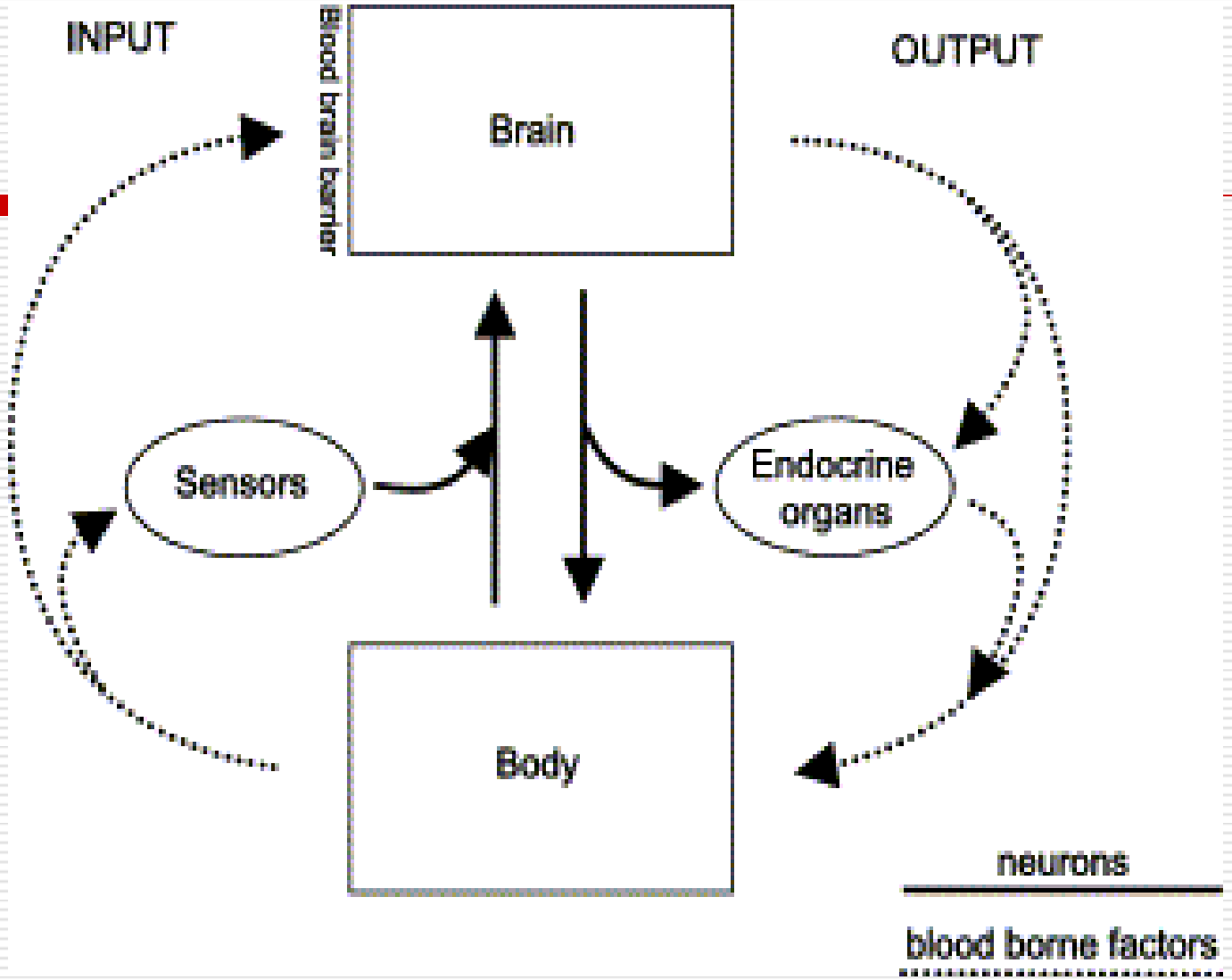
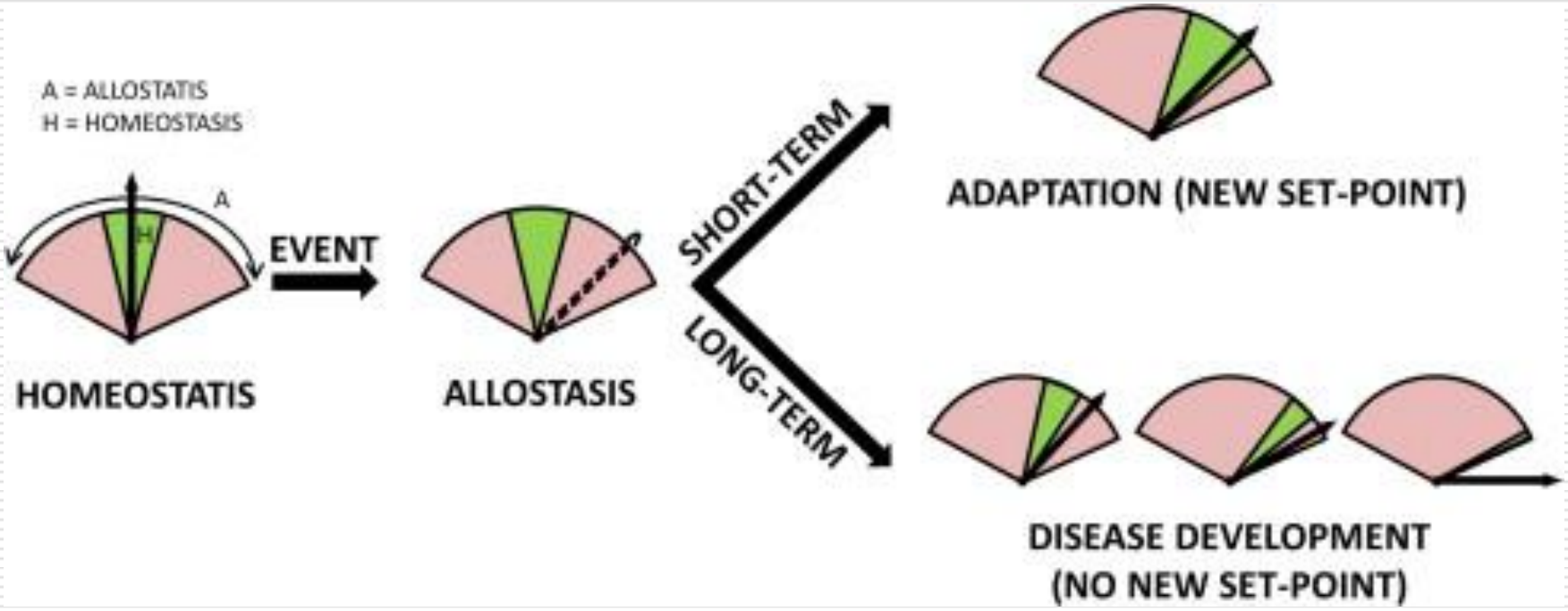
General Pathophysiology of Endocrine System

March 28, 2017

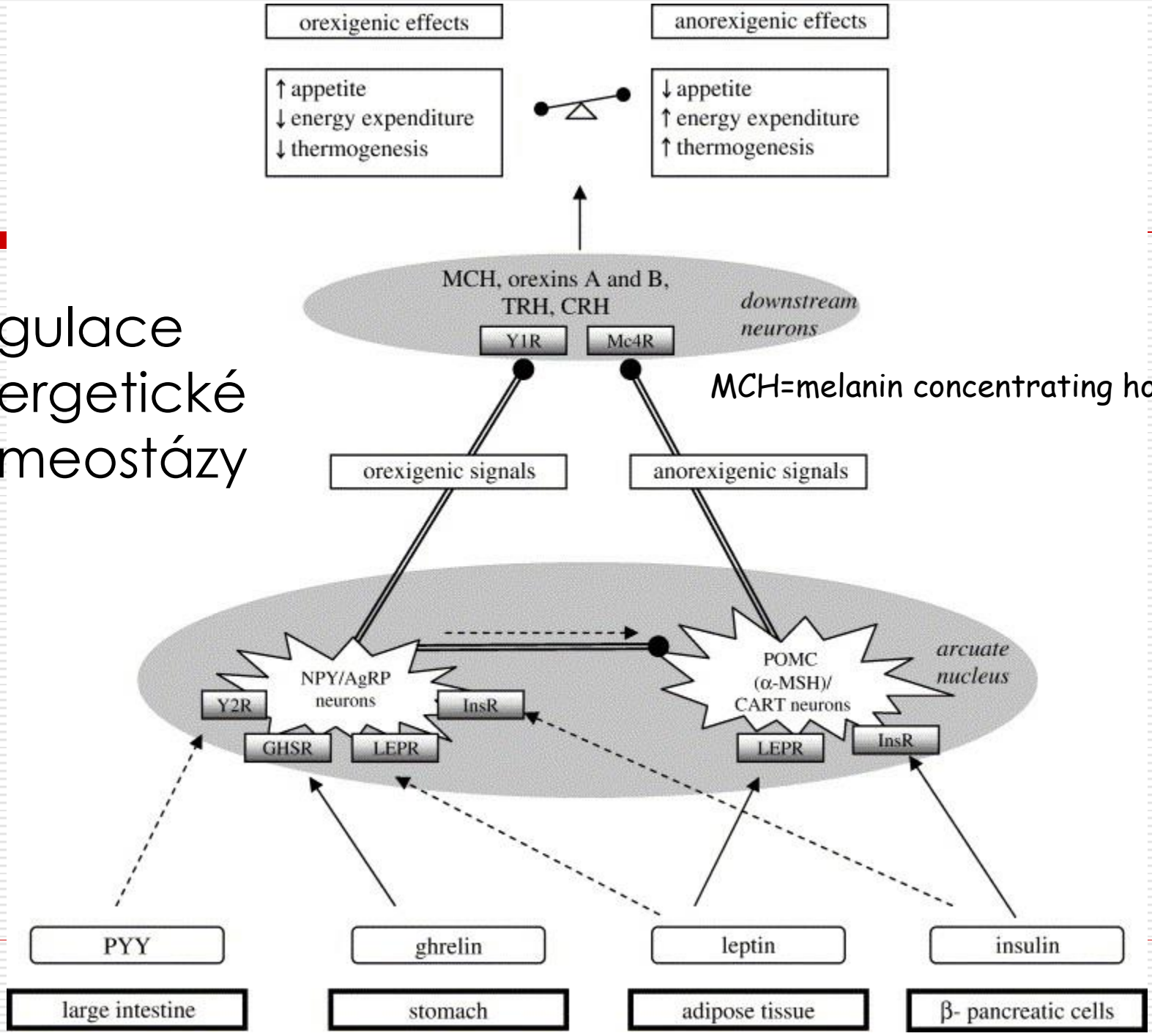


Interactive homeostatic system: communication between body and brain by means of neurons and factors circulating in blood



Bienertová-Vašků J, Zlámal F, Nečesánek I, Konečný D, Vasku A. PLoS One. 2016 Jan 15;11(1)

Regulace energetické homeostázy



MCH=melanin concentrating hormon

Effects of hormones

- **Pleoitrophism:**

- **one hormon has more effects in different tissue**
- **more hormones modulate one function**

Effects of hormones

- *Acute - posttranslational effects*
- *Chronic→genomic effects-→*trophic (cell growth and division)

Receptor regulation types:

- *up-regulation* (genomic effect)
- *down-regulation* (membrane effect)

Hormone action and receptors

- Hormones act by binding to specific receptors in the target cell, which may be at the cell surface and/or within the cell.
- Most hormone receptors are proteins with complex tertiary structures, parts of which complement the tertiary structure of the hormone to allow highly specific interactions, while other parts are responsible for the effects of the activated receptor within the cell.
- Many hormones bind to specific cell-surface receptors where they trigger internal messengers, while others bind to nuclear receptors which interact directly with DNA.

Hormone action and receptors

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- Cell-surface receptors usually contain hydrophobic sections which span the lipid-rich plasma membrane, while nuclear receptors contain characteristic amino-acid sequences to bind nuclear DNA (e.g. so-called 'zinc fingers') as in the glucocorticoid receptor.

Hormone classes according to the structure

Amines and amino acids	Peptides, polypeptides and proteins	Steroids
Adrenaline Noradrenaline Dopamine Thyreoid hormones	ACTH, angiotensine calcitonine erythropoietine FSH gastrine glucagone STH insulin LH, Oxytocin PTH, prolactine secretine, TSH, ADH	Aldosterone Glucokortikoids Estrogenes Progesterone Testosterone

Hormonal activity

- At the molecular level there is little difference in the way cellular activity is regulated between classical neurotransmitters that act across synaptic clefts, intercellular factors acting across gap junctions, classic endocrine and paracrine activity and a variety of other chemical messengers involved in cell regulation - such as cytokines, growth factors and interleukins; progress in basic cell biology has revealed the biochemical similarities in the messengers, receptors and intracellular post-receptor mechanisms underlying all these aspects of cell function.

