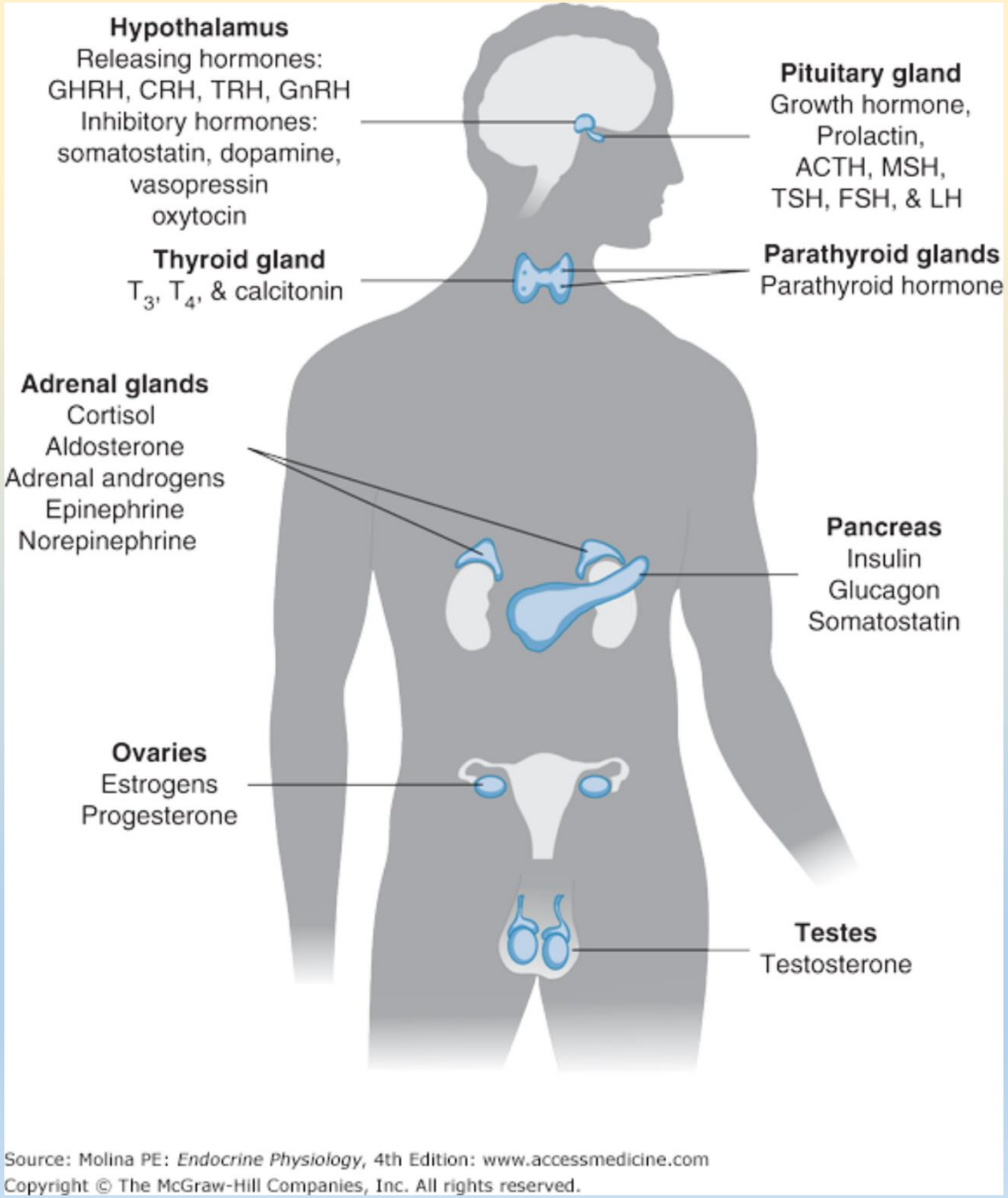
General principles of endocrine functions

MUNI MED

Hormones

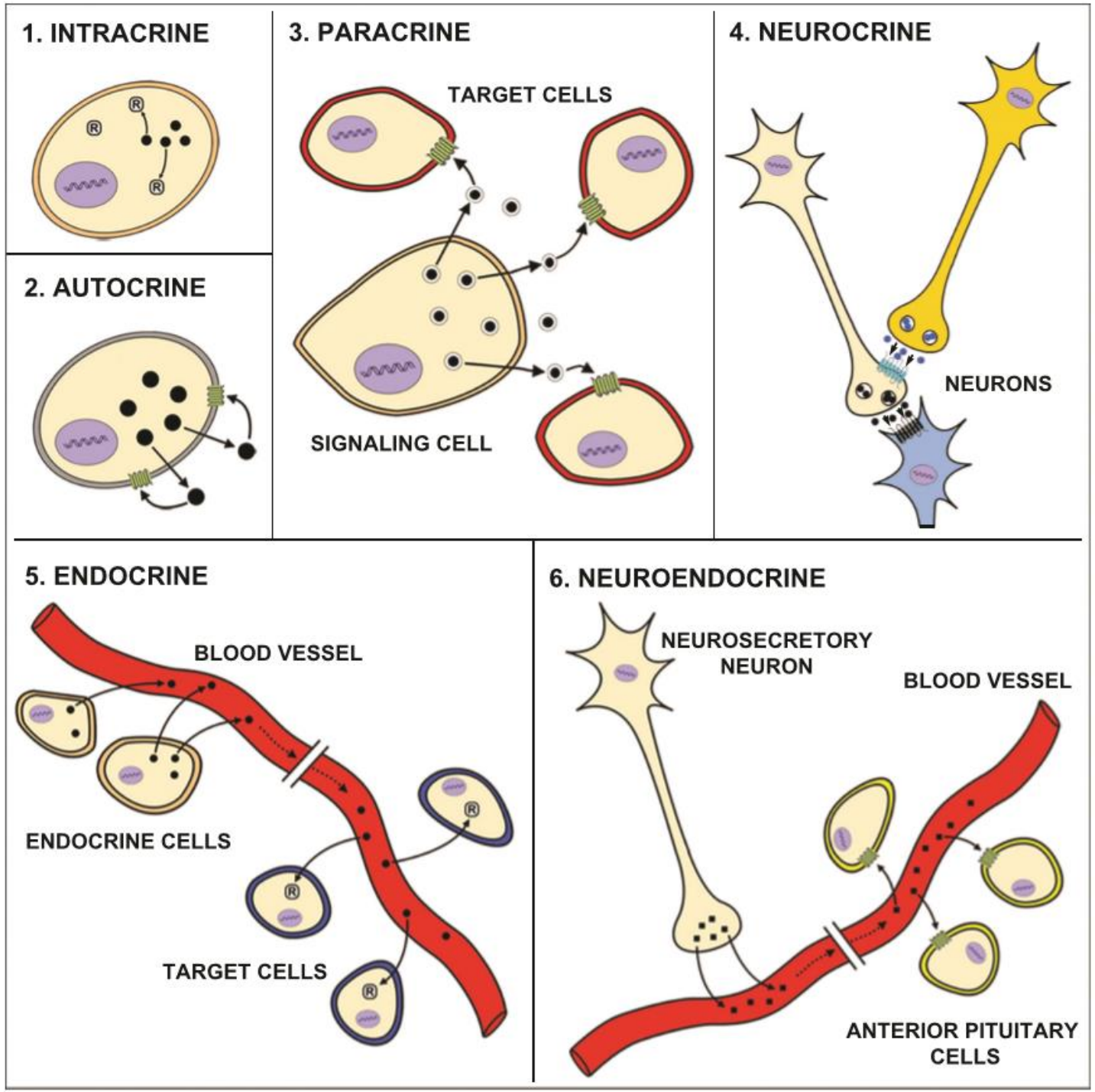
- **Starling 1905 - *secretin***
- **Definition?**
- **Glandotropic** hormones
- **Aglandotropic** hormones



How do cells communicate?

- **Intracrine**
- **Autocrine**
- **Paracrine**
- **Neurocrine**
- **Endocrine**
- **Neuroendocrine**

source → environment → target cell



source

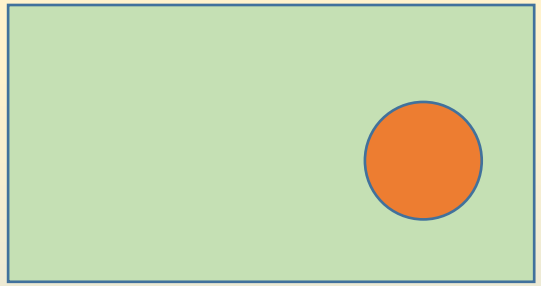
environment

target cell

endocrine

gland

blood



- synthesis/secretion
- no influence on specificity of effect

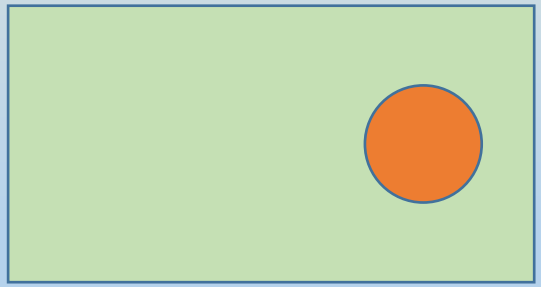
- universal environment
- dilution and interactions

- receptor = specificity
- cell response
  - number of receptors
  - signaling pathways
  - other ligands
  - metabolisation of ligand/receptor

paracrine, autocrine

cell

matrix/interstitial fluid



- synthesis/secretion
- main determinant of target cell (determined by localization)

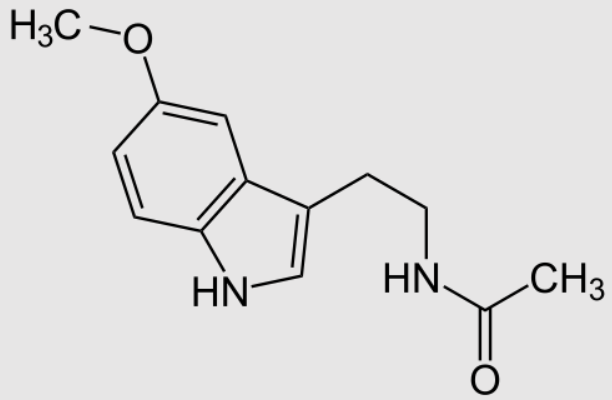
- diffusion
- binding proteins
- proteases
- components of extracellular matrix

- specificity and sensitivity
- diffusion barrier
- determinants of gradient
- inhibition signaling pathways
- effect of other ligands
- binding proteins

Chemical nature of hormones

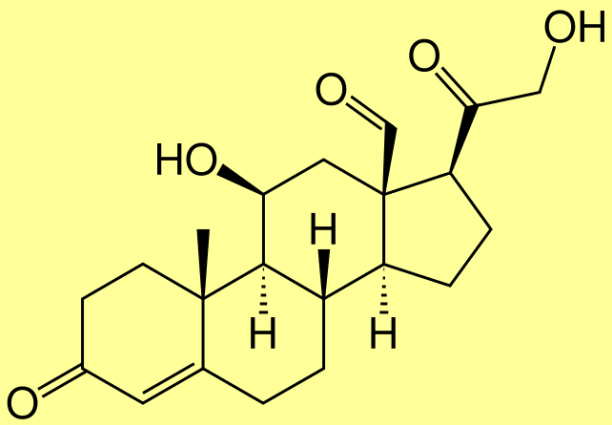
DERIVED FROM AMINOACIDS

-Adrenaline
-Noradrenaline
-Dopamine
-Melatonine
-T3/T4



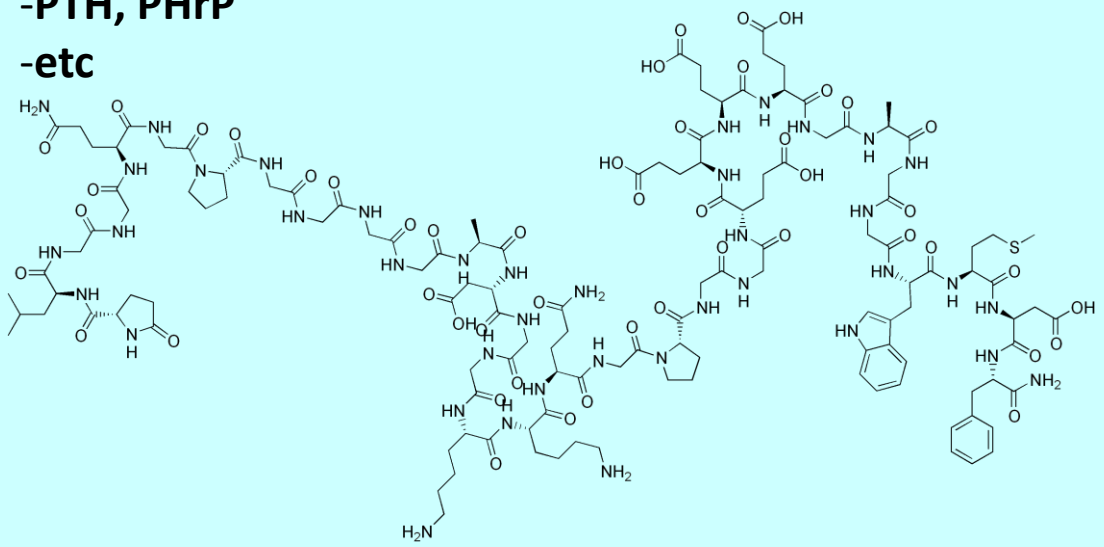
STEROID

-Cortisol
-Aldosterone
-Testosterone
-Progesterone
-Estradiol
-Calcitriol



PEPTIDES AND PROTEINS

-Hypothalamic hormones
-Adenohypophyseal hormones
-Insulin, glucagon, somatostatin
-Gastrin, cholecystokinin, secretin
-Natriuretic peptides
-Erythropoietin, thrombopoietin
-PTH, PHrP
-etc



