucocorticoids (cortisol in humans). These glucocorticoids exert a classical negative feedback influence on the pituitary, where they inhibit the effect of CRF and VP, and on the PVN, where they inhibit the synthesis of CRF. Thus, after a stimulus stimulates CRF and ACTH release, the production of glucocorticoids will eventually terminate this release, thereby ensuring the maintenance of homeostasis.

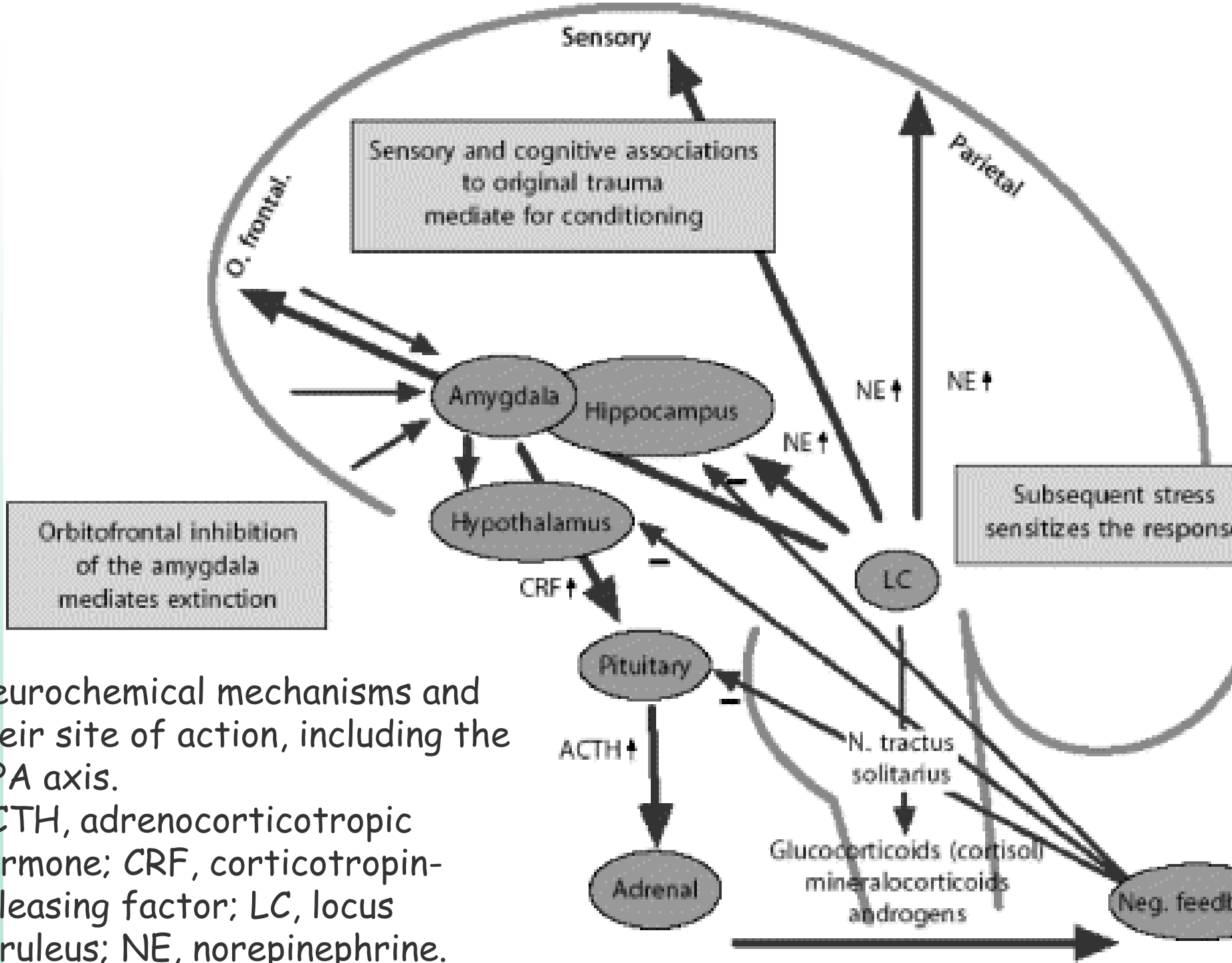
Stimuli triggering 'reactive' vs. 'anticipatory' HPA stress responses

'Reactive' responses	'Anticipatory' responses
Pain	Innate Programs
Visceral	Predators
Somatic	Unfamiliar environments/situations
Neuronal homeostatic signals	Social challenges
Chemoreceptor stimulation	Species-specific threats (e.g., illuminated spaces for rodents, dark spaces for humans)
Baroreceptor stimulation	
'Osmoreceptor' stimulation	
Humoral homeostatic signals	Memory programs
Glucose	Classically conditioned stimuli
Leptin	Contextually conditioned stimuli
Insulin	Negative reinforcement/frustration
Renin–angiotensin	
Atrial natriuretic peptide	
Others	
Humoral inflammatory signals	
IL-1	
IL-6	
TNF-α	
Others	

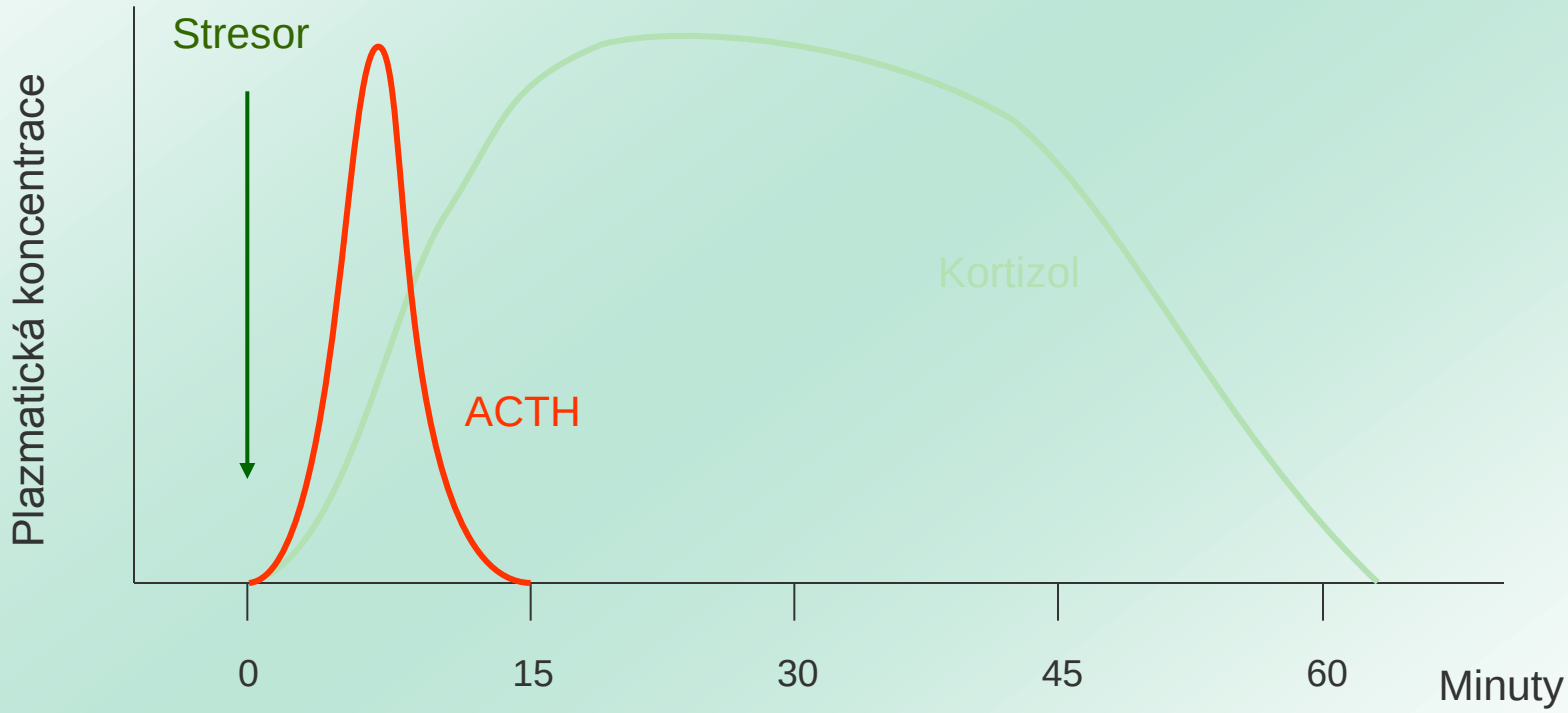

Hypothalamus
XRH
XIH
X
Long loop
Ultra-short loop
XRH
Short loop
XTH
XTH
X
Pituitary
Long loop
X
X
Peripheral gland
Stimulate
Inhibit