Output of the cell

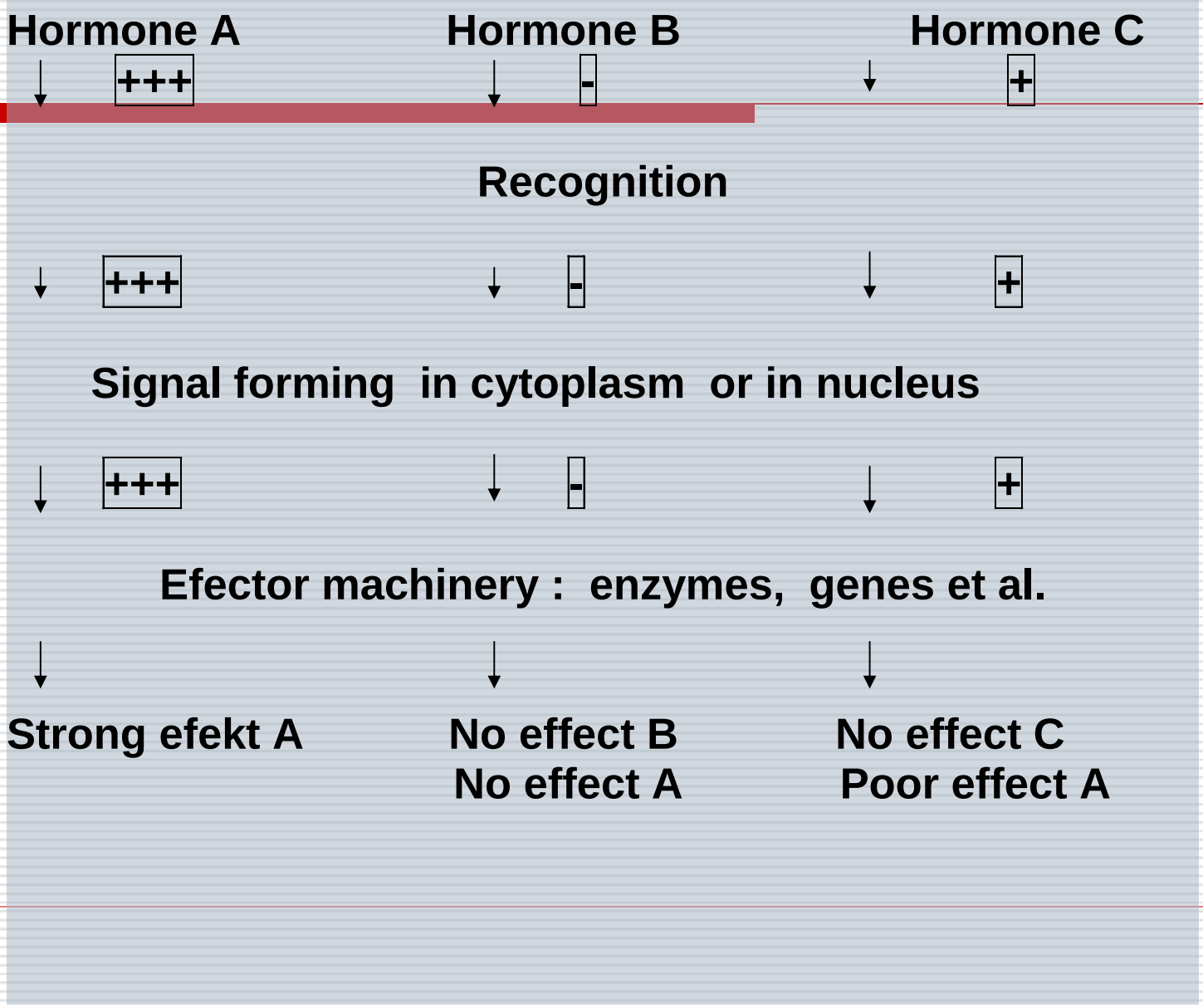
- *Acute* - monotrophic
- *Chronic*-pleiotrophic

- *Responsive cell-* the cell able to realize postreceptively adequate response
- *Receptive cell-* the cell appointed by receptors

Manner of hormone secretion

- *Endocrine secretion* – directly to the blood or indirectly through extracellular water compartment
- *Paracrine secretion* – the hormone has not must not be secreted to the blood (growth factors, neuroparakrinia)
- *Autocrine secretion* - f.i. presynaptic neuromodulation of NE release

Interaction hormone-receptor



Interaction hormone-receptor

Interactions fixed with messenger	Mobile interactions hormone-receptor-nucleus
Glucagone Insulin Noradrenaline PTH TSH ACTH FSH LH ADH Secretine	Estrogenes Testosterone Progesterone Adrenal cortical hormones Thyreoid hormons

Hormone binding globulins

- *with small affinity and specifity for the hormone*
- albumine, orozomukoid, α_1- acid glycoprotein
- *with high affinity and higher specifity for the hormone*
- TBG, Transkortine (CBG), SHBG

↓ binding proteins:

- Dysproteinemia acute and chronic

↑ binding proteins

- Liver cirrhosis

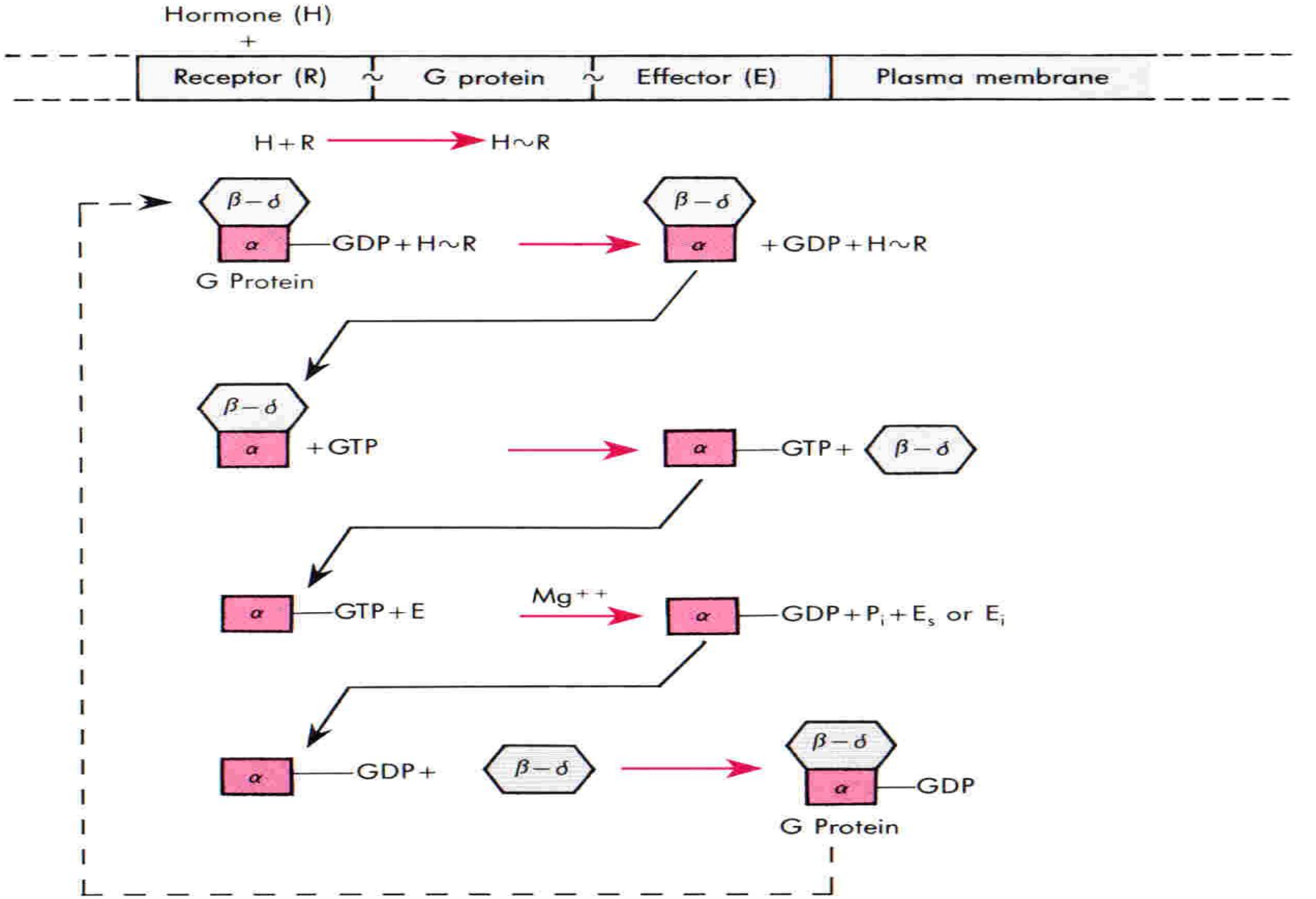
Feedback control

Hormone-hormone
Substrat-hormone

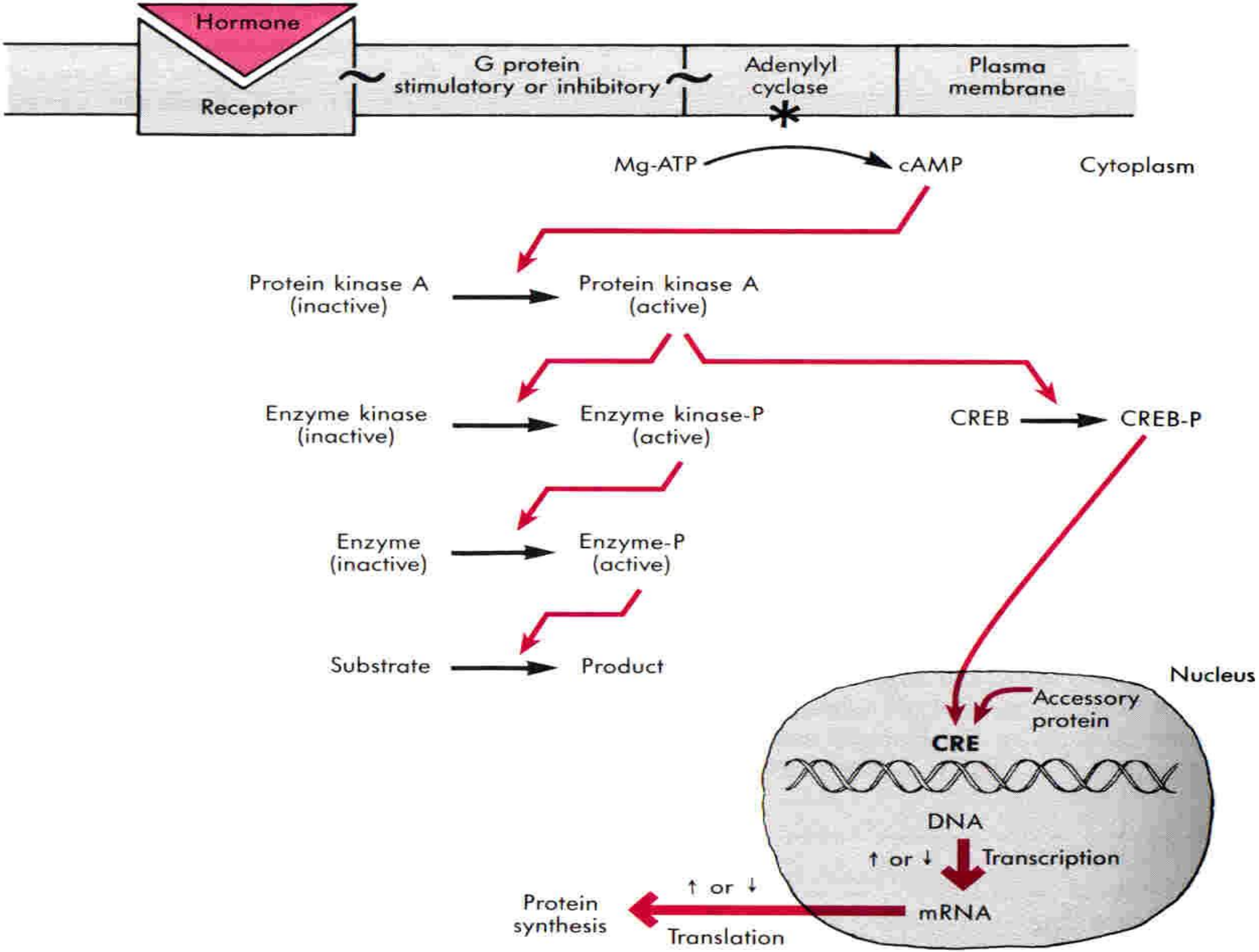
Neuronal control
Adrenergic
Cholinergic
Dopaminergic
Serotoninergic
Endorfinergic
-enkefalinergic
Gabaergic

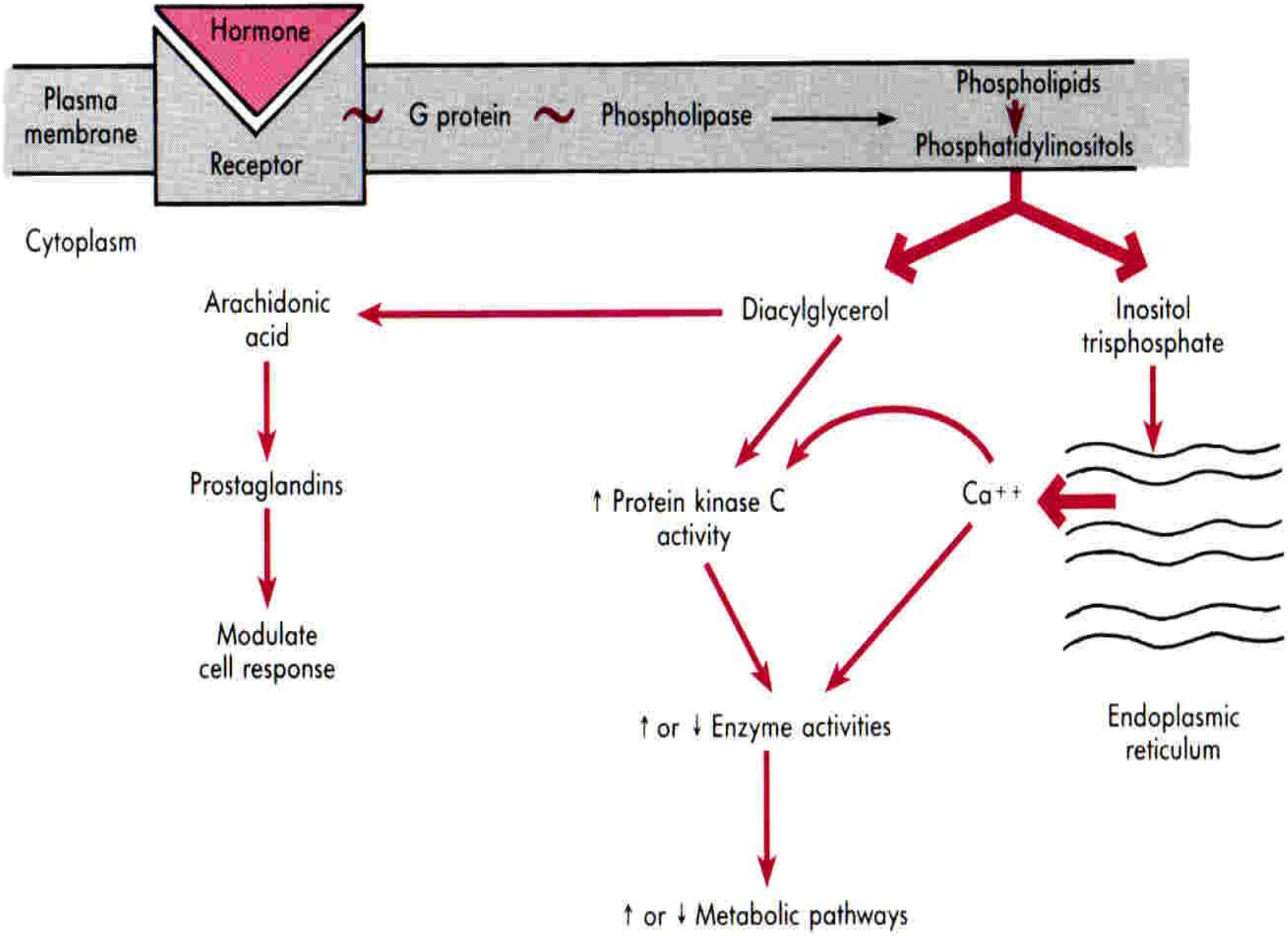
Chronotrophic control
Oscillated
Pulzatile
Diurnal rhythm
Sleep-wake rhythm
Menstrual rhythm
Sesonal rhythm
Development rhythm