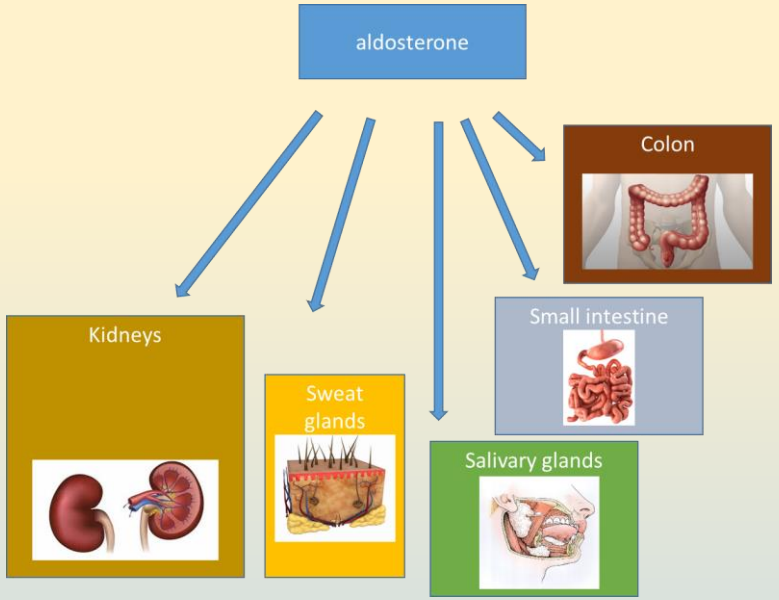
Chemical nature of hormones

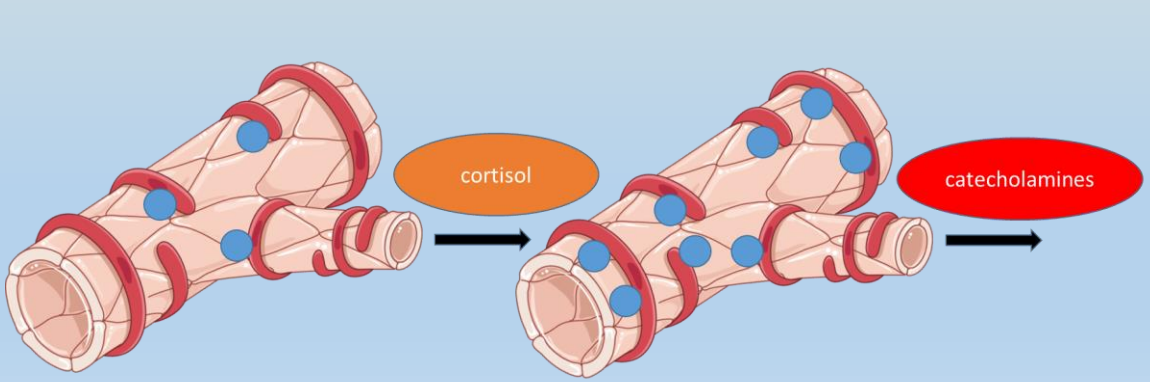
Hormone – characteristics	Peptides – proteins	Catecholamines	Steroid hormones	Thyroid hormones
Ph-CH properties	hydrophilic	hydrophilic	lipophilic	lipophilic
synthesis	proteosynthesis	Tyr modification	CH precursors	Tyr modifications
storage	secretory granules	secretory granules	not present	colloid
secretion	controlled exocytosis	controlled exocytosis	diffusion	diffusion
transport	free	free/weakly bound	bound	bound
elimination half-life	short (4 – 40 – 170 min)	very short (2 – 3 min)	moderate (up to 180 min)	long (20 hours – 7 days)
receptors	membrane	membrane	cytosol	nuclear
effect	short-term	very short-term	long-term	long-term
cell response	quick	very quick	slow	slow

CHEMICAL STRUCTURE OF HORMONES DETERMINES THEIR BIOSYNTHESIS, STORAGE, RELEASE, TRANSPORTATION, ELIMINATION HALF-LIFE, WAY OF ELIMINATION AND THE MECHANISM OF EFFECT ON TARGET CELLS

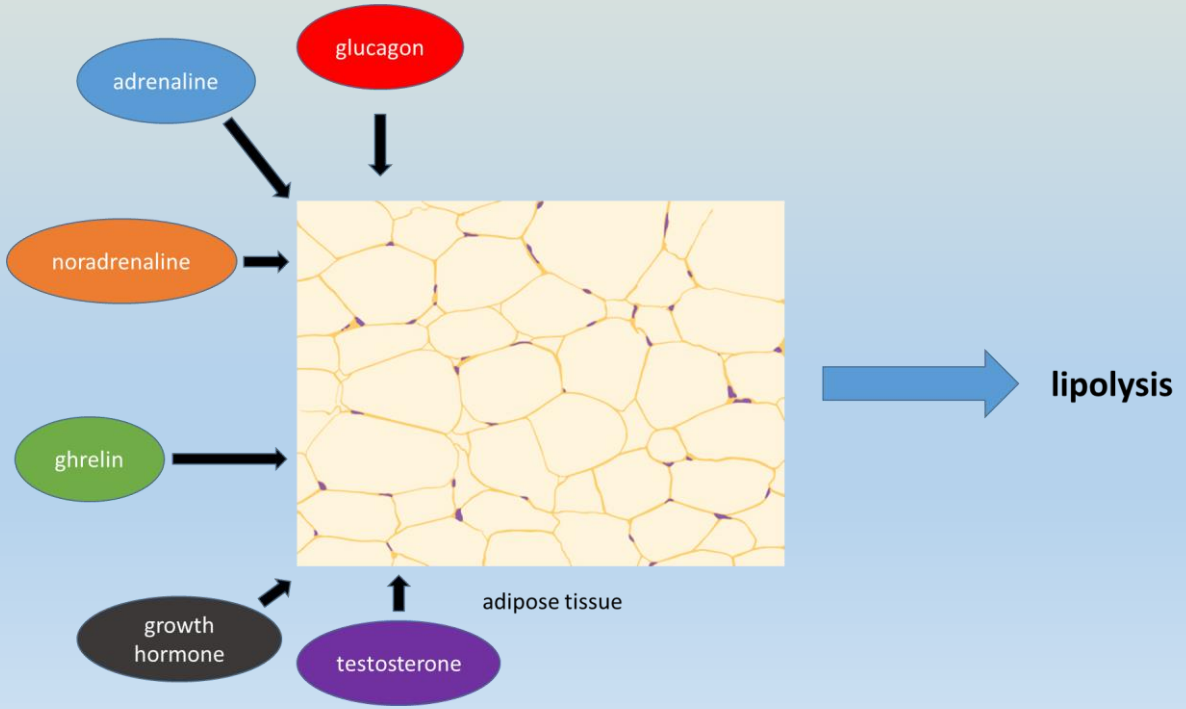
Hormones

- Pleiotropic effects
- Multiplicity
- Permissive effect



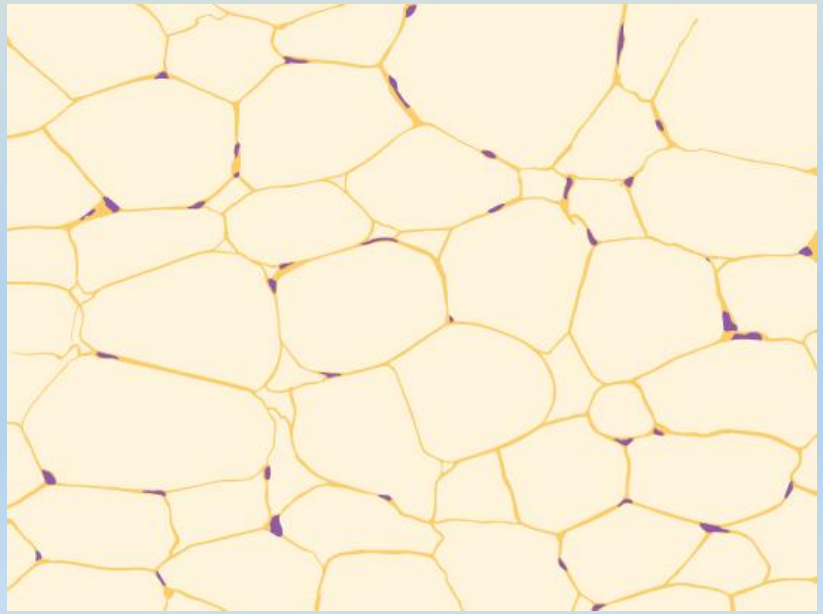


vasoconstriction

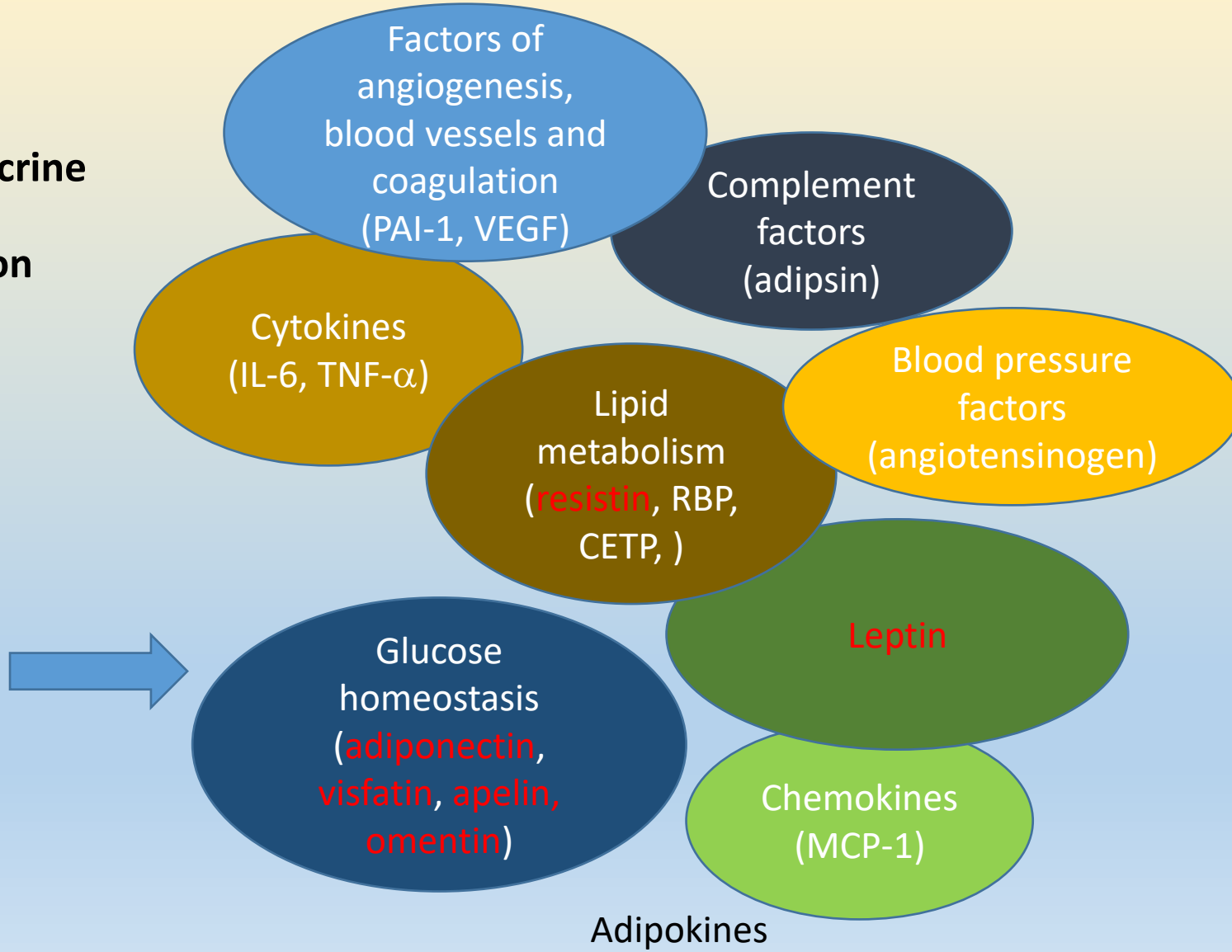


Endocrine organs

- **specialised cells – specialised organs („endocrine“)**
- **„secretory“ cells – organs with endocrine function**
- **cells without specialised secretory function**
- **cells converting hormone precursors**



adipose tissue



Adipokines

Clinical aspects

- Production of hormones by tumors – PARANEOPLASTIC SYNDROMES

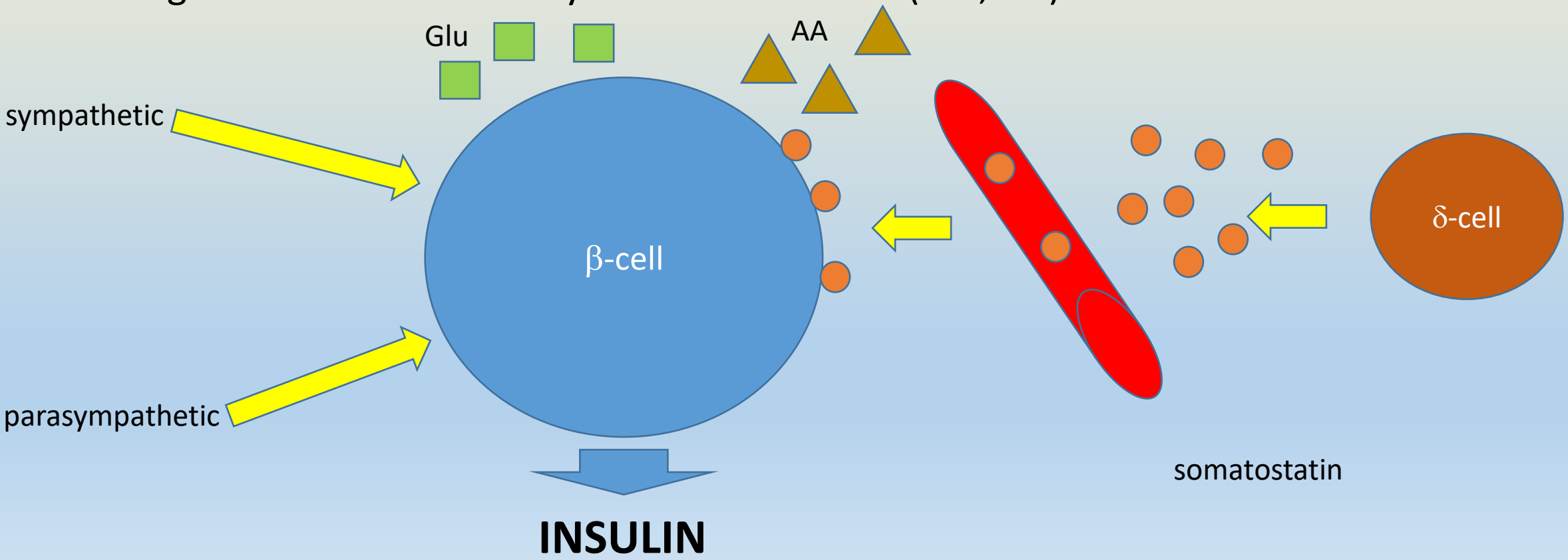
Lung tumors
– ADH (hyponatremia)
– ACTH (Cushing syndrome)
– PTHrP (hypercalcaemia)

Liver and kidney tumors
– erythropoietin (polycythemia)

