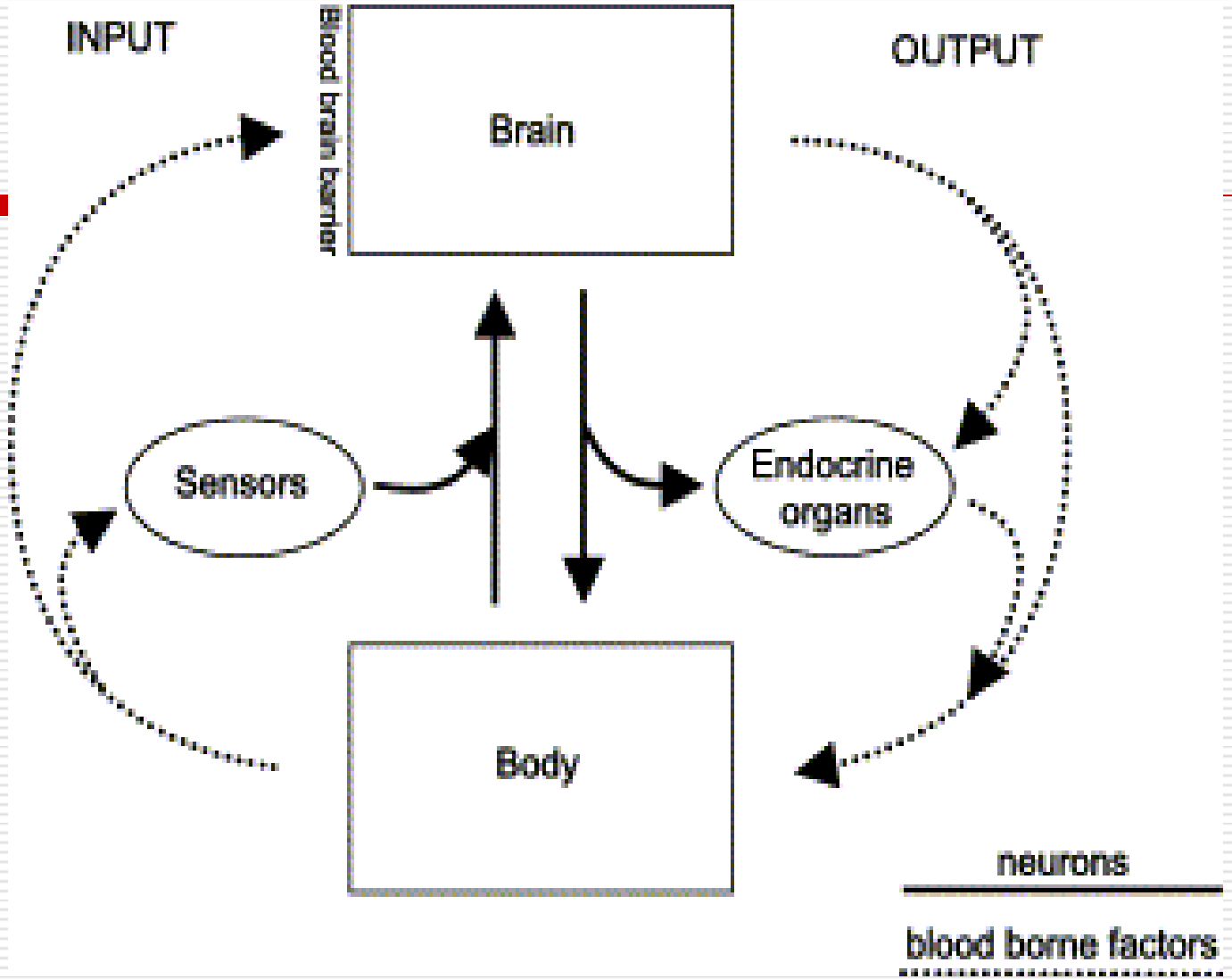
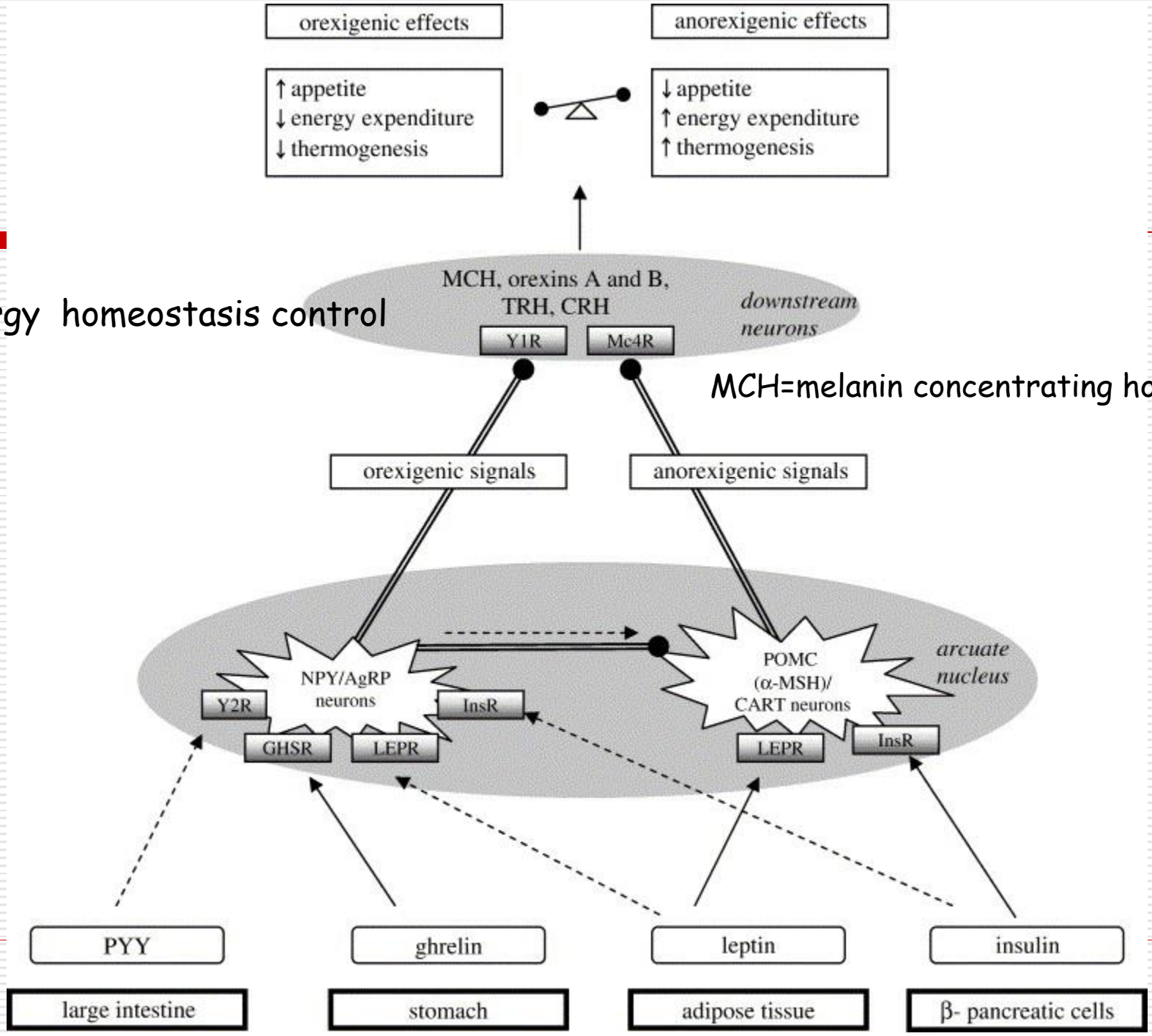
General Pathophysiology of Endocrine System

March 9, 2018

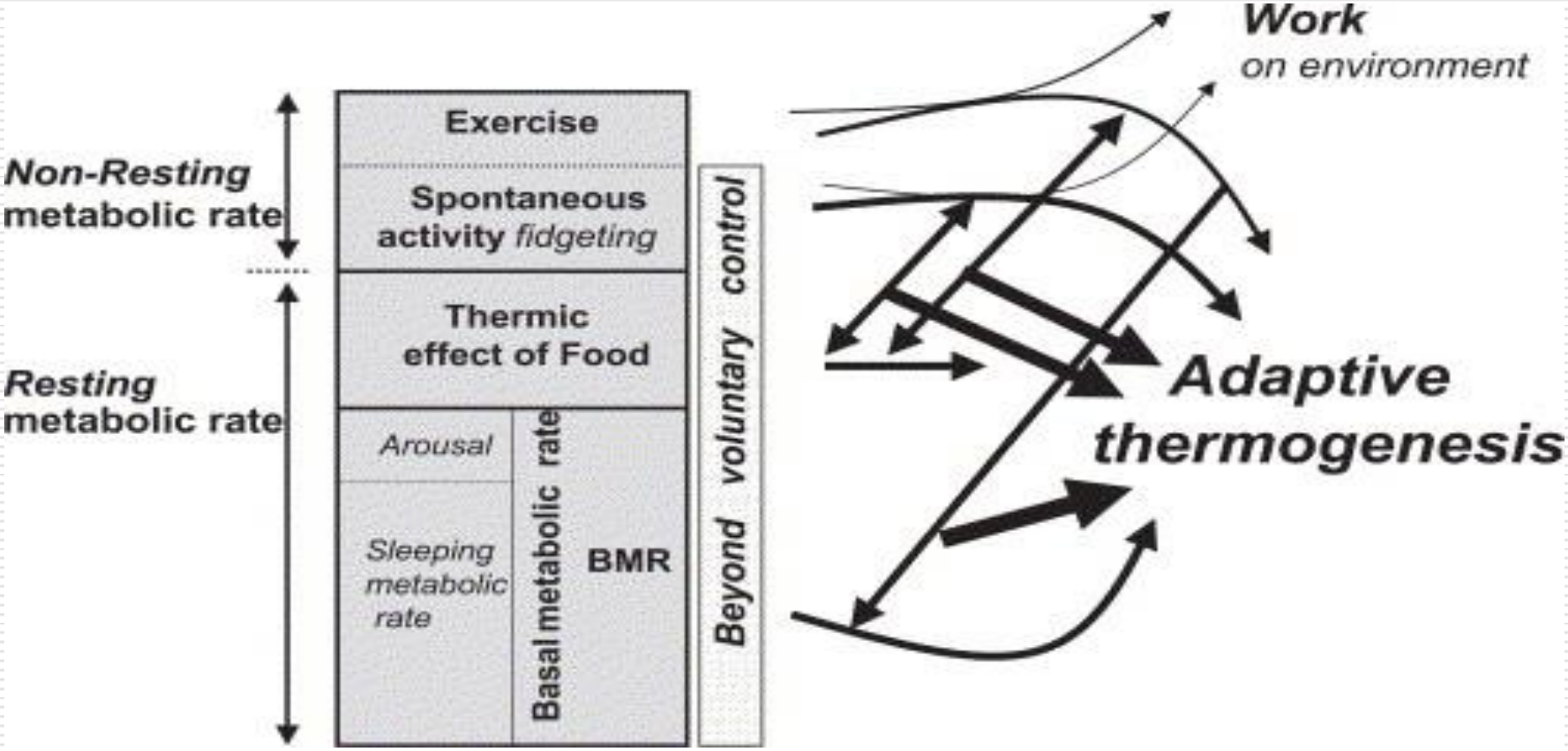


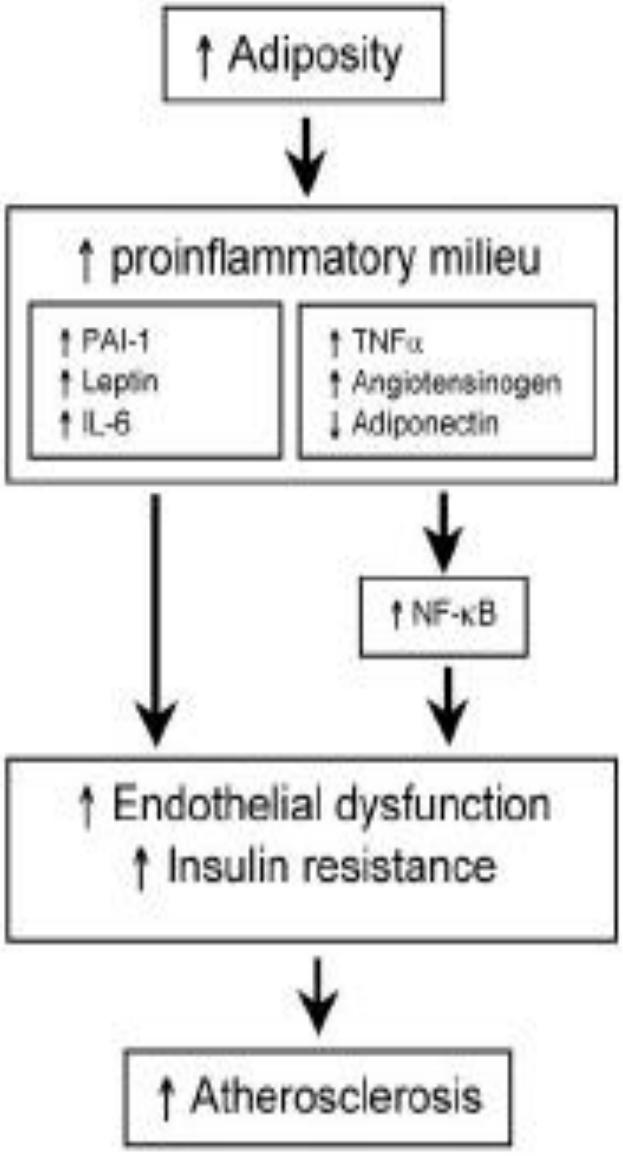
Interactive homeostatic system: communication between body and brain by means of neurons and factors circulating in blood