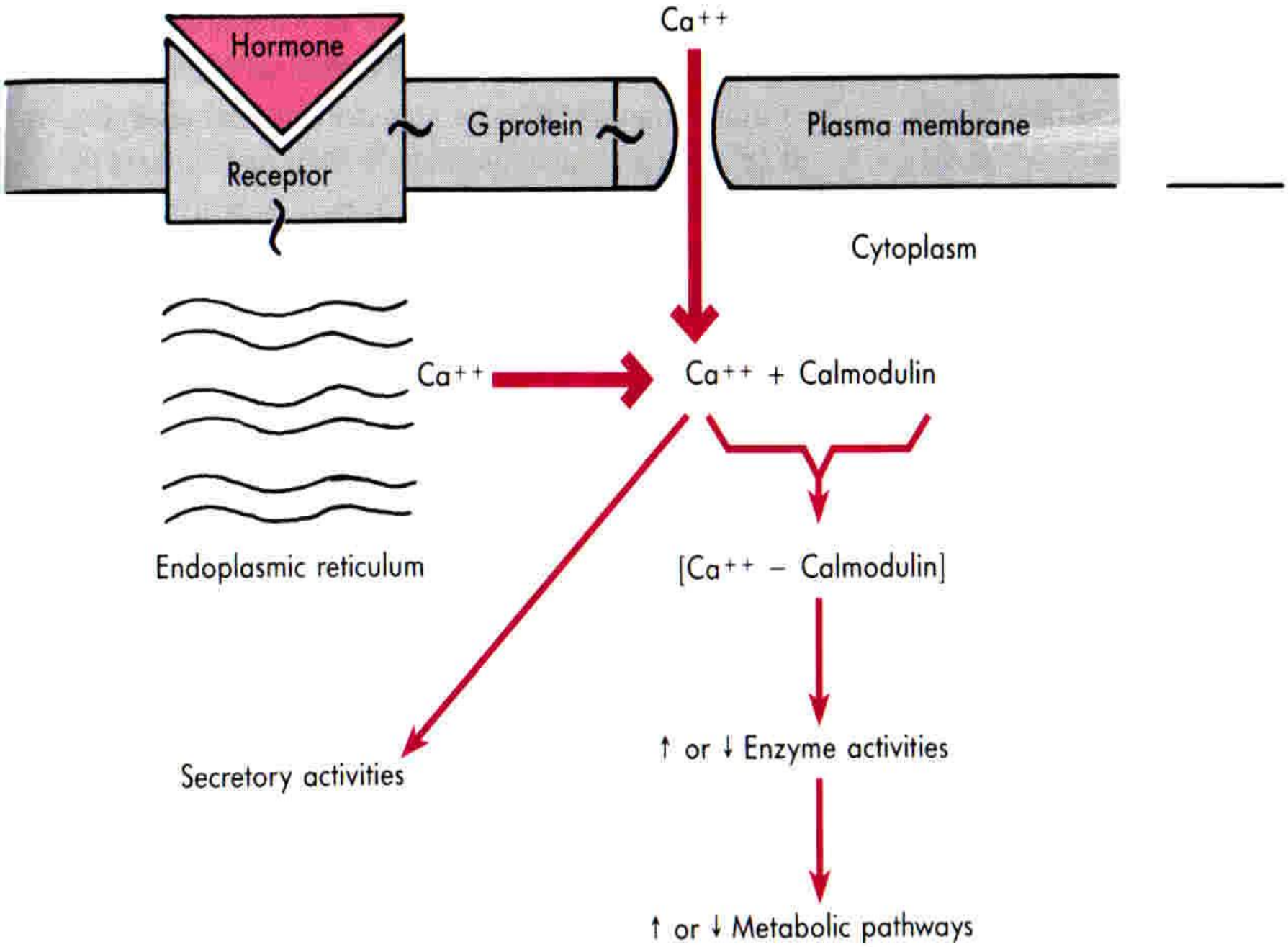
Koncepce multireceptivní buňky

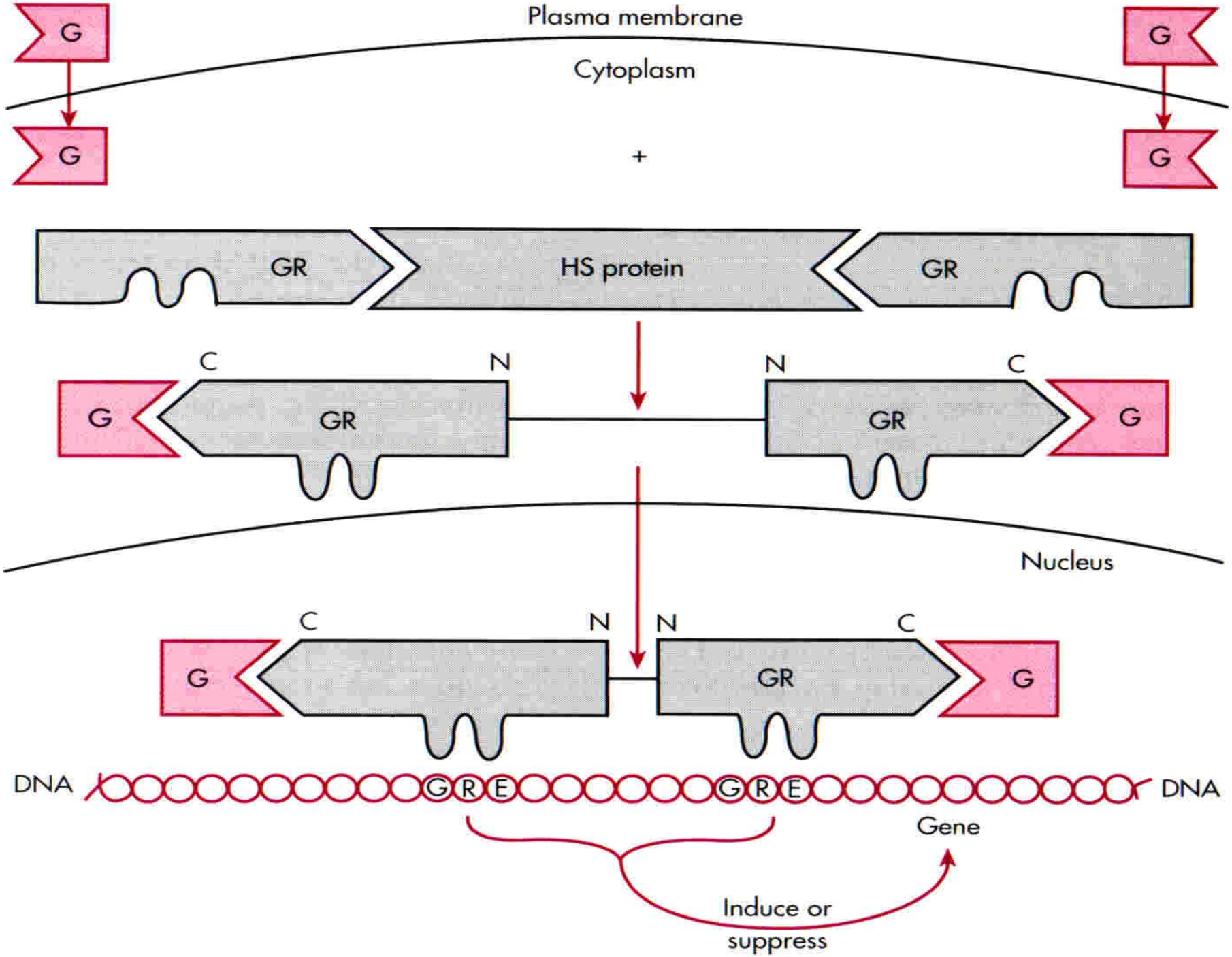


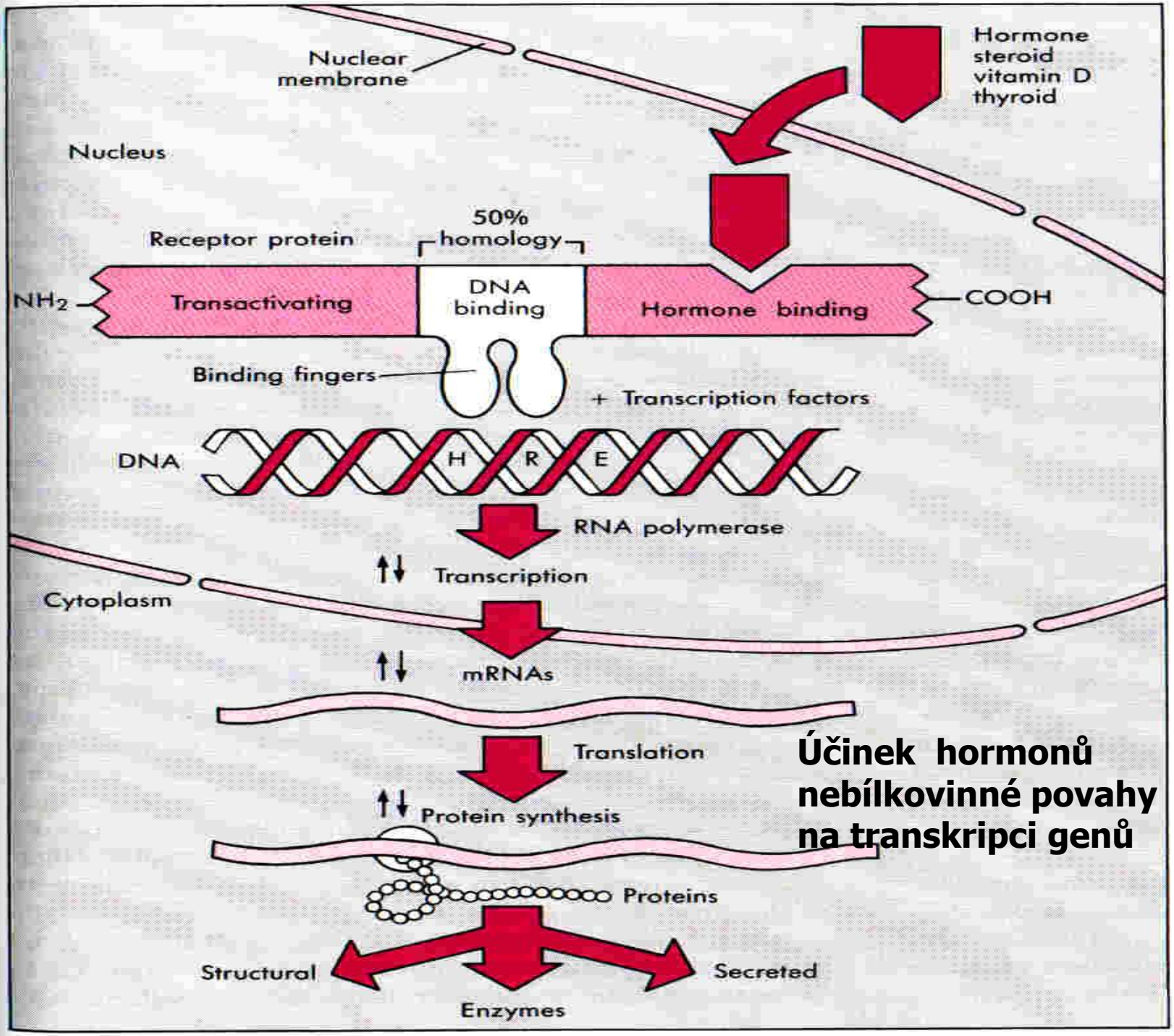
GDP = Guanosine diphosphate
GTP = Guanosine triphosphate
P_i = Inorganic phosphate
E = Effector
E_s = Stimulated effector
E_i = Inhibited effector


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


Hormone
Plasma membrane
Receptor
G protein
Phospholipase
Phospholipids
Phosphatidylinositols
Cytoplasm
Arachidonic acid
Diacylglycerol
Inositol trisphosphate
Prostaglandins
↑ Protein kinase C activity
Ca++
Modulate cell response
↑ or ↓ Enzyme activities
Endoplasmic reticulum
↑ or ↓ Metabolic pathways

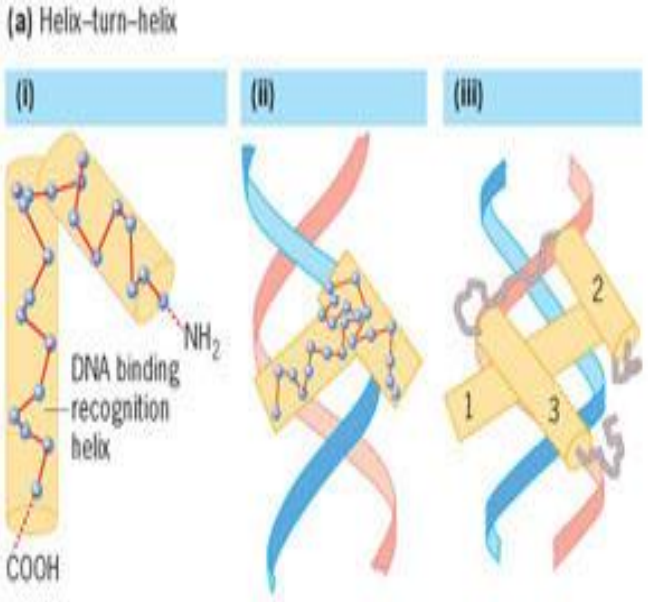

Hormone
Receptor
G protein
Plasma membrane
Ca++
Cytoplasm
Endoplasmic reticulum
Ca++
Ca++ + Calmodulin
[Ca++ – Calmodulin]
Secretory activities
↑ or ↓ Enzyme activities
↑ or ↓ Metabolic pathways