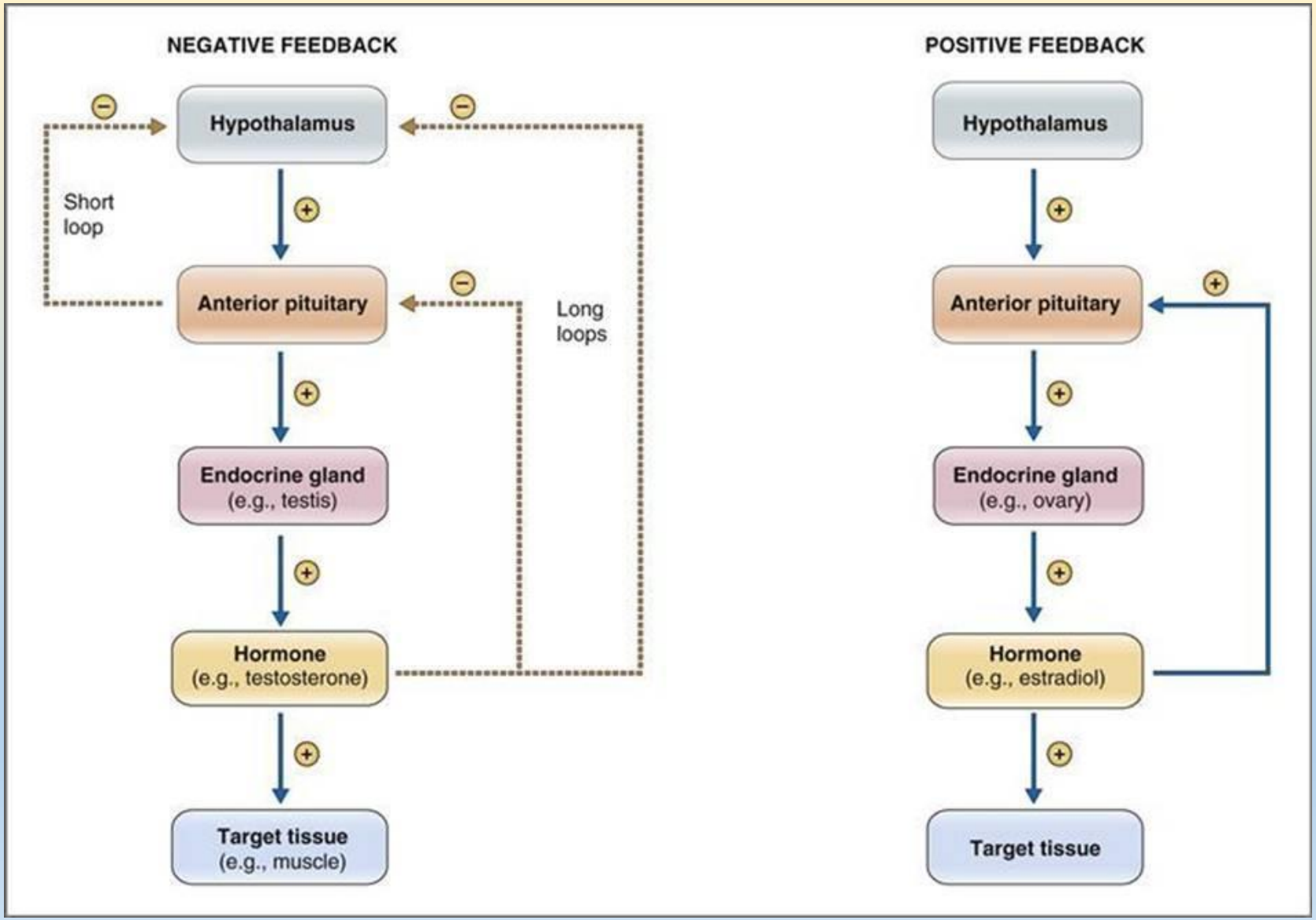
GIT tumors
– ACTH (Cushing syndrome)

Secretion of hormones and its regulation

- Neuronal control
  - hypothalamus
  - sympathetic/parasympathetic nervous system
- Hormonal control
- Regulation od secretion by ions or substrates (Glu, AA)

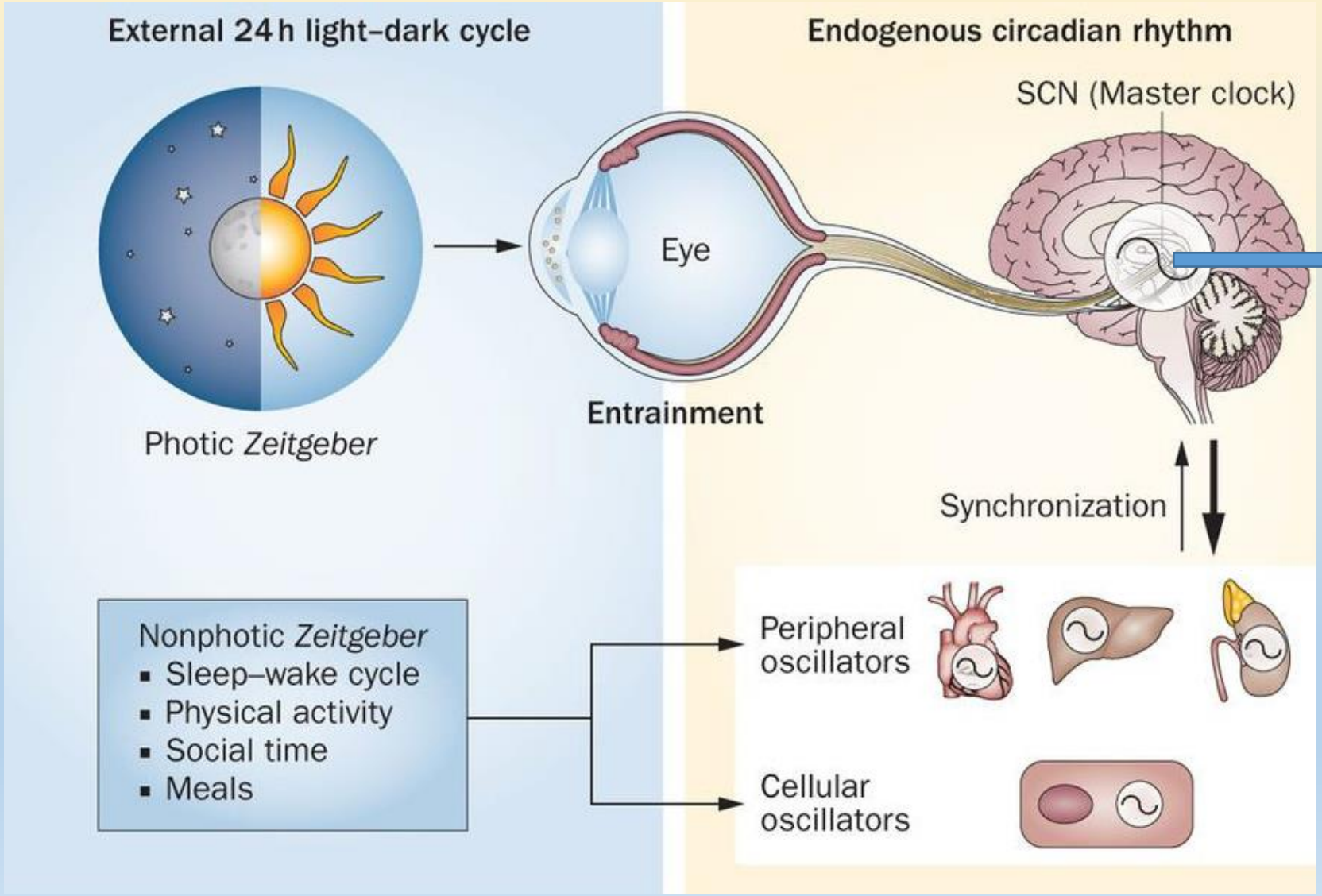


Hormone secretion is controlled by feedback system



Cyclic changes in hormone secretion

SCN:
- Afferent – retina
- Efferent – hypothalamic nucleus



- Melatonin
- GHRH/GHIH
- ADH
- ACTH
- Insulin
- Ghrelin
- Adiponectin
- Leptin

Neuronal/hormonal = SNC-dependent

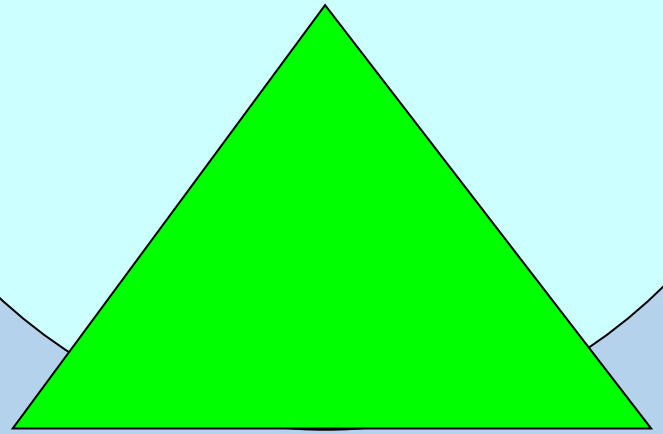
Satiety/fasting

Body temperature

Hormone transport

- Physico-chemical properties
- Transport protein(s)
  - Albumin
  - Globulins
  - Specific proteins – TBG, SHBG, CBG
- Bond strength
- „Alternative“ binding – TBG versus transthyretin

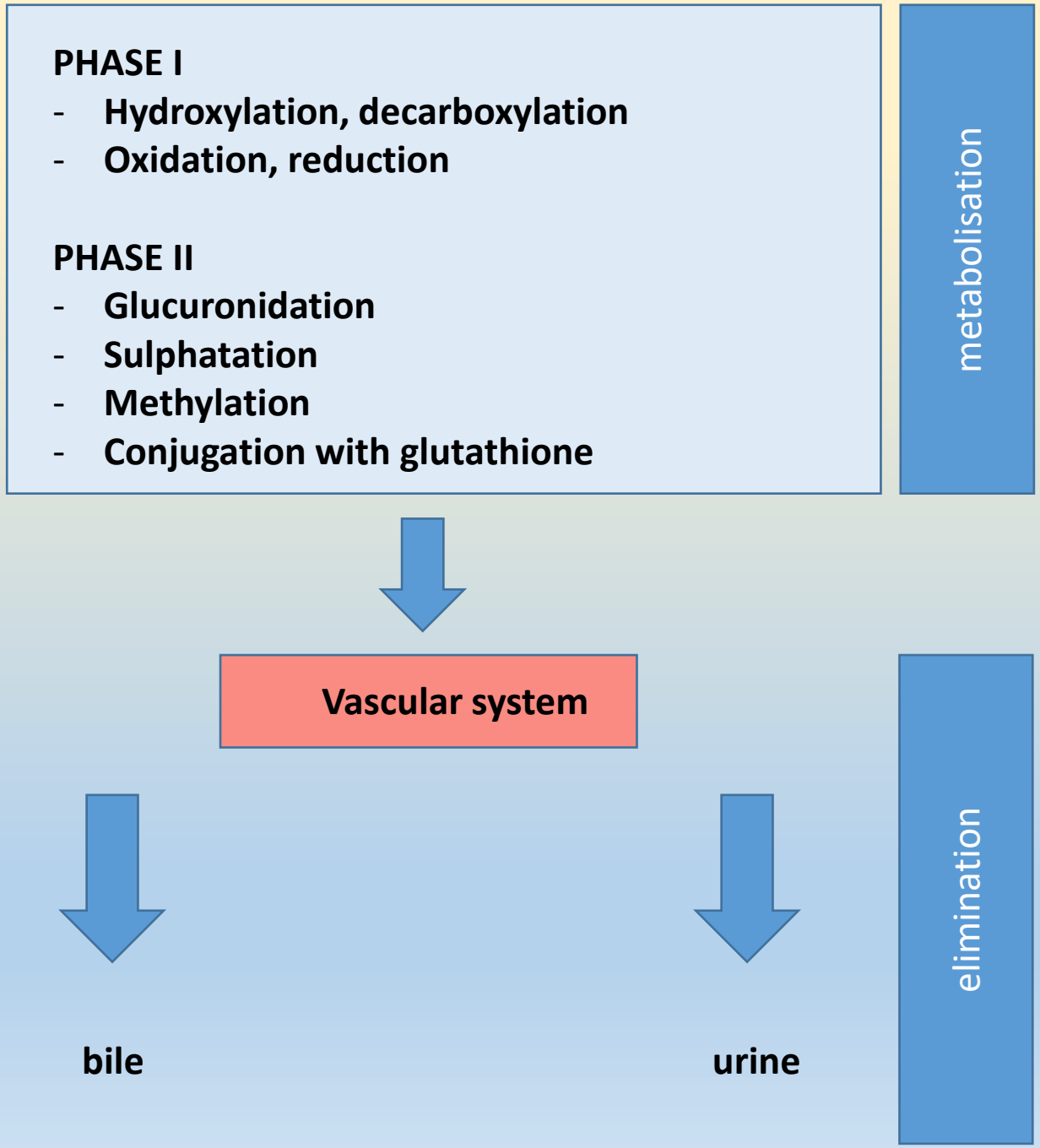
- Protection
- Reservoir
- Ubiquitous distribution
- Transport across plasmatic membrane (SHBG – megalin)



DYNAMIC BALANCE BETWEEN HORMONE AND TRANSPORT PROTEIN

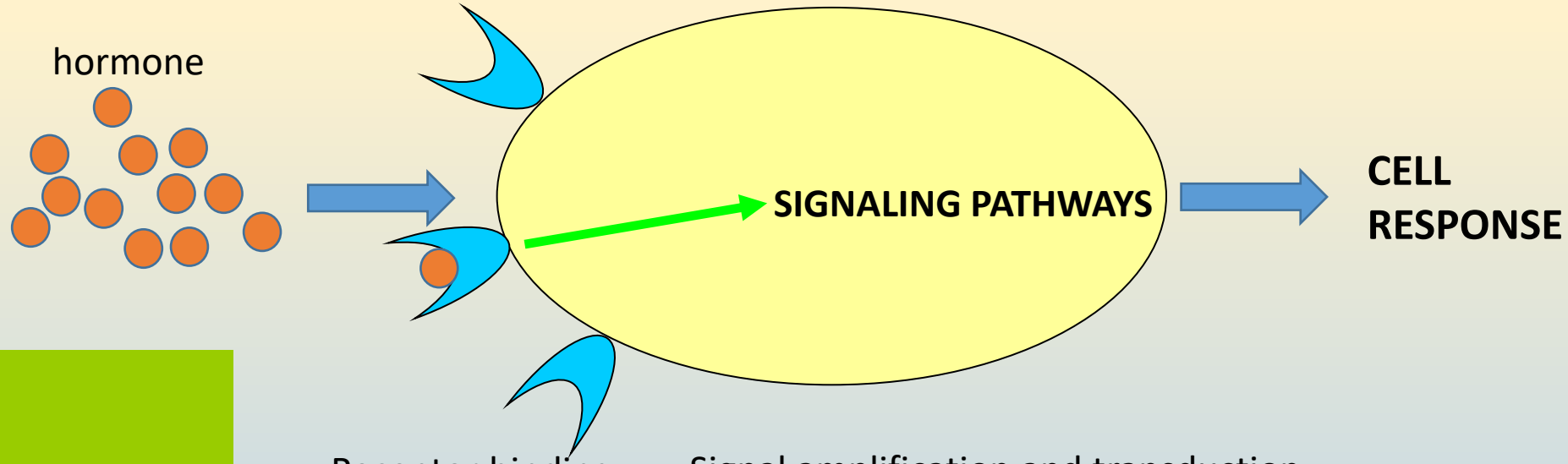
Hormone elimination

- Different length of time in circulation
- Metabolisation by
  - Target cells
  - Enzymatic systems in blood
  - Organs – mainly liver
- Elimination
  - Liver
  - Kidneys



Hormones and cell response

- Target cells
- Specificity
- High affinity
- Selectivity



MECHANISMS
Conformation changes
Phosphorylation/dephosphorylation + protein recruitment
GTP binding (G proteins)
cAMP binding (efector proteins)
Precursor molecule generation in PM
Non-covalent Ca^{2+} bond