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

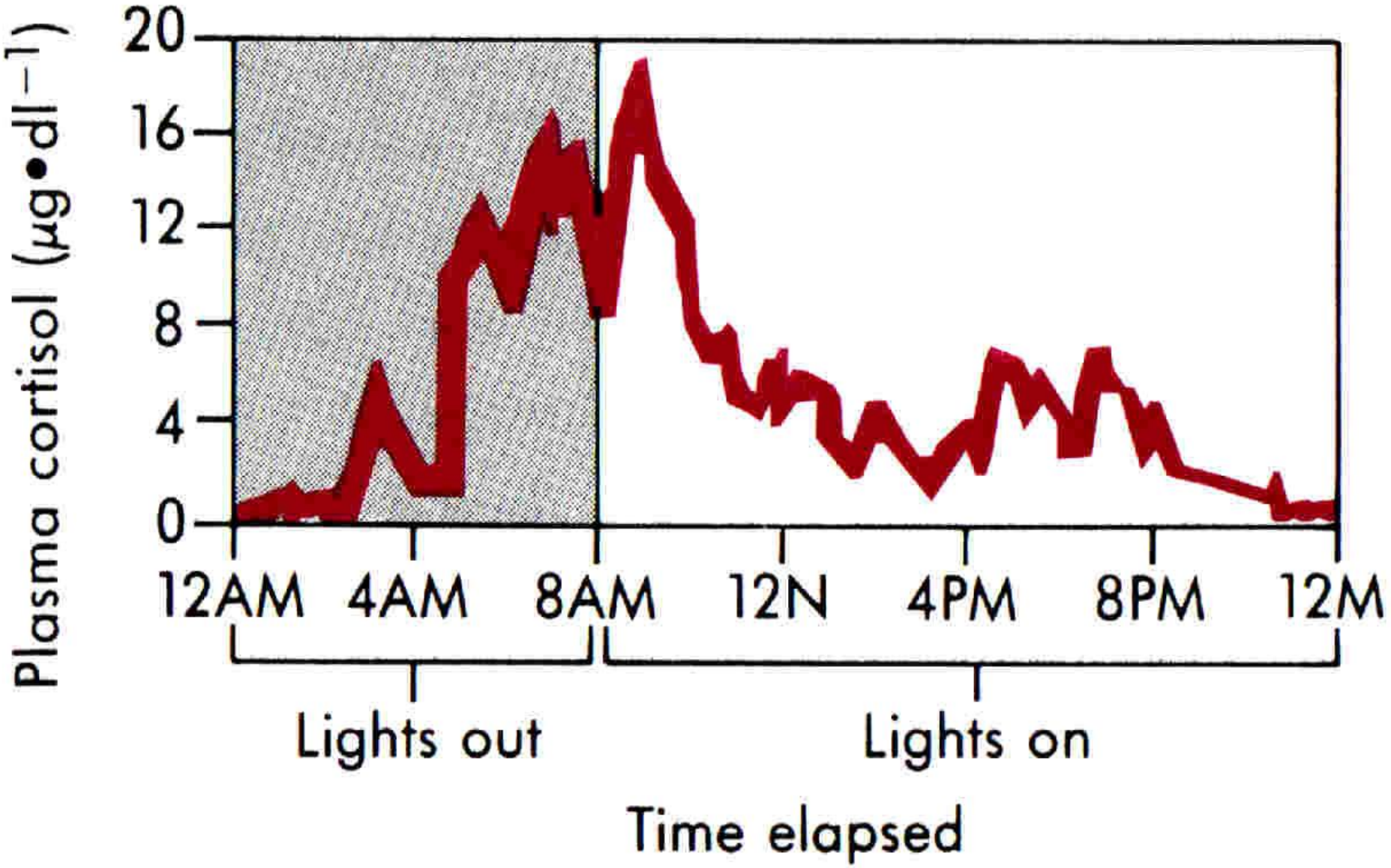


Neurochemical mechanisms and their site of action, including the HPA axis.
ACTH, adrenocorticotropic hormone; CRF, corticotropin-releasing factor; LC, locus ceruleus; NE, norepinephrine.

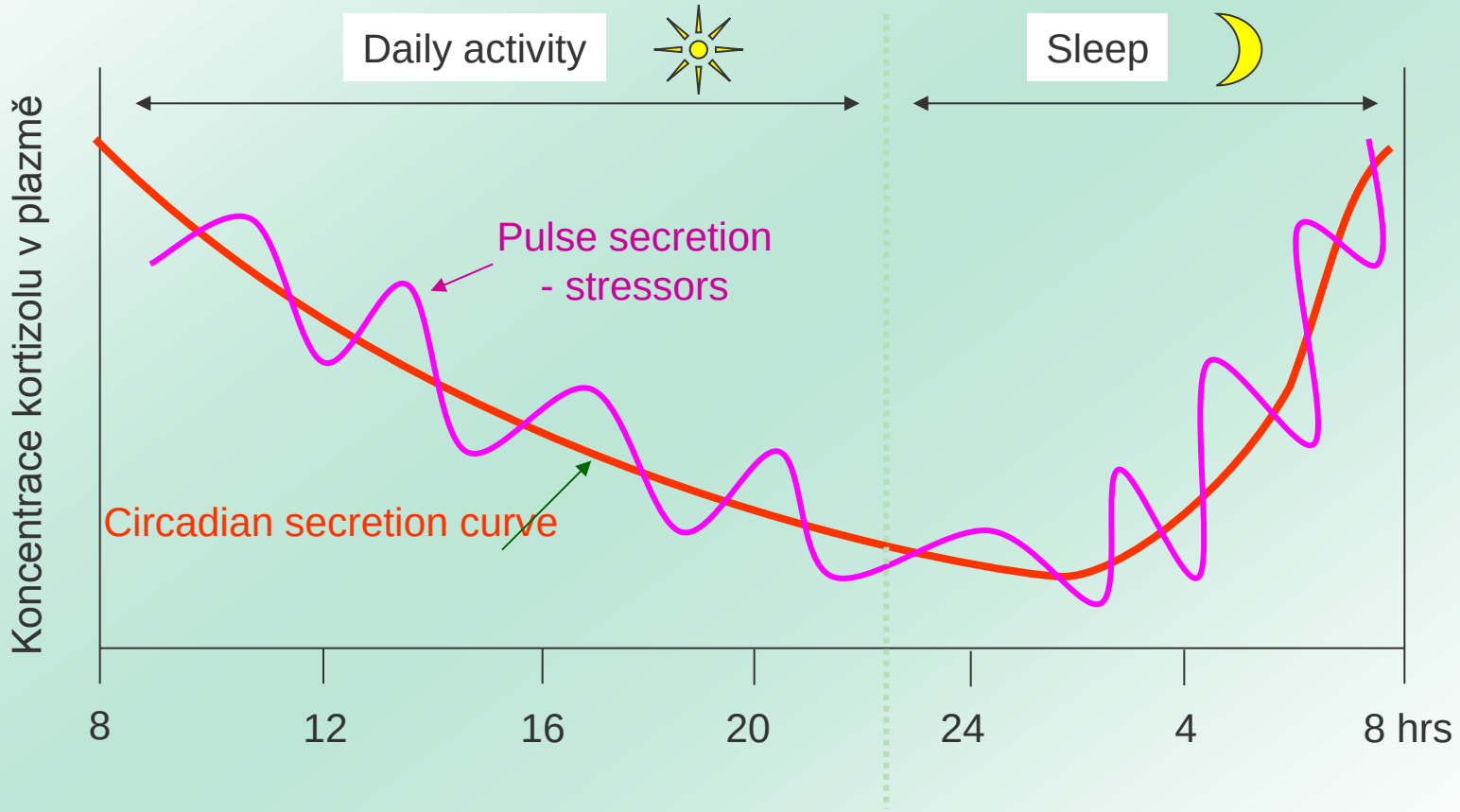


(Podle Felker B and Hubbard JR: In Handbook of Stress Medicine, CRC Press, Boca Raton, FL, 1998)