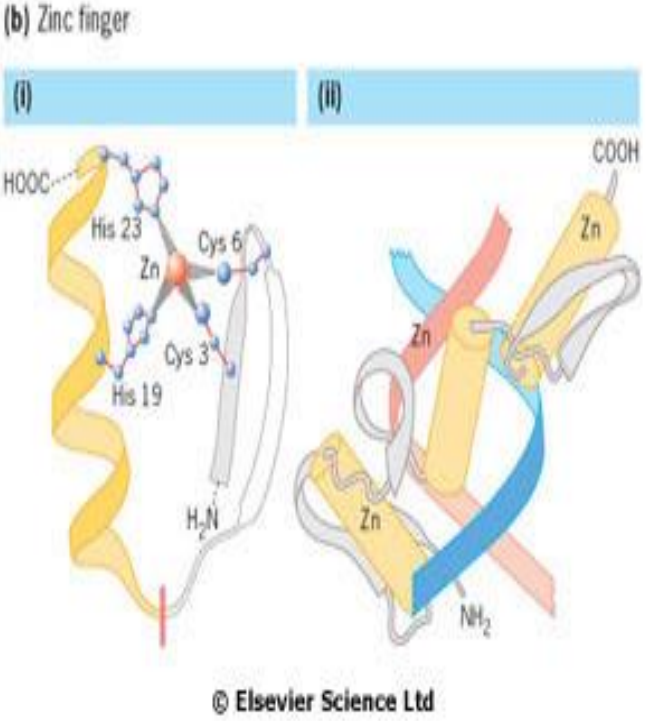

Plasma membrane
Cytoplasm
G
G
+
G
G
GR
HS protein
GR
C
N
N
C
G
GR
GR
G
Nucleus
C
N
N
C
G
GR
G
DNA
G R E
G R E
DNA
Gene
Induce or
suppress

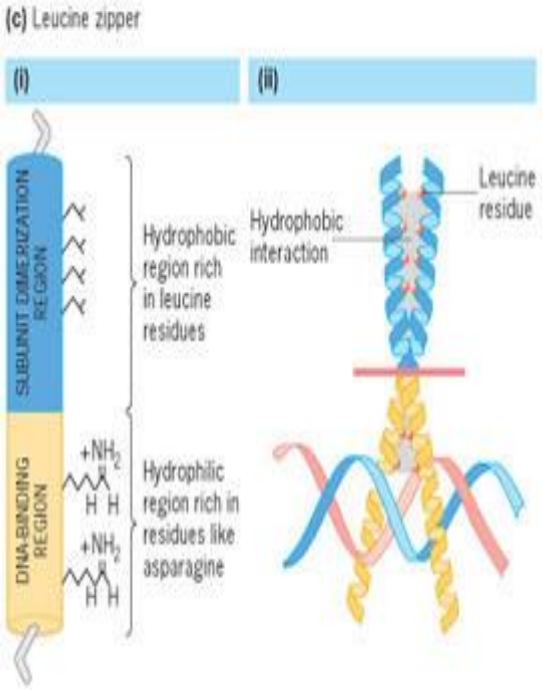


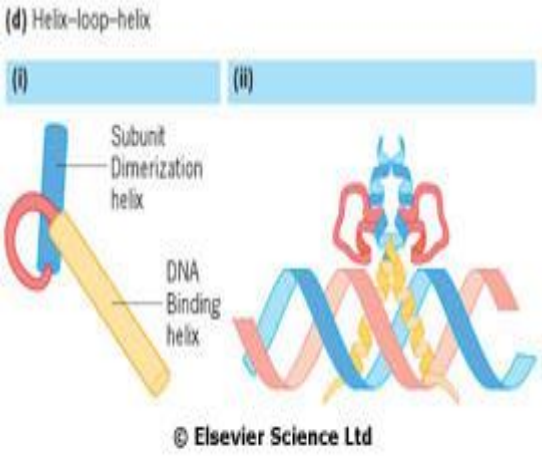
Účinek hormonů nebílkovinné povahy na transkripci genů