Receptor binding

% of occupied receptors
conformation change

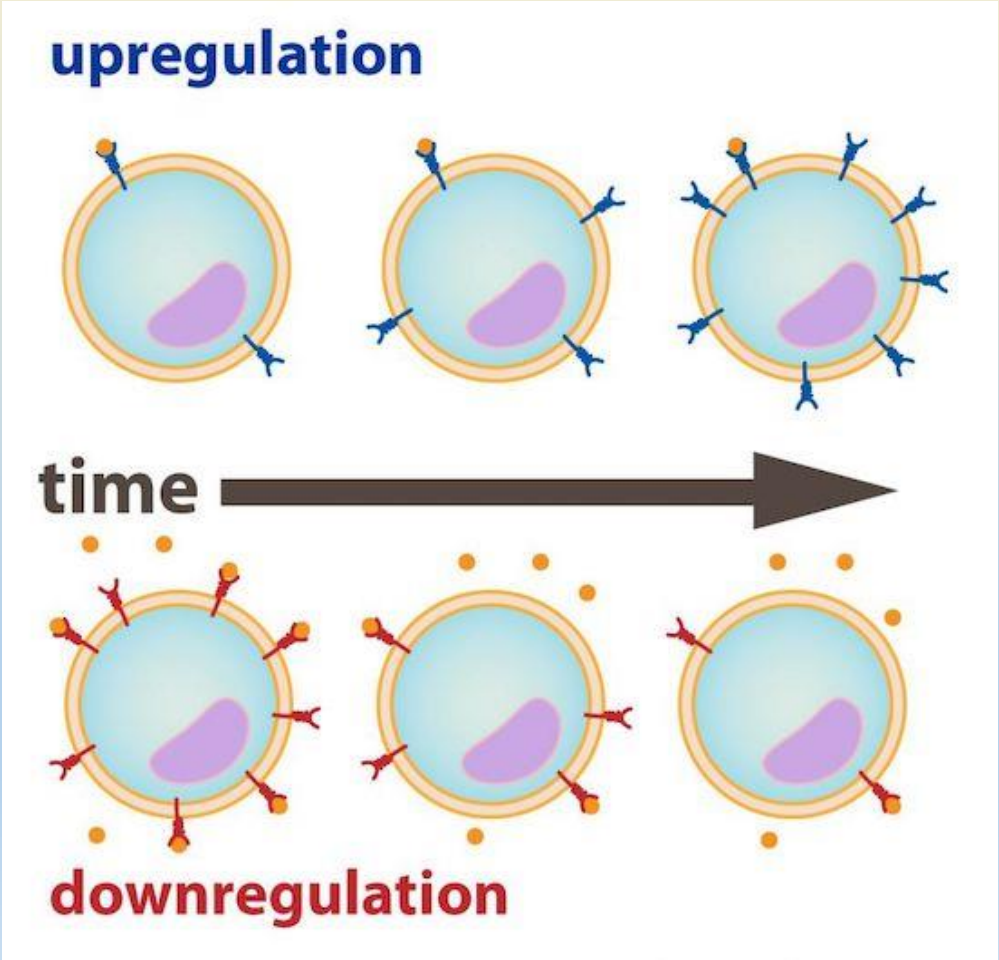
Signal amplification and transduction efector molecules

synergy
antagonism
possible loss of sensitivity
feedback-loop regulation

CELL RESPONSE IS MEDIATED BY RELEVANT RECEPTORS

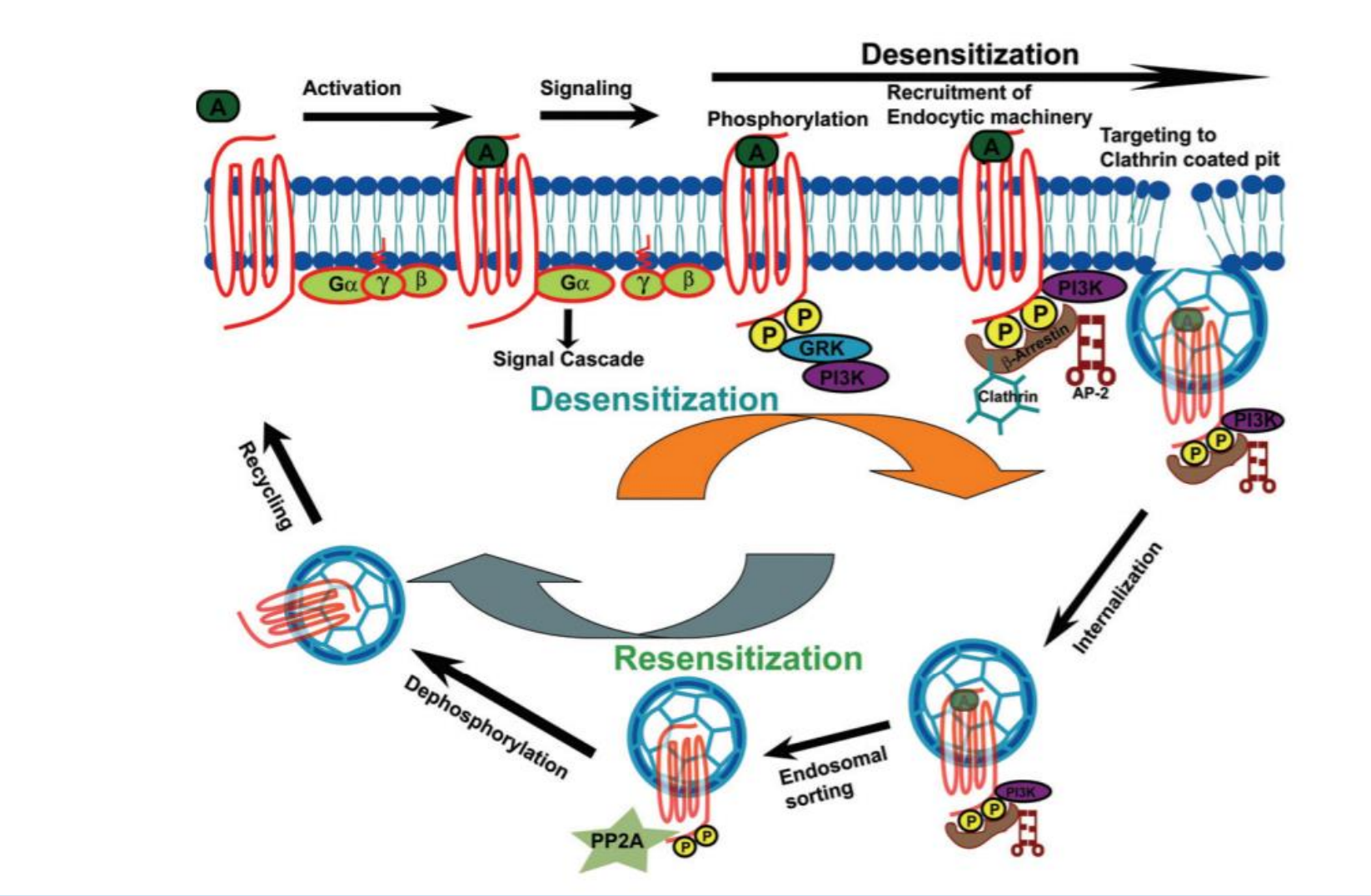
Regulation of cell response at receptor level

Downregulation versus upregulation

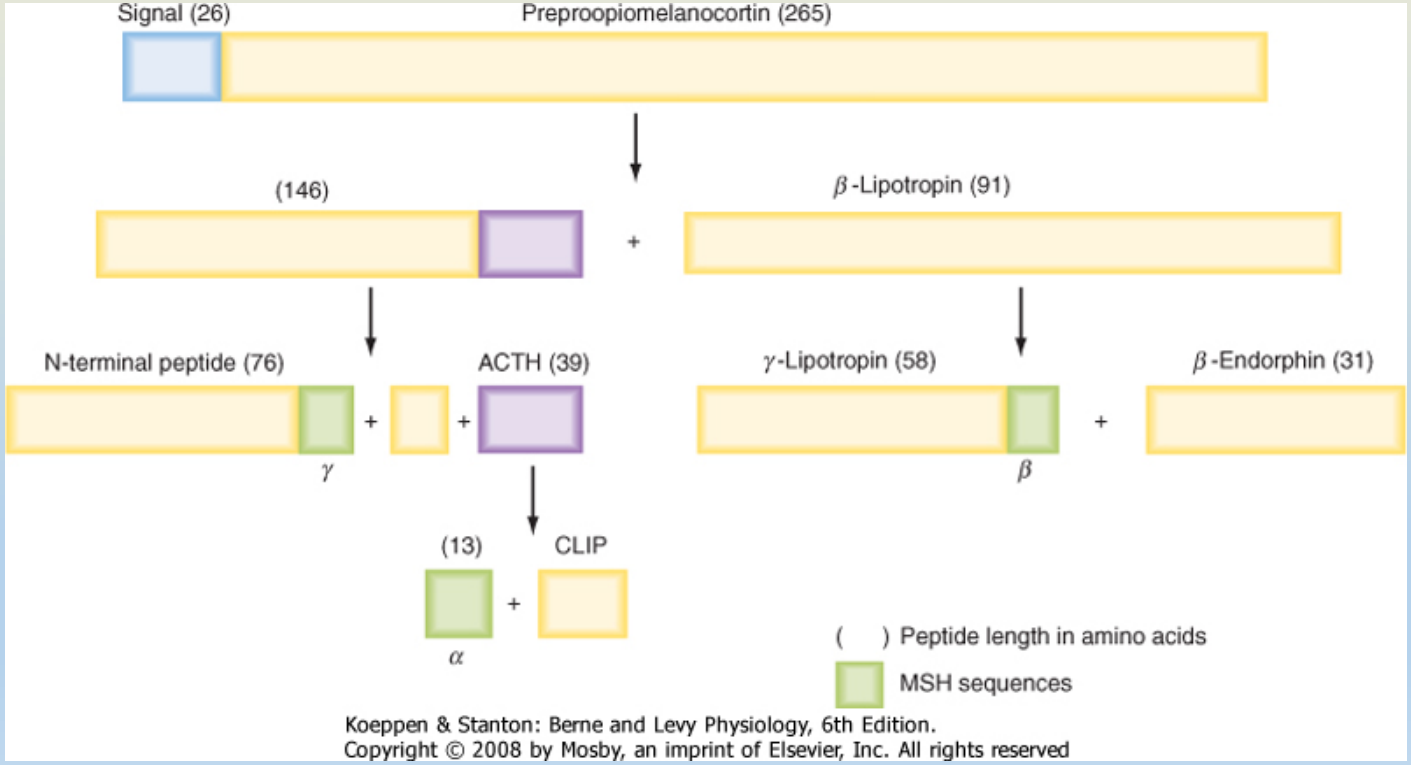


Regulation of cell response at receptor level

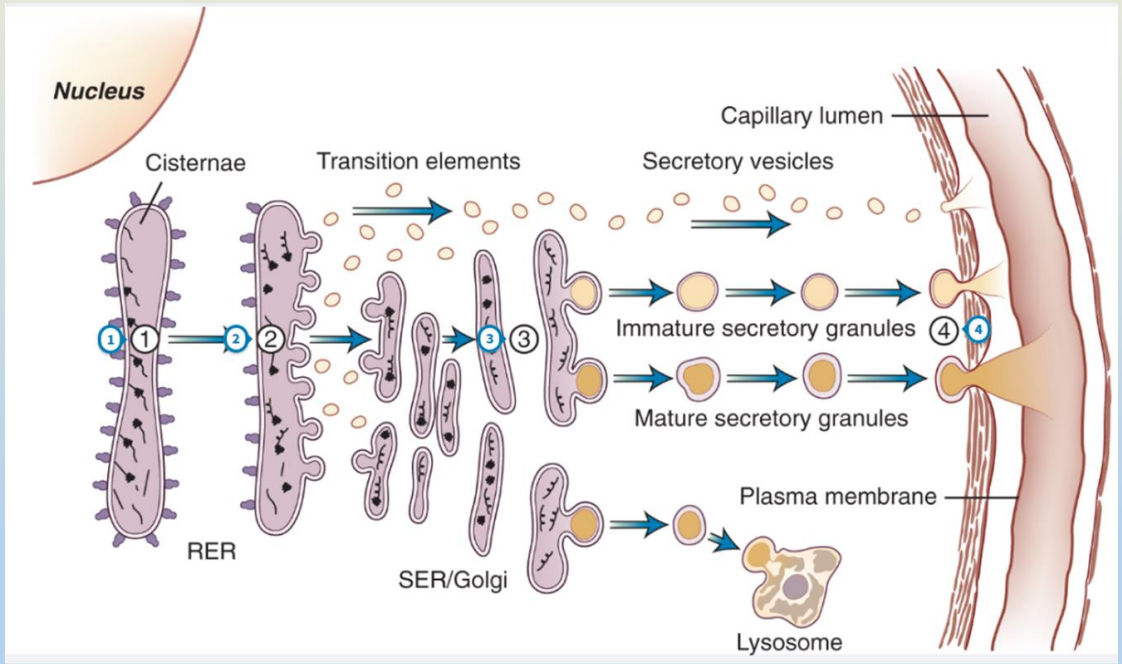
Homologous desensitization („with ligand“) X Heterologous desensitization („without ligand“)



Hormones – proteins and peptids



Koeppen & Stanton: Berne and Levy Physiology, 6th Edition.



preprohormone – prohormone – hormone (+ fragments)

G protein-coupled receptors (GPCR)