Pulsatile and diurnal character of glucocorticoid secretion



Pulse and diurnal secretion of glucocorticoids



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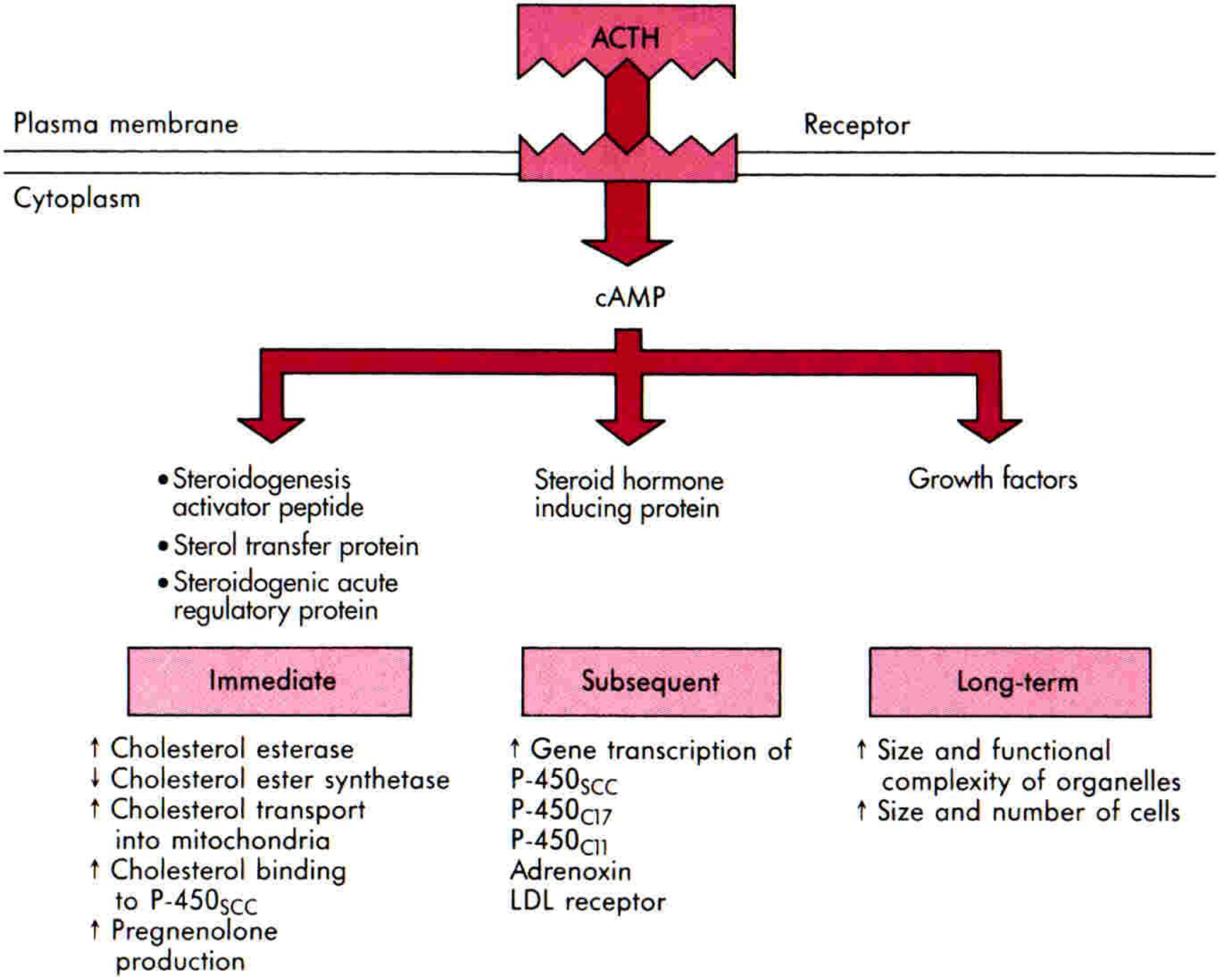
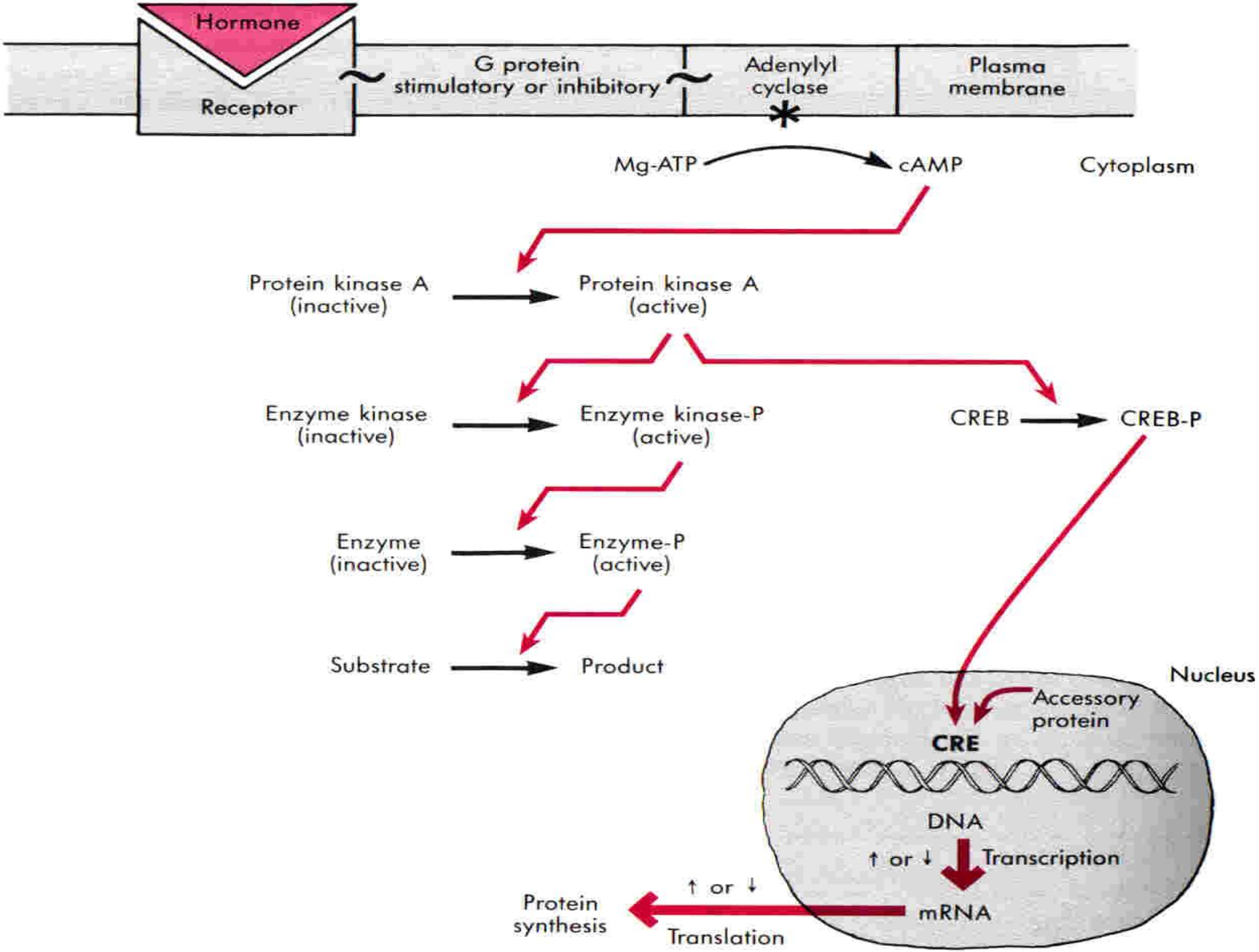
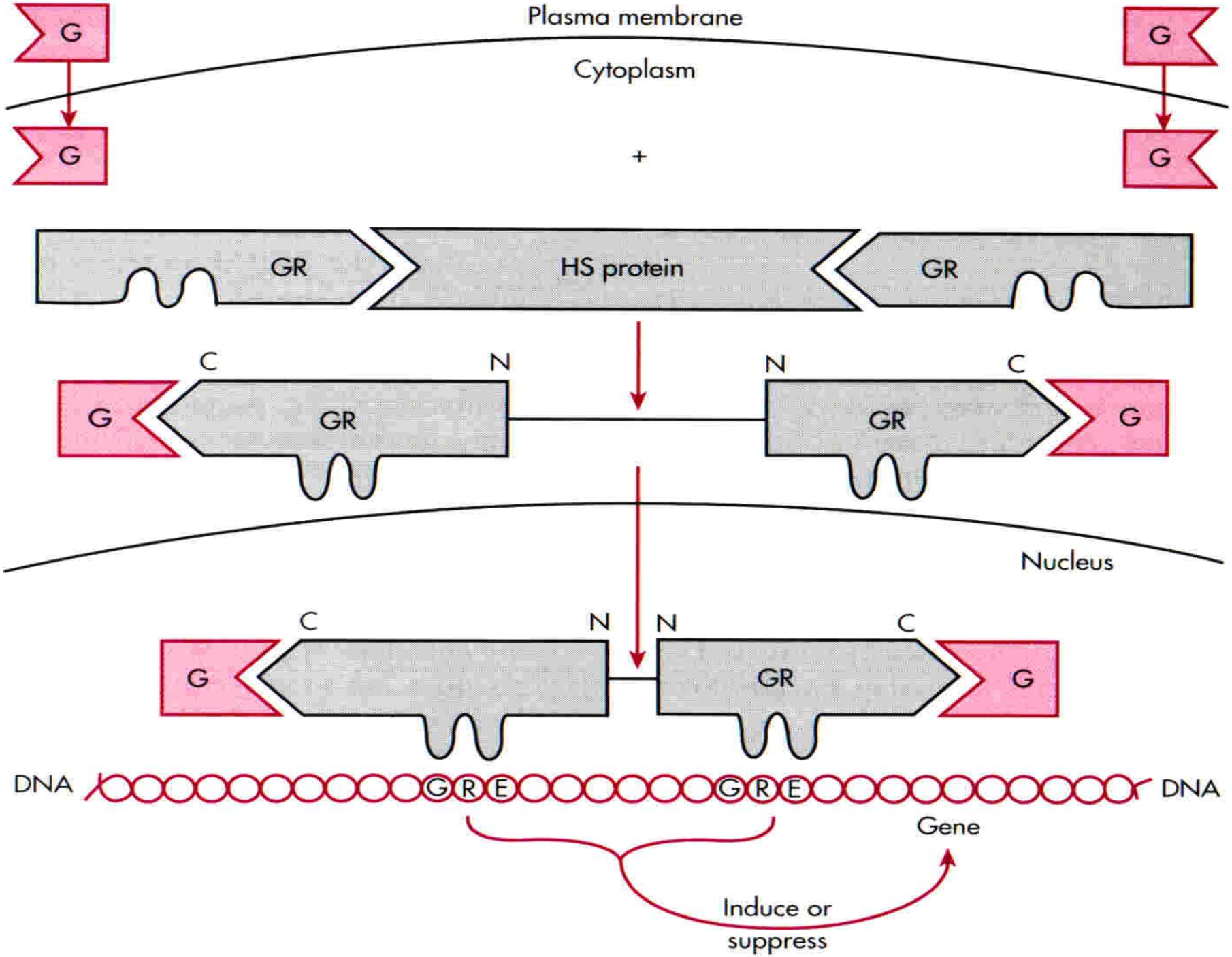
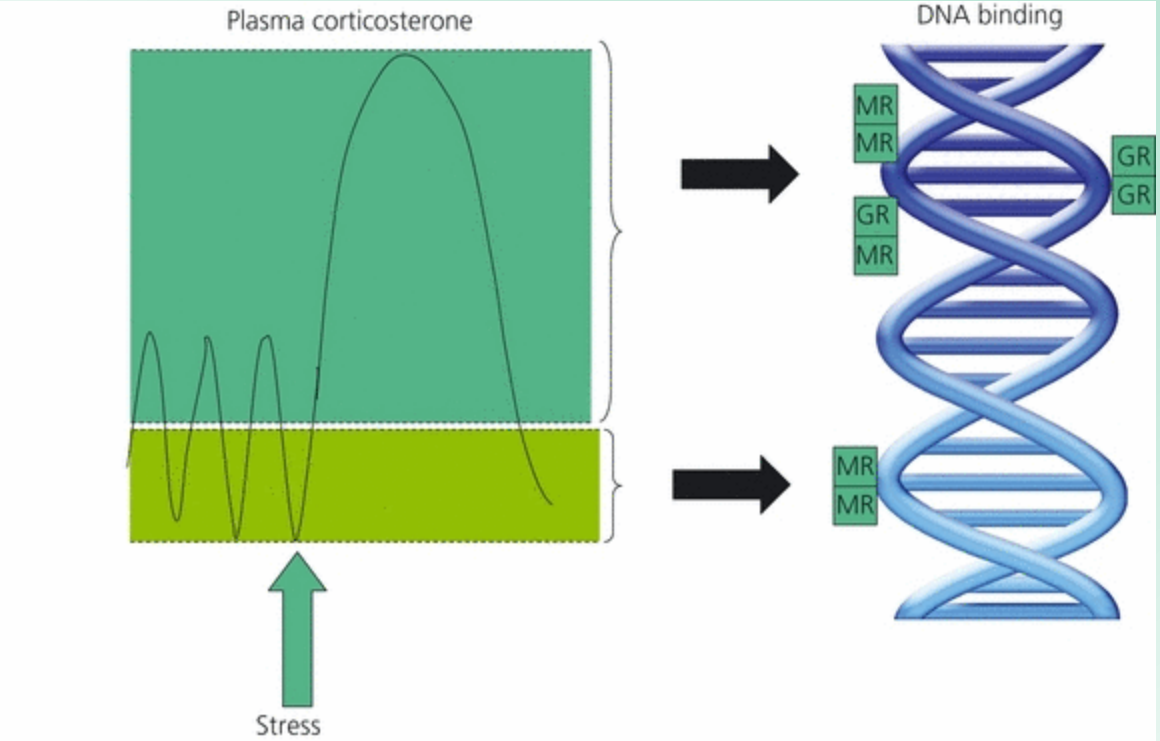