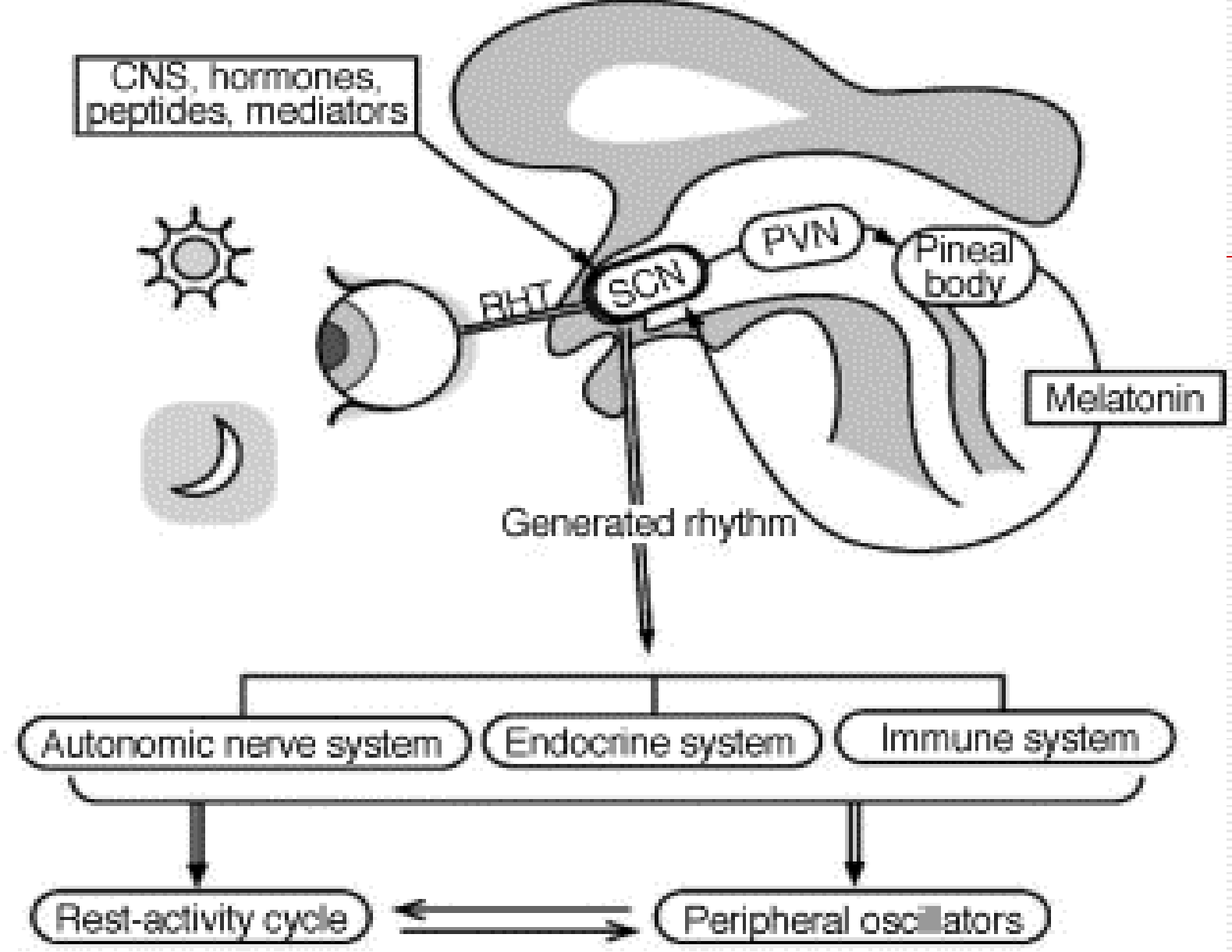
4 třídy DNA-vazných proteinů



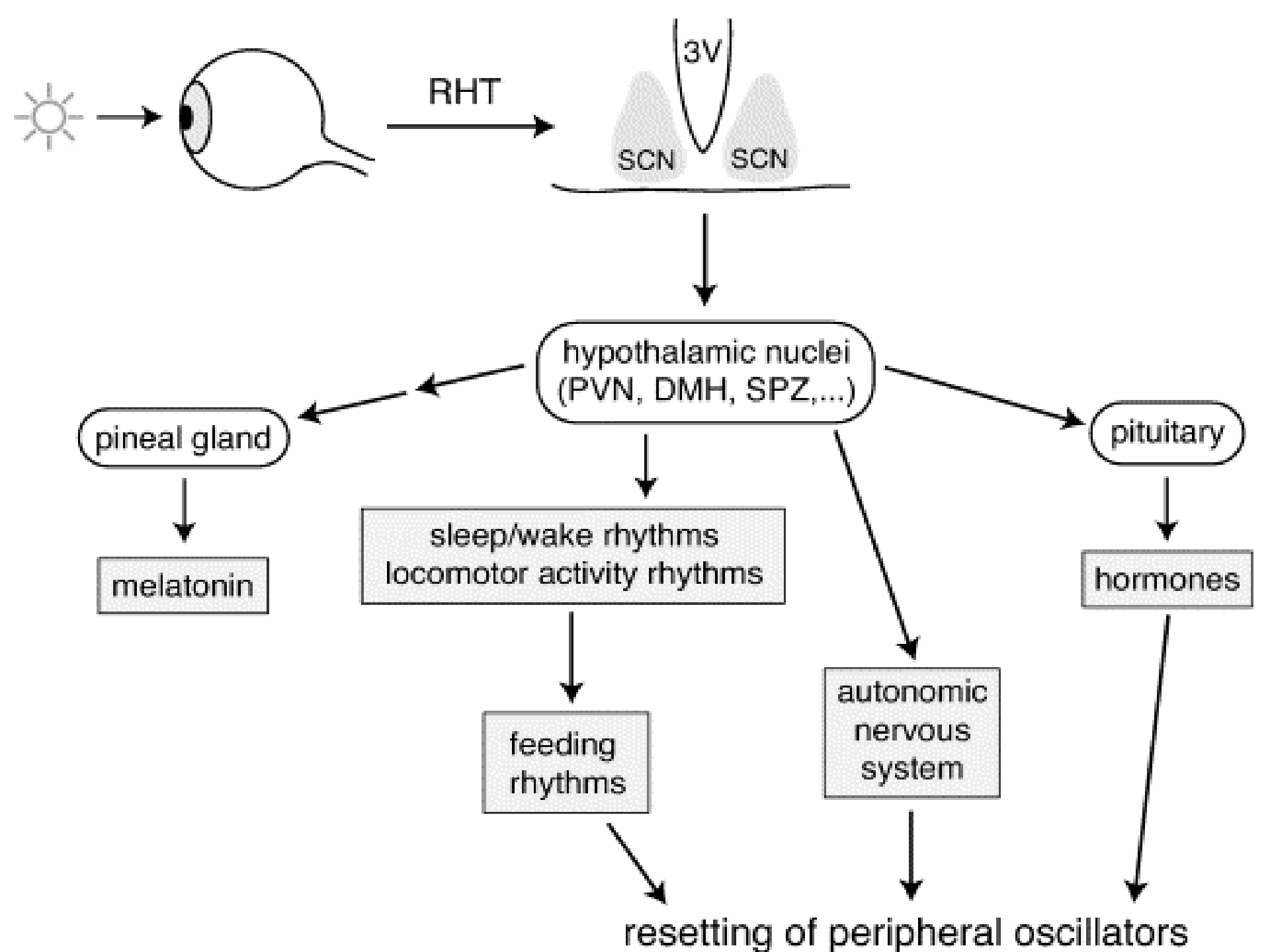




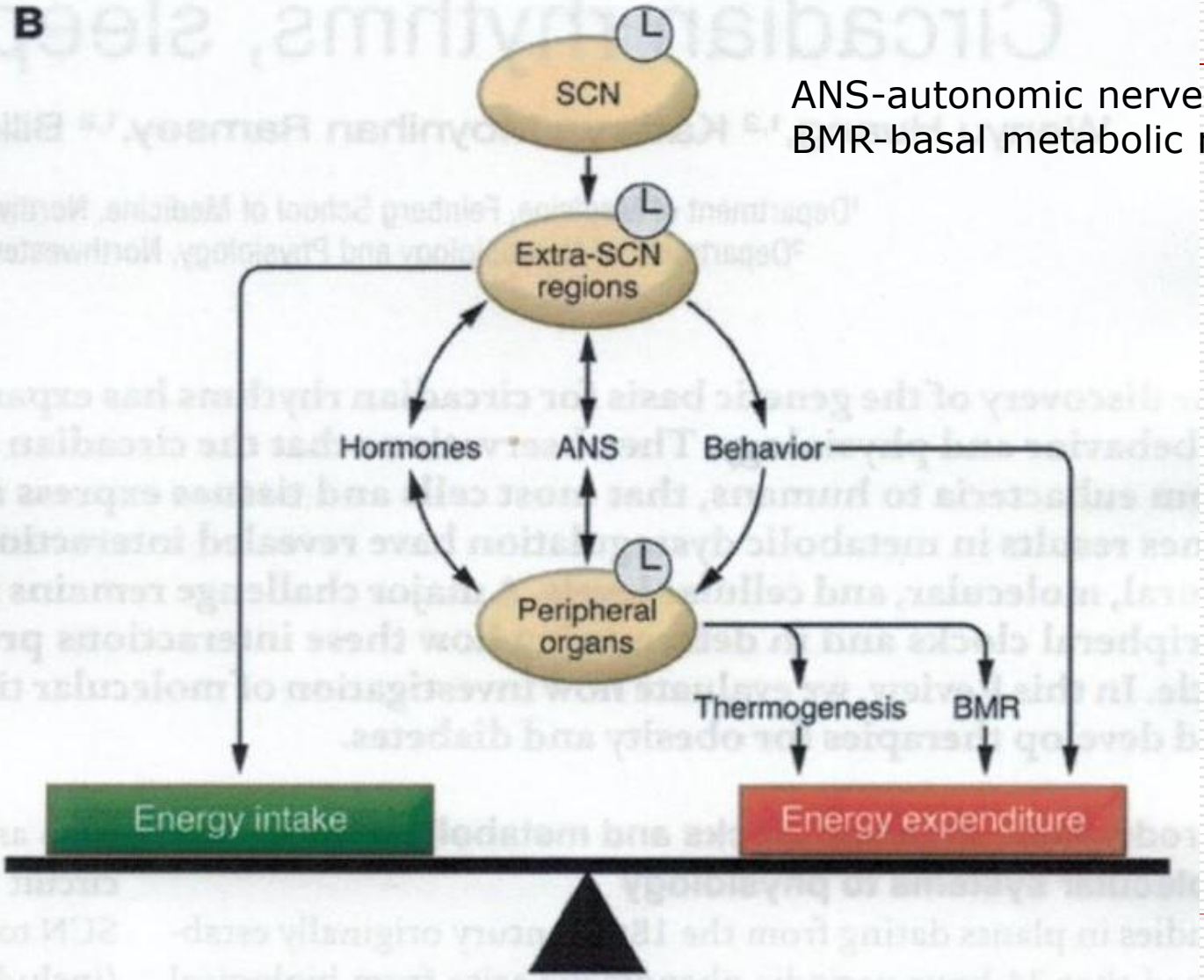




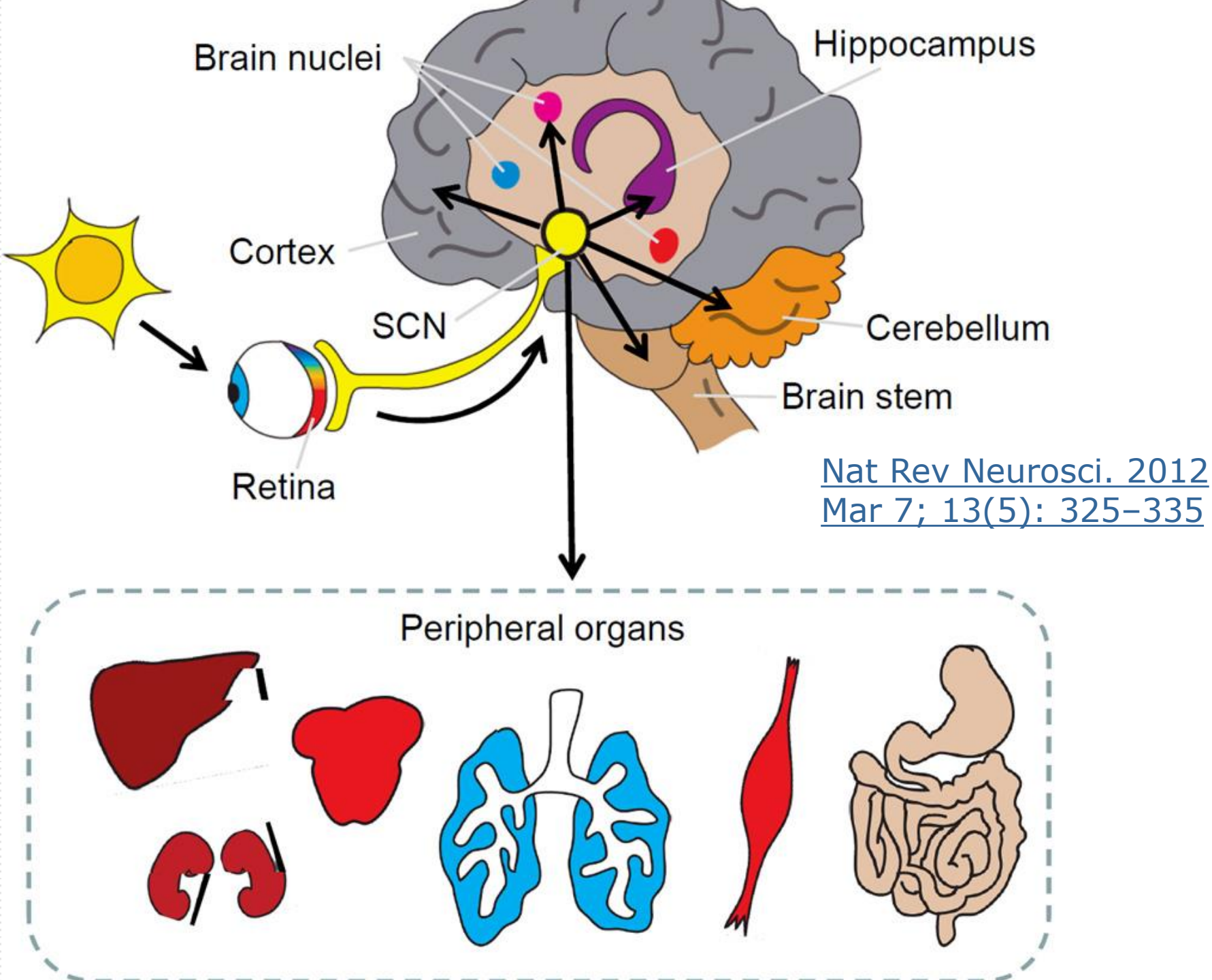
Schema of human circadian system. RHT, retinohypothalamic tract; SCN, suprachiasmatic nucleus; PVN, paraventricular nucleus


RHT
3V
SCN
SCN
hypothalamic nuclei
(PVN, DMH, SPZ,...)
pineal gland
melatonin
sleep/wake rhythms
locomotor activity rhythms
feeding
rhythms
autonomic
nervous
system
pituitary
hormones
resetting of peripheral oscillators

Clin Invest. 2011 Jun;121(6):2133-41. **Circadian rhythms, sleep, and metabolism.**
Huang W[1], Ramsey KM, Marcheva B, Bass J.



ANS-autonomic nerve system
BMR-basal metabolic rate



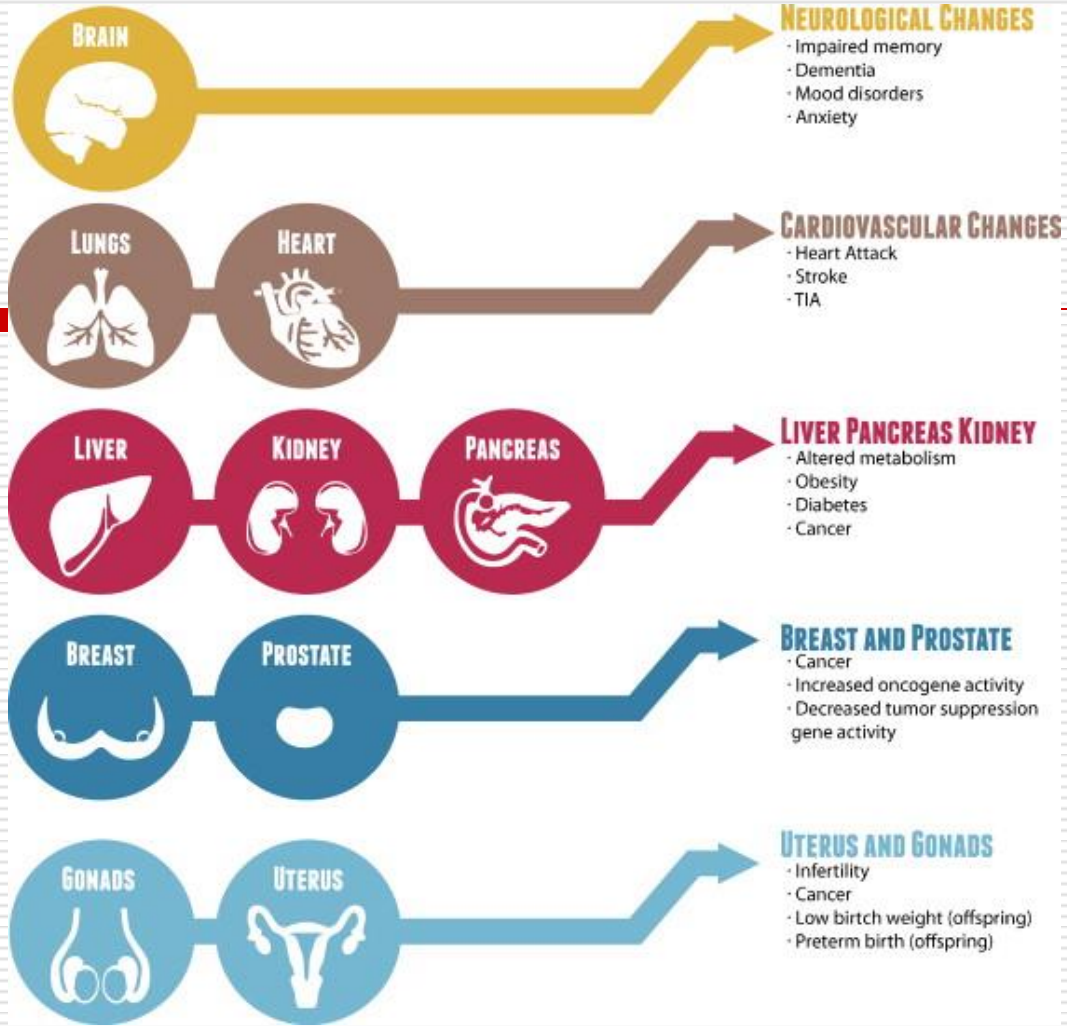
Nat Rev Neurosci. 2012 Mar 7; 13(5): 325–335

Circadian rhythmicity

- Central clocks - n. suprachiasmaticus (SCN- anterior hypothalamus). SCN neurons generate rhythmicity, electric activity and produce synchronizing signals.
- These signals control phase of peripheral clocks oscillations (liver, muscles, kidneys, heart)

Circadian rhythmicity

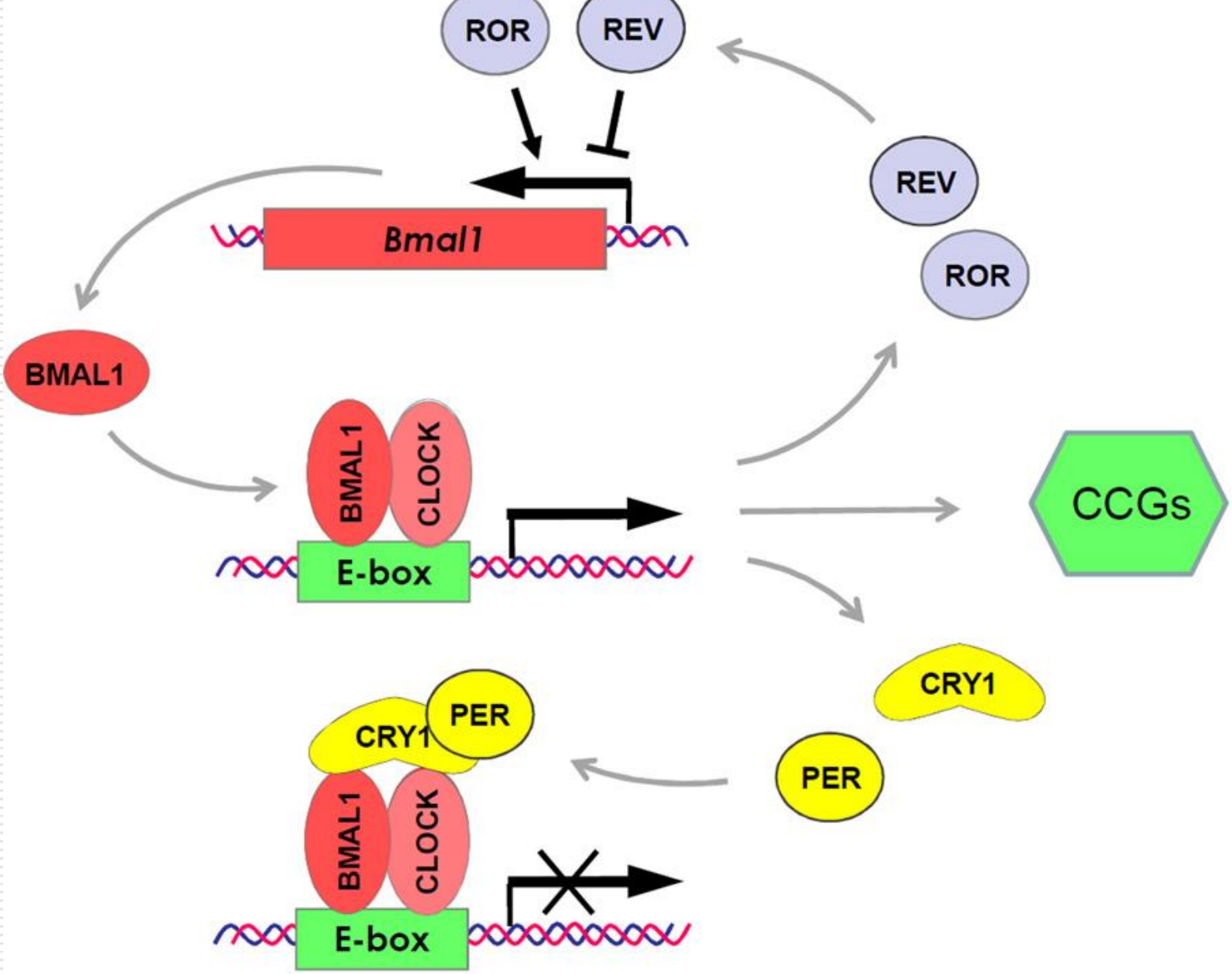
- Rhythmic activity of central clocks synchronized by external light (trc. retinohypothalamicus)
- Peripheral tissues produce rhythmic physiological outputs which optimize action of the body in interaction with environmental conditions during day and/ or night time.



Circadian disruption affects multiple organ systems. The diagram provides examples of how circadian disruption negatively impacts the brain and the digestive, cardiovascular, and reproductive systems. Though the diagram displays unidirectional affects, there are various feedback loops that exist within the system and interactions that occur between these systems.

Circadian rhythmicity

Circadian oscillations are leaing to modification of gene expression and production of proteins.