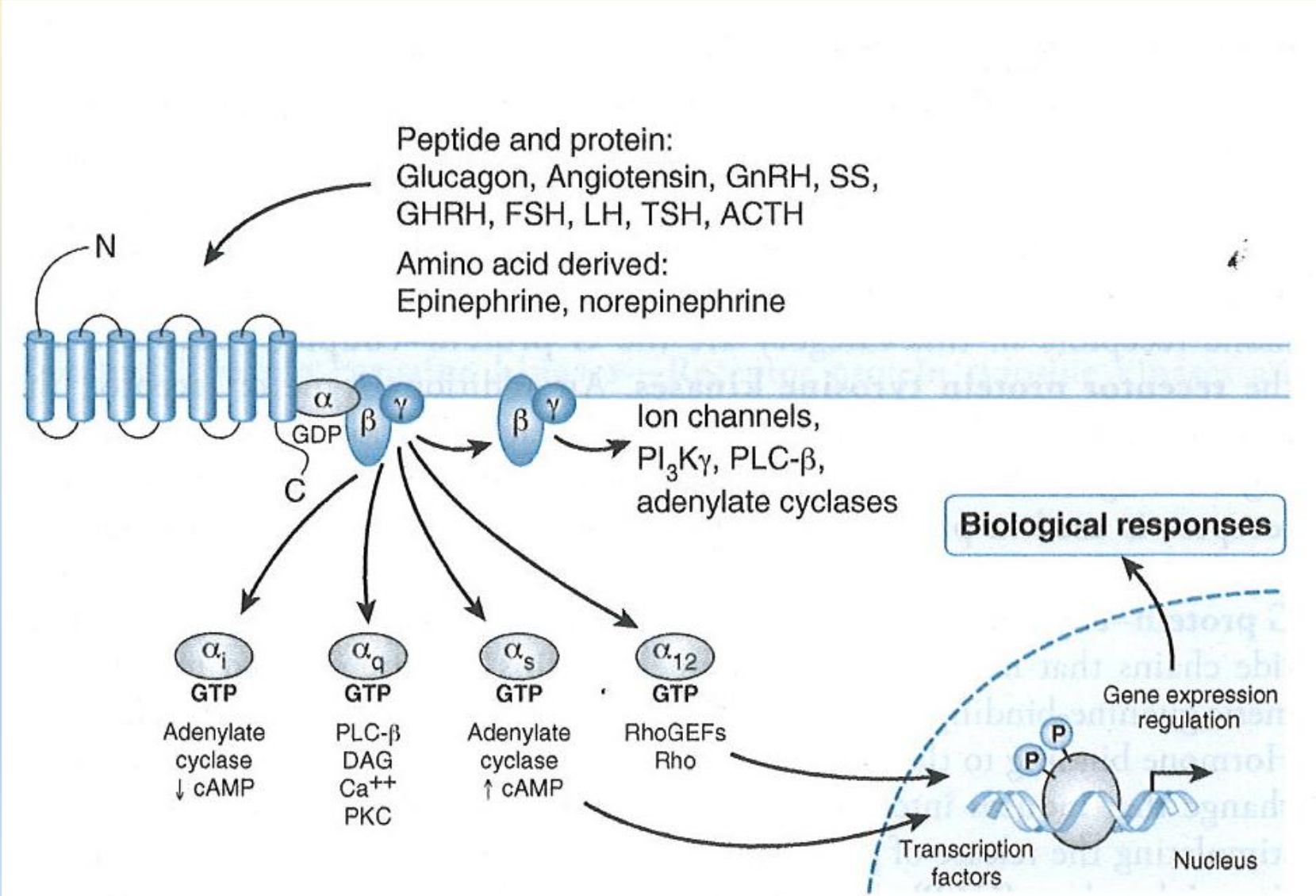
G_s – G_s, G_{olf}

G_i

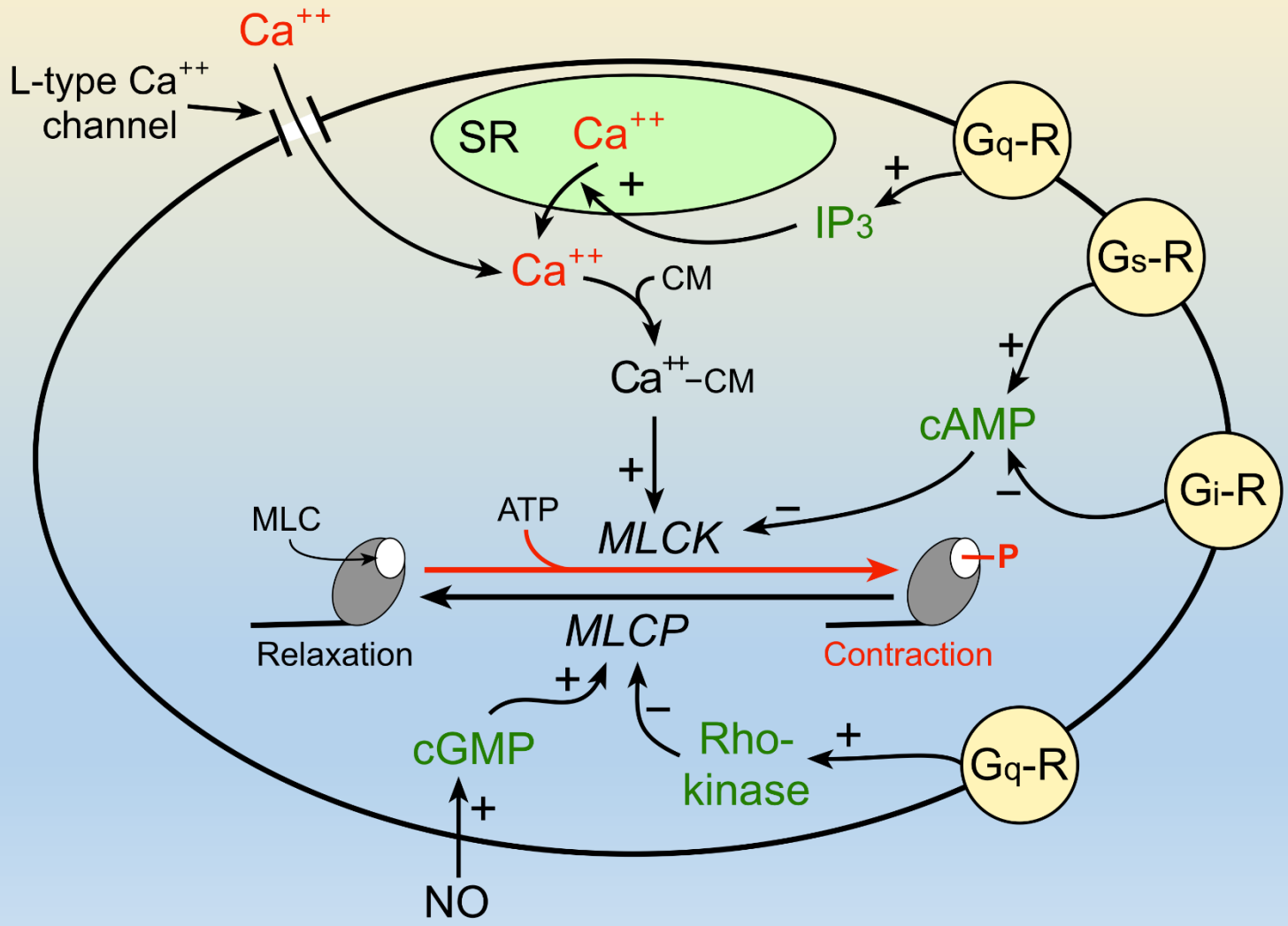
- G_0 (2, brain)
- G_t (2, photorec. – cAMP-PDE)
- G_z (inhibition of K^+ channels)