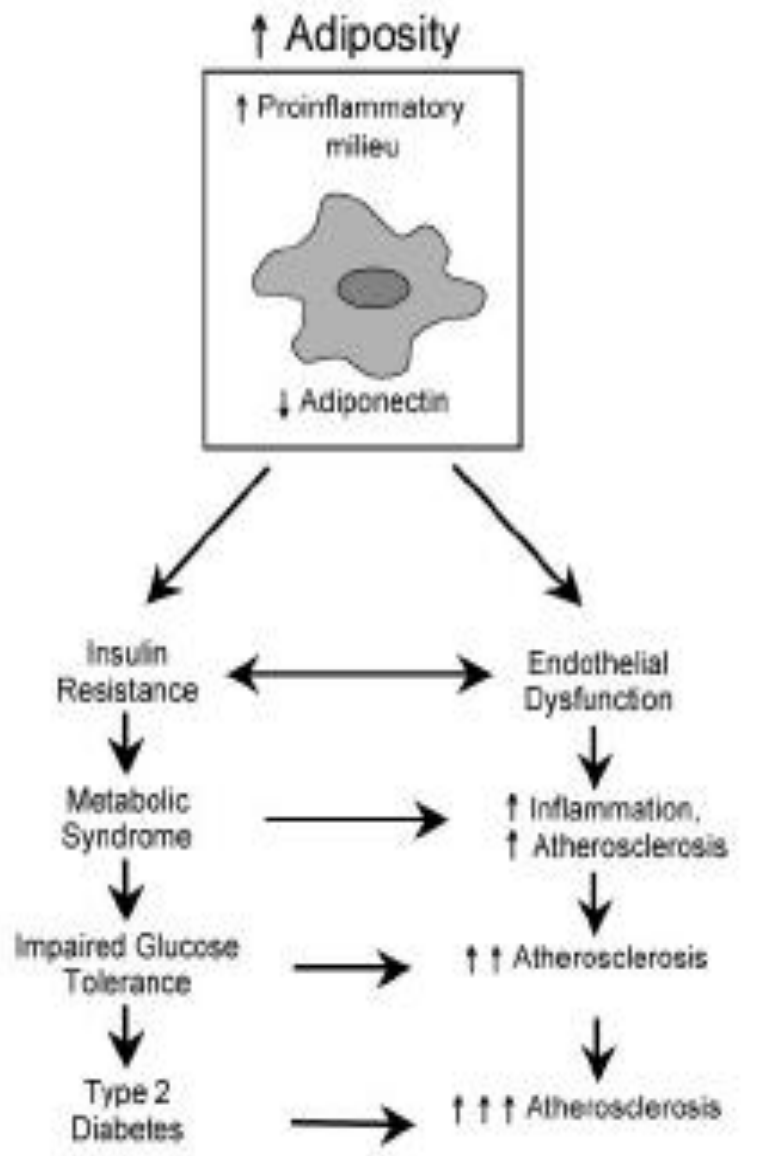
Energy homeostasis control

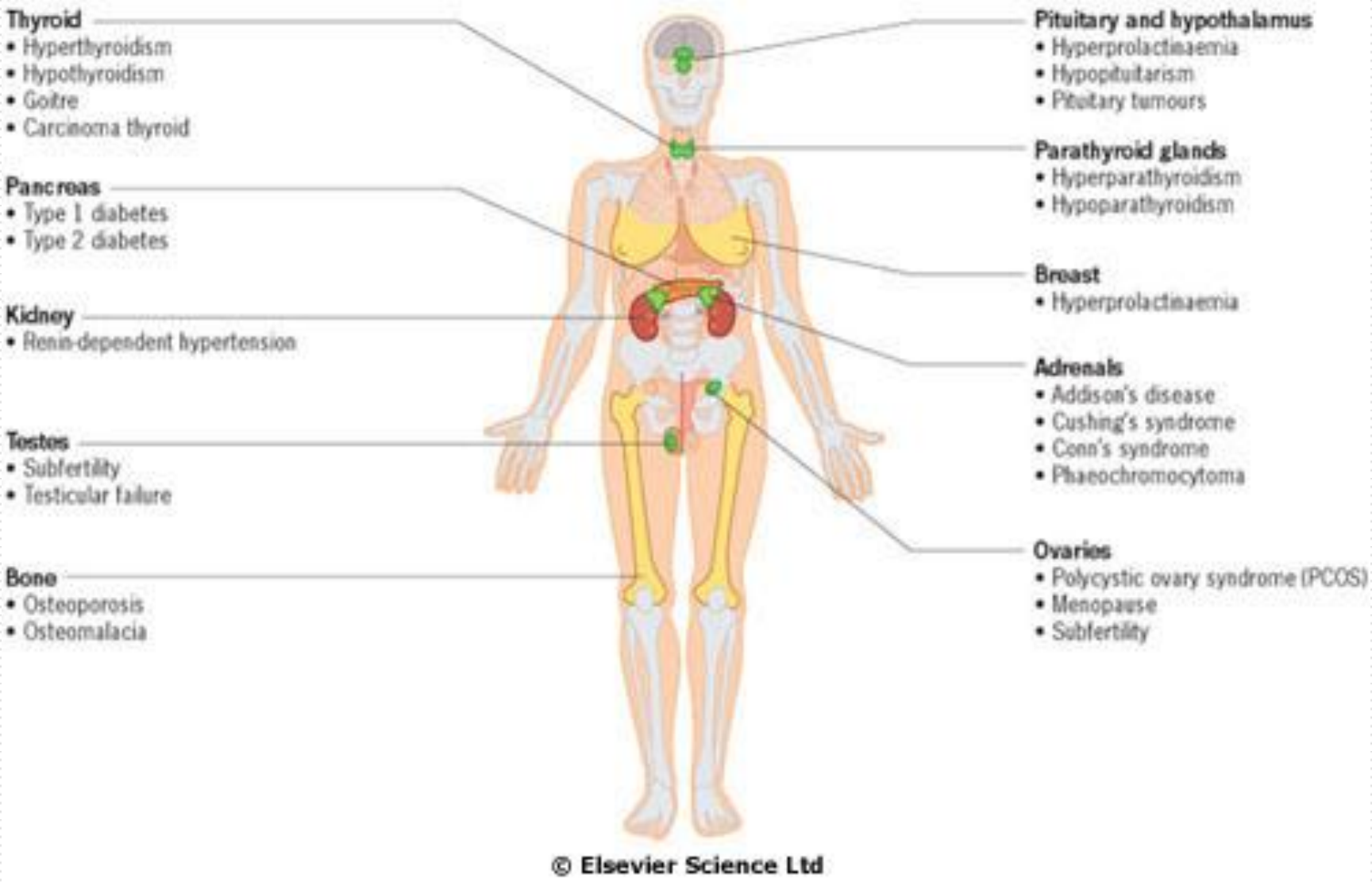


MCH=melanin concentrating hormon


Non-Resting metabolic rate
Resting metabolic rate
Exercise
Spontaneous activity fidgeting
Thermic effect of Food
Arousal
Sleeping metabolic rate
Basal metabolic rate
BMR
Beyond voluntary control
Work
on environment
Adaptive thermogenesis


↑ Adiposity
↑ proinflammatory milieu
↑ PAI-1
↑ Leptin
↑ IL-6
↑ TNFα
↑ Angiotensinogen
↓ Adiponectin
↑ NF-κB
↑ Endothelial dysfunction
↑ Insulin resistance
↑ Atherosclerosis


↑ Adiposity
↑ Proinflammatory milieu
↓ Adiponectin
Insulin Resistance
Endothelial Dysfunction
Metabolic Syndrome
↑ Inflammation, ↑ Atherosclerosis
Impaired Glucose Tolerance
↑ ↑ Atherosclerosis
Type 2 Diabetes
↑ ↑ ↑ Atherosclerosis



Endocrinopathies

Effects of hormones

- **Pleoitrophism:**

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

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

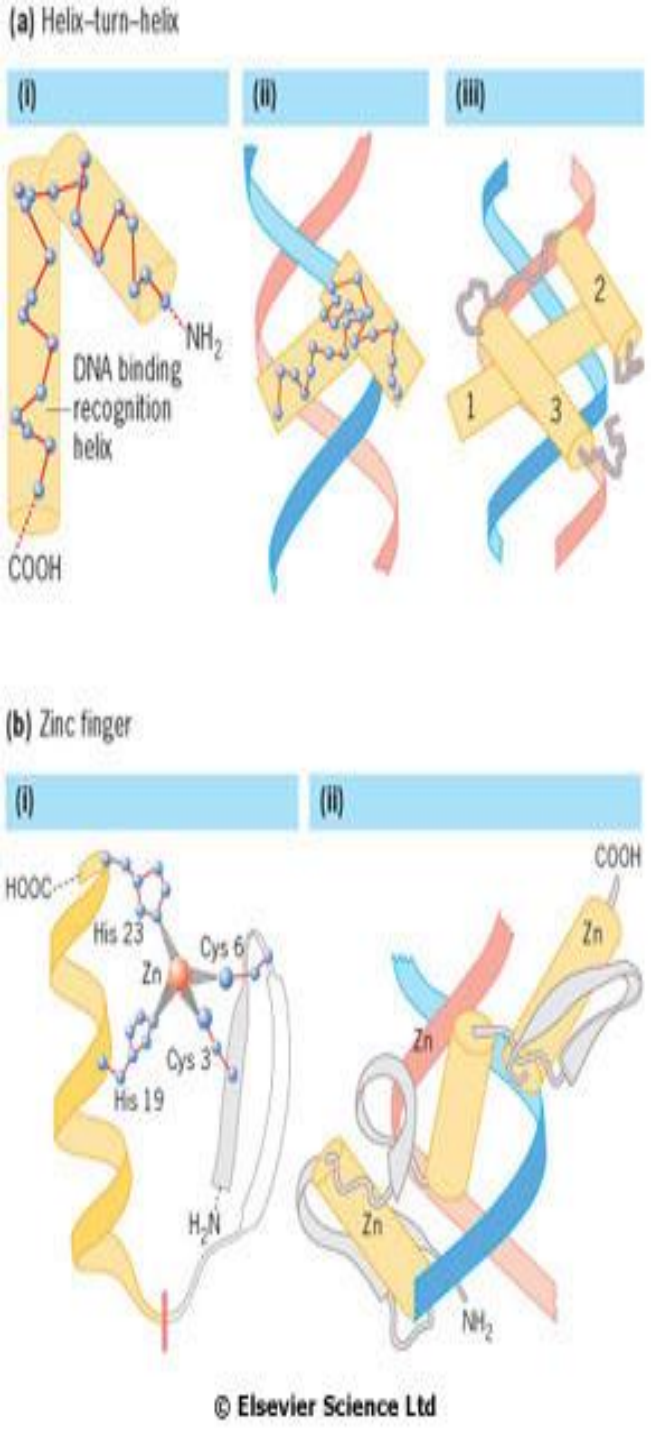
- Hormones act by binding to specific receptors in the target cell, which may be at the cell surface and/or within the cell.
- Most hormone receptors are proteins with complex tertiary structures, parts of which complement the tertiary structure of the hormone to allow highly specific interactions, while 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.

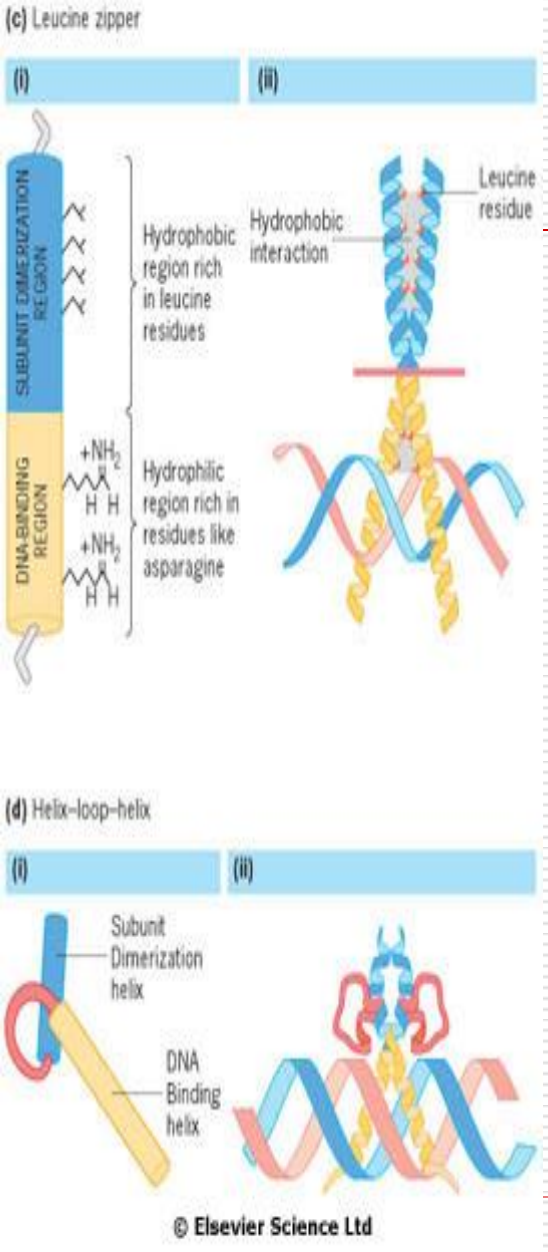
Hormone action and receptors

.

- 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.