ACTH
Plasma membrane
Receptor
Cytoplasm
cAMP
• Steroidogenesis activator peptide
• Sterol transfer protein
• Steroidogenic acute regulatory protein
Steroid hormone inducing protein
Growth factors
Immediate
Subsequent
Long-term
↑ Cholesterol esterase
↓ Cholesterol ester synthetase
↑ Cholesterol transport 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

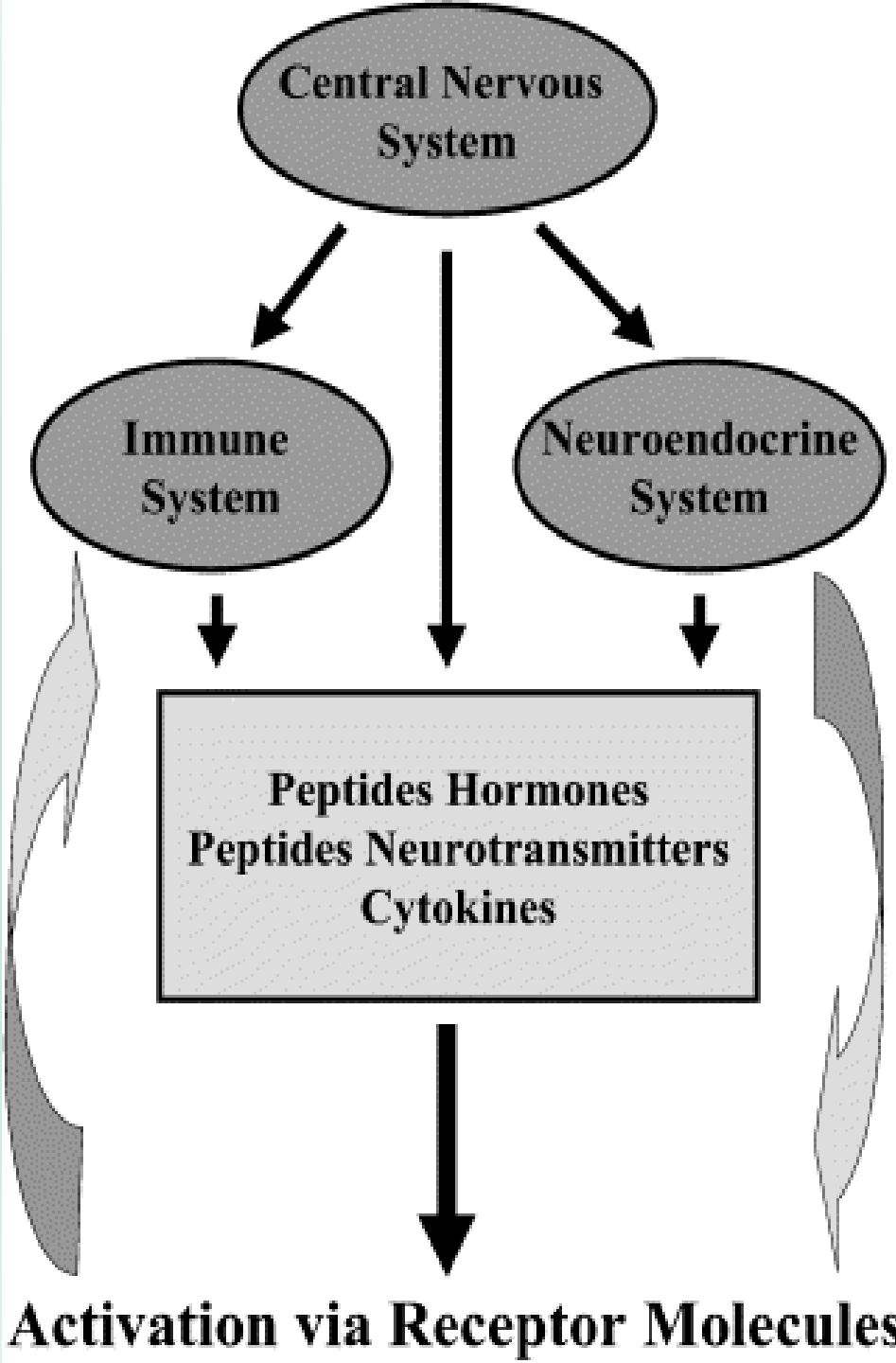

Hormone
Receptor
G protein
stimulatory or inhibitory
Adenylyl
cyclase
Plasma
membrane
Mg-ATP
cAMP
Cytoplasm
Protein kinase A
(inactive)
Protein kinase A
(active)
Enzyme kinase
(inactive)
Enzyme kinase-P
(active)
CREB
CREB-P
Enzyme
(inactive)
Enzyme-P
(active)
Substrate
Product
Nucleus
Accessory
protein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

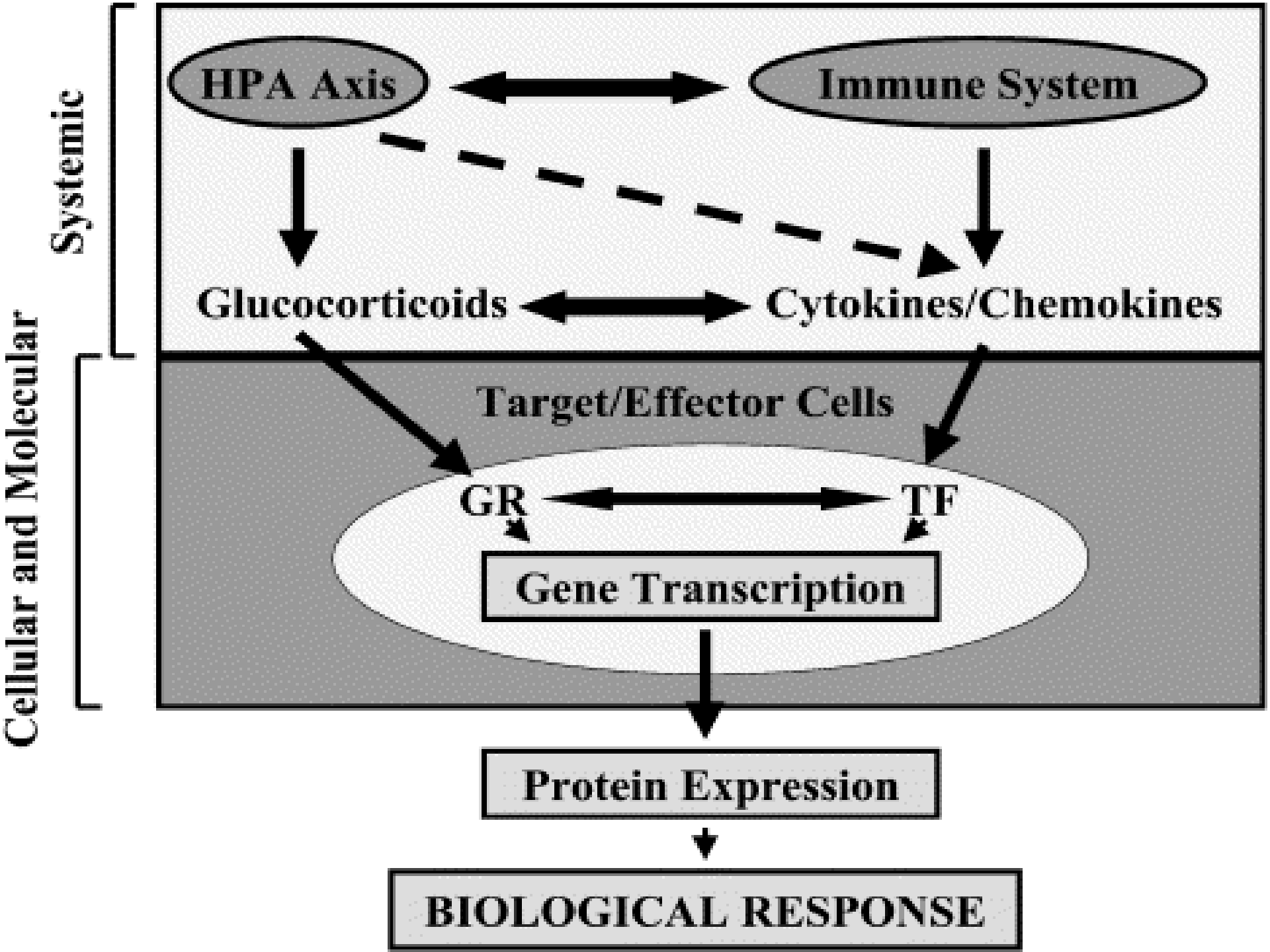

Plasma membrane
Cytoplasm
G
G
G
G
+
GR
HS protein
GR
C
N
N
C
G
GR
GR
G
Nucleus
C
N
N
C
G
GR
G
DNA
G R E
G R E
DNA
Gene
Induce or
suppress



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.