$G_{q/11}$

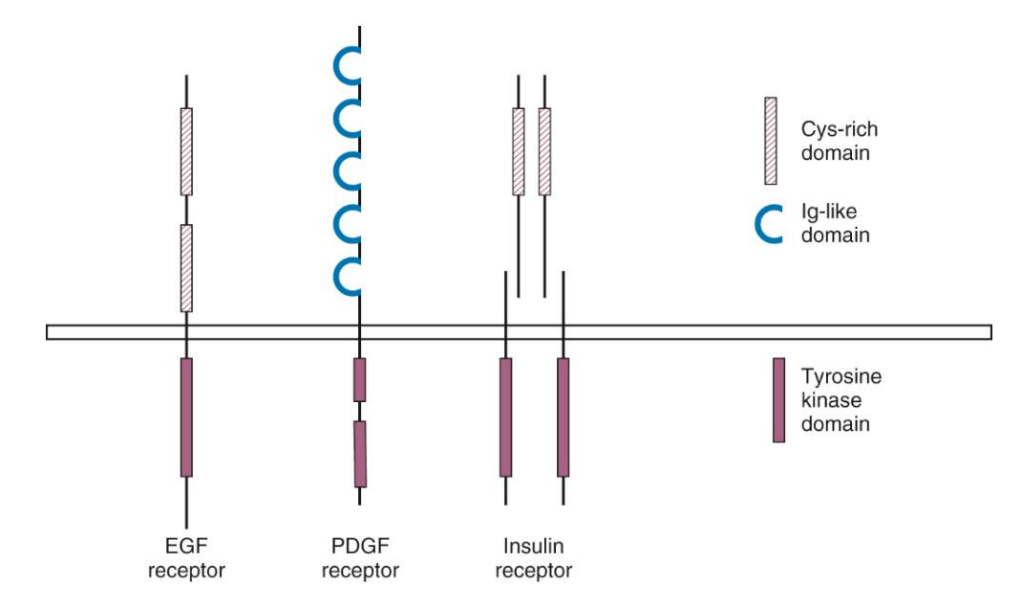
$G_{12/13}$

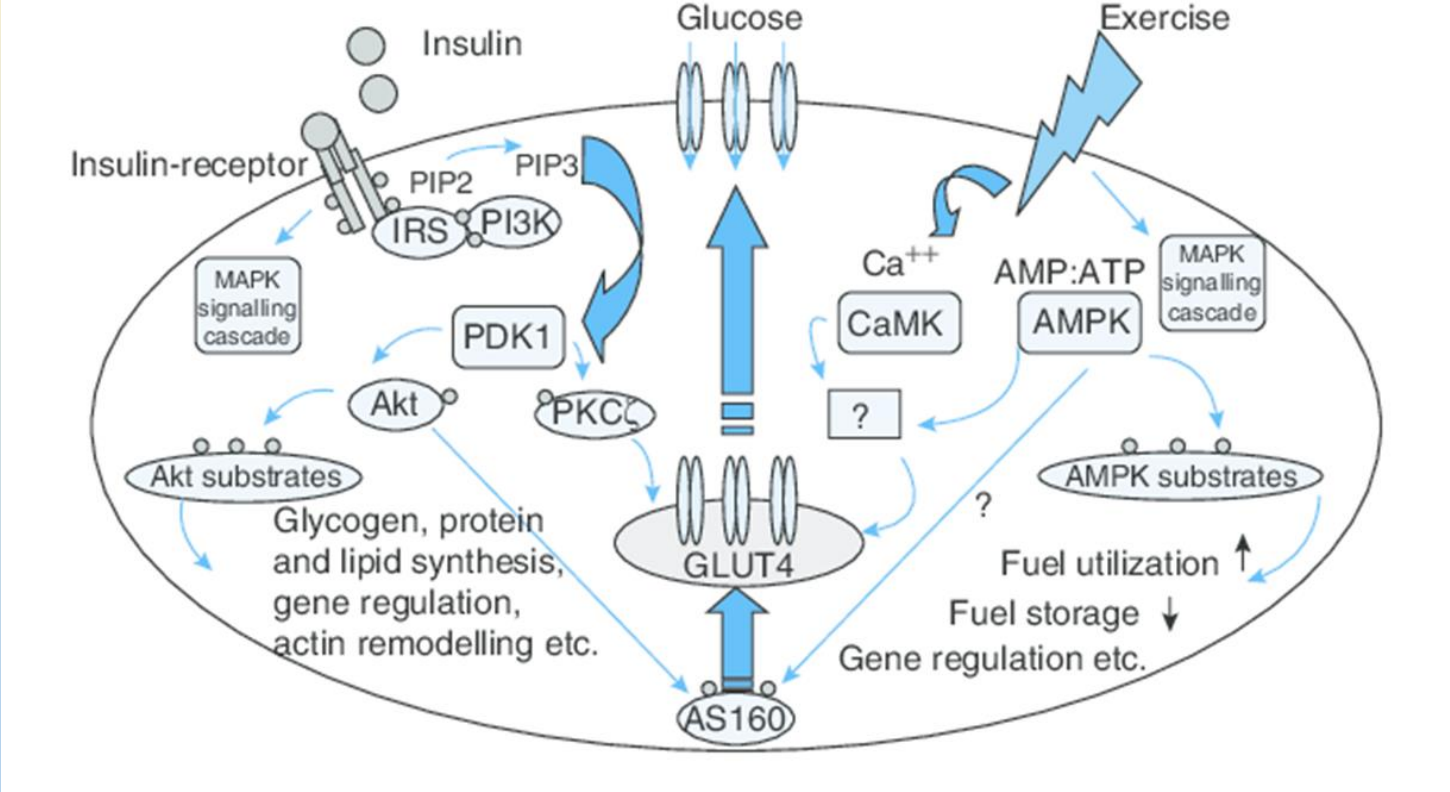


Example – G-protein coupled receptors and smooth muscle



Receptor tyrosinkinases

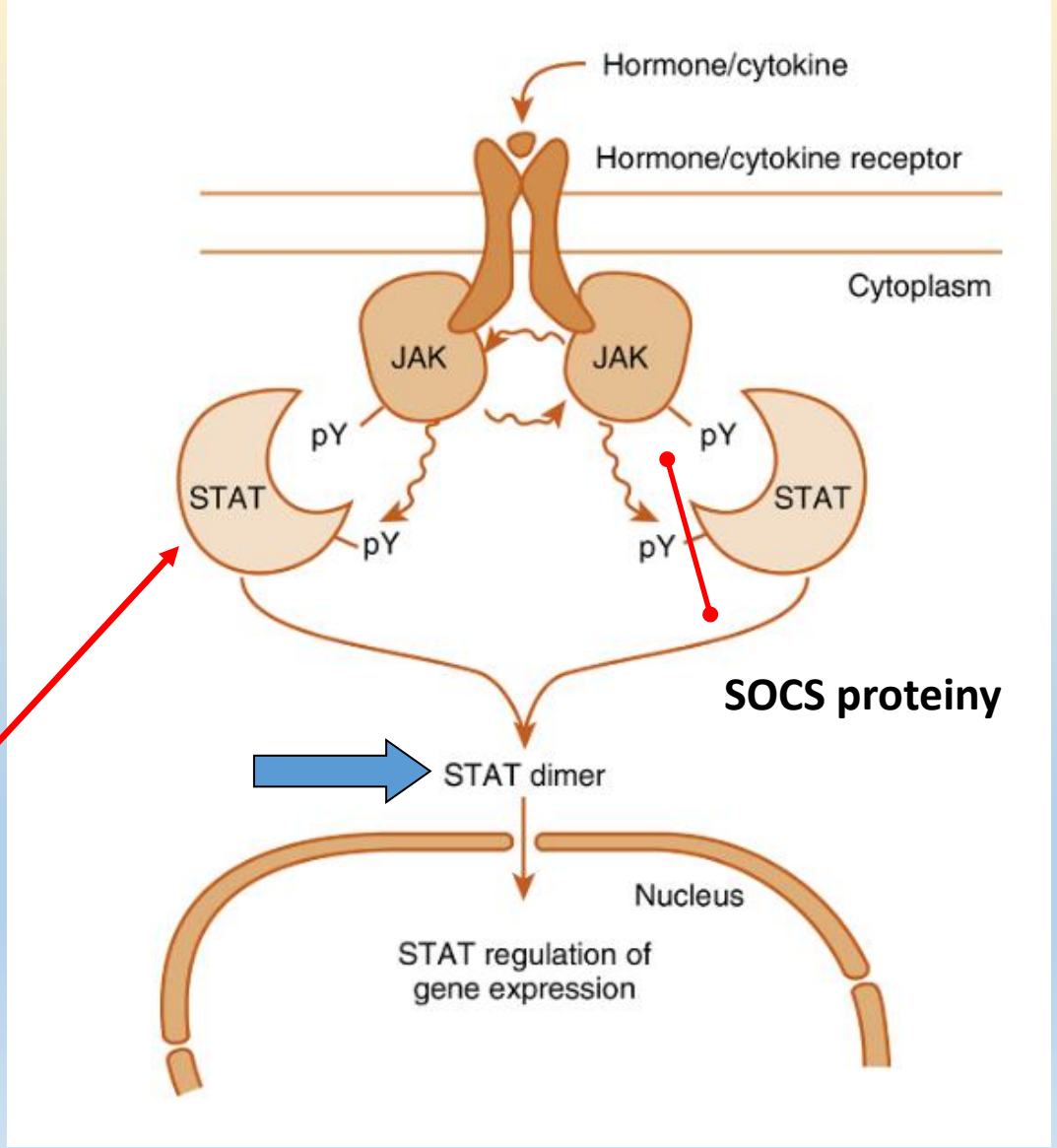




Receptors associated with cytosolic TK

- GH
- Prolactin
- Leptin
- erythropoietin

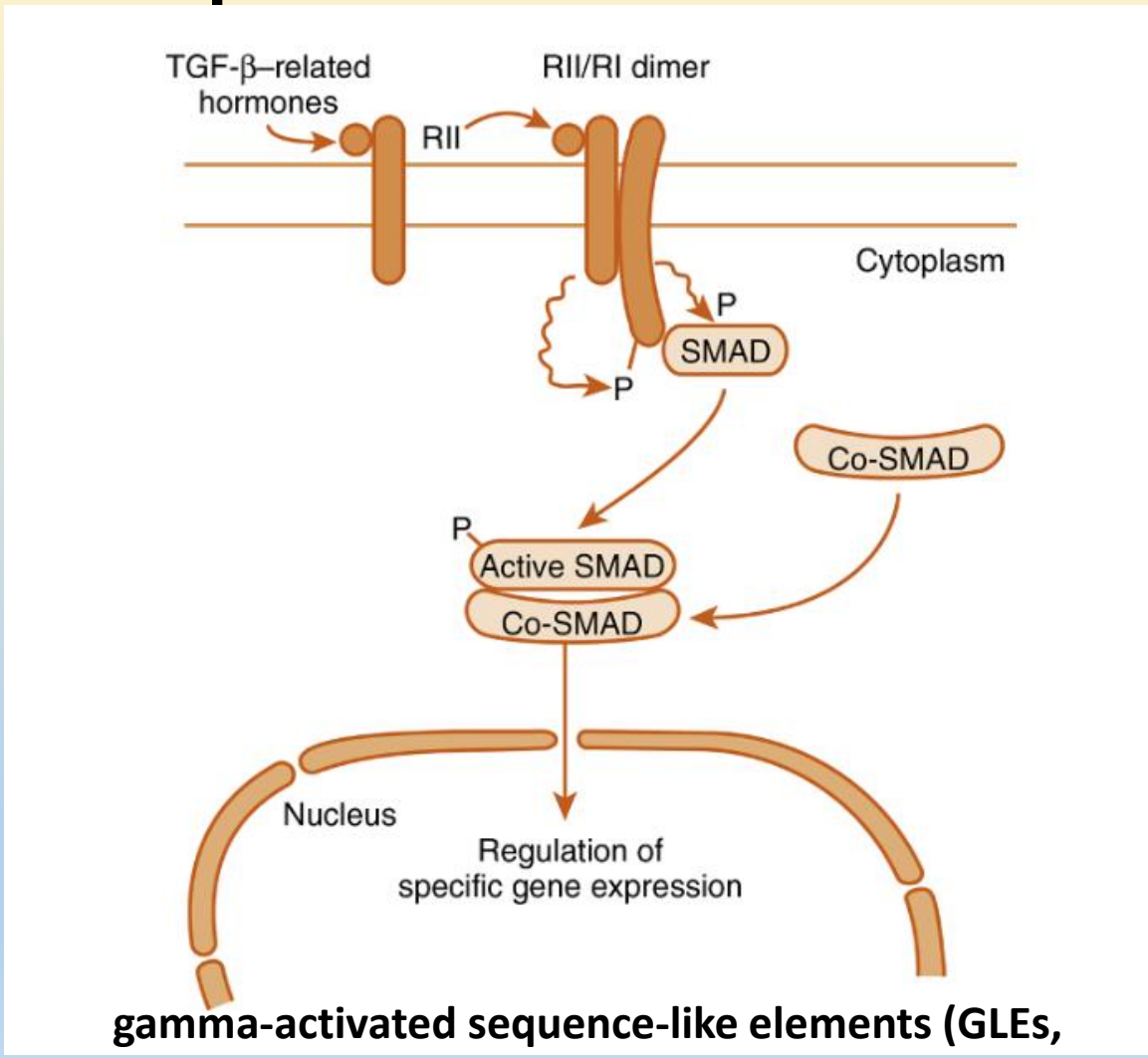
signal transducers and activators of transcription



Receptor serine/threonine protein kinases

- Anti-Müllerian hormone
- inhibitin

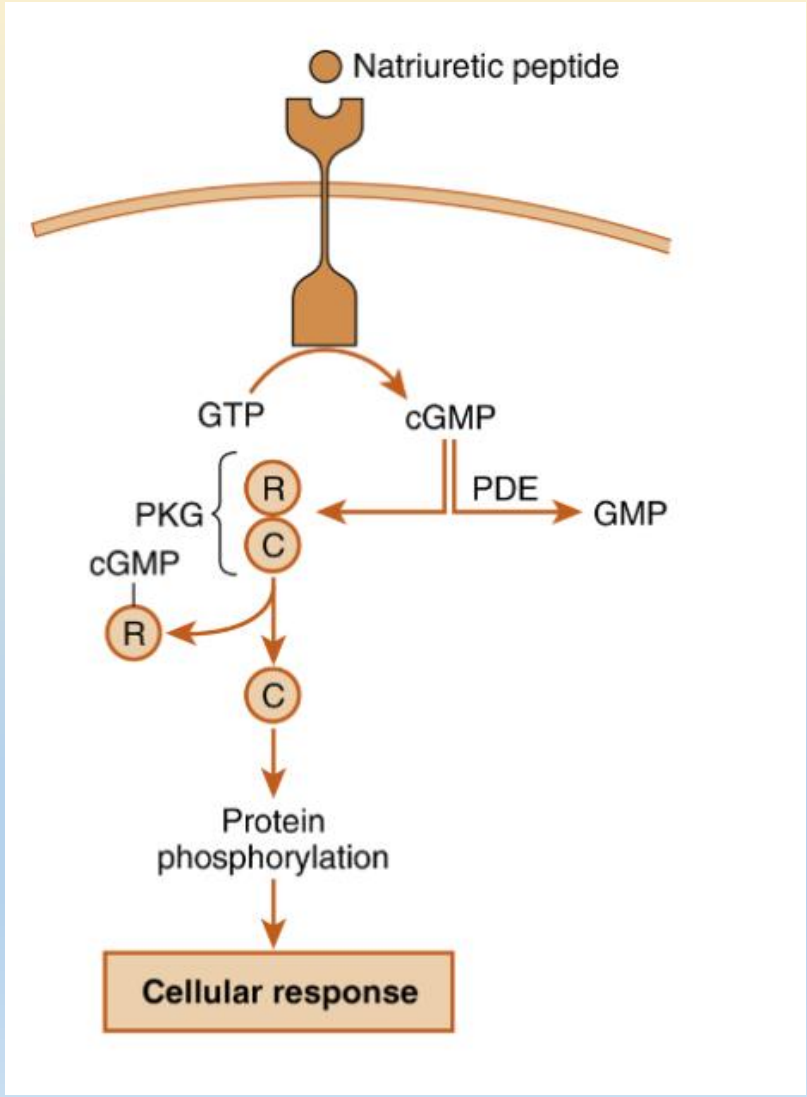
- SMAD = „latent transcription factors“



gamma-activated sequence-like elements (GLEs, promotor region of some genes)

Receptor guanylate cyclase

- Natriuretic peptides:
  - ANP, BNP, CNP



Signal transduction – system of second messengers

HORMONE = FIRST MESSENGER

INTRACELLULAR SIGNALING MOLECULE GENERATED AFTER HORMONE-RECEPTOR BONDING = SECOND MESSENGER

- cAMP
  - TSH, glucagon, ACTH, hypothalamic hormones, ADH etc.
  - Proteinkinase A
- Modulation of signaling pathways by compartmentalization (A-kinase anchoring proteins (AKAPs))

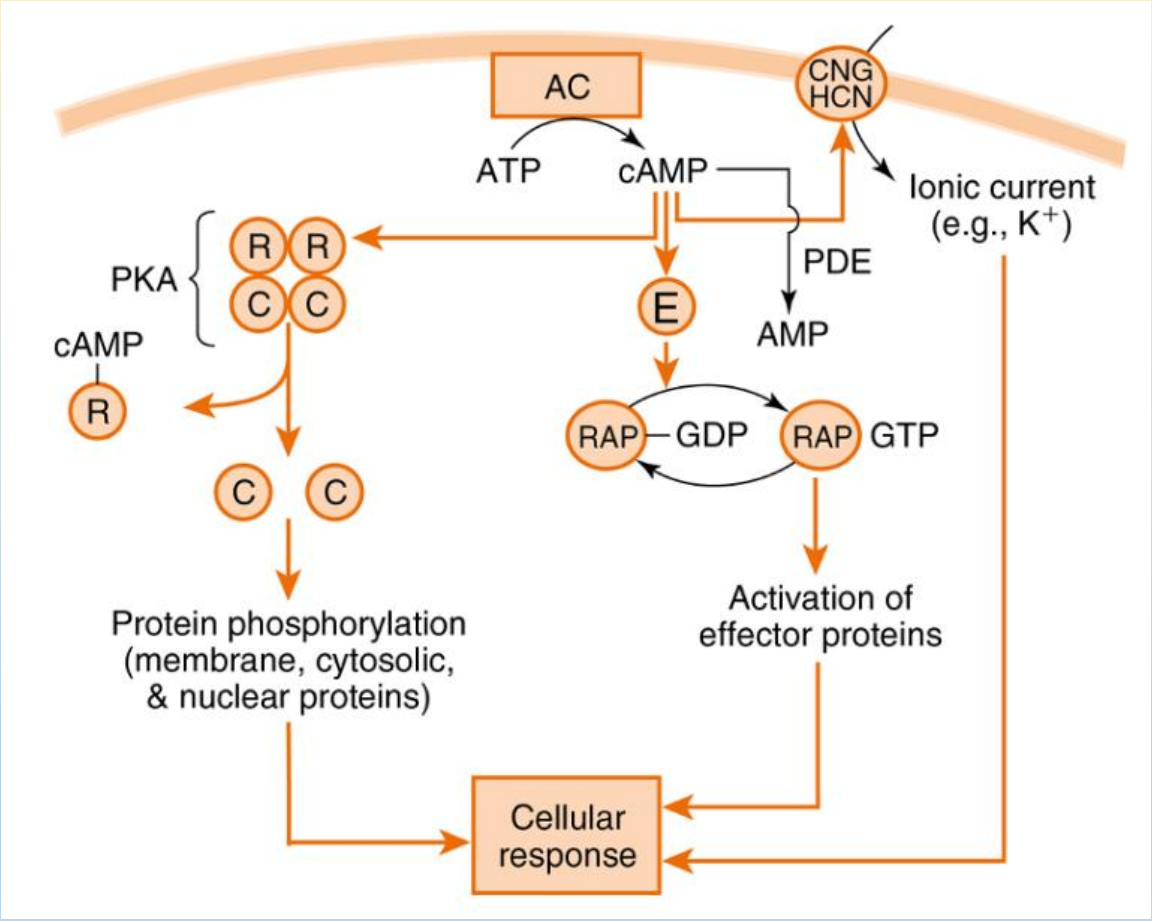
- cGMP
  - ANP, BNP, CNP
  - NO (sGC)
  - Proteinkinase G

- DAG and IP_3
  - PIP_2 – phospholipase C system

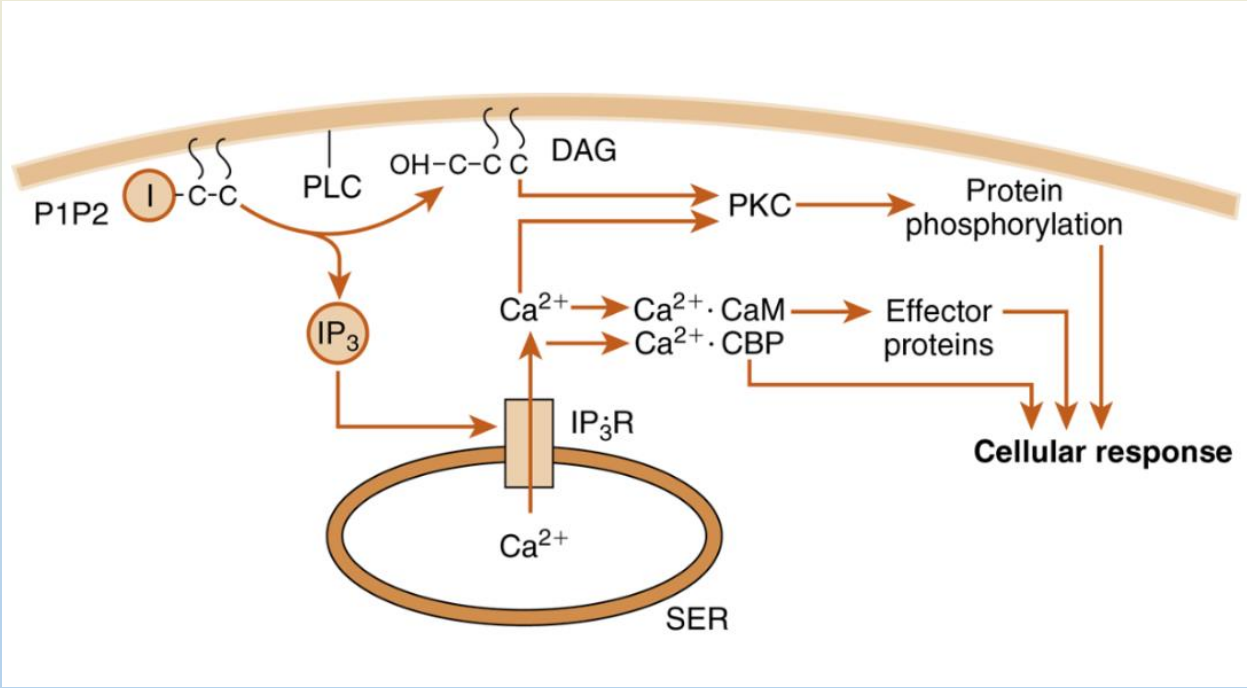
- Ca^{2+}
  - Ca^{2+}/Ca^{2+}- calmodulin