The four classes of DNA-binding pro

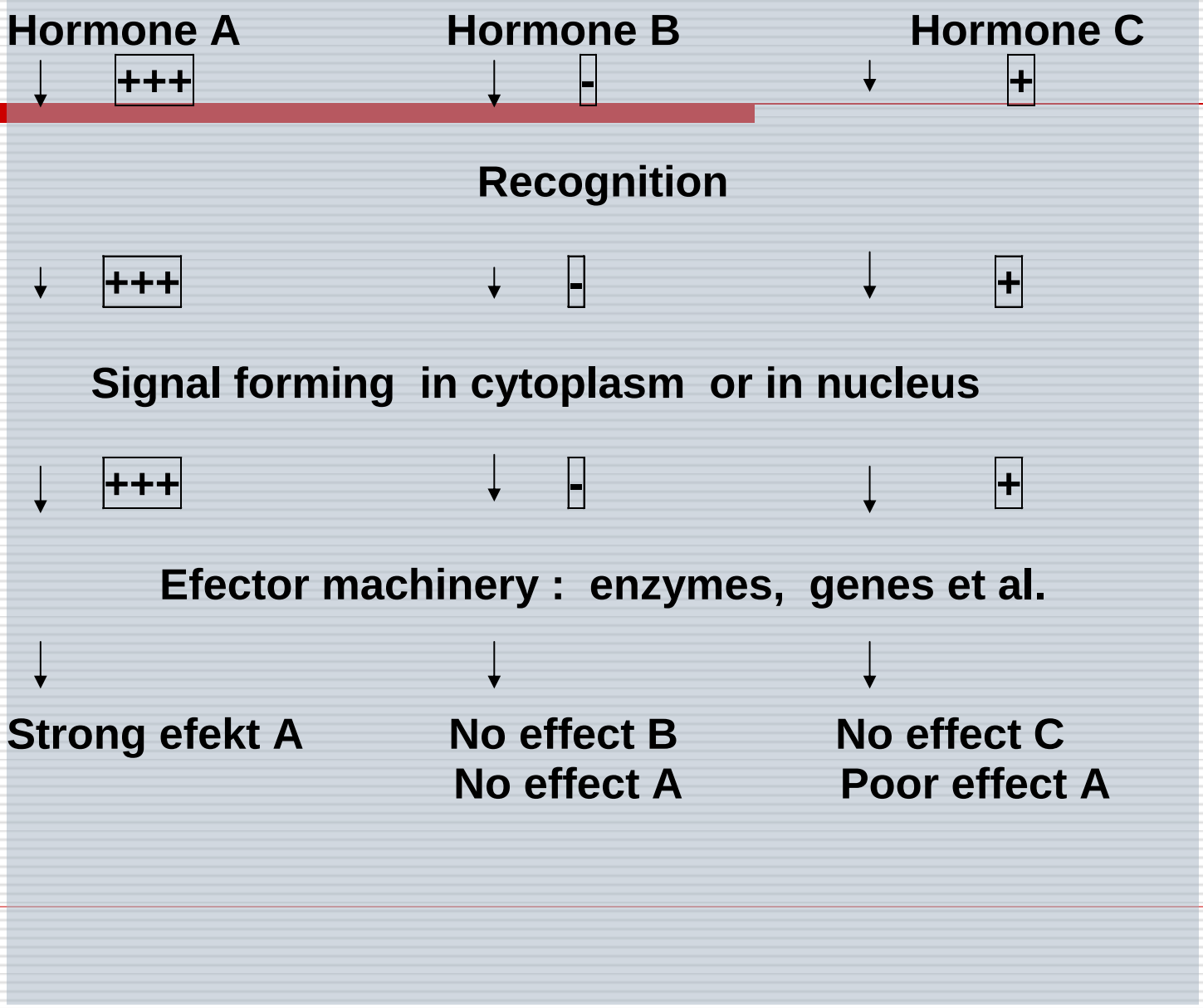




Manner of hormone secretion

- *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



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

Interaction hormone-receptor

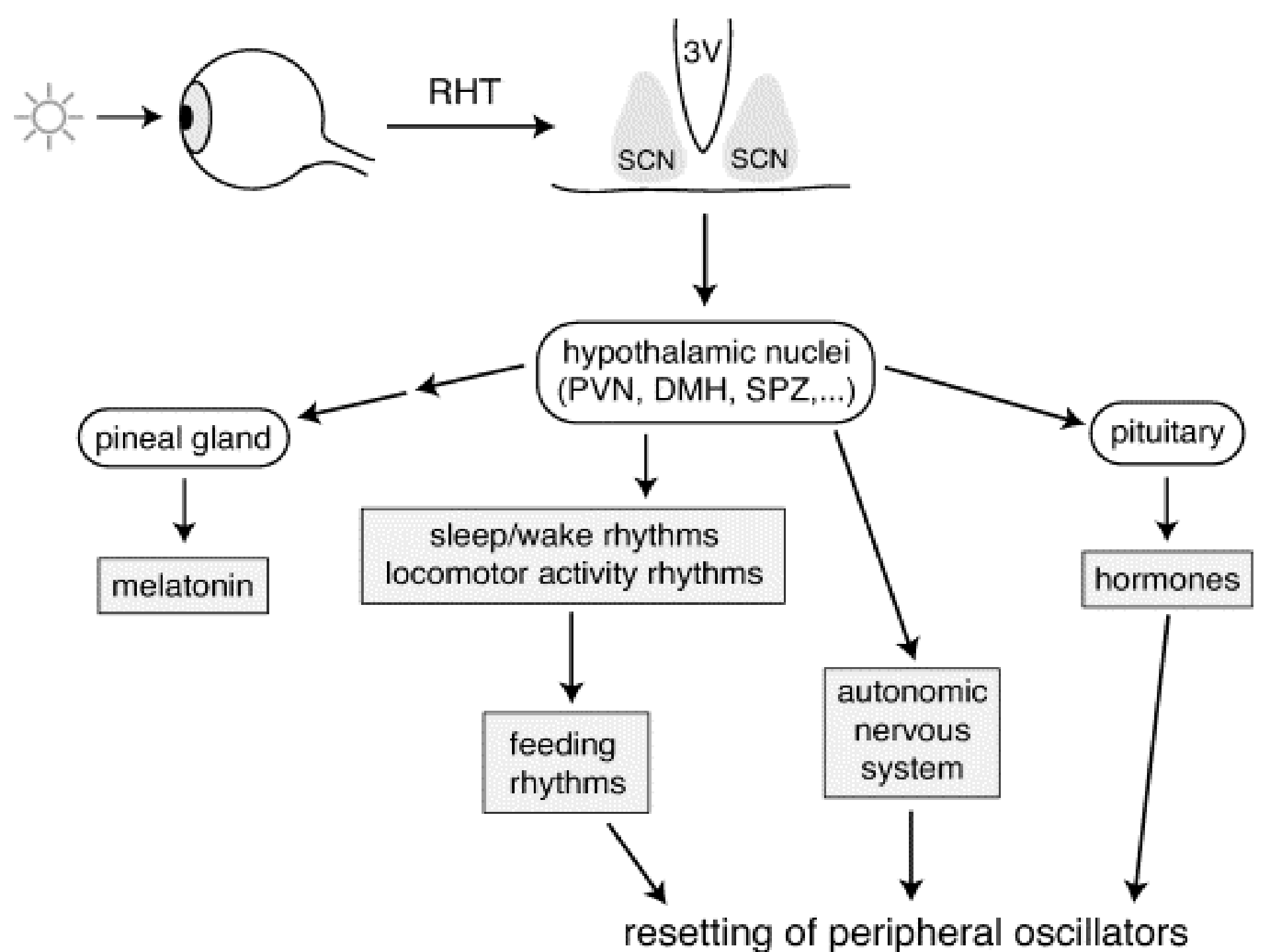
Interactions fixed with messenger	Mobile interactions hormone-receptor-nucleus
Glucagone Insulin Noradrenaline PTH TSH ACTH FSH LH ADH Secretine	Estrogenes Testosterone Progesterone Adrenal cortical hormones Thyreoid hormons

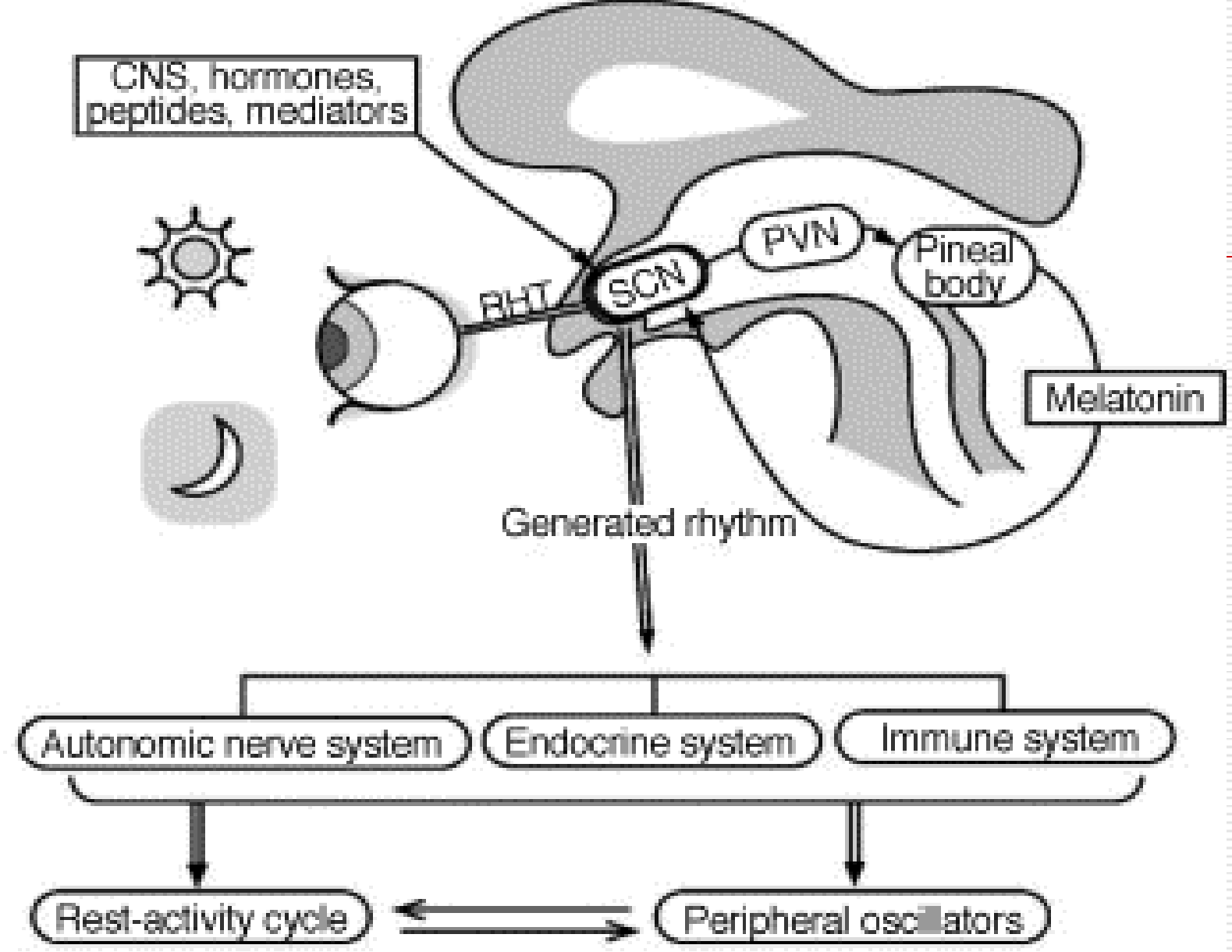
Feedback control

Hormone-hormone
Substrat-hormone

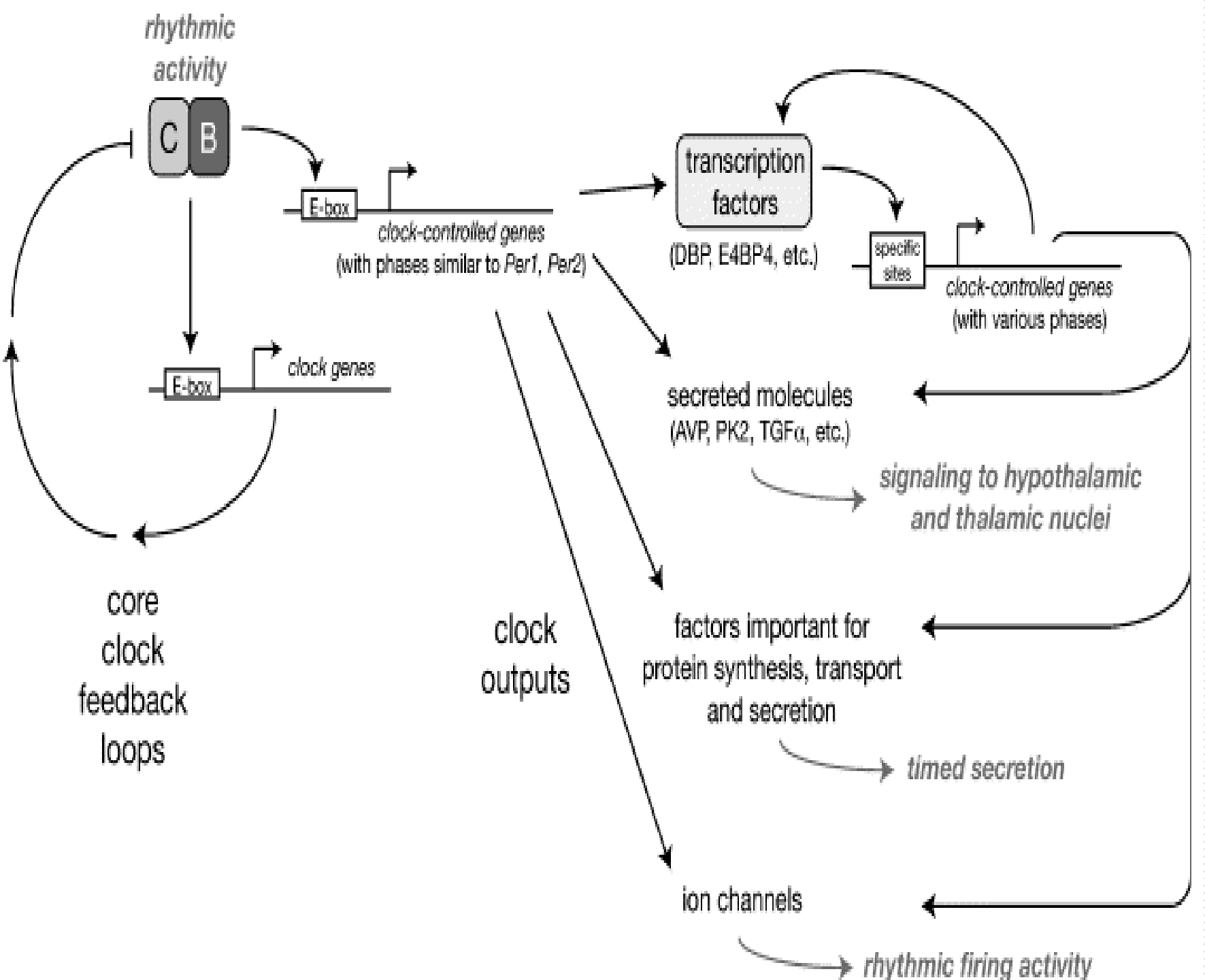
Neuronal control
Adrenergic
Cholinergic
Dopaminergic
Serotoninergic
Endorfinergic
-enkefalinergic
Gabaergic

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

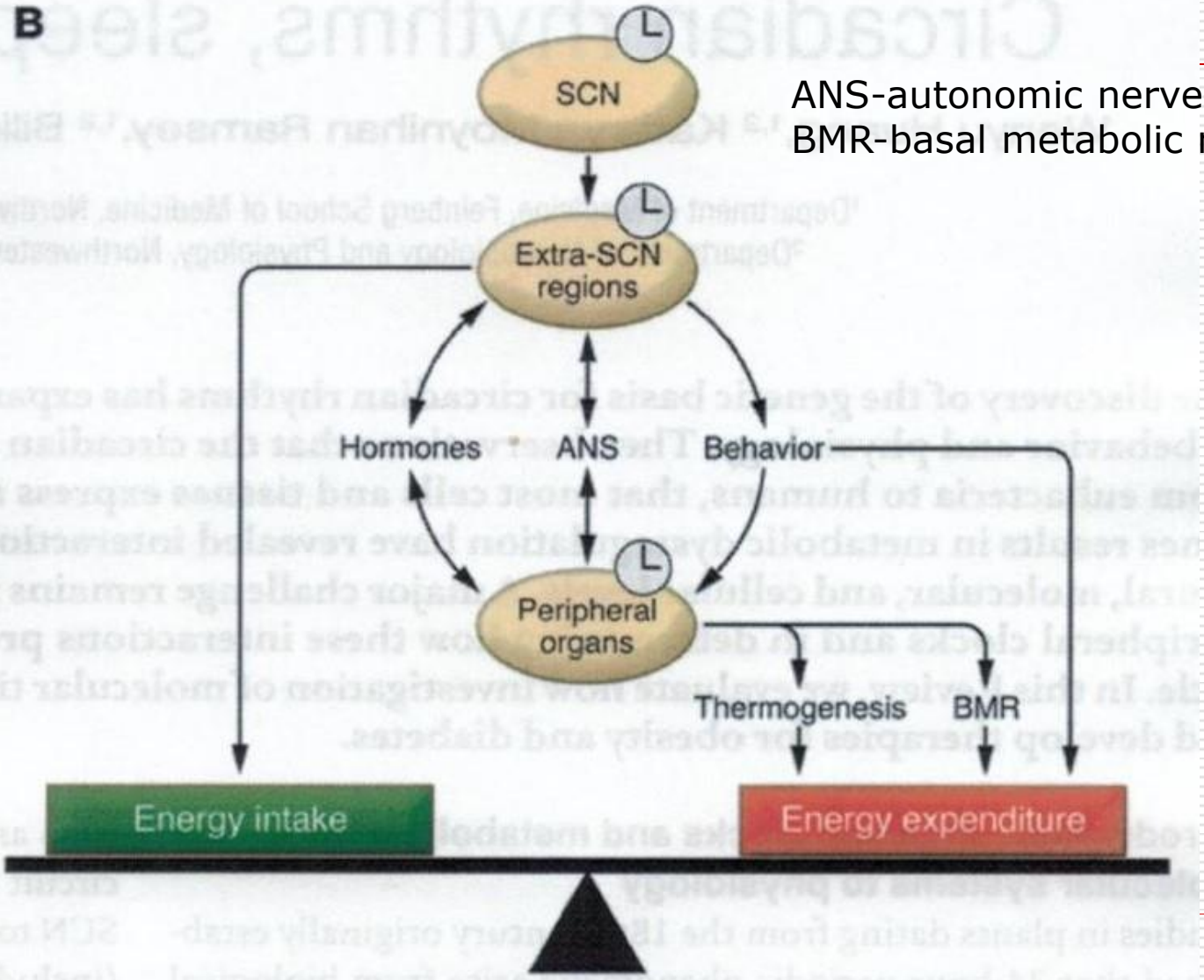

RHT
3V
SCN
SCN
hypothalamic nuclei
(PVN, DMH, SPZ,...)
pineal gland
melatonin
sleep/wake rhythms
locomotor activity rhythms
feeding
rhythms
autonomic
nervous
system
pituitary
hormones
resetting of peripheral oscillators