Scheme for molecular communications circuits existing between the immune
and neuroendocrine systems and involving shared ligands and receptors

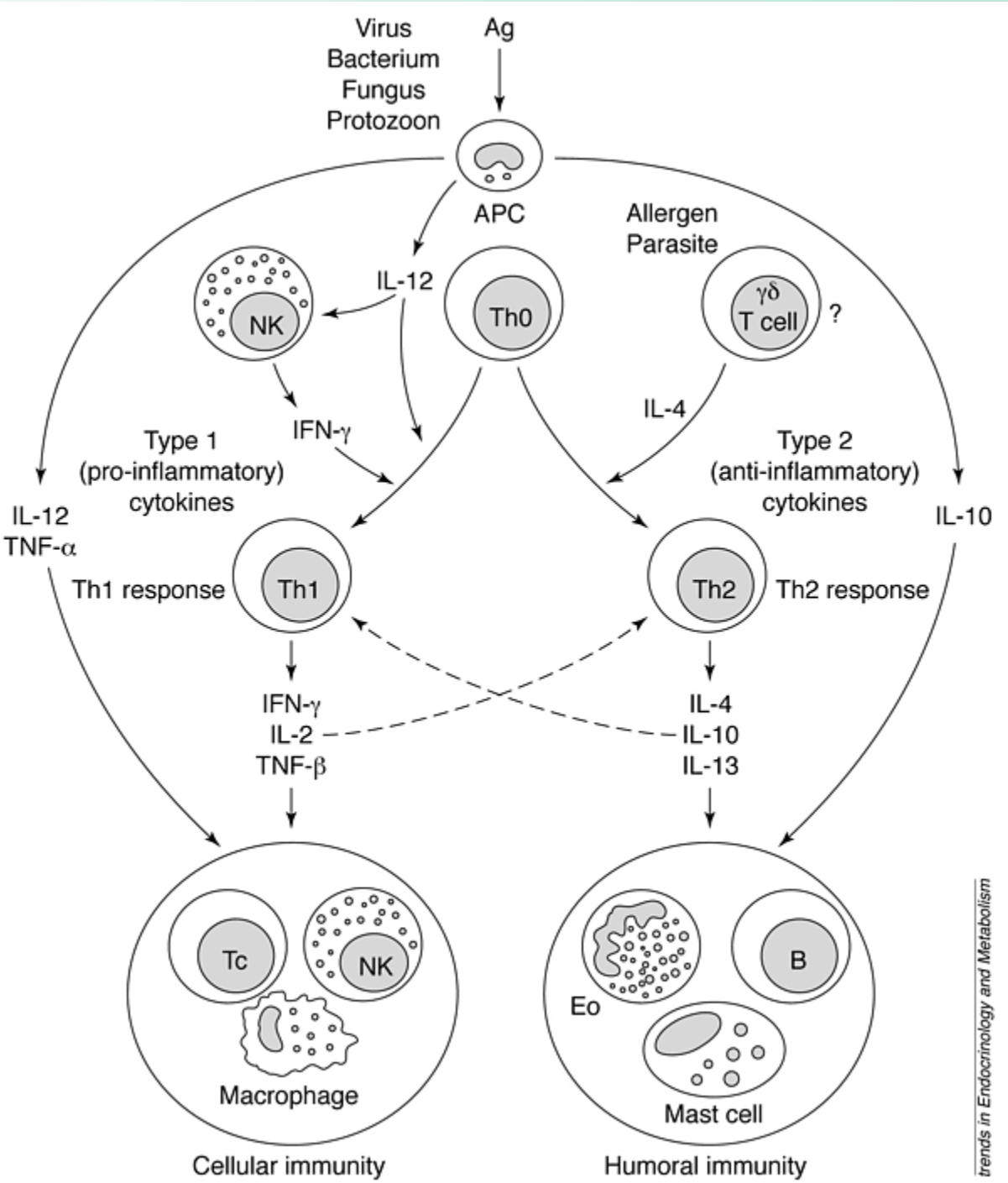


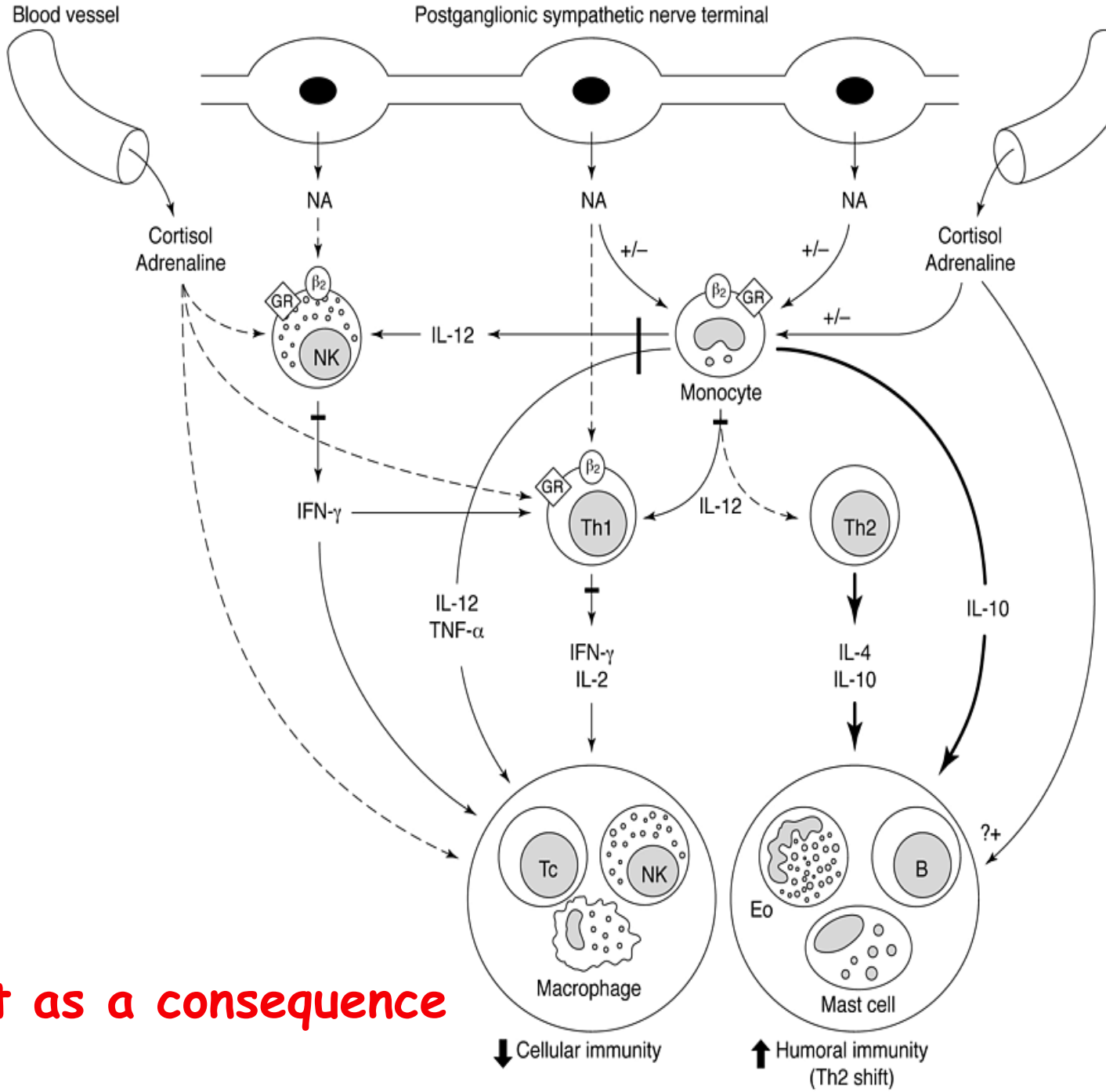

Systemic
Cellular and Molecular
HPA Axis
Immune System
Glucocorticoids
Cytokines/Chemokines
Target/Effector Cells
GR
TF
Gene Transcription
Protein Expression
BIOLOGICAL RESPONSE

To the previous figure:

- Scheme depicting systemic and cellular/molecular interplay between the HPA axis and the immune system in the regulation of glucocorticoid/cytokine secretion and gene expression.
- Abbreviations: GR, glucocorticoid receptor; TF, transcription factors.