EXTRACELLULAR SIGNAL MUST BE CONVERTED TO INTRACELLULAR RESPONSE

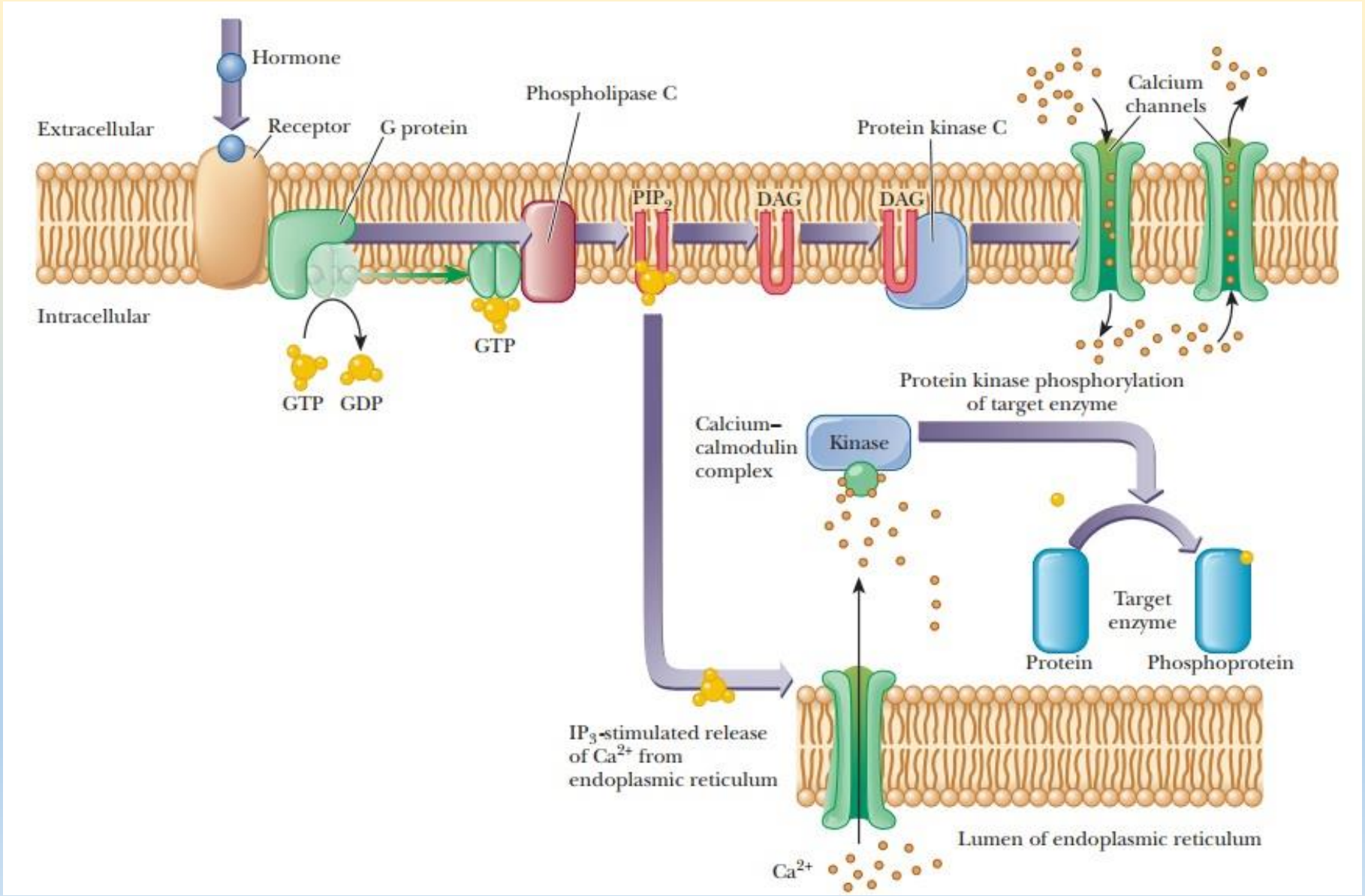
AC – cAMP system



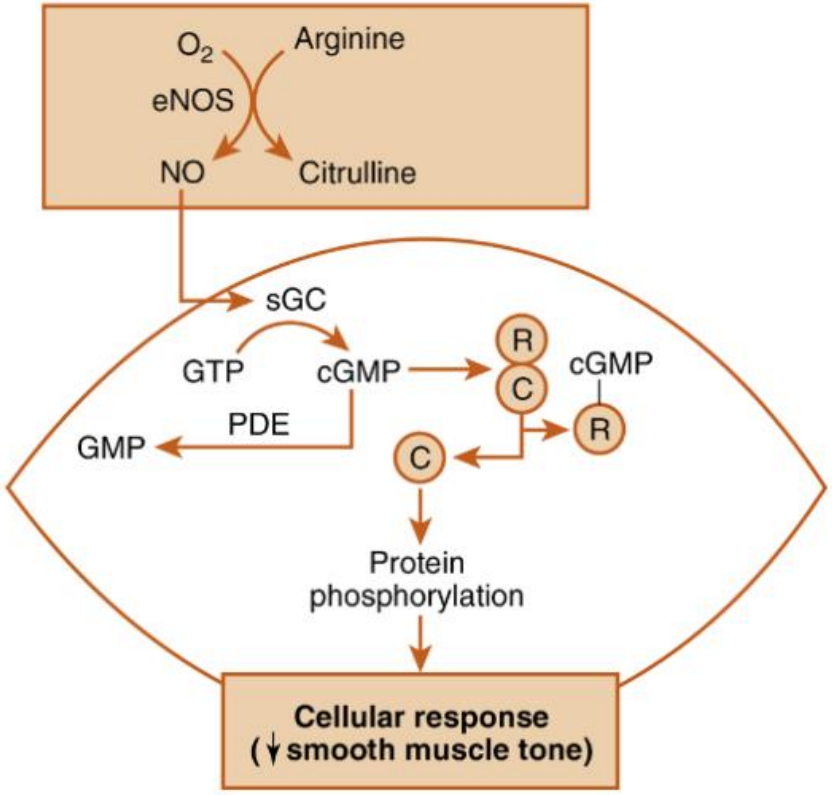
PLC - DAG and IP_3 system

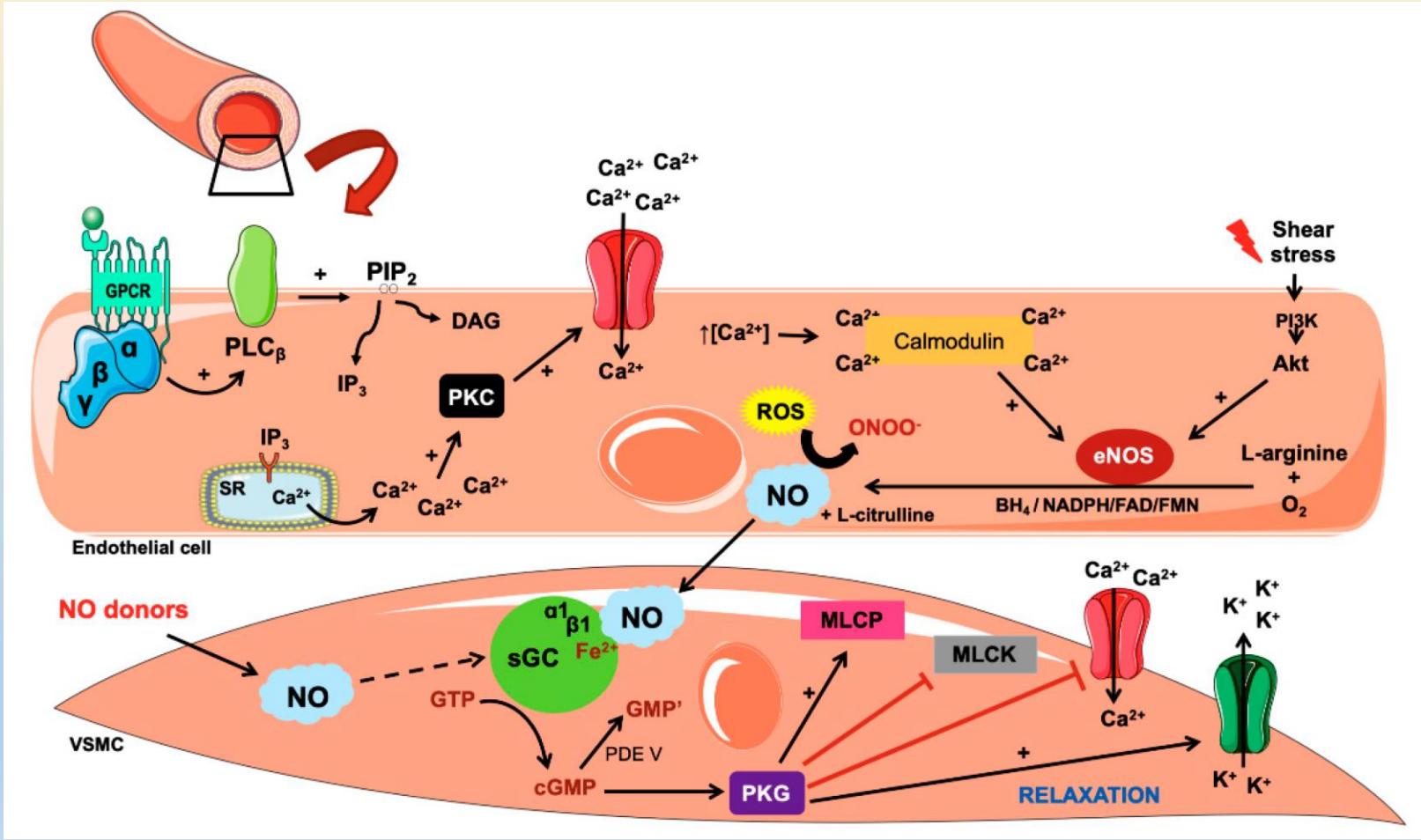


Ca^{2+} - calmodulin system



NO as a signalling molecule - cGMP





Clinical aspects

- Syndromes of resistance to hormones (i.e. IR, IGF-1, TRβ)

- Syndromes caused by CPCRs and G proteins mutations
  - ADH – nephrogenic diabetes insipidus
  - ACTH – familiar ACTH resistance
  - GnRH – hypogonadotrophic hypogonadism
  - FSH – hypergonadotrophic ovarial dysgenesis
  - LH – male pseudohermaphroditism
  - Melanocortin 4 – obesity
  - PTH/PTHrP – Blomstrand lethal chondrodysplasia

Hormones acting through nuclear receptors

HORMONES

-Thyroid hormones – TRα/β ← heterodimers

-Estrogens – ERα/β

-Testosterone - AR

-Progesterone - PR

-Aldosterone - MR

-Cortisol - GR

homodimers

PRODUCTS OF METABOLISM AND XENOBIOTICS

-Fatty acids– PPAR α, β, γ

-Oxysterols – liver X receptor LXR α, β

-Bile acids - BAR

-Hem – RevErb α, β

-Phospholipids – homologue of liver receptor LRH-1, SF-1

-Xenobiotics – pregnane X receptor PXR

- constitutive androstane receptor CAR

VITAMINS

-1,25-[OH]2D3 - VDR

-All-*trans*-retinoic acid – RA receptors α, β, γ

-9-*cis*-retinoic acid – retinoid X receptor RXR α, β, γ

-Orphan receptors

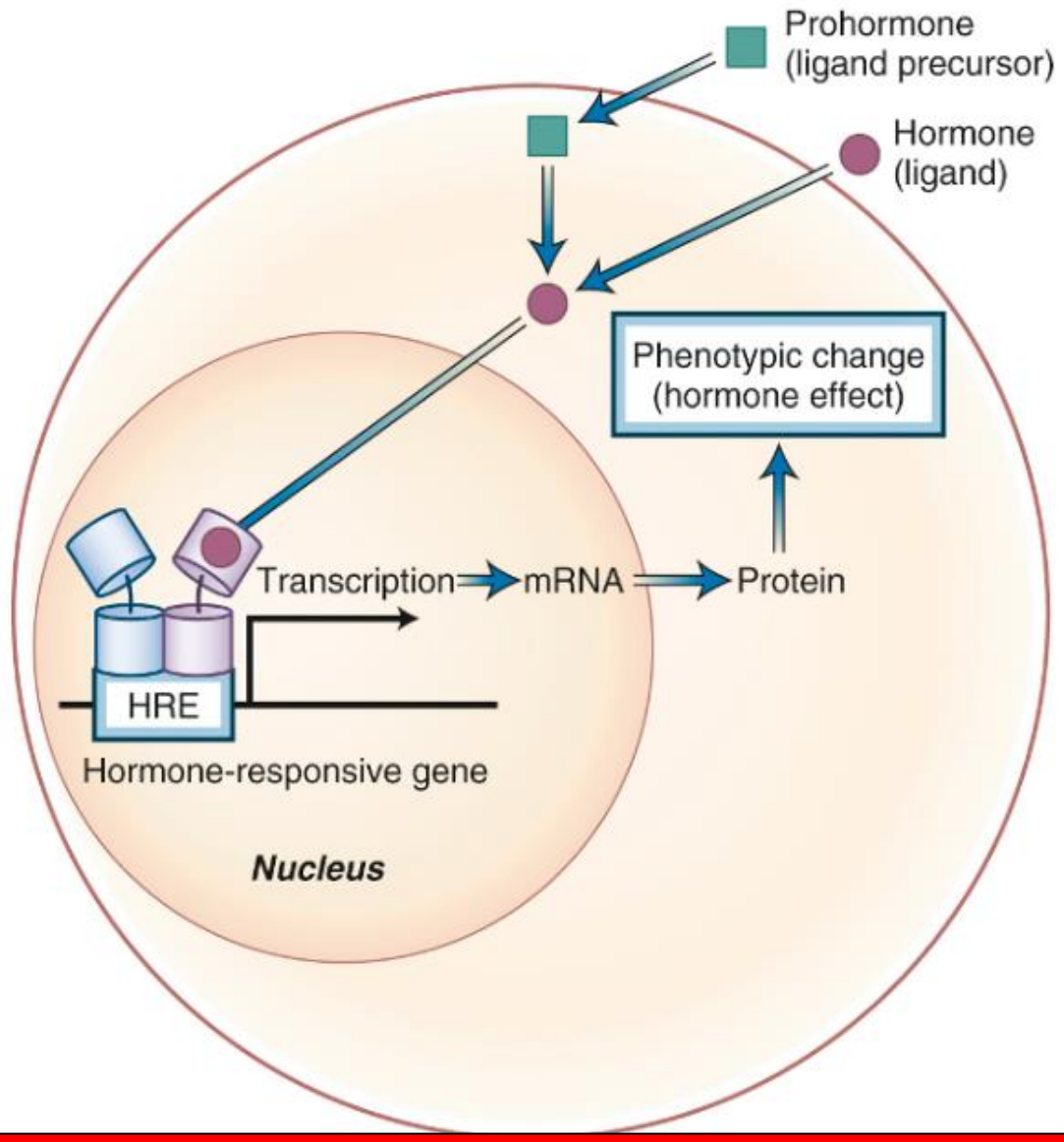
-Variable receptors

Explanation of some effects and pathologies

General mechanism of effect of hormones acting through nuclear receptors

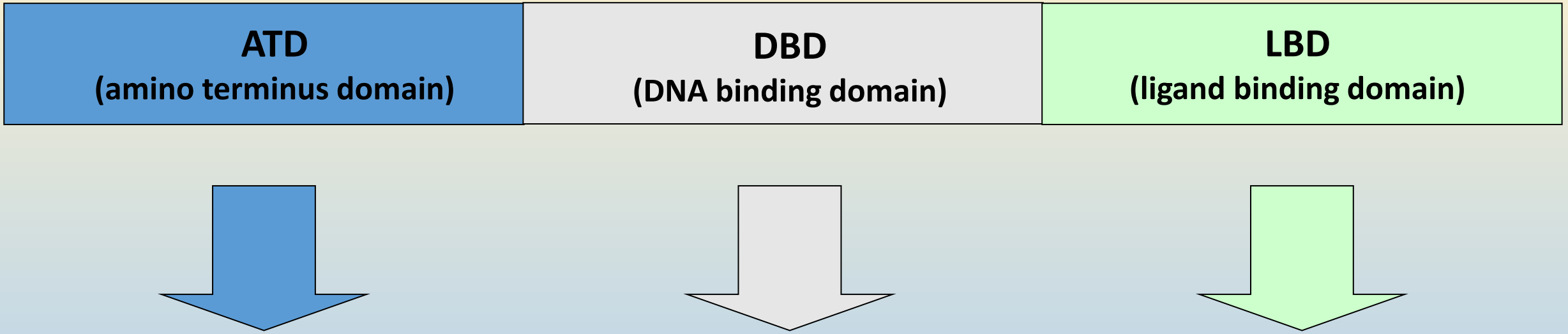
-High affinity of ligand bond = due to R structure
-Recognition of specific promotor region
-Dimerisation of receptors (homodimers, heterodimers)
-Remodelation of chromatin for gene expression (HDAC)
-Gene expression at the end decreased or increased