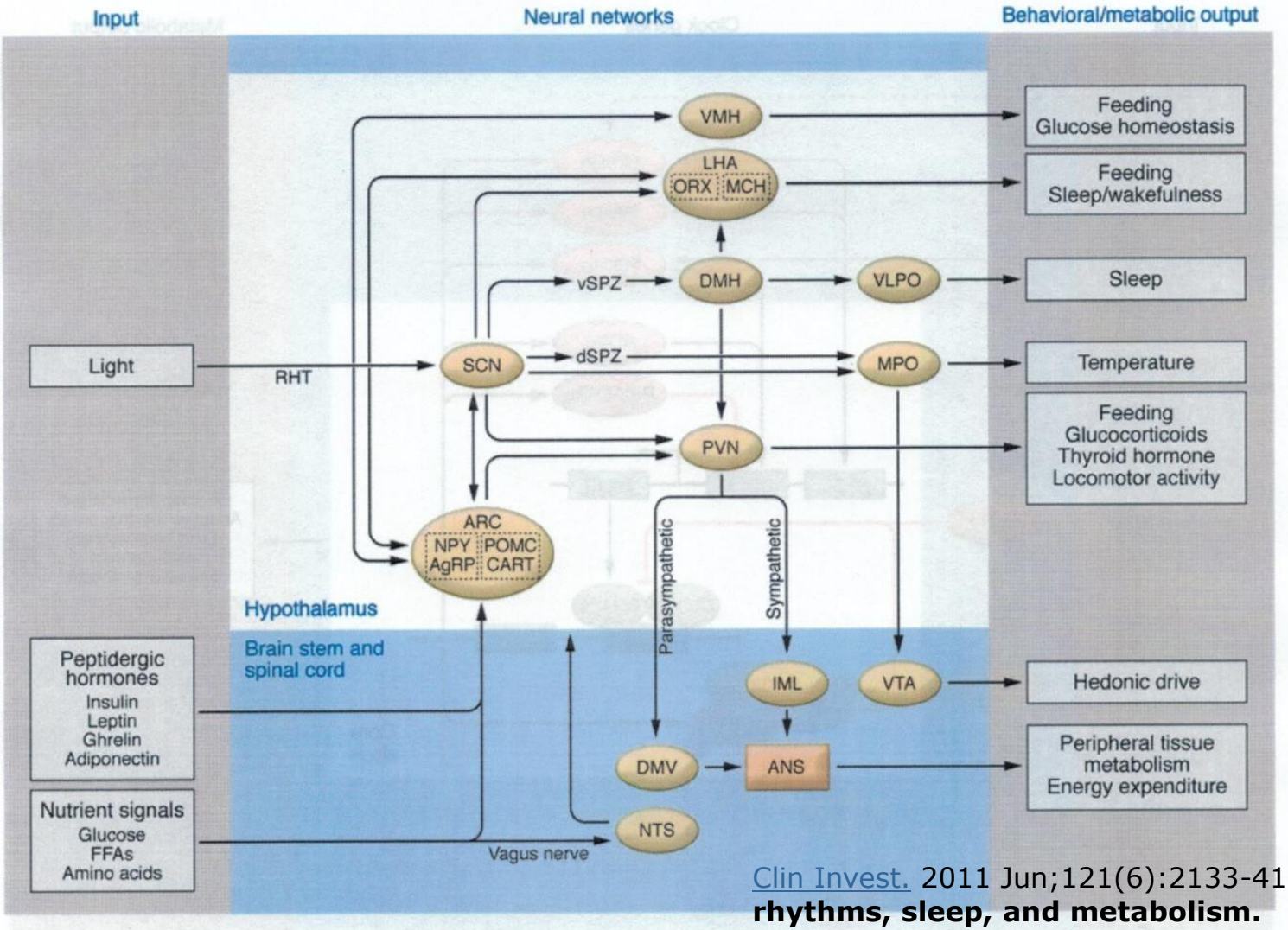
Schema of human circadian system. RHT, retinohypothalamic tract; SCN, suprachiasmatic nucleus; PVN, paraventricular nucleus


rhythmic activity
C
B
E-box
clock-controlled genes
(with phases similar to Per1, Per2)
transcription factors
(DBP, E4BP4, etc.)
specific sites
clock-controlled genes
(with various phases)
E-box
clock genes
secreted molecules
(AVP, PK2, TGFα, etc.)
signaling to hypothalamic and thalamic nuclei
core clock feedback loops
clock outputs
factors important for protein synthesis, transport and secretion
timed secretion
ion channels
rhythmic firing activity

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



Clin Invest. 2011 Jun;121(6):2133-41. **Circadian rhythms, sleep, and metabolism.**
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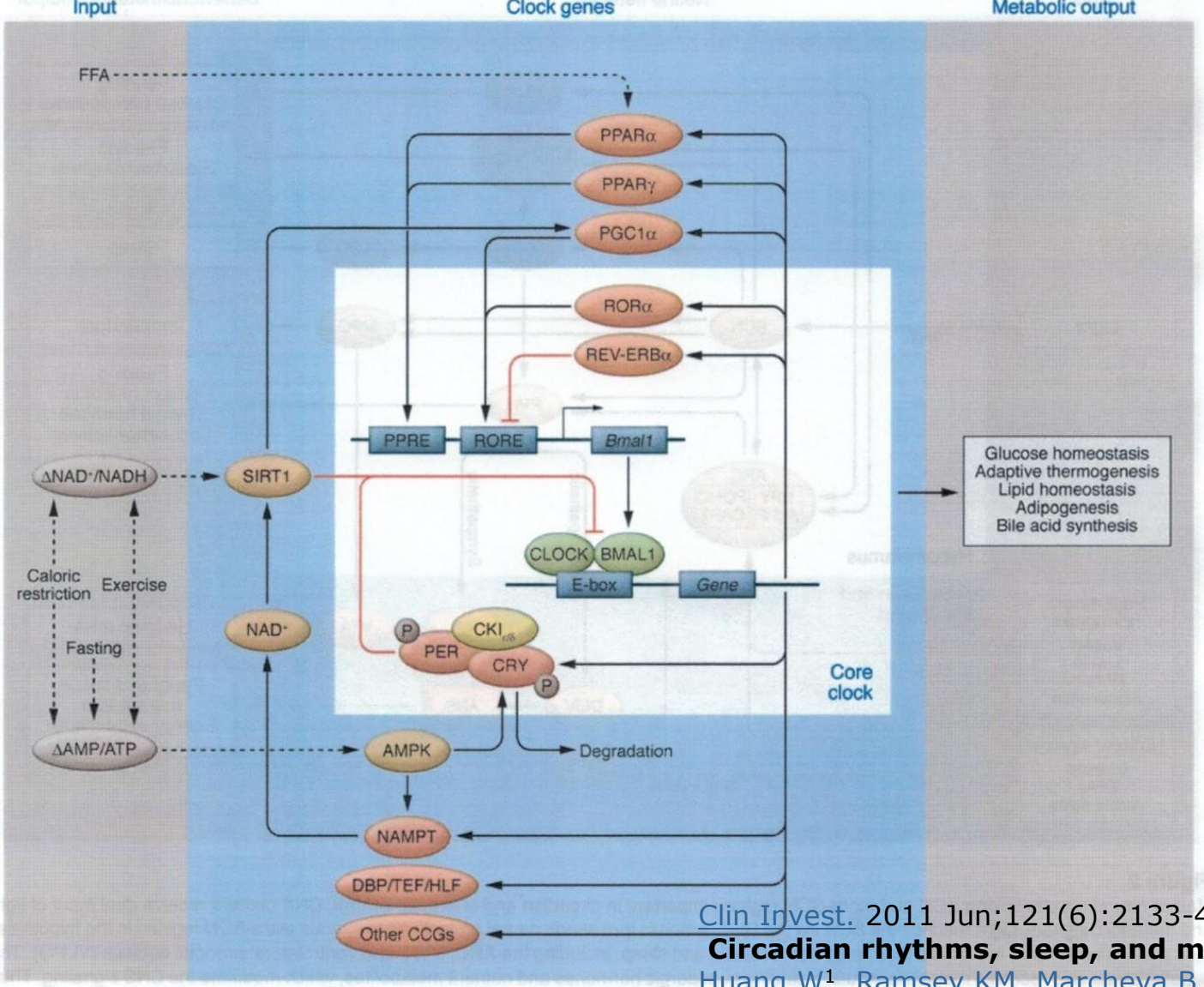
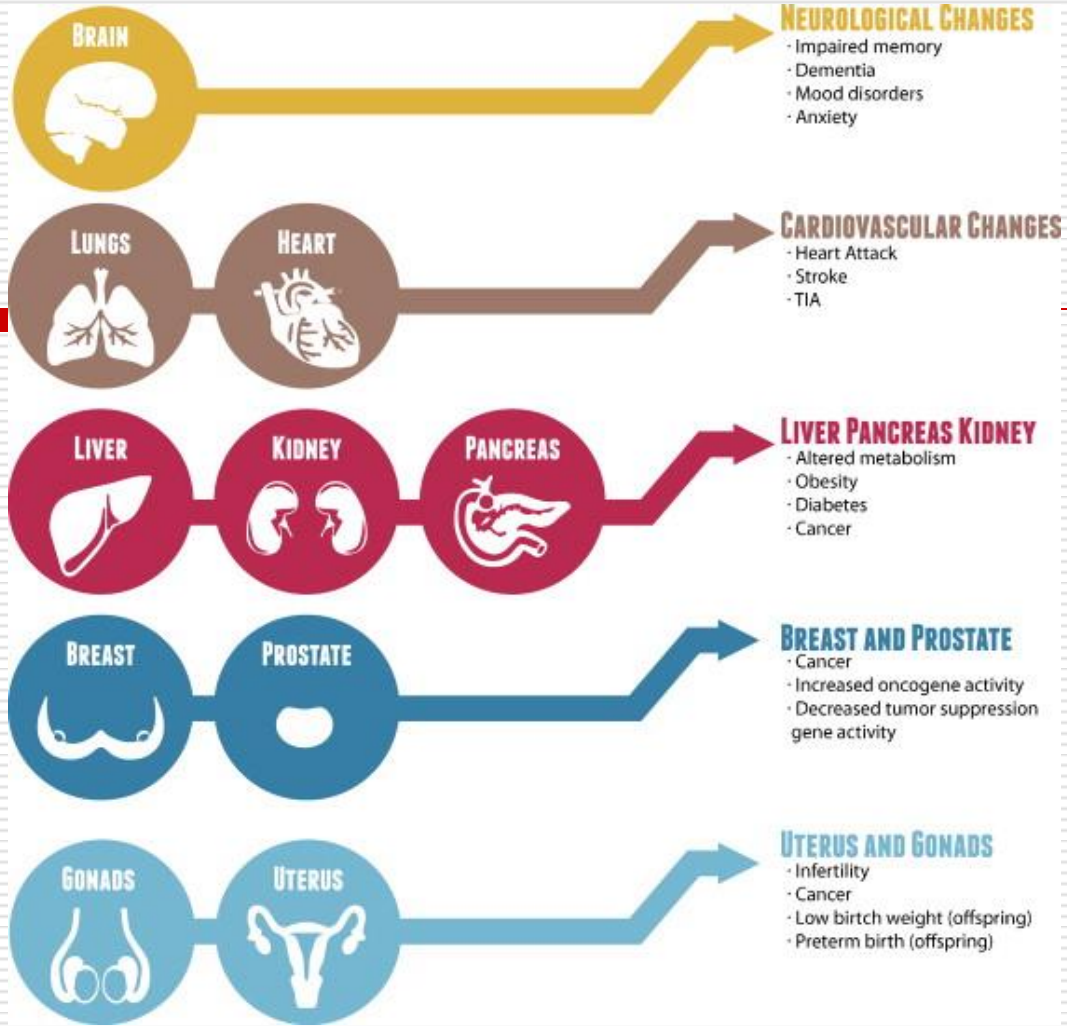
Figure 2

Map of neural circuits linking SCN and extra-SCN regions important in circadian and energetic control. CNS centers receive dual input of light and metabolic signals. Light reaches the SCN via the RHT, which in turn sends neural projections to various extra-SCN regions in the hypothalamus and brainstem that are critical for energy homeostasis and sleep, including the ARC, PVN, and ventrolateral preoptic nucleus (VLPO). The hypothalamus also receives metabolic inputs, including peptidergic hormones and nutrient metabolites, which modulate the CNS signaling. Thus signals from the exogenous environment (i.e., light) and endogenous metabolism (i.e., metabolic cues) are integrated in the CNS, the output of which in turn imparts rhythmicity on sleep and a variety of metabolic outputs, such as thermogenesis, feeding behavior, hormone secretion, and locomotor activity. IML, intermediolateral nucleus; NTS, nucleus tractus solitarius. dSPZ, dorsal subparaventricular zone; RHT, retinohypothalamic tract; vSPZ, ventral subparaventricular zone; MCH, melanocyte concentrating hormone.

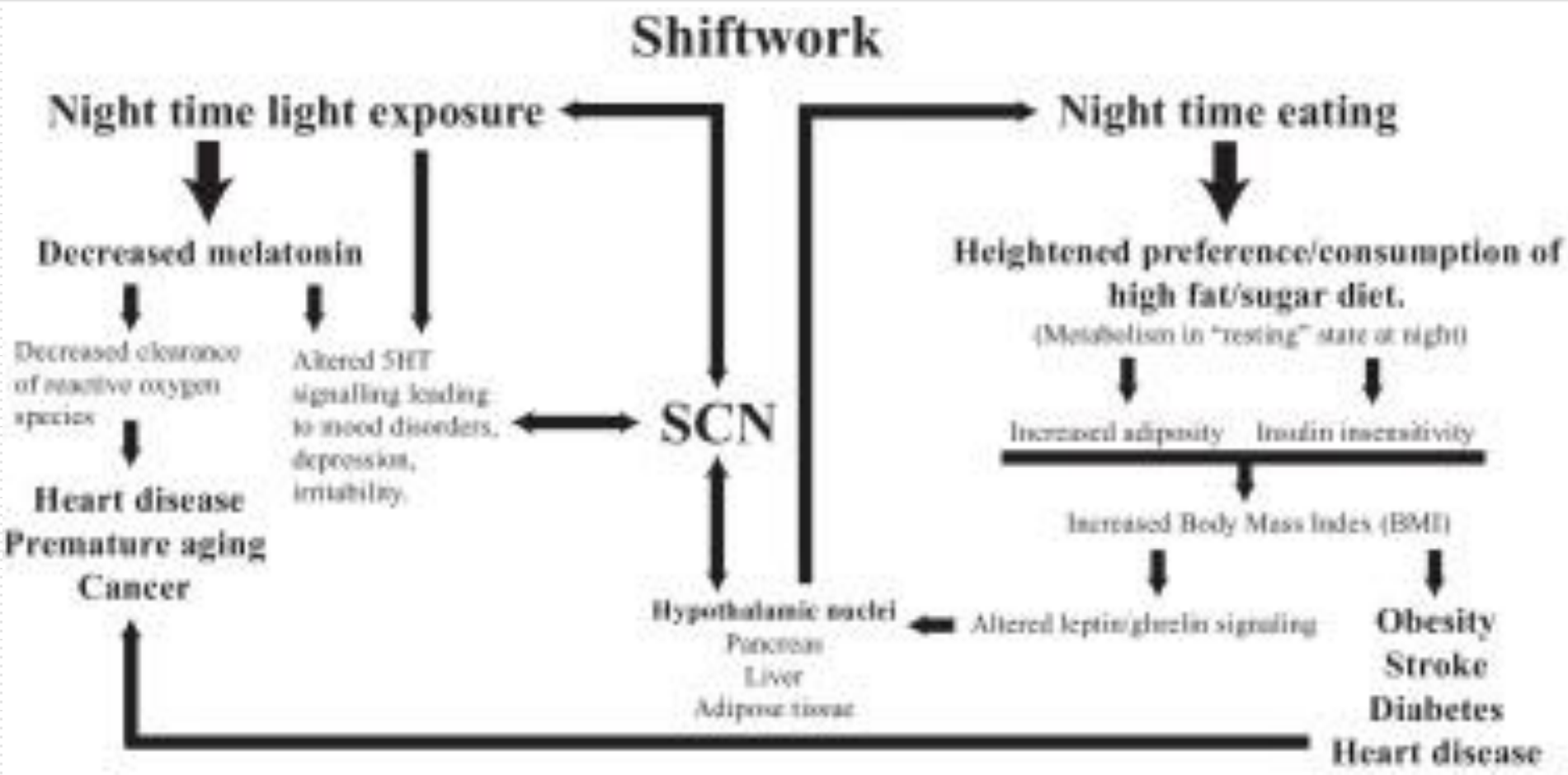


Clin Invest. 2011 Jun;121(6):2133-41.
Circadian rhythms, sleep, and metabolism.
Huang W[1], Ramsey KM, Marcheva B, Bass J.

Figure 3
Interactions between the molecular clock and downstream metabolic genes. The core molecular clock consists of several transcription/translation feedback loops, including posttranscriptional regulation (yellow), that oscillate with an approximately 24-hour periodicity. CLOCK and BMAL1 heterodimerize to drive rhythmic expression of downstream target genes (shown in red), which in turn regulate diverse metabolic processes, including glucose metabolism, lipid homeostasis, and thermogenesis. Many of these clock target genes in turn reciprocally regulate the clock in response to changes in nutrient status (shown in blue) via cellular nutrient sensors (shown in orange), generating a complex network of interlocking feedback loops that fine-tune the clock and coordinate metabolic processes with the daily cycles of sleep/wakefulness and fasting/feeding. Dashed lines represent metabolic inputs; solid lines depict interactions among core clock genes, clock-controlled genes, and nutrient sensors.