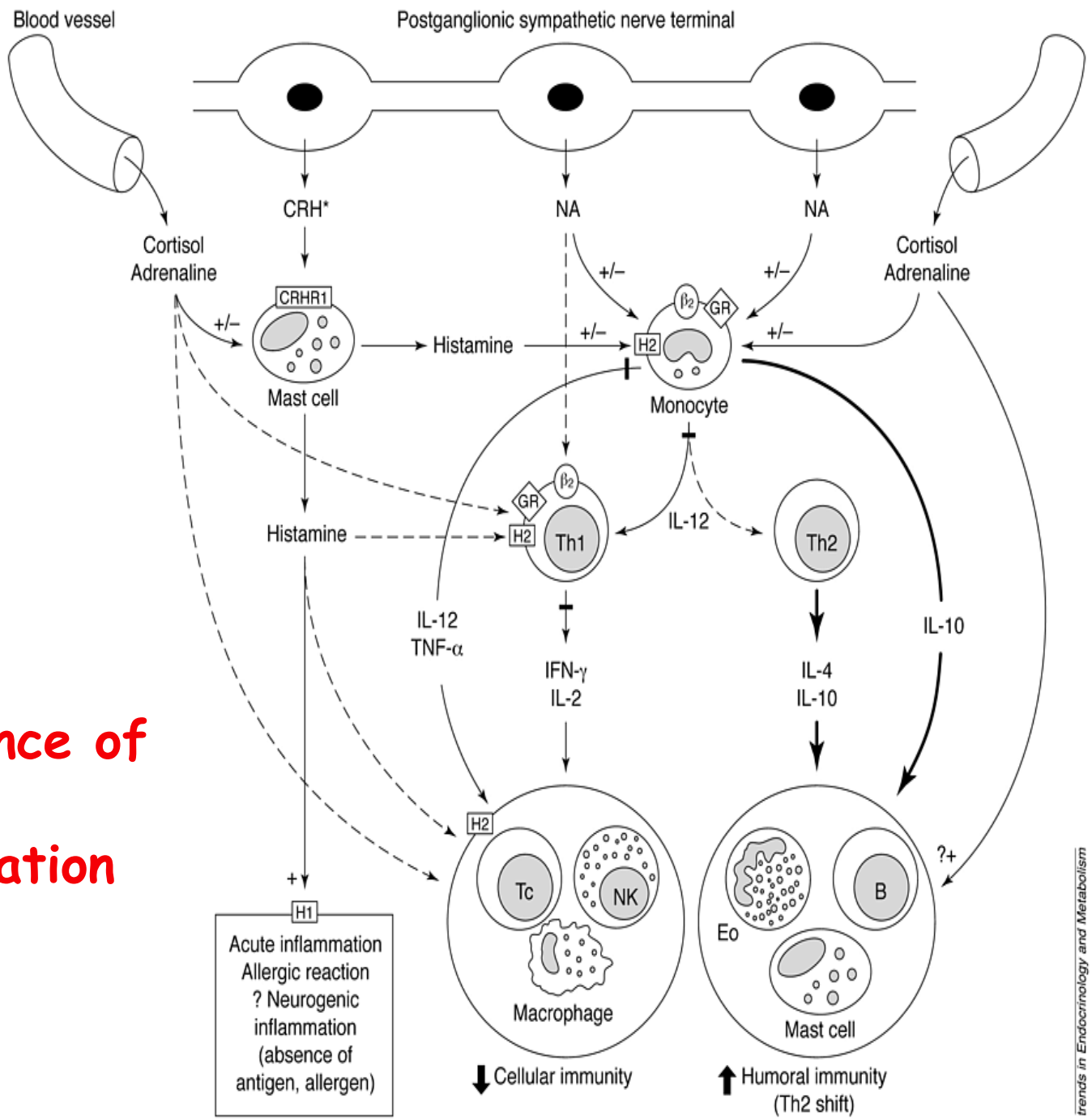
Balance of Th1/Th2 immune resposes





Th2 shift as a consequence of stress

Th2 shift as a consequence of stress and acute inflammation



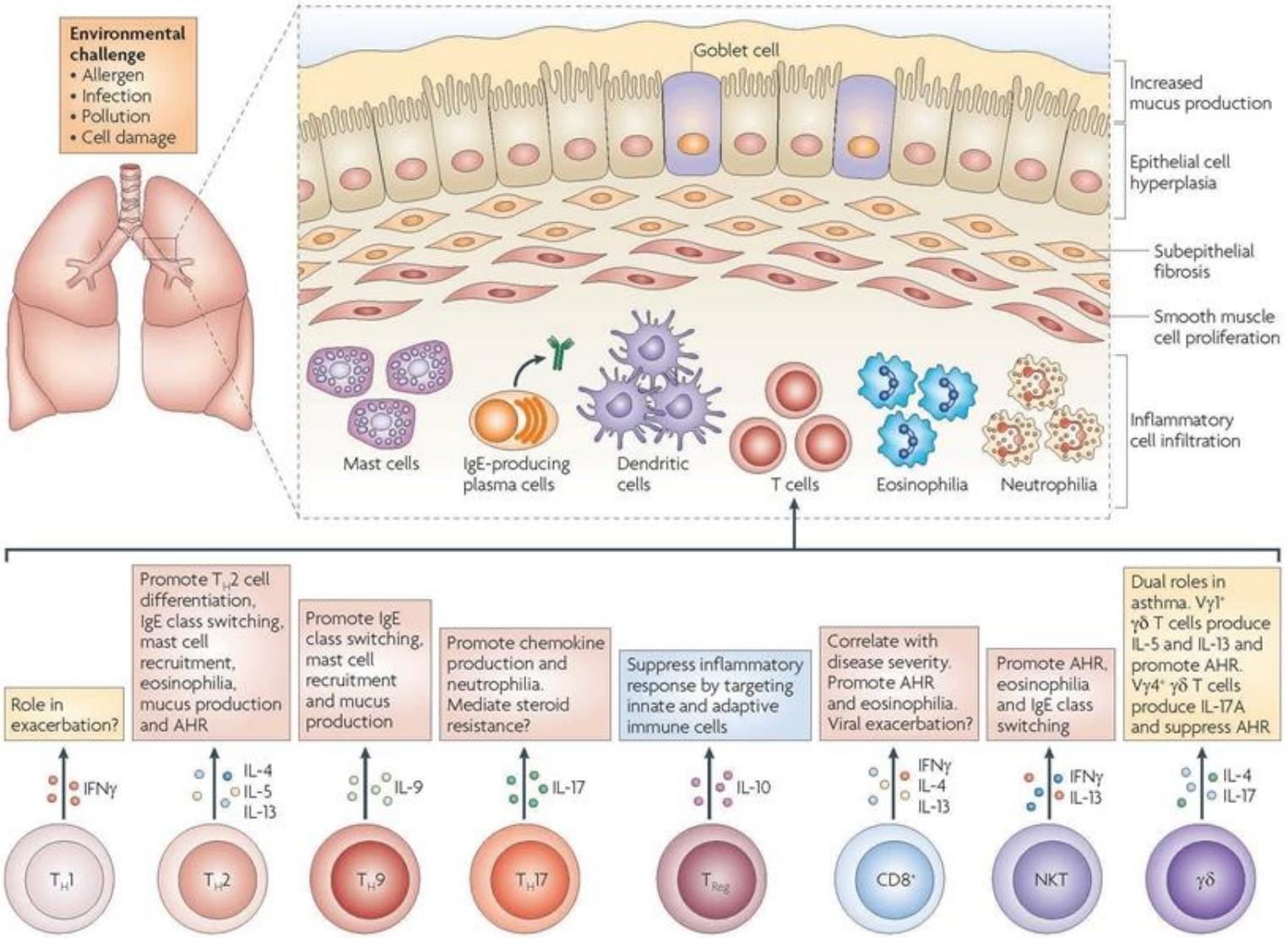
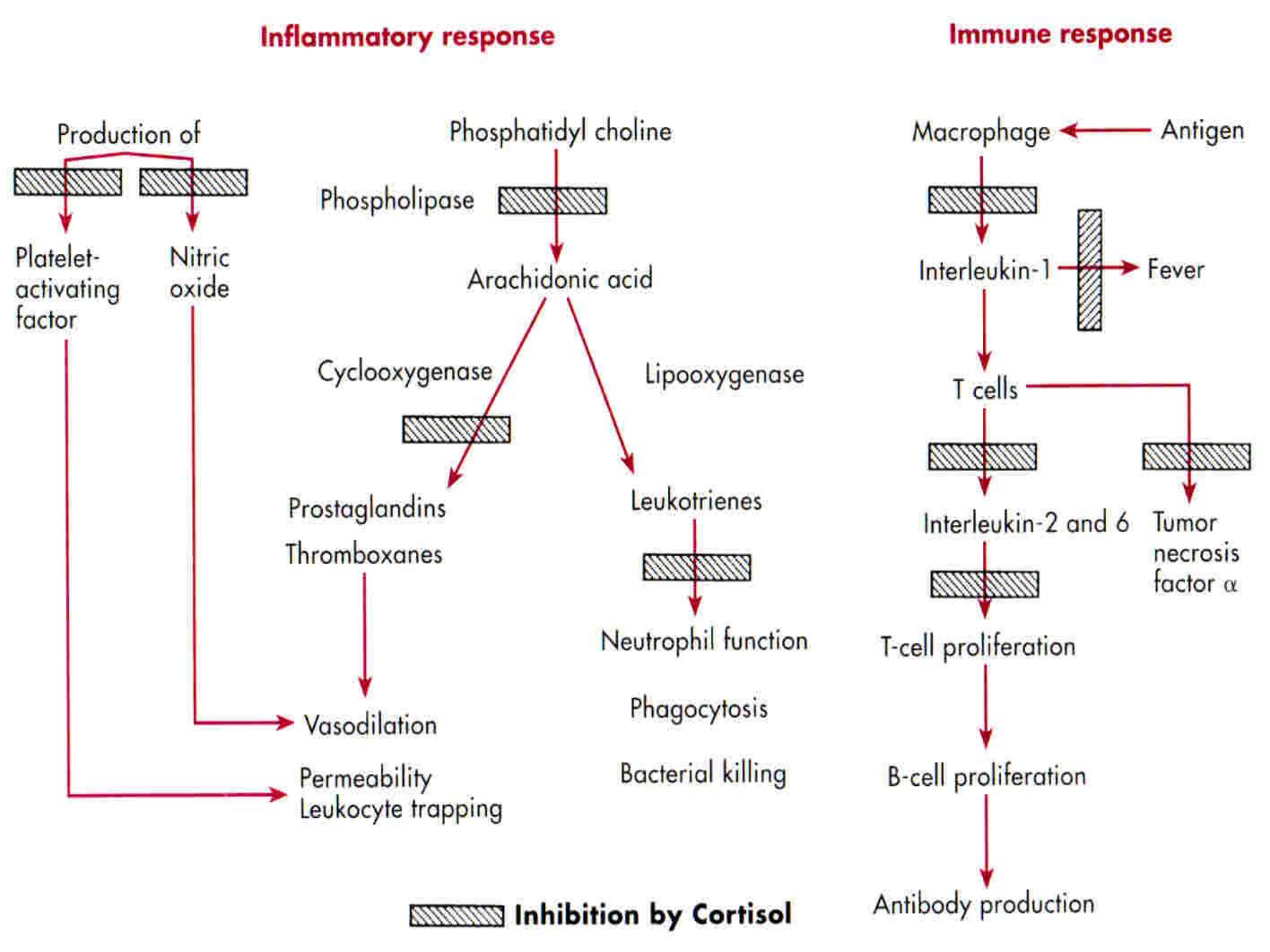


Figure 1 | **T cells involved in the induction of the allergic phenotype.** Asthma is a heterogeneous disease that is characterized by airway hyperresponsiveness (AHR), recruitment of inflammatory leukocytes to the lung and tissue remodelling, including mucus production and airway smooth muscle changes. 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
Phosphatidyl choline
Phospholipase
Arachidonic acid
Cyclooxygenase
Lipooxygenase
Prostaglandins
Thromboxanes
Leukotrienes
Neutrophil function
Phagocytosis
Bacterial killing
Vasodilation
Permeability
Leukocyte trapping
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

Treatment by glucocorticoids

Respiratory diseases

- Asthma
- Chronic obstructive pulmonary disease
- Sarcoidosis
- Prevention/treatment of ARDS

Cardiac diseases

- Post-myocardial infarction syndrome

Renal diseases

- Some nephrotic syndromes
- Some glomerulonephritides
- Gastrointestinal disease
- Ulcerative colitis
- Crohn's disease
- Autoimmune hepatitis

Treatment by glucocorticoids

Rheumatological diseases

- Systemic lupus erythematosus
- Polymyalgia rheumatica
- Cranial arteritis
- Juvenile idiopathic arthritis
- Vasculitides
- Rheumatoid arthritis