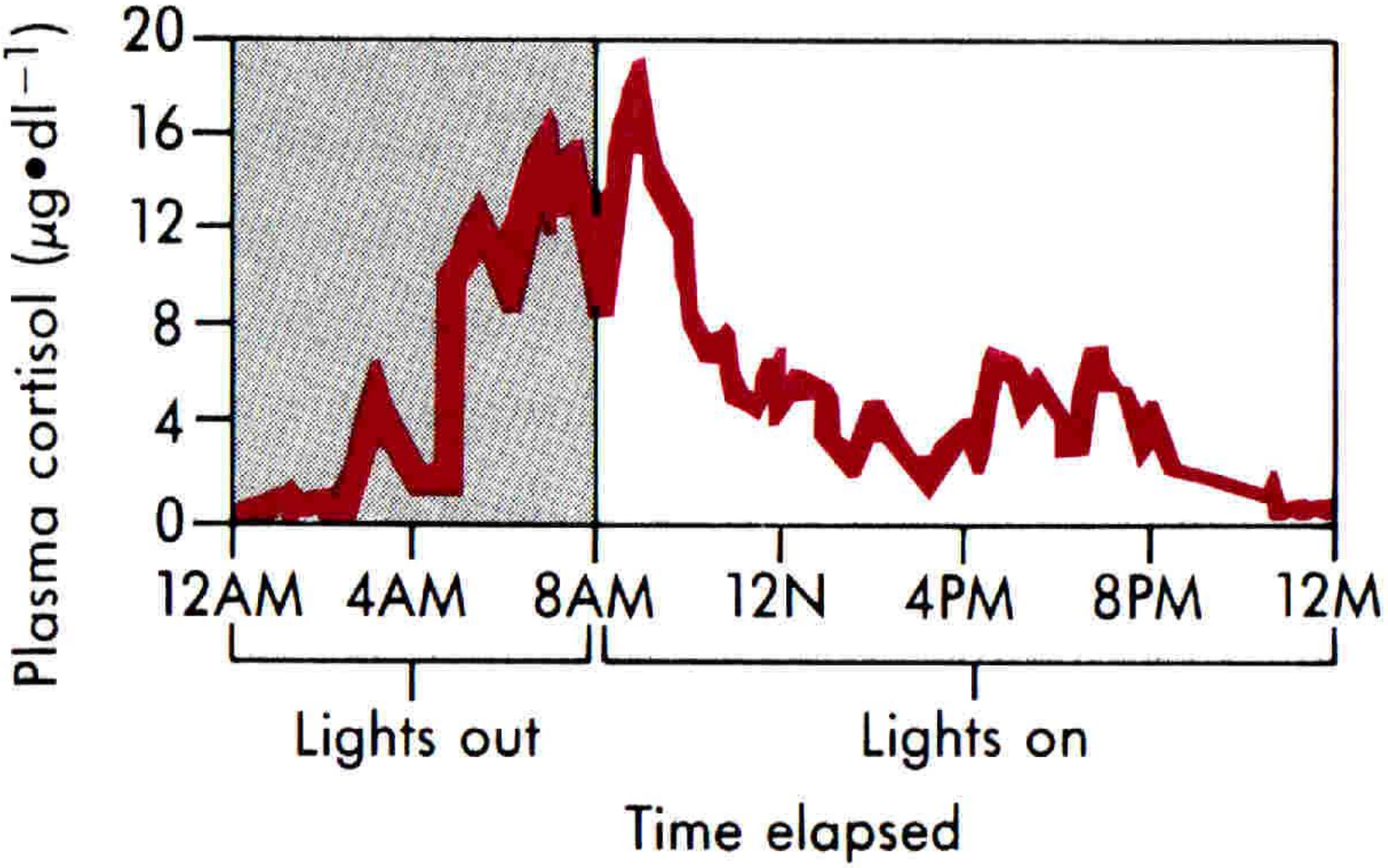


Nat Rev Neurosci. 2012 Mar 7; 13(5): 325–335

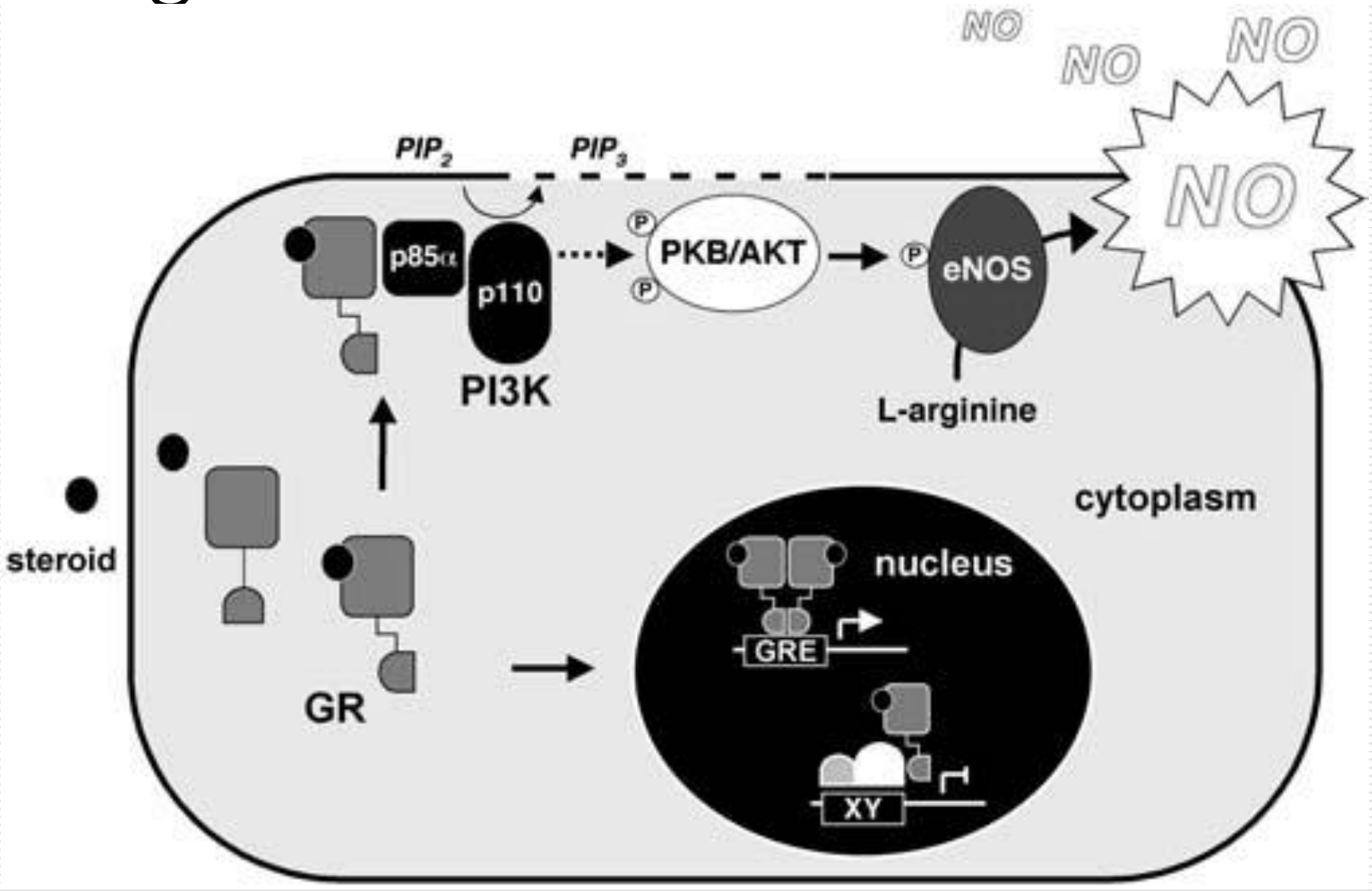
Circadian rhythmicity

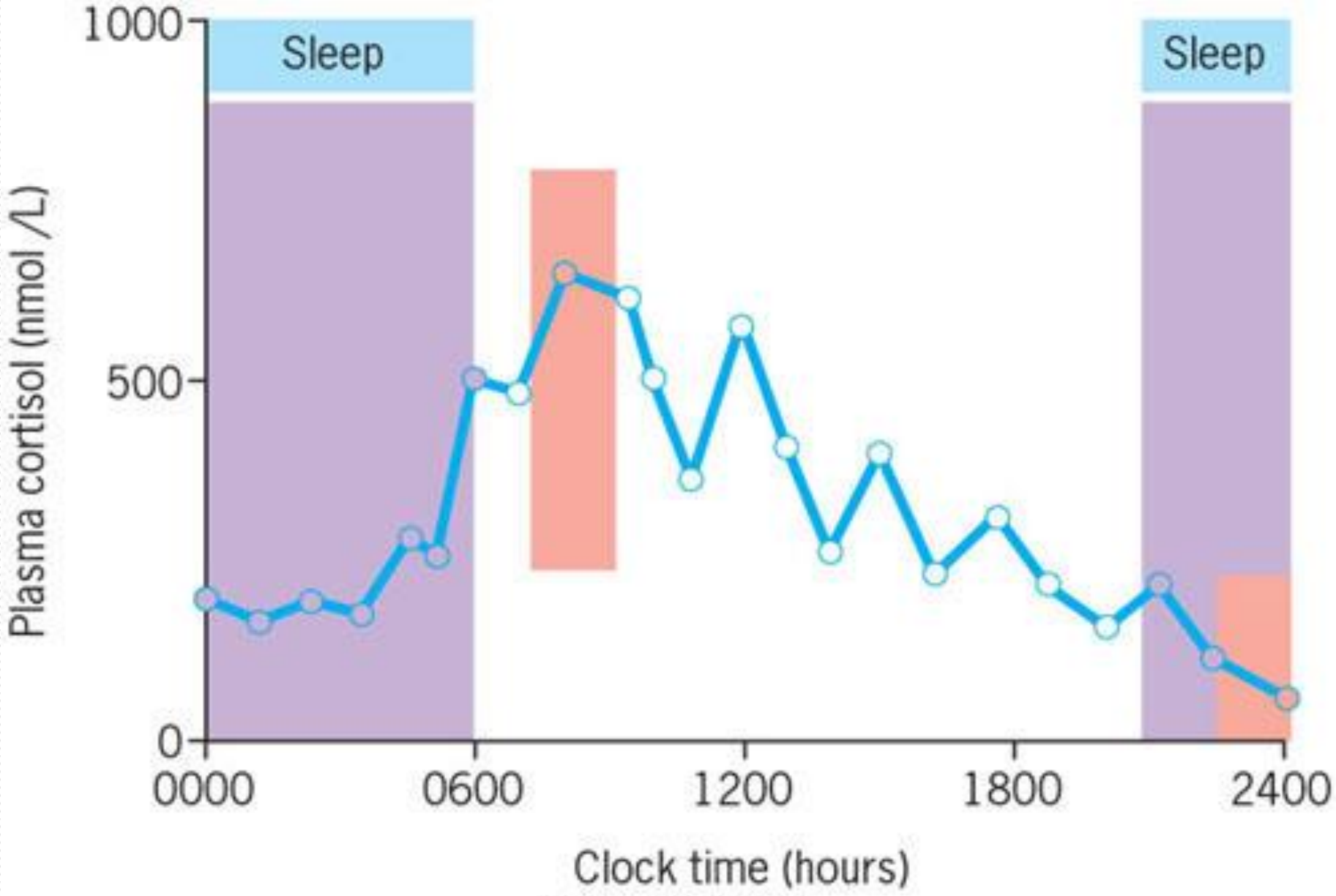
- Circadian system function decreases during aging.
- Earlier phases and lower amplitude of temperature and some hormone expressions can be observed (melatonin, cortisol).

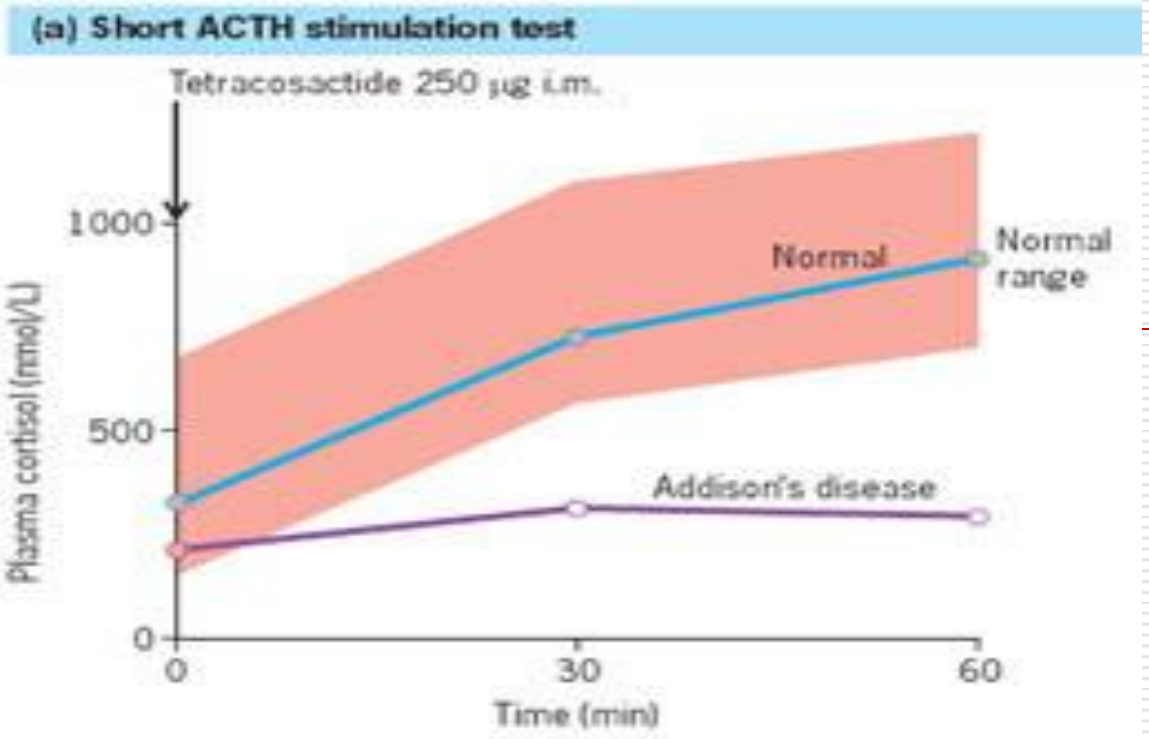
Pulsatile and diurnal glucocorticoid secretion