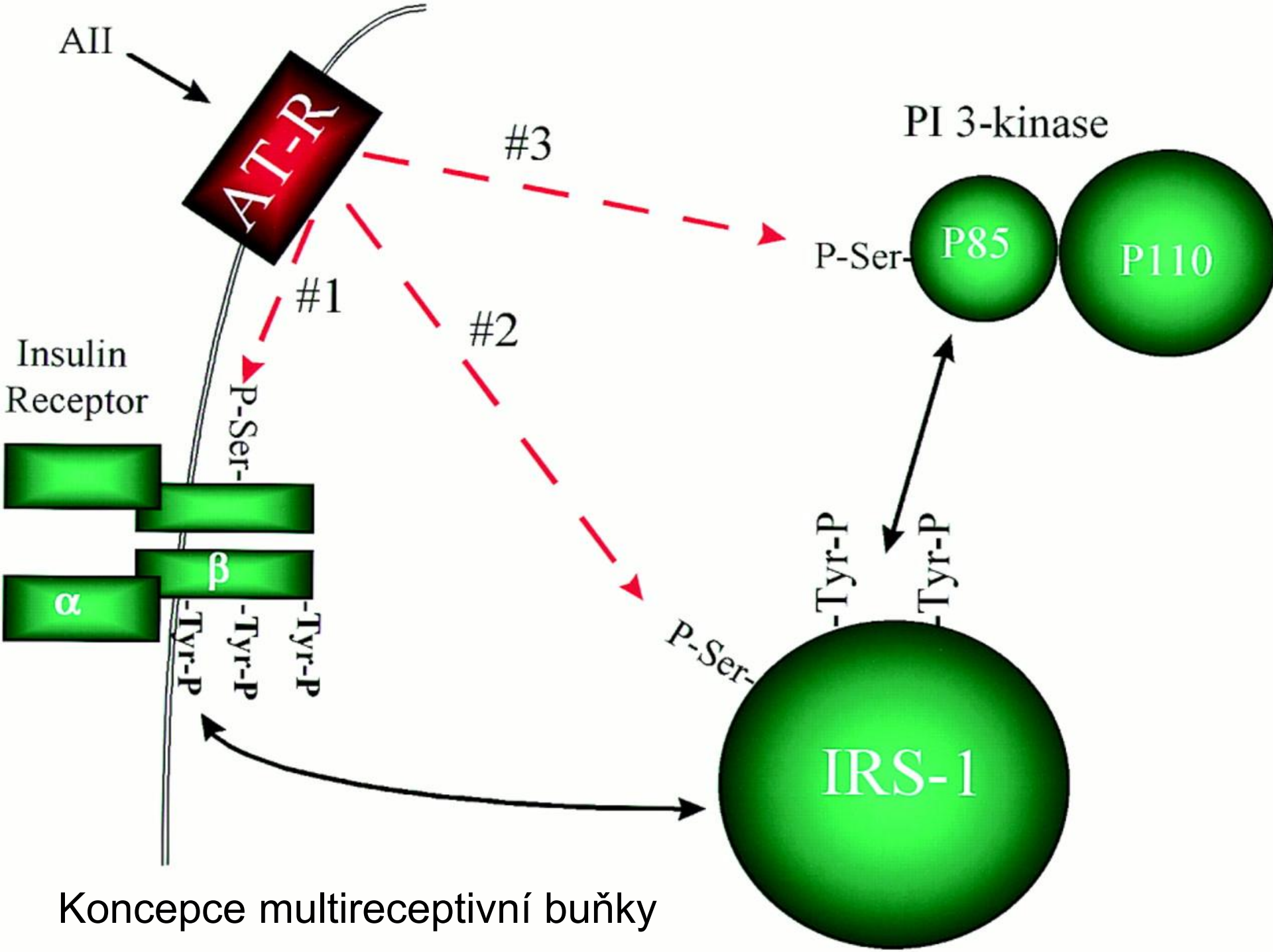
Circadian disruption affects multiple organ systems. The diagram provides examples of how circadian disruption negatively impacts the brain and the digestive, cardiovascular, and reproductive systems. Though the diagram displays unidirectional affects, there are various feedback loops that exist within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



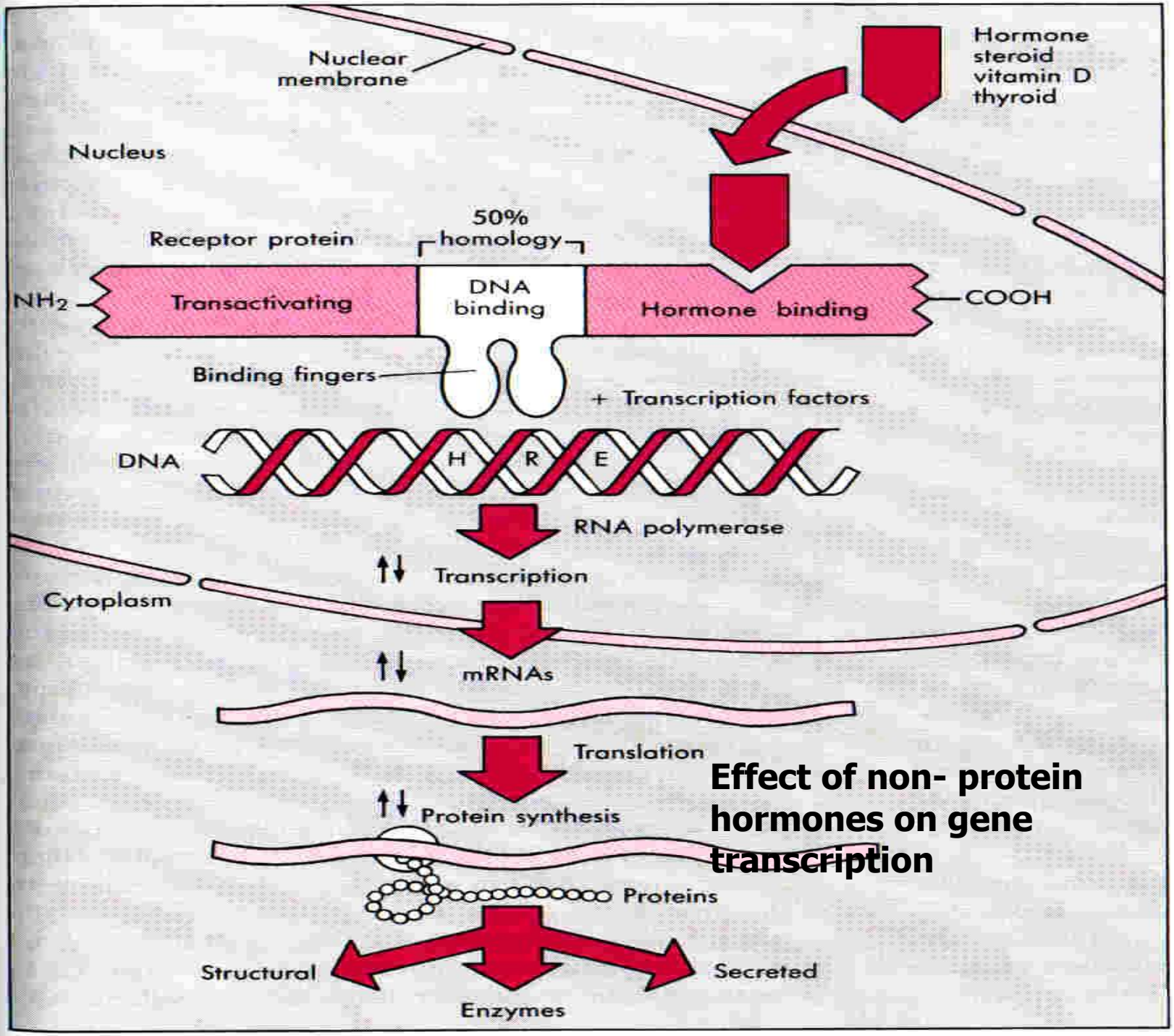
Erin L. Zelinski, Scott H. Deibel, Robert J. McDonald
Neuroscience and Biobehavioral Reviews 40 (2014) 80–101

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



Koncepce multireceptivní buňky

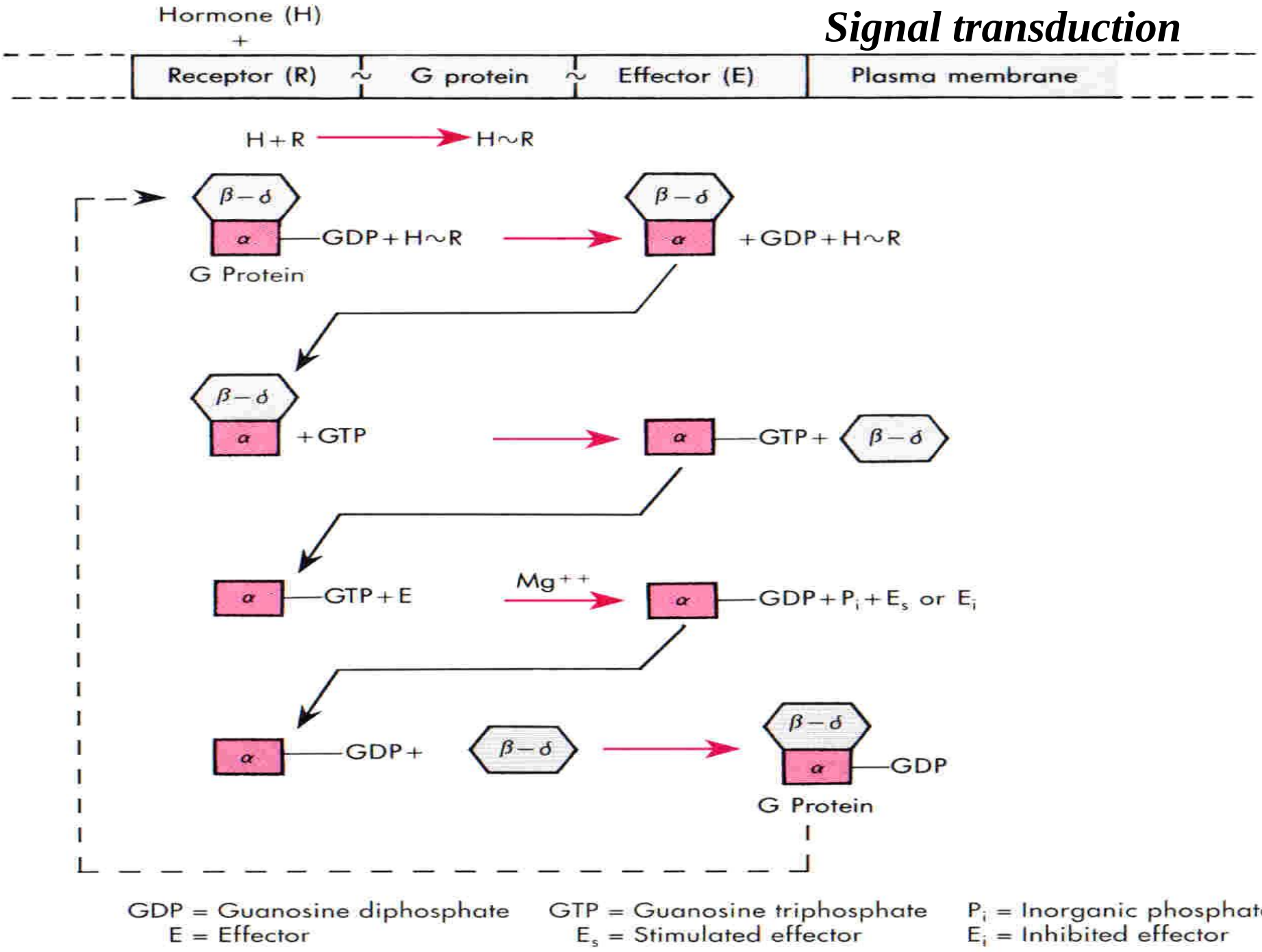


Effect of non- protein hormones on gene transcription

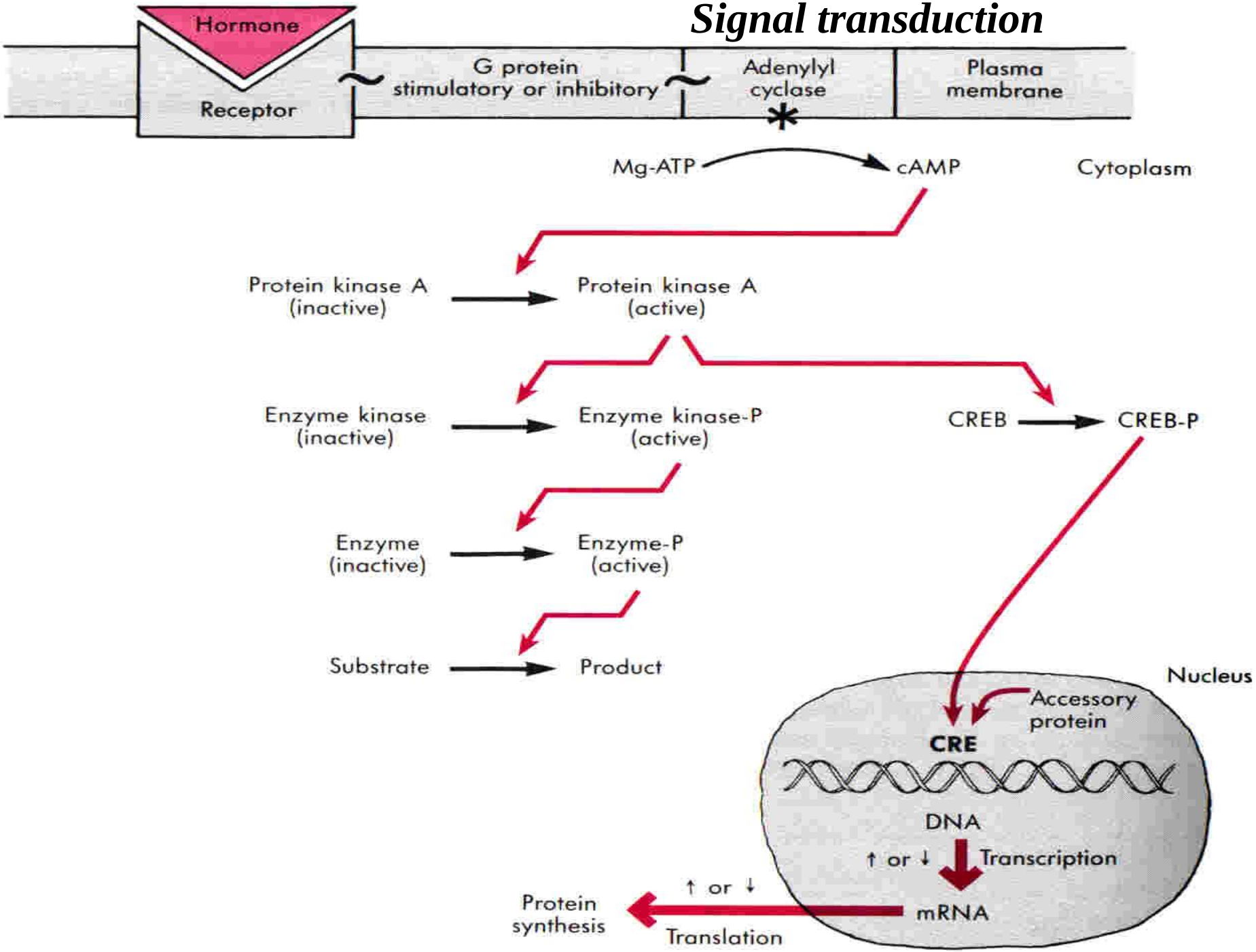
Hormonal activity

- 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.