Neurological diseases

- Cerebral oedema

Skin diseases

- Pemphigus, eczema

Tumours

- Hodgkin's lymphoma
- Other lymphomas

Transplantation

- Immunosuppression

Major adverse effects of corticosteroid therapy

Physiological

- Adrenal and/or pituitary suppression

Pathophysiological

Cardiovascular

- Increased blood pressure

Gastrointestinal

- Peptic ulceration exacerbation (possibly)
- Pancreatitis

Renal

- Polyuria
- Nocturia

Central nervous

- **Depression**
- **Euphoria**
- **Psychosis**
- **Insomnia**

Endocrine

- **Weight gain**
- **Glycosuria/ hyperglycaemia/diabetes**
- **Impaired growth**
- **Amenorrhoea**

Major adverse effects of corticosteroid therapy

Bone and muscles
- Osteoporosis
- Proximal myopathy and wasting
- Aseptic necrosis of the hip
- Pathological fractures

Skin
- Thinning
- Easy bruising

Eyes
- Cataracts (including inhaled drug)

Increased susceptibility to infection
- **(signs and fever are frequently masked)**
- **Septicaemia**
- **Reactivation of TB**
- **Skin (e.g. fungi)**

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

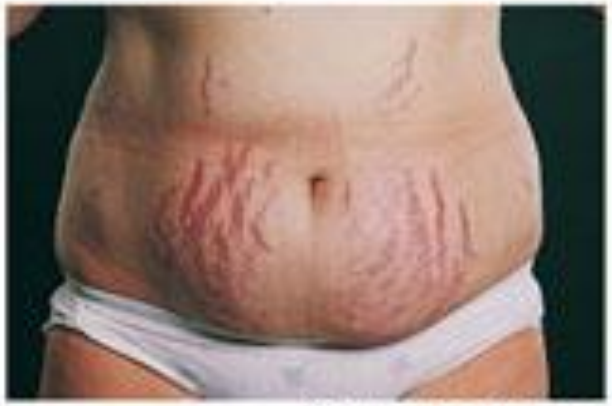
Others

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

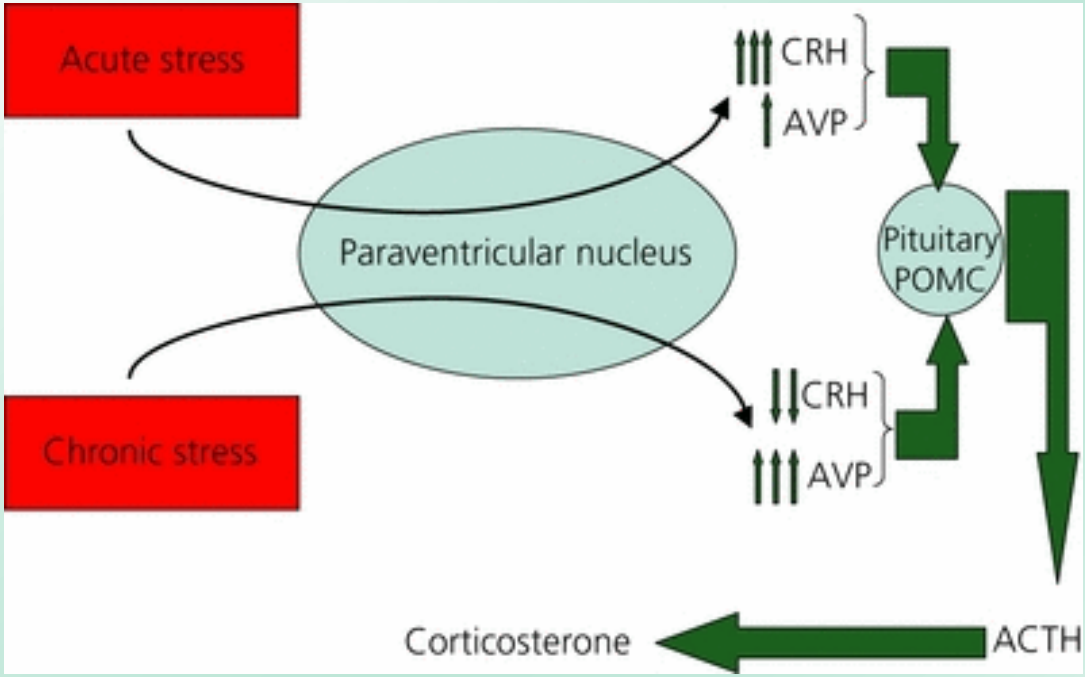


Signs

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
- akthough 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).

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

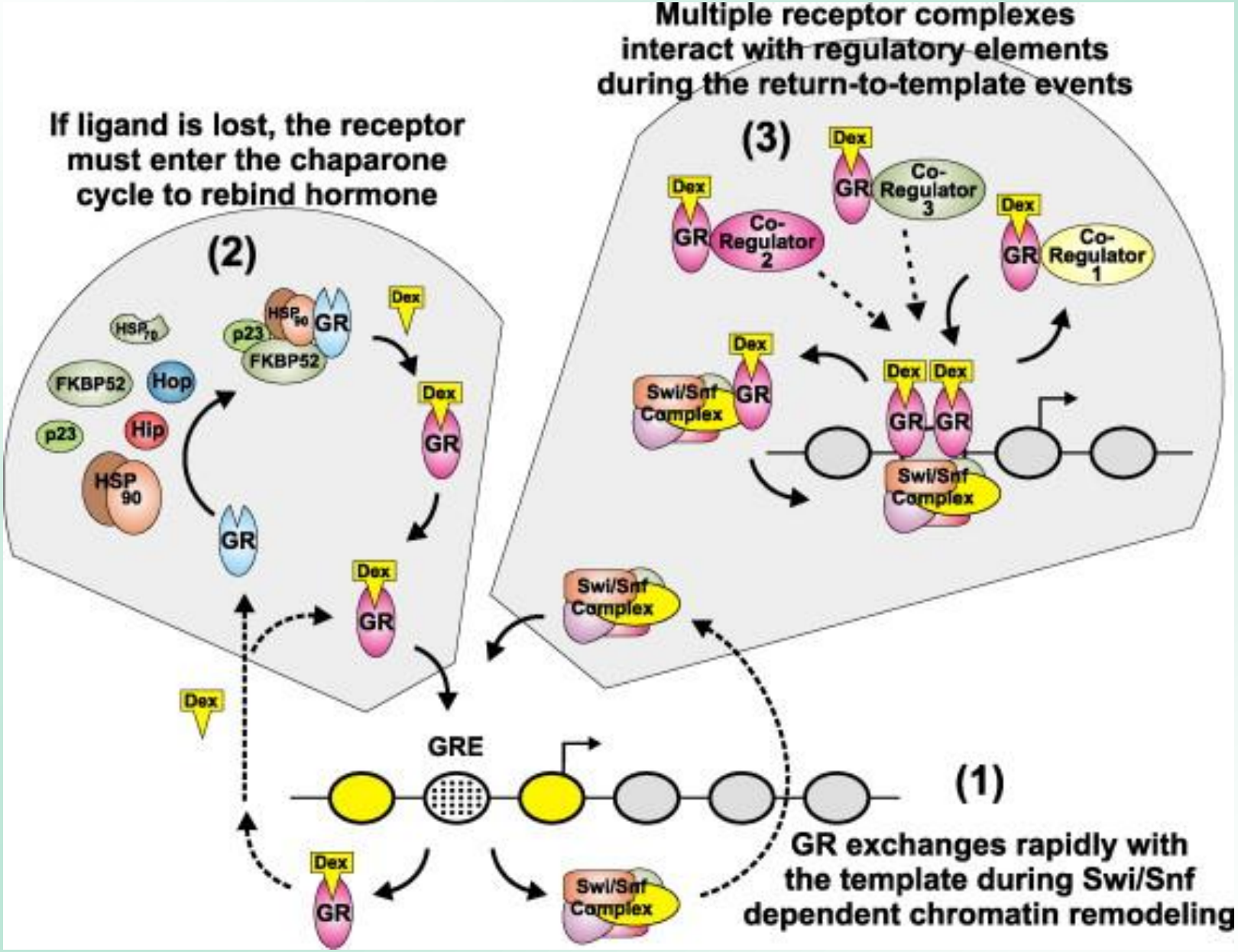
Acute stress response-cardiovascular/ respiratory effects

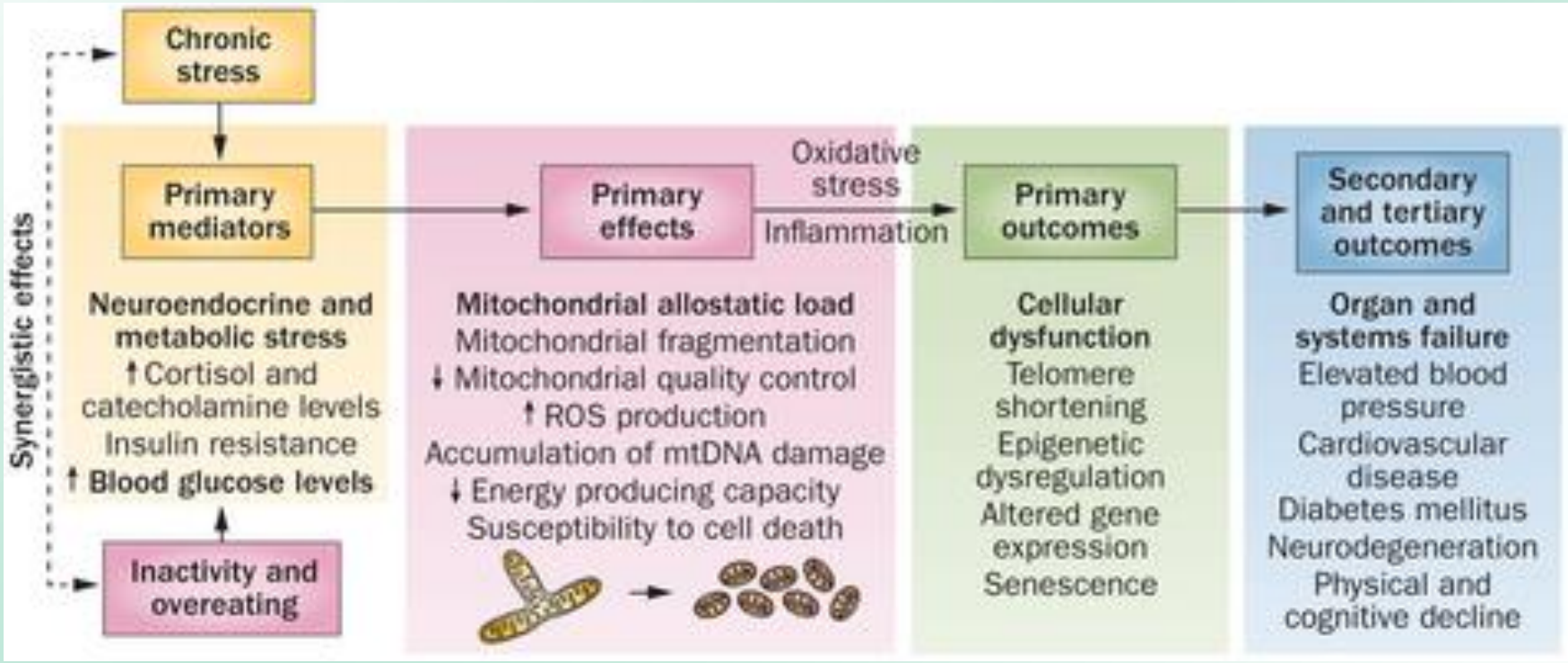
- Purpose: to increase cardiovascular tonus for a quick transport of mobilized glucose to the tissues with the highest oxygen consumption.
- Vasopressin release from axon neurohypophysal terminals leading to reabsorbtion of water in the kidney Purpose: to increase cardiovascular circulating volume