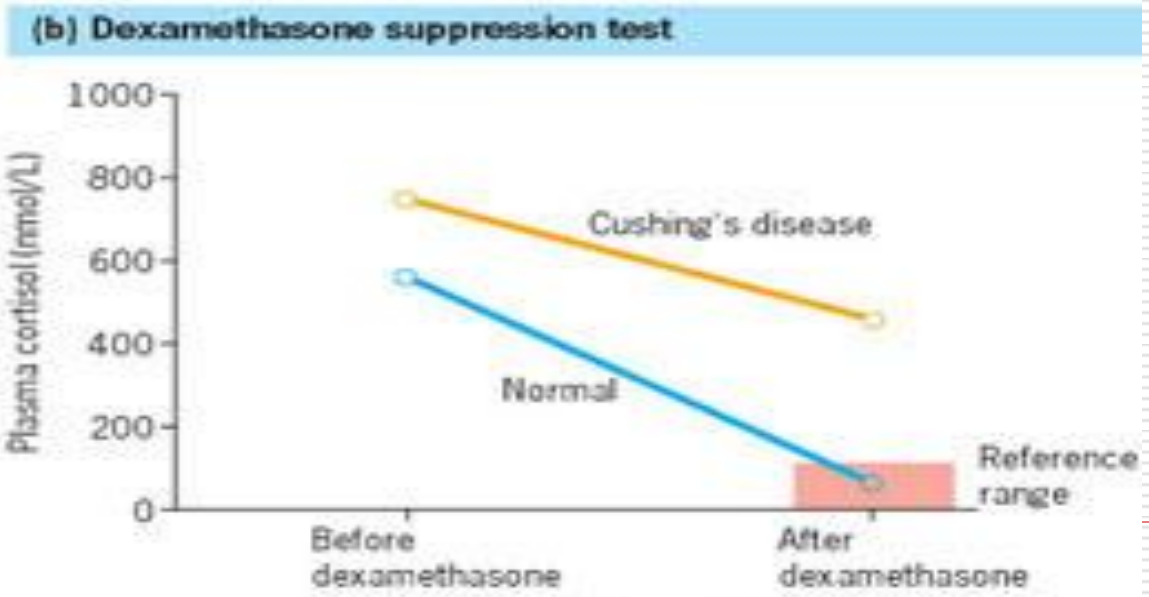


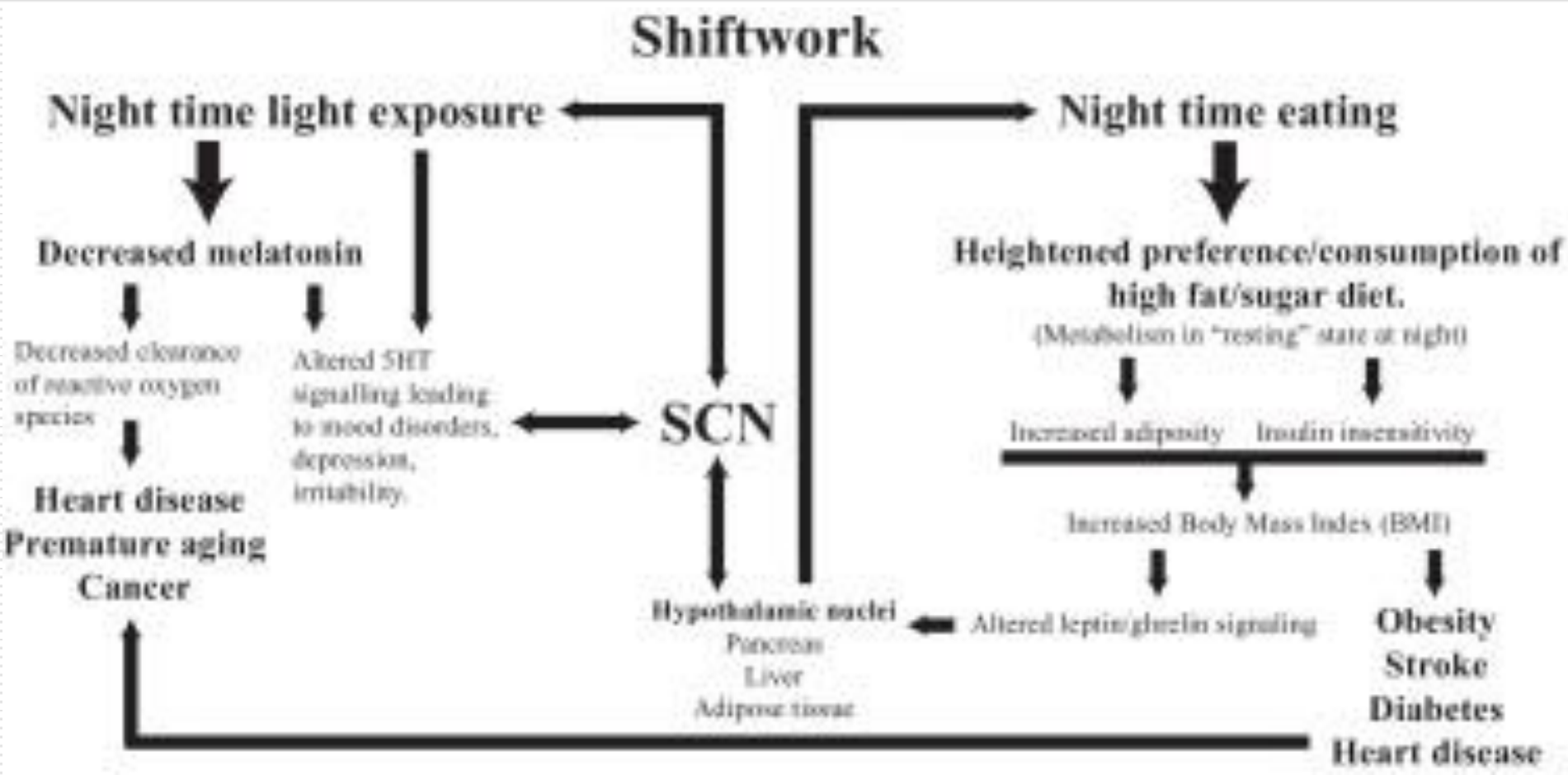
Nuclear and non nuclear actions of glucocorticoids











Erin L. Zelinski, Scott H. Deibel, Robert J. McDonald
Neuroscience and Biobehavioral Reviews 40 (2014) 80–101

Night time work

- Exposition to light during night time is leading to disturbances in serotonin production in SCN.
- This is leading to influencing of cognition functions, metabolic functions and peripheral circadian oscillators.
- Light during night time is influencing secretion of melatonin as well as melatonin receptor density.

Shift work

- Increased BMI leads to alteration of leptin/ghrelin signalling (worse homeostasis of energy state of the body)
- Higher risk of obesity, DM II and cardiovascular diseases

Night time work (shift work)

- Lower efficacy of melatonin as antioxidant.
- Premature aging, cardiovascular diseases, malignancy.
- Eating during night time work period with higher preference of food with high sugars and lipids content.
- Metabolism of sugars and lipids does not work optimally during night time period; higher risk of obesity and insulin resistance.

Jet lag

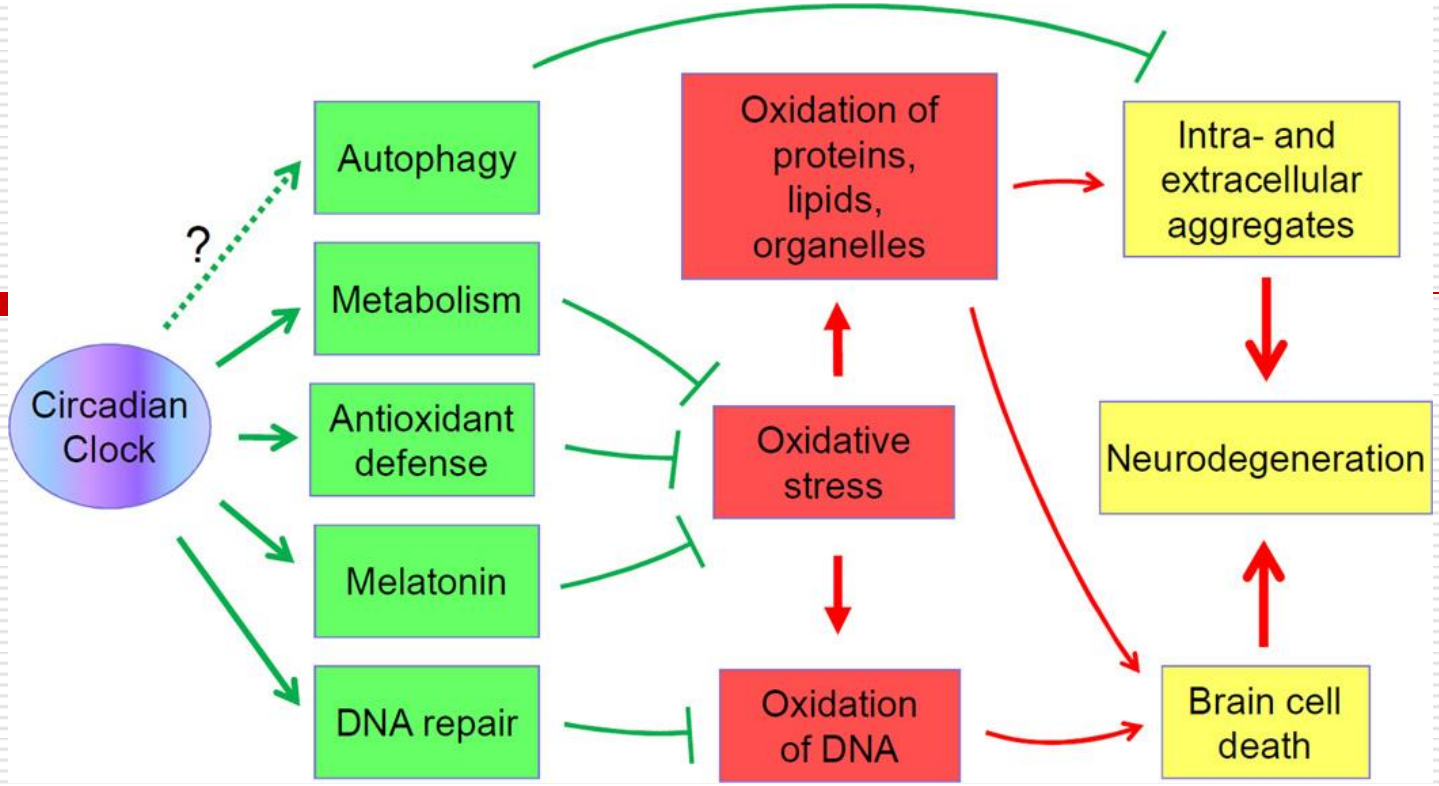
- Upon arrival at his destination, the jet traveler who has crossed multiple time zones experiences a mismatch between his/her endogenous bodily rhythms and the new light/dark cycle that is being imposed. This environmental change produces a variable response in the body's circadian rhythms, each having different time requirements for establishing their normal phase relationships not only with other internal rhythms but with the environmental cycle as well. It is during this adjustment period that jet lag symptoms are most severe, although their severity varies widely among individuals.

Jet lag

- Eastbound travel causes a phase advance in all body's circadian rhythms while westward flight has the opposite effect, i.e., it produces a phase delay. Consequently, travelers tend to synchronize their bodily rhythms at a speed of 1.5 h a day after westward and 1 h a day after eastward flight irrespective of whether they travel during the day or at night.

Signs of jet lag

- Reduced alertness,
- Daytime fatigue,
- Loss of appetite,
- Reduced cognitive skills
- Disruption of the sleep/wake cycle.



Potential mechanisms of circadian clock-dependent regulation of neurodegeneration The circadian clock regulates metabolism, ROS homeostasis, DNA repair and, probably, autophagy (circadian clock controlled systems and pathways are shown in green). Disruption of circadian system function will compromise the activities of these systems, which will lead to oxidative stress (shown in red) and accumulation of intra- and extra-cellular aggregates in the brain. This in turn will lead to brain cell death and degeneration of brain structures (shown in yellow). Similar mechanisms can contribute to the changes in the brain during the normal ageing.

Table 18.5

Nomenclature and biochemistry of hypothalamic, pituitary and peripheral hormones

Hypothalamic hormones	Pituitary hormones	Peripheral hormones
Gonadotrophin-releasing hormone (GnRH, LHRH) (*Decapeptide*)	Luteinizing hormone (LH) Follicle-stimulating hormone (FSH) (*Two-chain α, β peptides*)	Oestrogens/androgens (*Steroid ring*)
Prolactin inhibiting factor (PIF – dopamine) (*Amine*)	Prolactin (PRL) (*Single chain peptide*)	–
Growth hormone-releasing hormone (GHRH) (*Peptide*) Somatostatin (GHRIH) (*Cyclic peptide*)	Growth hormone (GH) (*Peptide*)	Insulin-like growth factor-I (IGF-1) (*Peptide*)
Thyrotrophin-releasing hormone (TRH) (*Tripeptide*)	Thyroid-stimulating hormone (TSH) (*Two-chain α, β peptide*)	Thyroxine (T_4), triiodothyronine (T_3) (*Thyronines*)
Corticotropin-releasing hormone (CRH) (*Single-chain peptide*)	Adrenocorticotrophic hormone (ACTH) (*Single-chain peptide*)	Cortisol (*Steroid ring*)
Vasopressin (antidiuretic hormone; ADH) (*Nonapeptide*)	–	–
Oxytocin (*Nonapeptide*)	–	–

NB: The α chains of LH, FSH and TSH are identical
GHRIH, growth hormone release inhibitory hormone

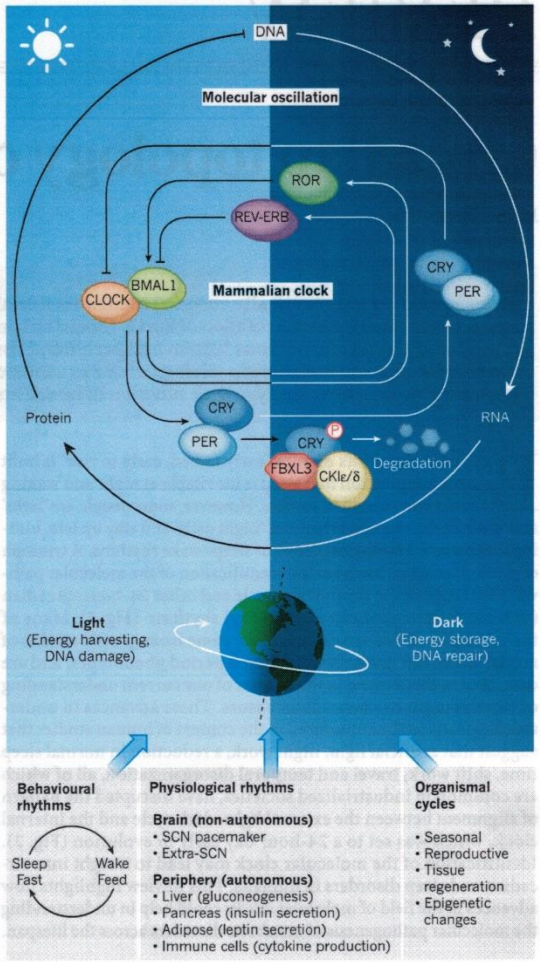


Figure 1 | Circadian adaptation as a unifying model that integrates behaviour and physiology. The circadian clock allows light-sensitive organisms to synchronize their daily molecular oscillations, behavioural rhythms, physiological rhythms and organismal cycles with the rotation of Earth on its axis. 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.