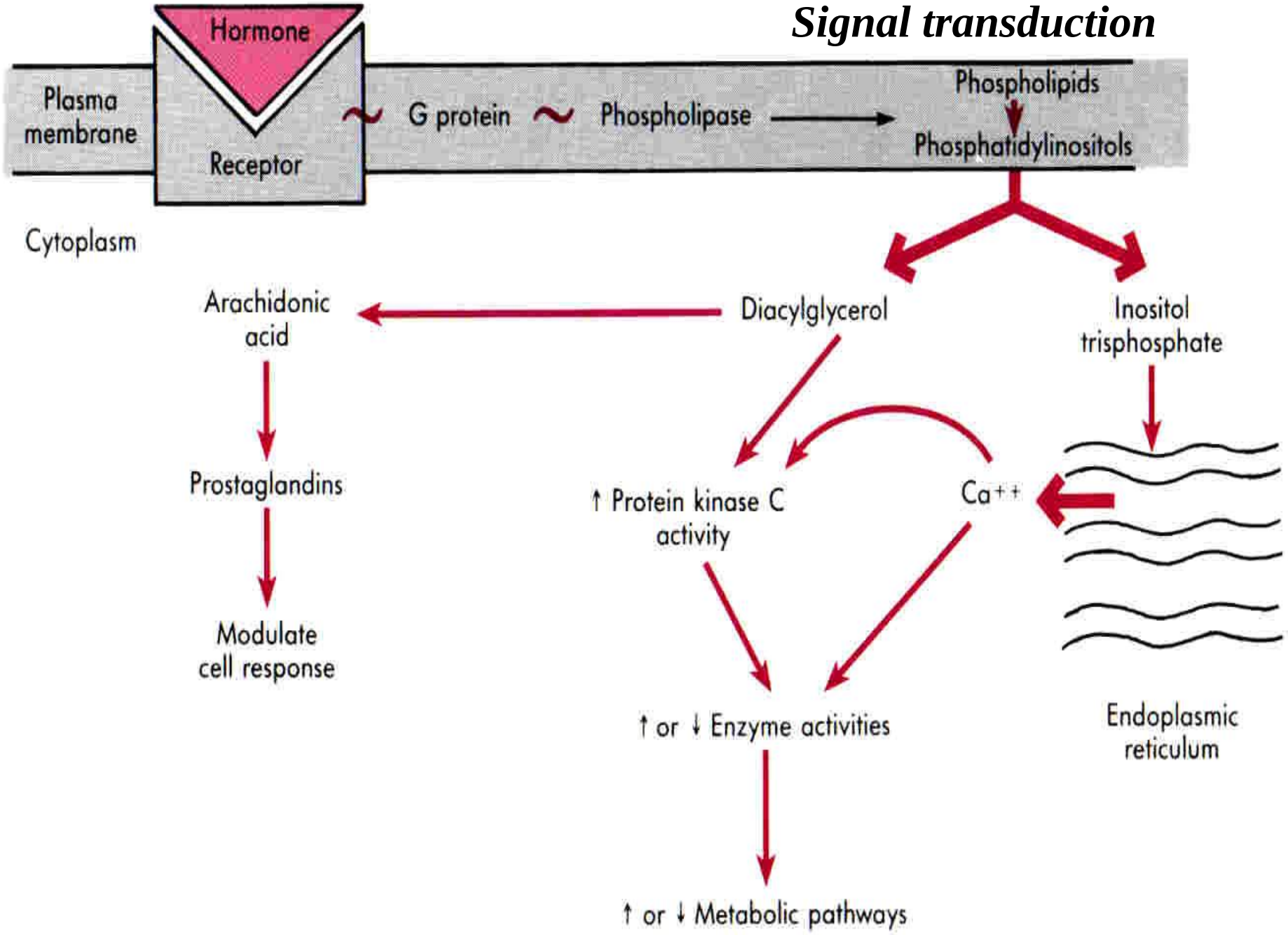
Signal transduction



Signal transduction



Signal transduction



Signal transduction

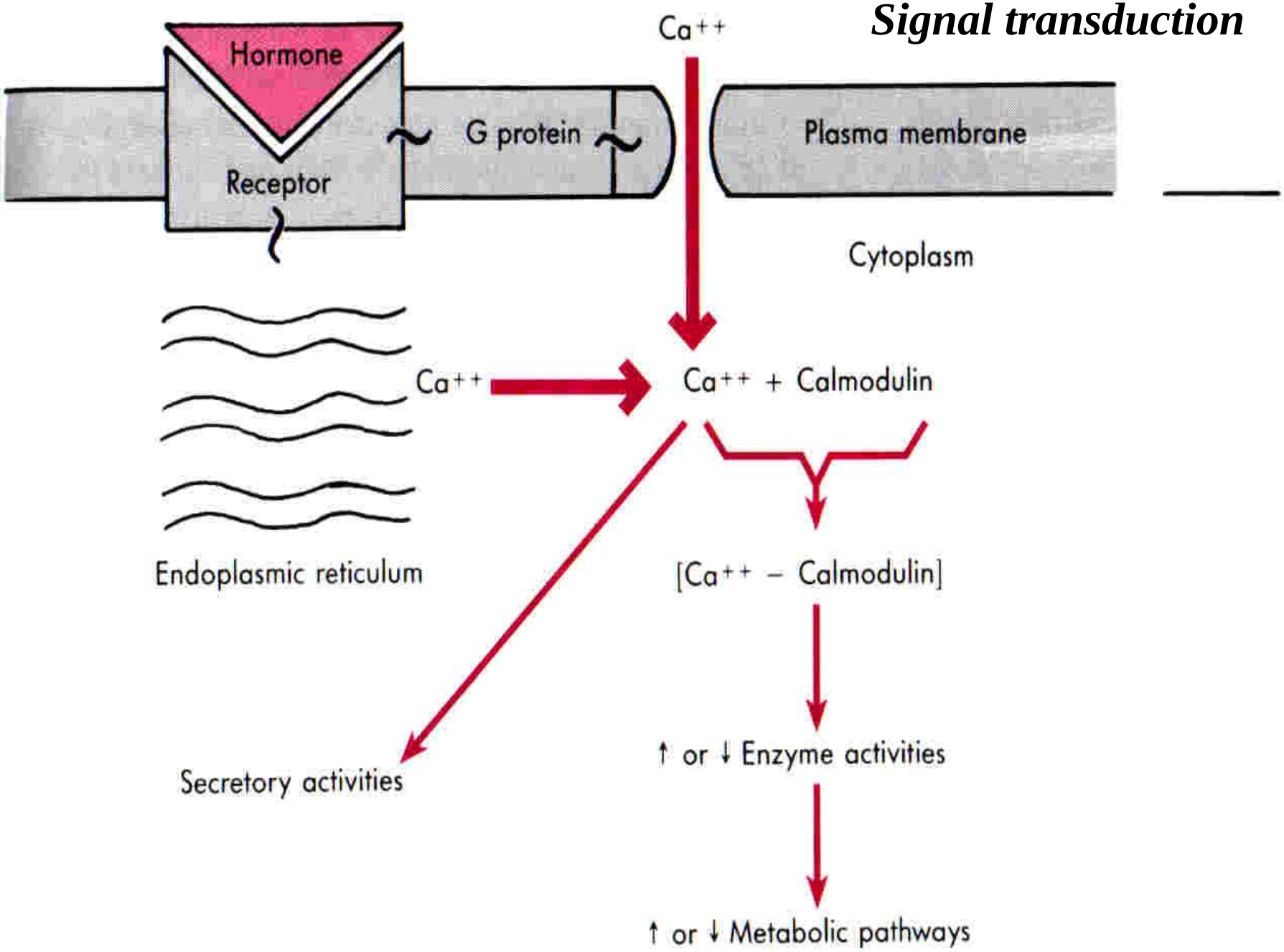
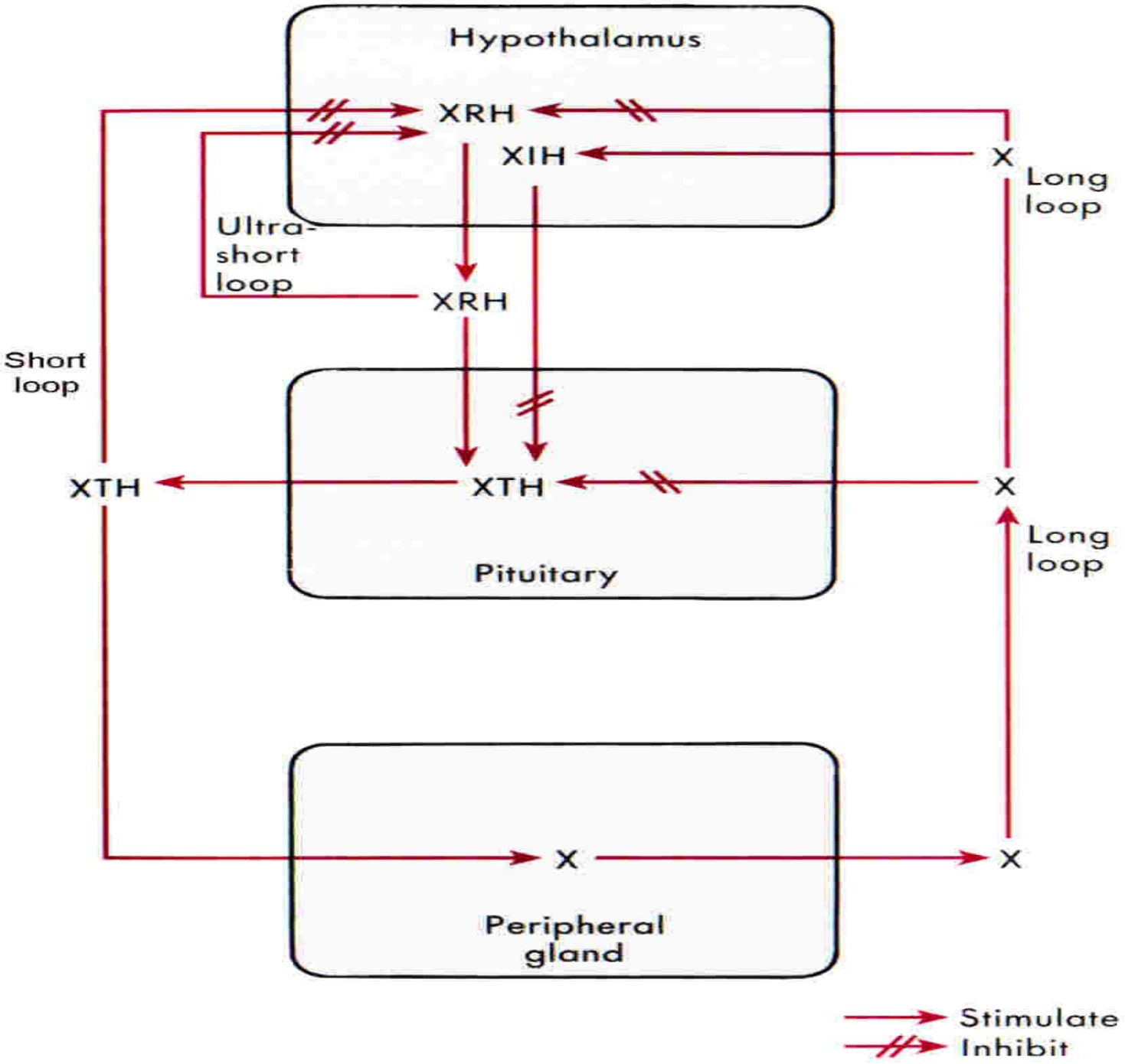