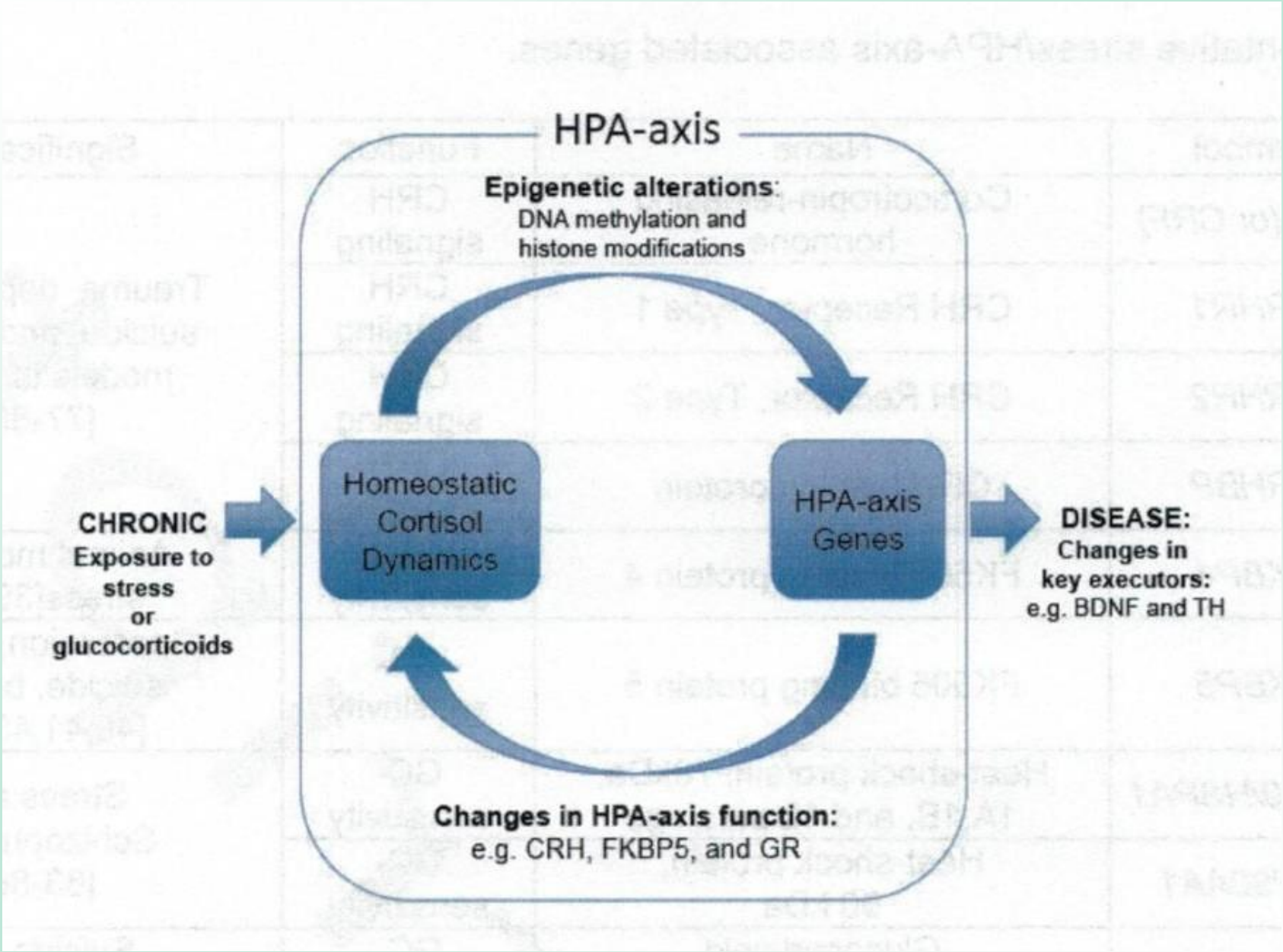
Acute stress response-analgesia

- 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.


Multiple receptor complexes
interact with regulatory elements
during the return-to-template events
If ligand is lost, the receptor
must enter the chaparone
cycle to rebind hormone
(3)
(2)
(1)
Dex
GR
Co-
Regulator
3
Co-
Regulator
2
Co-
Regulator
1
Swi/Snf
Complex
HSP90
HSP70
p23
FKBP52
Hop
Hip
GRE
GR exchanges rapidly with
the template during Swi/Snf
dependent chromatin remodeling


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


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

Chronic stress response

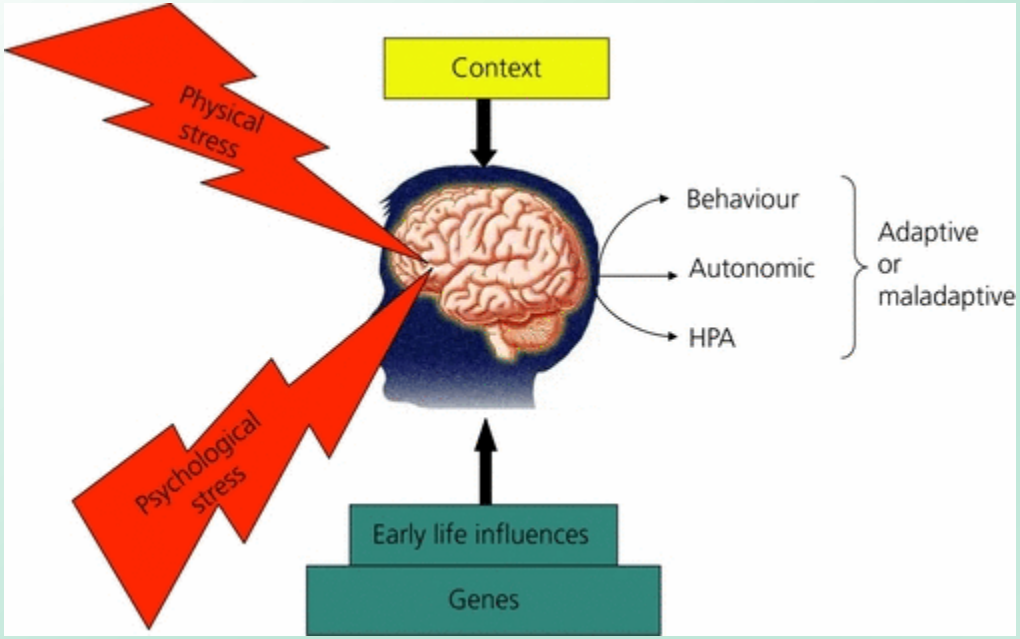
☹maladaptive = imparing effects

☹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.



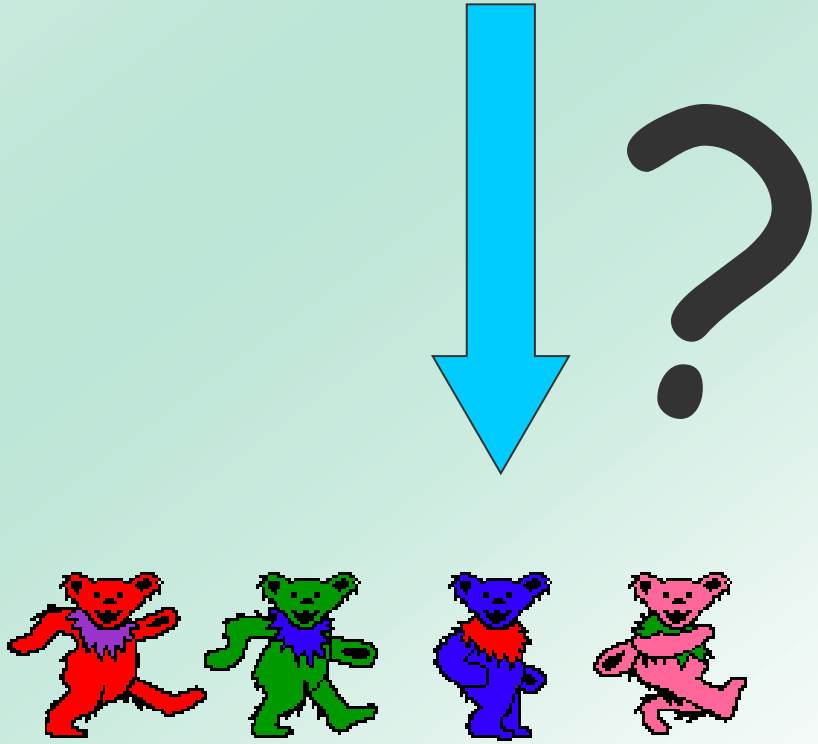
Physiological and pathological responses to stress. The resilience or vulnerability of any one individual to stressful situations in adulthood will depend upon that person's genetic inherence and early life experiences.

Stress and multiplex factors role

- Dominant and subdominant primates (males):
- In stable conditions (no teritorial emergency), dominant males have lower glucocorticoids levels than subdominat 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.

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)



Děkuji vám za pozornost