Nature, 491 (2012), pp. 348–356

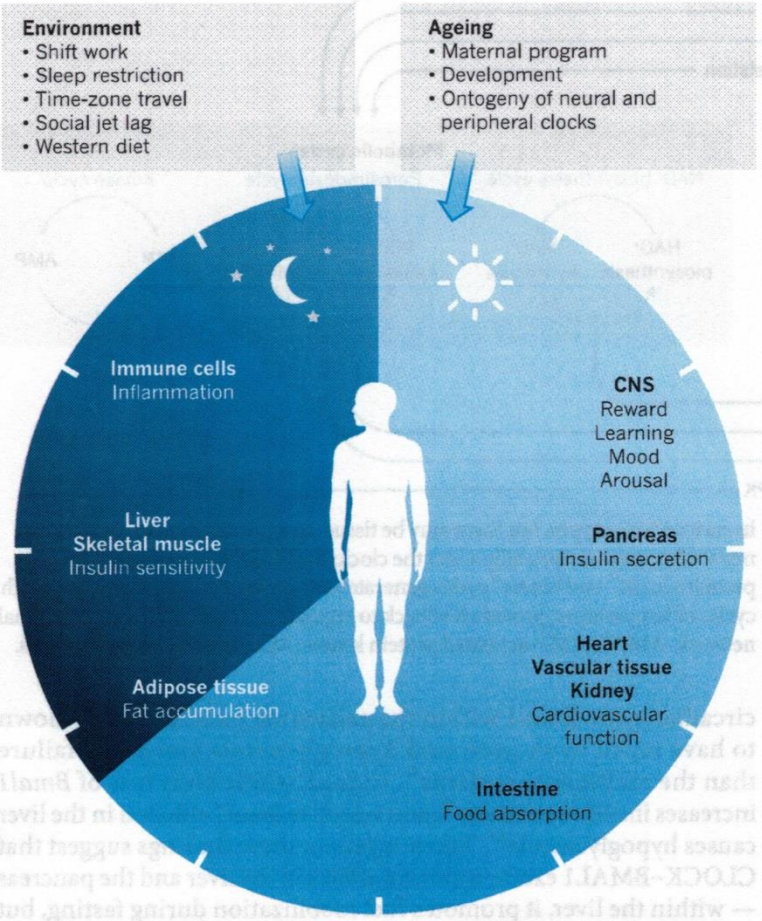
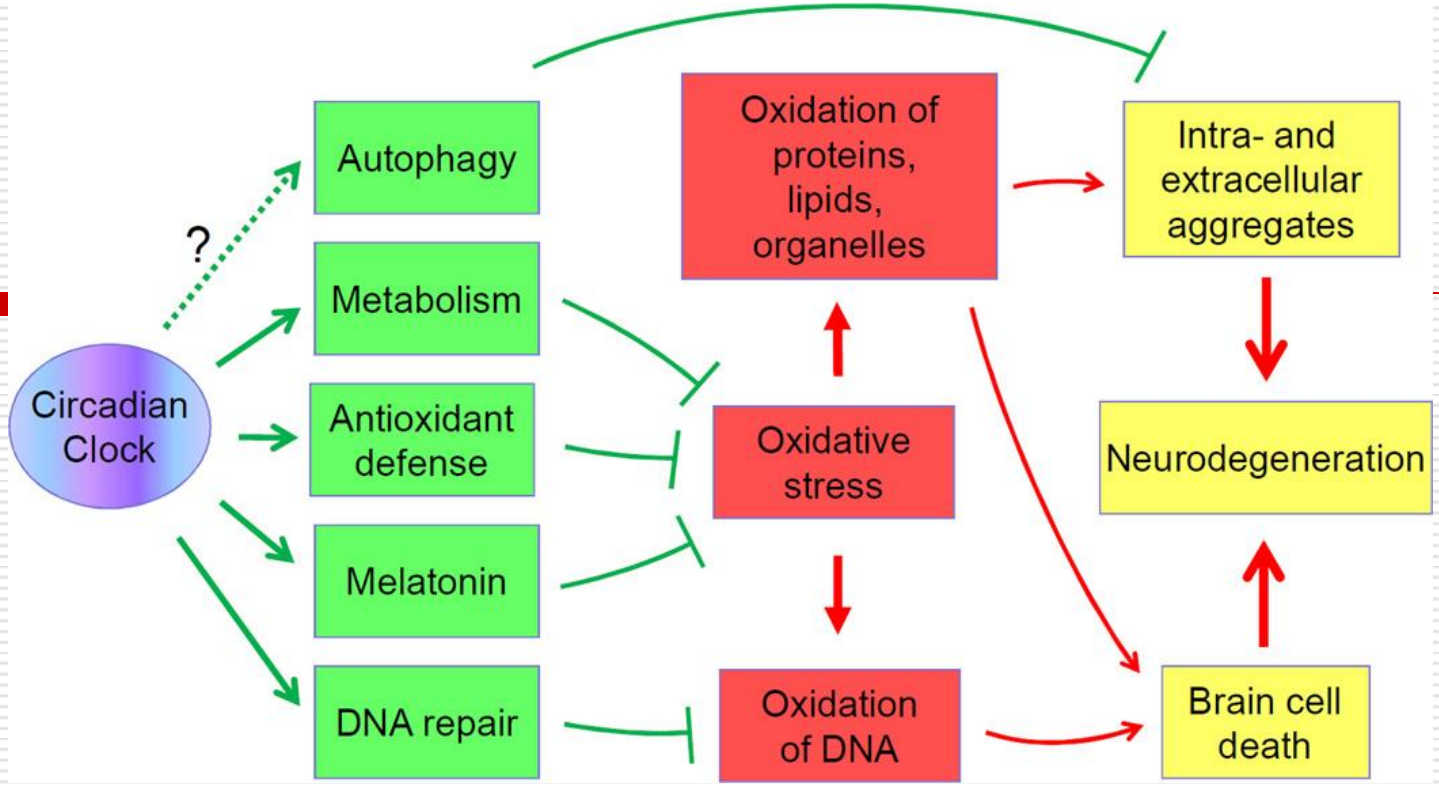
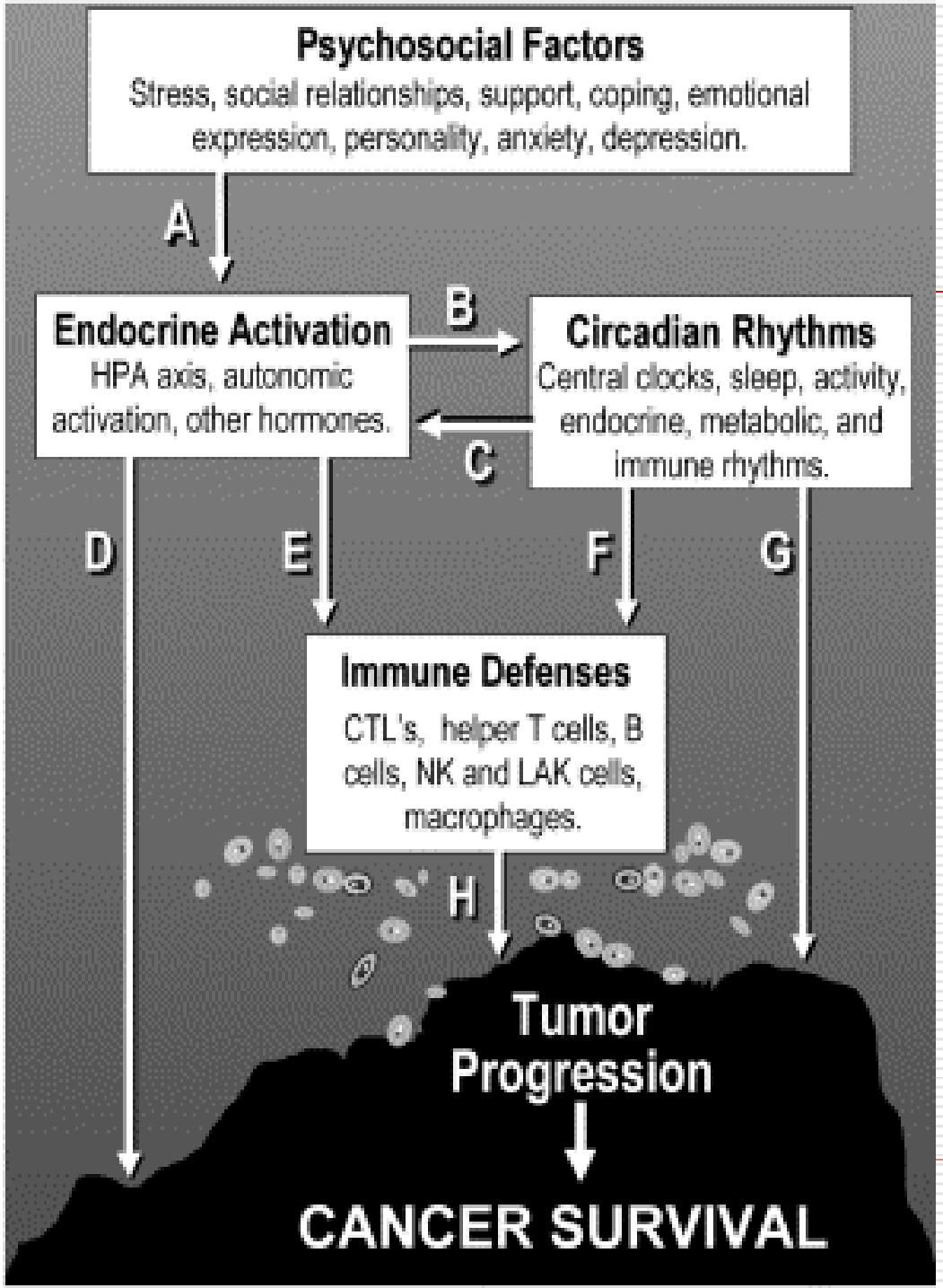


Figure 2 | Affect of ageing and environmental disruption on circadian control of metabolic processes. The circadian clock partitions metabolic processes within the peripheral tissues according to whether we are asleep or awake; for example, the pancreatic clock promotes insulin secretion during the wake–feeding period[52], but the adipose tissue clock promotes fat accumulation during the sleep as well as the wake period. Synchronization of peripheral tissue clocks and downstream metabolic processes with the environmental cycle is crucial for the maintenance of the health of the organism[35,39]. We are only just beginning to gain an appreciation of how both ageing[26,28] and environmental disruption (including changes in diet, time of feeding or jet lag) perturb the integration of the circadian and metabolic networks[100]. CNS, central nervous system.

Nature, 491 (2012), pp. 348–356



Potential mechanisms of circadian clock-dependent regulation of neurodegeneration The circadian clock regulates metabolism, ROS homeostasis, DNA repair and, probably, autophagy (circadian clock controlled systems and pathways are shown in green). Disruption of circadian system function will compromise the activities of these systems, which will lead to oxidative stress (shown in red) and accumulation of intra- and extra-cellular aggregates in the brain. This in turn will lead to brain cell death and degeneration of brain structures (shown in yellow). Similar mechanisms can contribute to the changes in the brain during the normal ageing.


Psychosocial Factors
Stress, social relationships, support, coping, emotional expression, personality, anxiety, depression.
A
Endocrine Activation
HPA axis, autonomic activation, other hormones.
B
Circadian Rhythms
Central clocks, sleep, activity, endocrine, metabolic, and immune rhythms.
C
D
E
F
G
Immune Defenses
CTL's, helper T cells, B cells, NK and LAK cells, macrophages.
H
Tumor Progression
CANCER SURVIVAL

Potential pathways by which circadian dysregulation may mediate psychosocial effects on cancer progression

- Arrow (A) represents activation of endocrine stress-responses associated with psychological distress and other psychosocial factors. Repeated stress-response activation may hypothetically lead to dysregulation of circadian rhythms (B), while aberrations in sleep–wake cycles, rest-activity rhythms, genetic, or suprachiasmatic control of circadian rhythms would engender endocrine abnormalities (C). Hypotheses regarding direct effects of hormones on tumor growth involve metabolic pathways or influences on oncogene expression (D).

Potential pathways by which circadian dysregulation may mediate psychosocial effects on cancer progression

- Neuroimmune effects are widespread and include modulation of innate immunity, T and B cell function, cytokine and adhesion molecule expression, cell trafficking, and immune cell differentiation (E). Circadian rhythm aberration is associated with abnormalities of immune cell trafficking and cell proliferation cycles (F). It has been hypothesized that circadian clock genes are tightly linked with genes related to tumor growth and that tumors may be a direct consequence of circadian dysregulation (G). Immune defenses against tumor growth include both specific mechanisms (e.g., killing by cytotoxic T lymphocytes aided by helper T cells, B cell-mediated antibody-dependent lysis) and non-specific immunity (e.g., lytic activity of NK, LAK, and A-NK cells, macrophages, and granulocytes; H).

Děkuji za pozornost