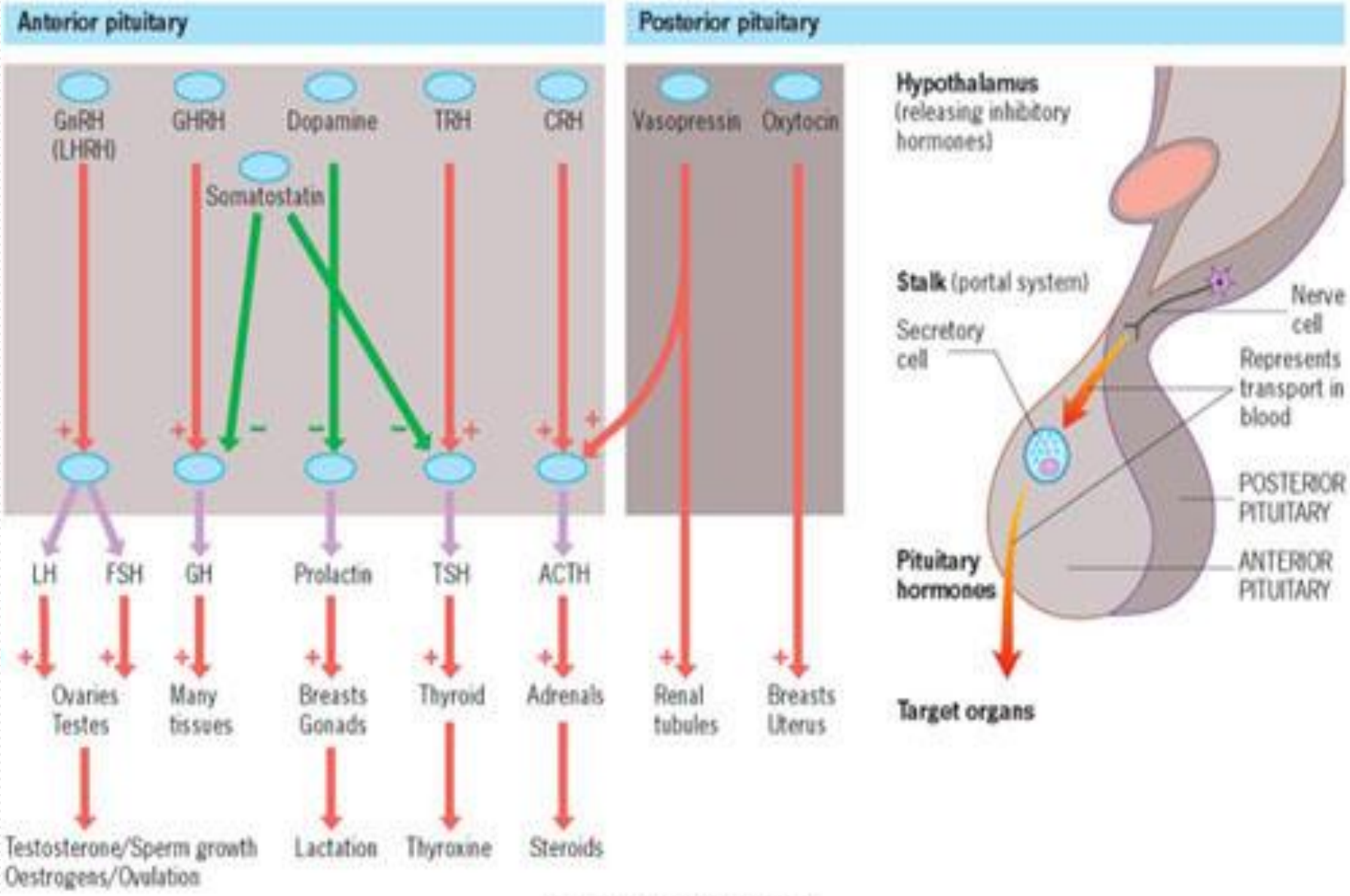
Table 18.5

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


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



Hypothalamic releasing hormones and the pituitary trophic hormo

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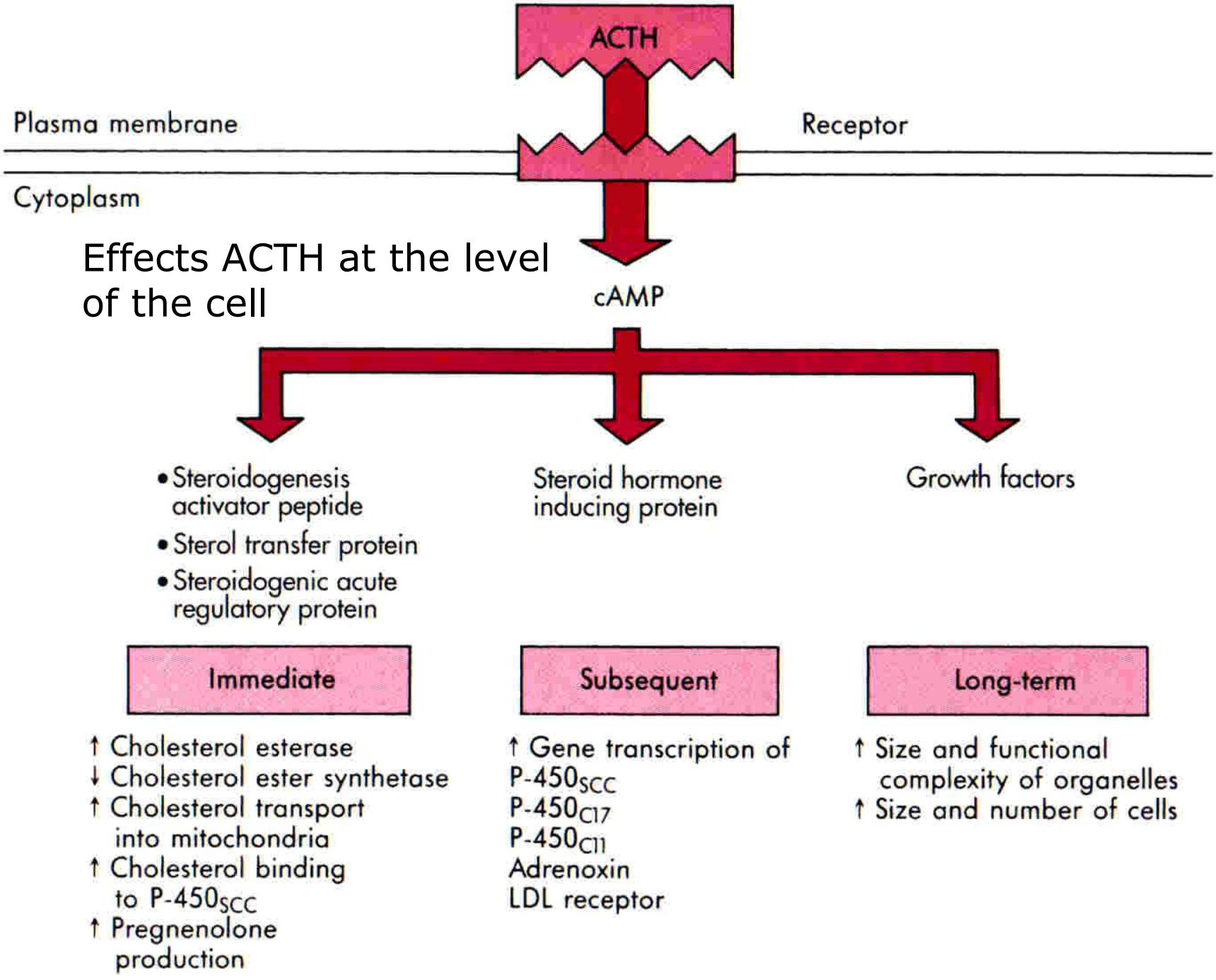
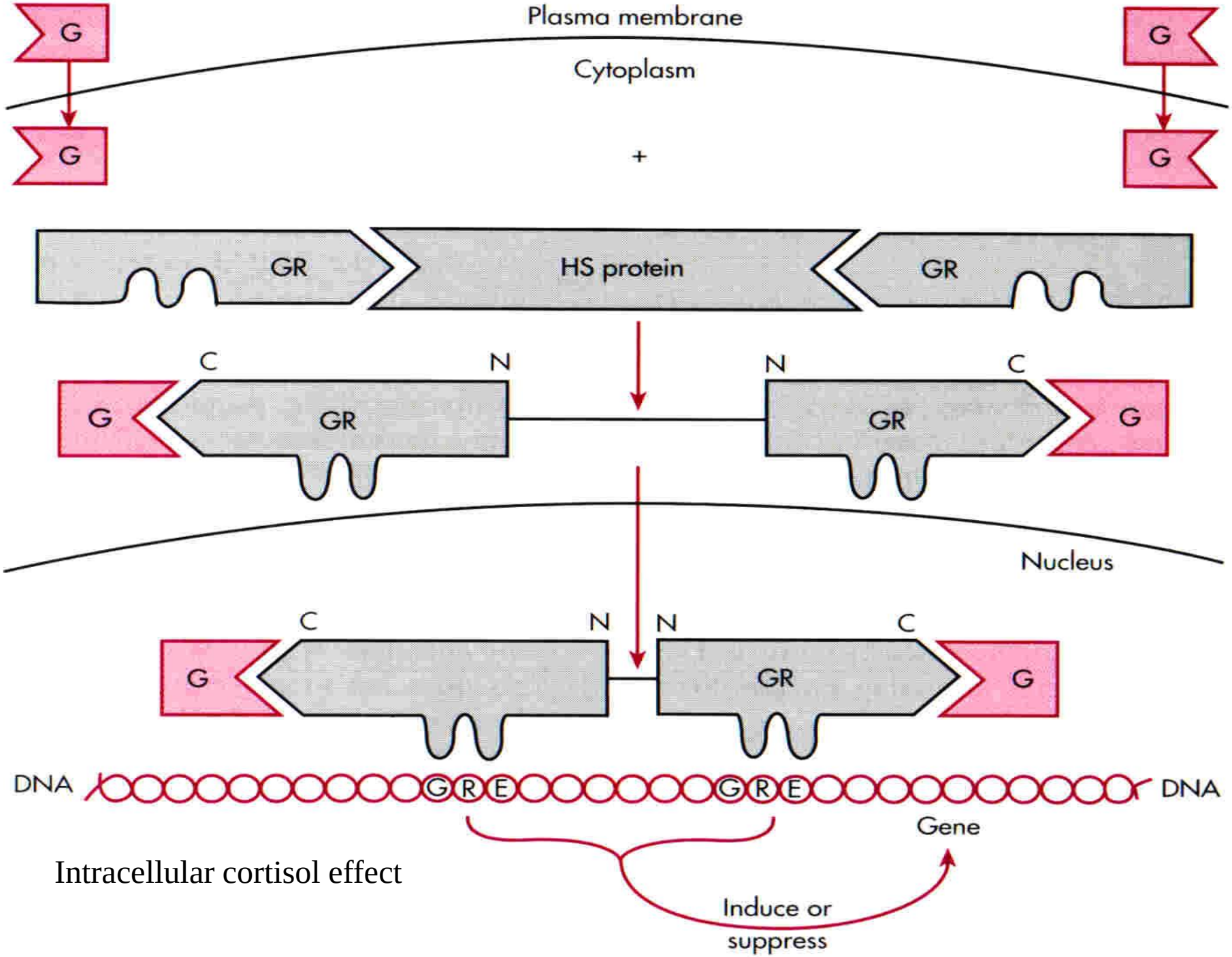
Vasopressin (antidiuretic hormone; ADH) (*Nonapeptide*)	–	–
Oxytocin (*Nonapeptide*)	–	–

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

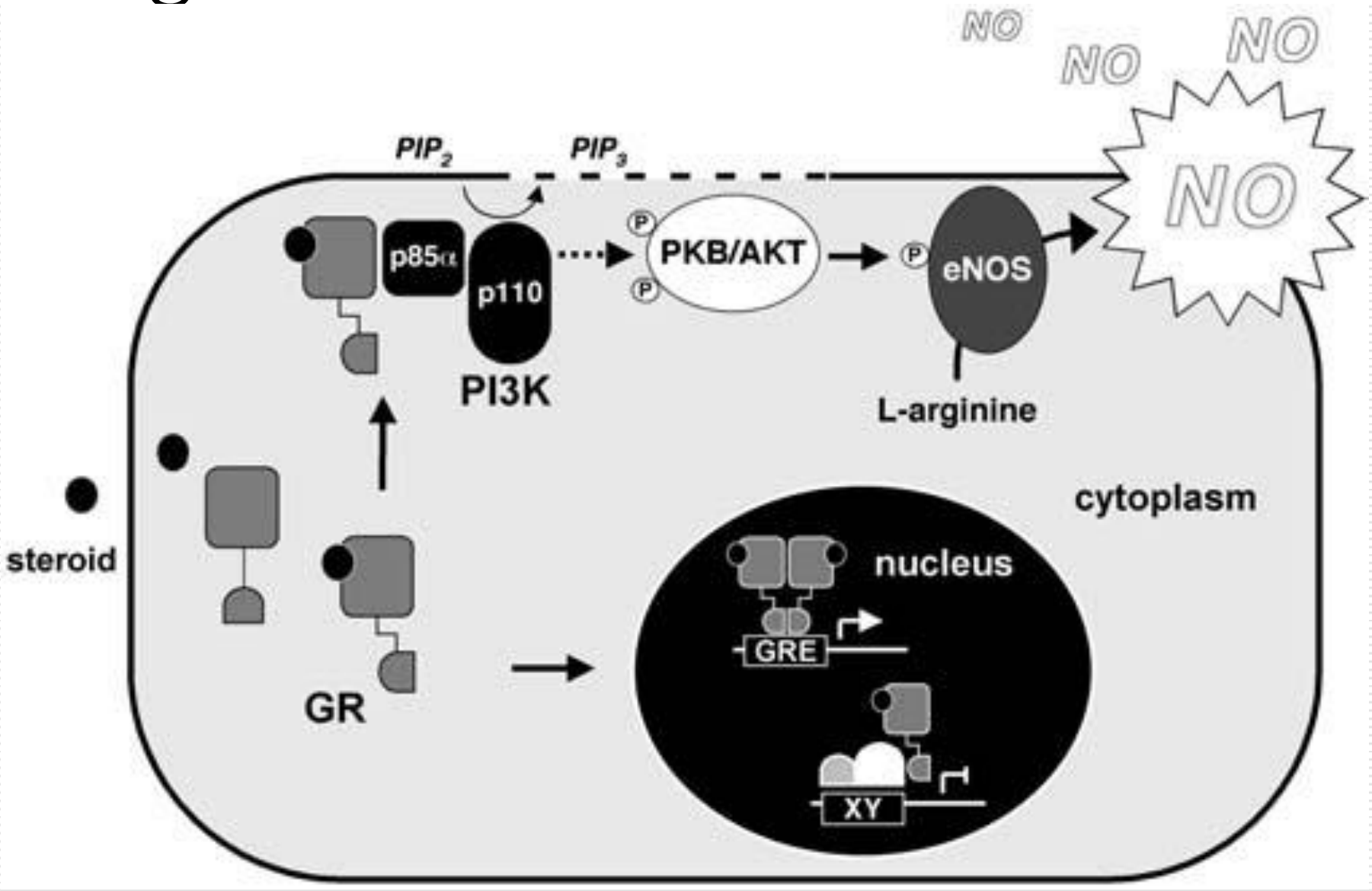


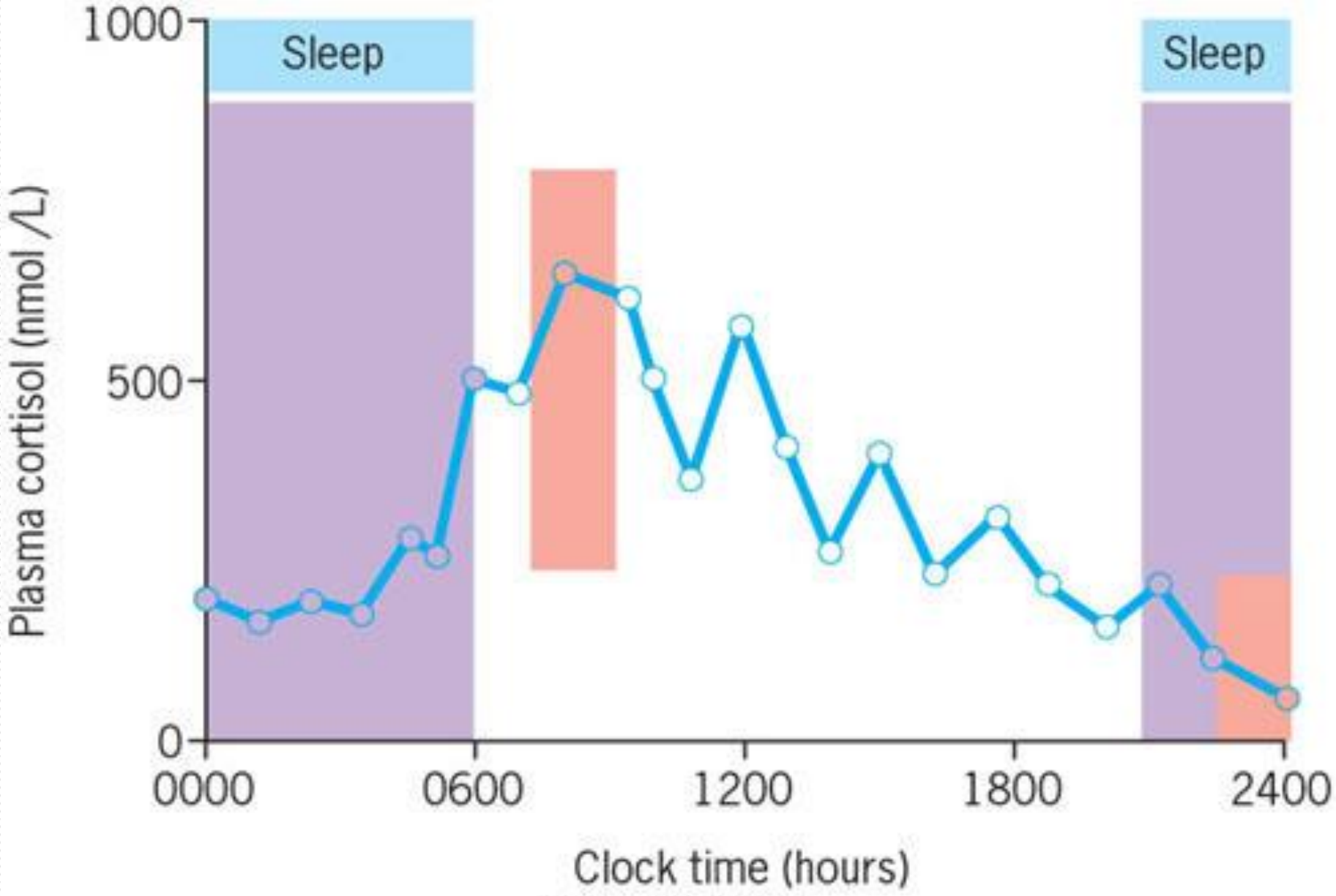
Effects ACTH at the level of the cell

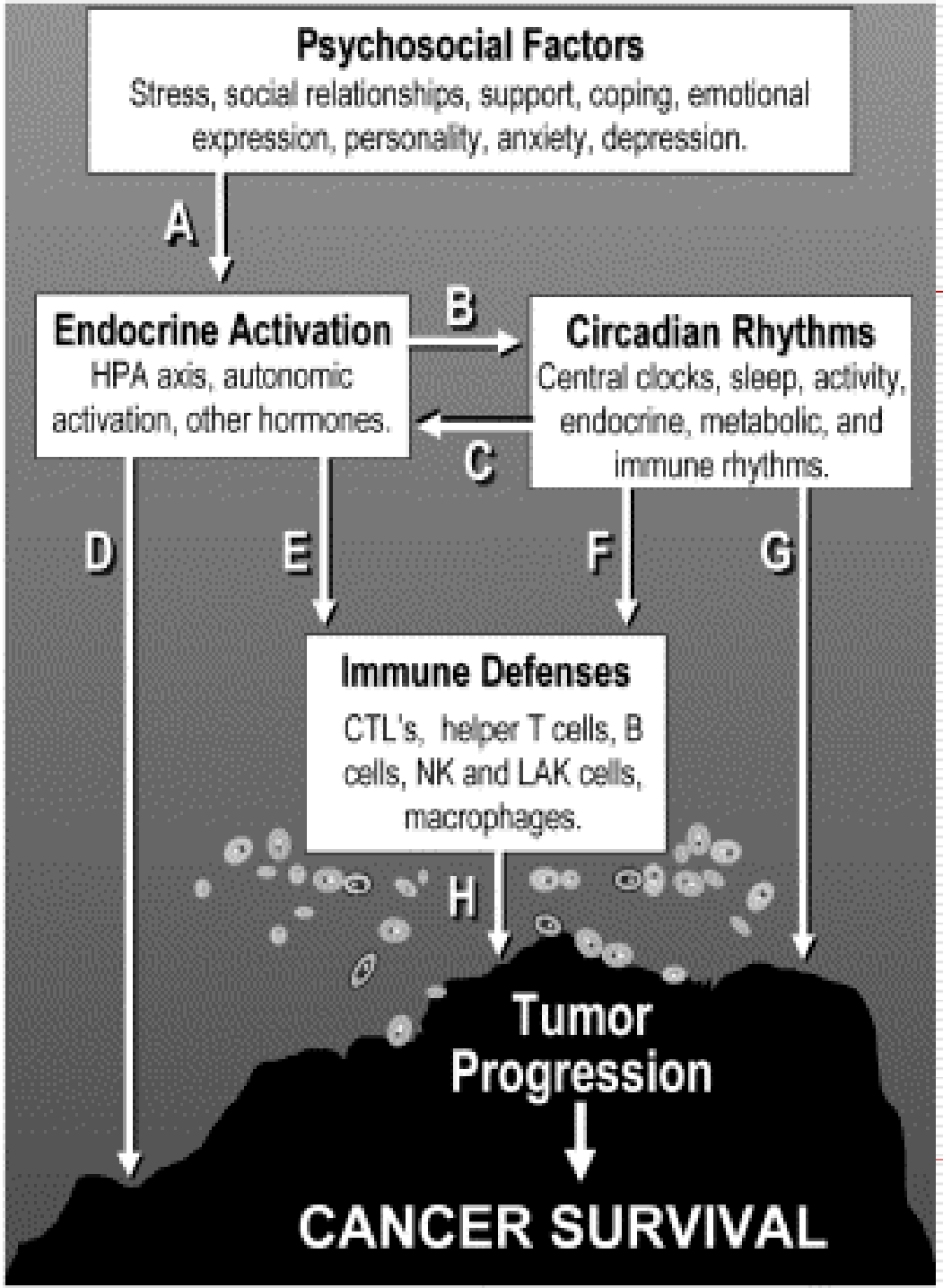


Intracellular cortisol effect

Nuclear and non nuclear actions of glucocorticoids





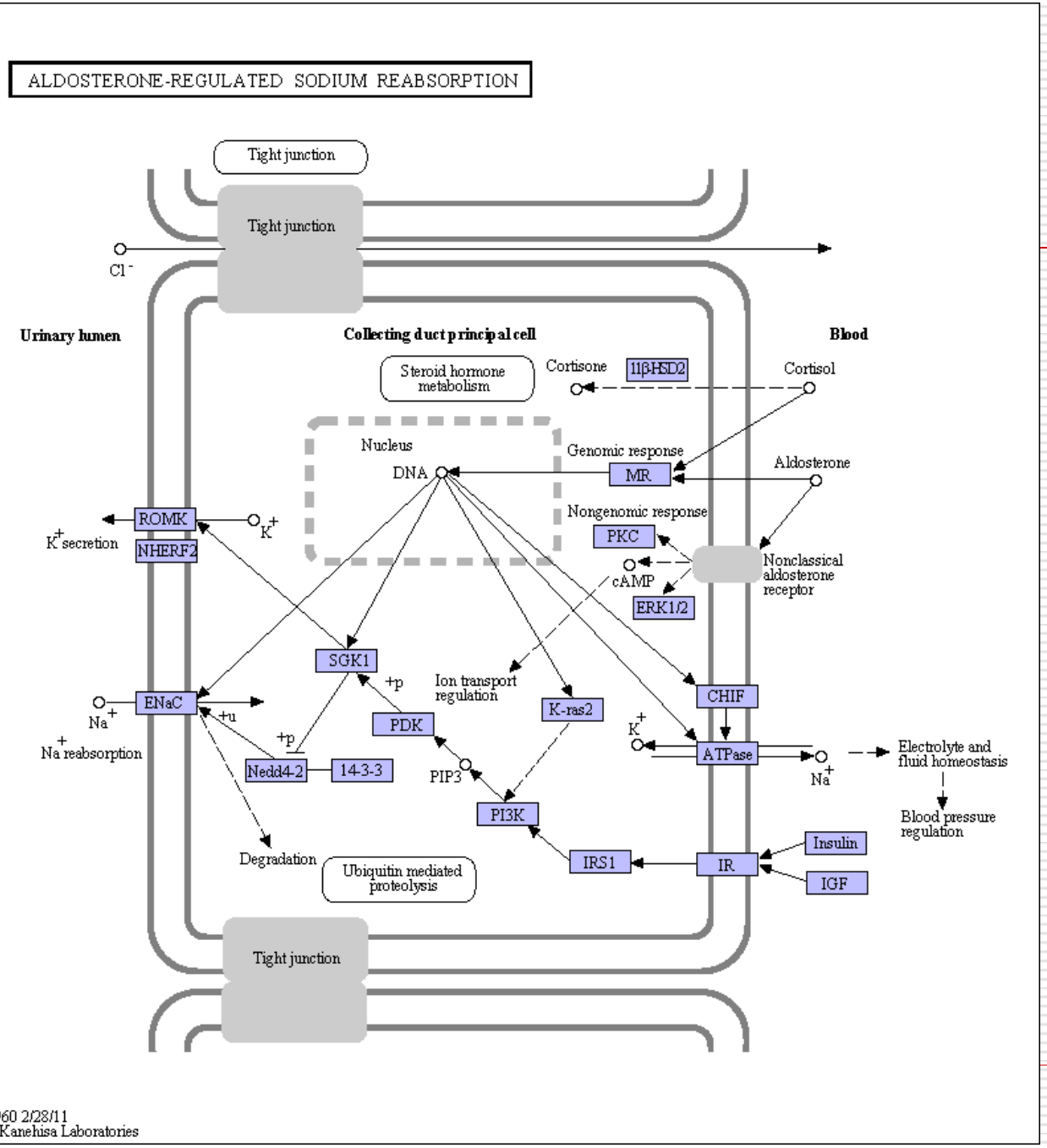

Psychosocial Factors
Stress, social relationships, support, coping, emotional expression, personality, anxiety, depression.
A
Endocrine Activation
HPA axis, autonomic activation, other hormones.
B
Circadian Rhythms
Central clocks, sleep, activity, endocrine, metabolic, and immune rhythms.
C
D
E
F
G
Immune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

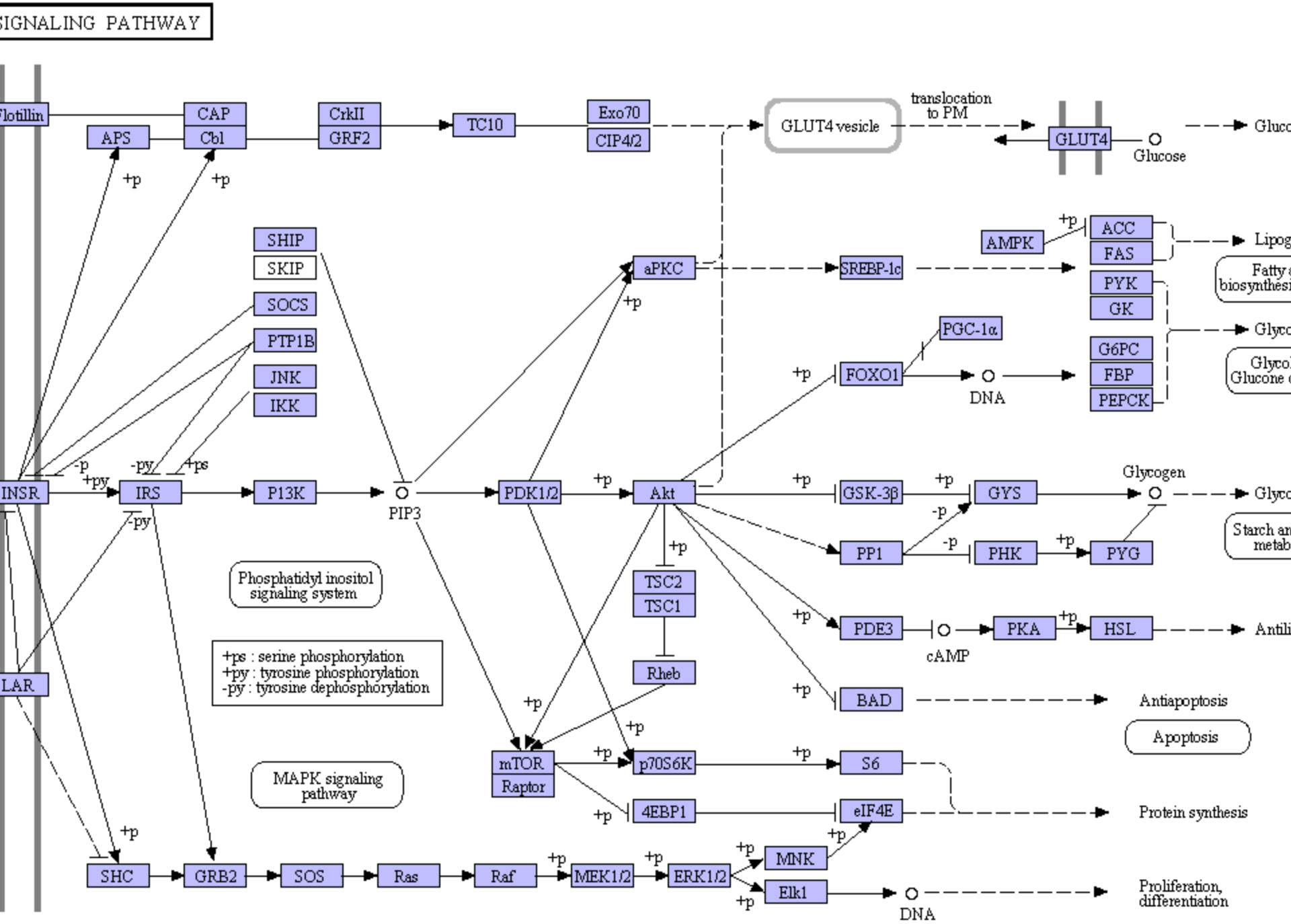
Potential pathways by which circadian dysregulation may mediate psychosocial effects on cancer progression

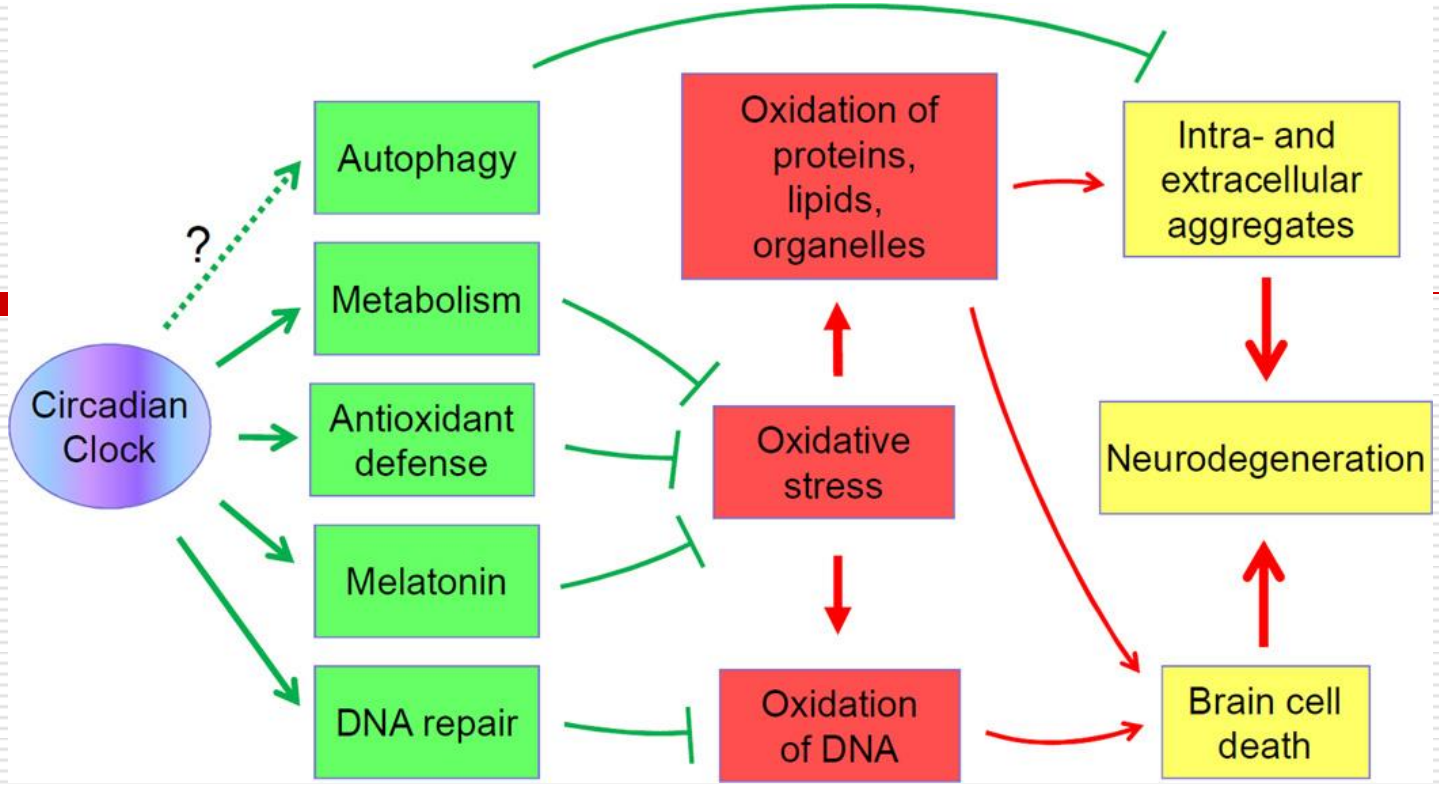
- Arrow (A) represents activation of endocrine stress-responses associated with psychological distress and other psychosocial factors. Repeated stress-response activation may hypothetically lead to dysregulation of circadian rhythms (B), while aberrations in sleep–wake cycles, rest-activity rhythms, 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).


ALDOSTERONE-REGULATED SODIUM REABSORPTION
Tight junction
Tight junction
Cl-
Urinary lumen
Collecting duct principal cell
Blood
Steroid hormone metabolism
Cortisone
11βHSD2
Cortisol
Nucleus
DNA
Genomic response
MR
Aldosterone
Nongenomic response
PKC
cAMP
ERK1/2
Nonclassical aldosterone receptor
ROMK
K+ secretion
NHERF2
K+
SGK1
+p
Ion transport regulation
K-ras2
CHIF
ENaC
Na+
+u
Na+ reabsorption
+p
PDK
Nedd4-2
14-3-3
PIP3
K+
ATPase
Na+
Electrolyte and fluid homeostasis
Blood pressure regulation
PI3K
Degradation
Ubiquitin mediated proteolysis
IRS1
IR
Insulin
IGF
Tight junction
04960 2/28/11
(c) Kanehisa Laboratories


SIGNALING PATHWAY
Flotillin
CAP
Cbl
APS
CrkII
GRF2
TC10
Exo70
CIP4/2
GLUT4 vesicle
translocation to PM
GLUT4
Glucose
+p
SHIP
SKIP
SOCS
PTP1B
JNK
IKK
aPKC
SREBP-1c
AMPK
ACC
FAS
PYK
GK
G6PC
FBP
PEPCK
PGC-1α
FOXO1
DNA
Lipog
Fatty
biosynthesi
Glyco
Glucone
INSR
IRS
P13K
PIP3
PDK1/2
Akt
GSK-3β
GYS
Glycogen
PP1
PHK
PYG
Starch an
metab
-p
+py
-py
+ps
Phosphatidyl inositol signaling system
+ps : serine phosphorylation
+py : tyrosine phosphorylation
-py : tyrosine dephosphorylation
TSC2
TSC1
Rheb
PDE3
cAMP
PKA
HSL
Antili
BAD
Antiapoptosis
Apoptosis
LAR
mTOR
Raptor
p70S6K
S6
4EBP1
eIF4E
Protein synthesis
MAPK signaling pathway
SHC
GRB2
SOS
Ras
Raf
MEK1/2
ERK1/2
MNK
Elk1
DNA
Proliferation, differentiation



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.

Děkuji za pozornost