WHY ONLY NUCLEAR RECEPTORS?
-Synthesis in cytoplasm
-Stay until ligand binding or until transport to nucleus



-Regulation mechanism – modification, count of receptors
-Important parameter – selectivity of target cells
-Tissue-specific factors, coactivators and corepressors

Nuclear receptors

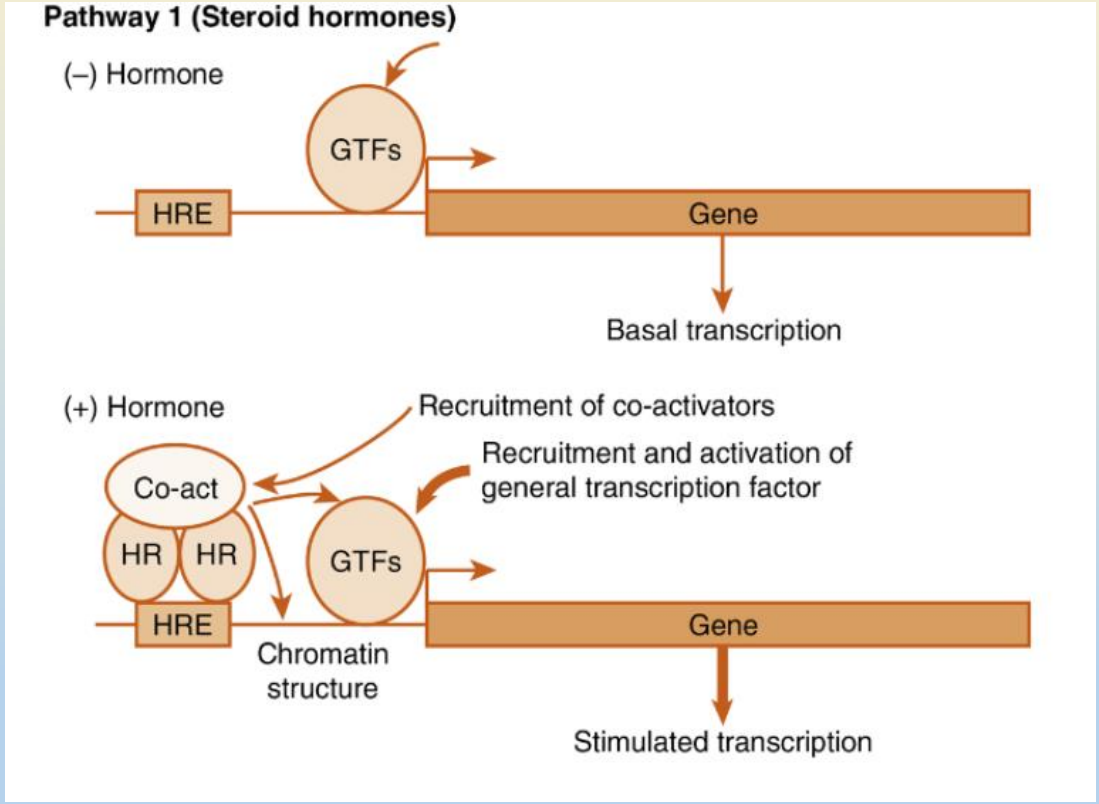


-Coregulatory proteins binding (independent on ligand)
- Phosphorylation sites

-DNA binding (zinc fingers)
-Dimerisation
-ERE, PRE, GRE, MRE, ARE

-Ligand binding (agonist, antagonist)
-Coregulatory proteins binding (dependent on ligand)
-Dimerisation
-Nuclear translocation
-Chaperone association (HSP)

Example – steroid hormones X thyroid hormones

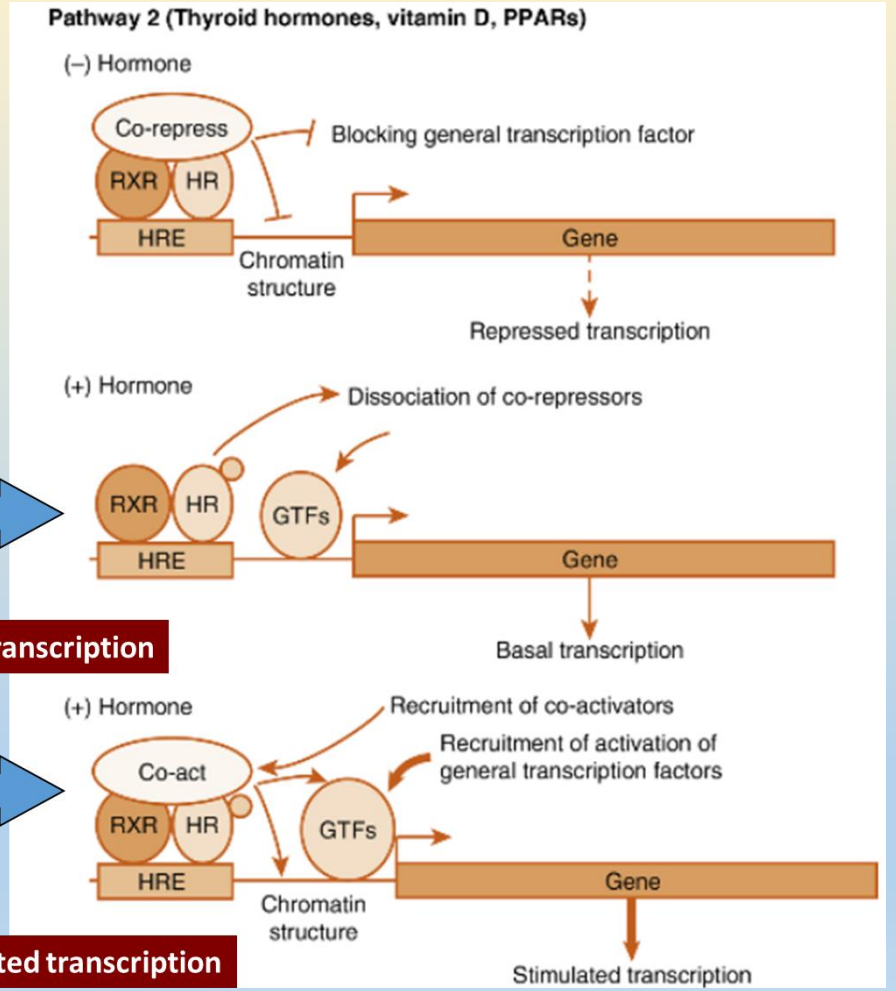


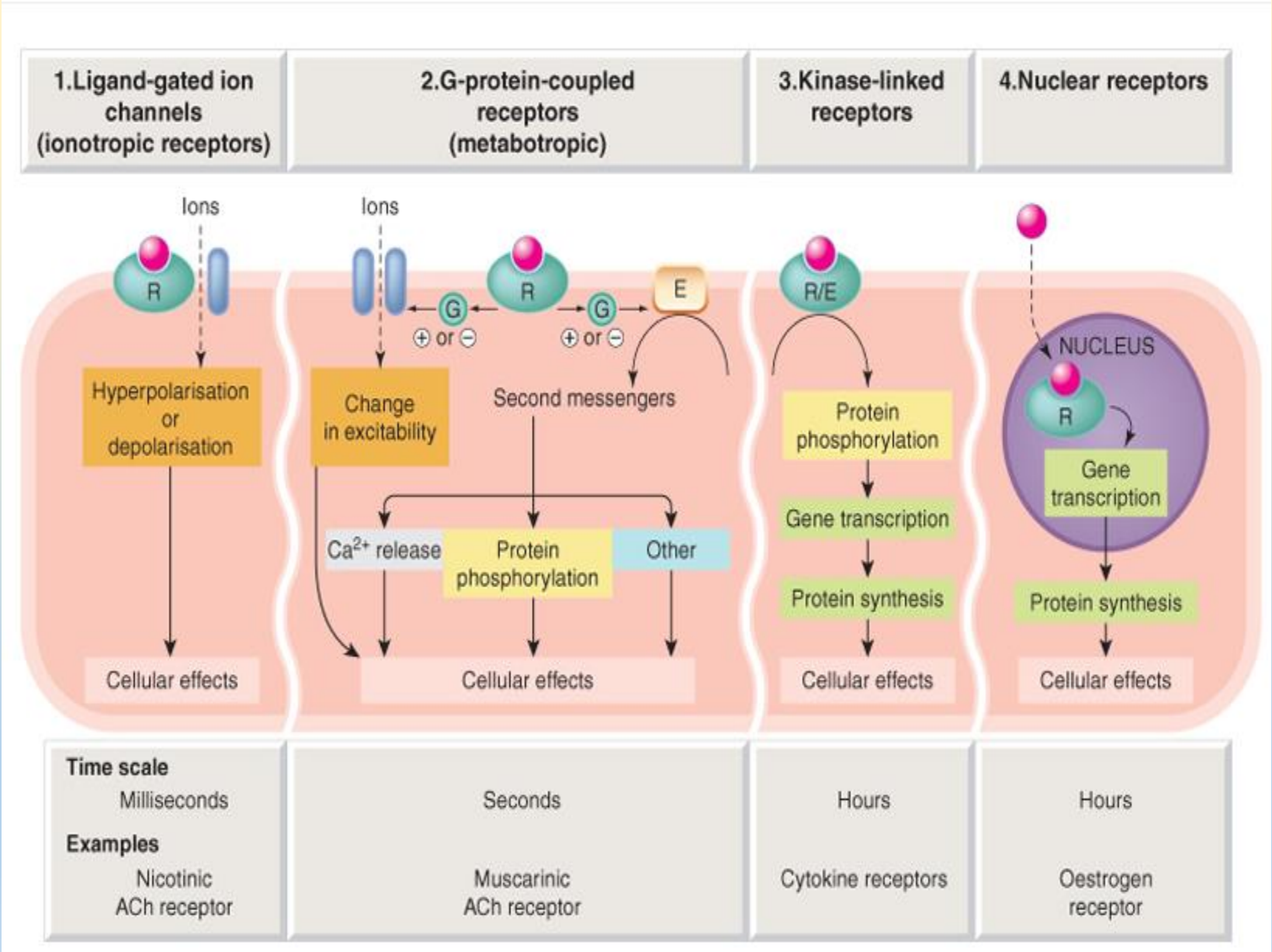
hormone

basic transcription

hormone + RA

stimulated transcription




1.Ligand-gated ion channels (ionotropic receptors)
2.G-protein-coupled receptors (metabotropic)
3.Kinase-linked receptors
4.Nuclear receptors
Ions
Ions
R
G
R
G
E
⊕ or ⊖
⊕ or ⊖
R/E
NUCLEUS
R
Hyperpolarisation or depolarisation
Change in excitability
Second messengers
Protein phosphorylation
Gene transcription
Gene transcription
Ca2+ release
Protein phosphorylation
Other
Protein synthesis
Protein synthesis
Cellular effects
Cellular effects
Cellular effects
Cellular effects
Time scale
Milliseconds
Seconds
Hours
Hours
Examples
Nicotinic ACh receptor
Muscarinic ACh receptor
Cytokine receptors
Oestrogen receptor

Termination of hormone action

Receptor-mediated endocytosis and subsequent lysosome degradation

Phosphorylation/ dephosphorylation of receptor or proteins of signaling pathway

Ubiquitination and proteosomal degradation

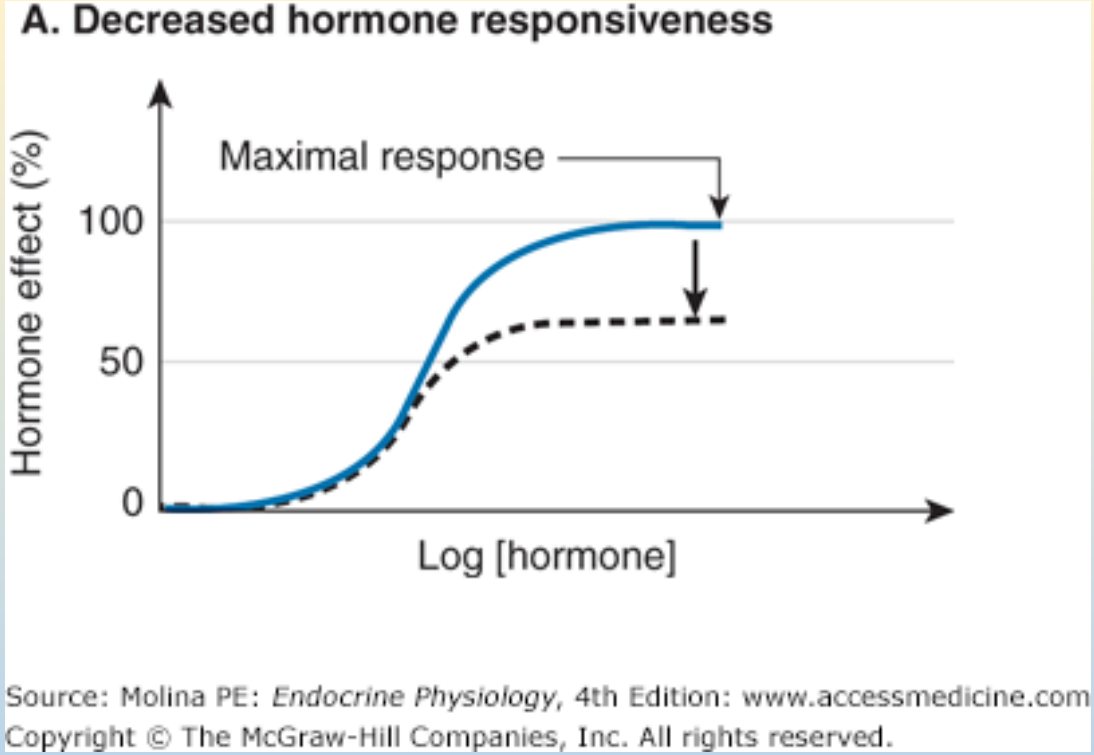
Binding of regulatory factor on corresponding protein (enzyme)

Inner enzymatic activity and its regulation

Clinical aspects

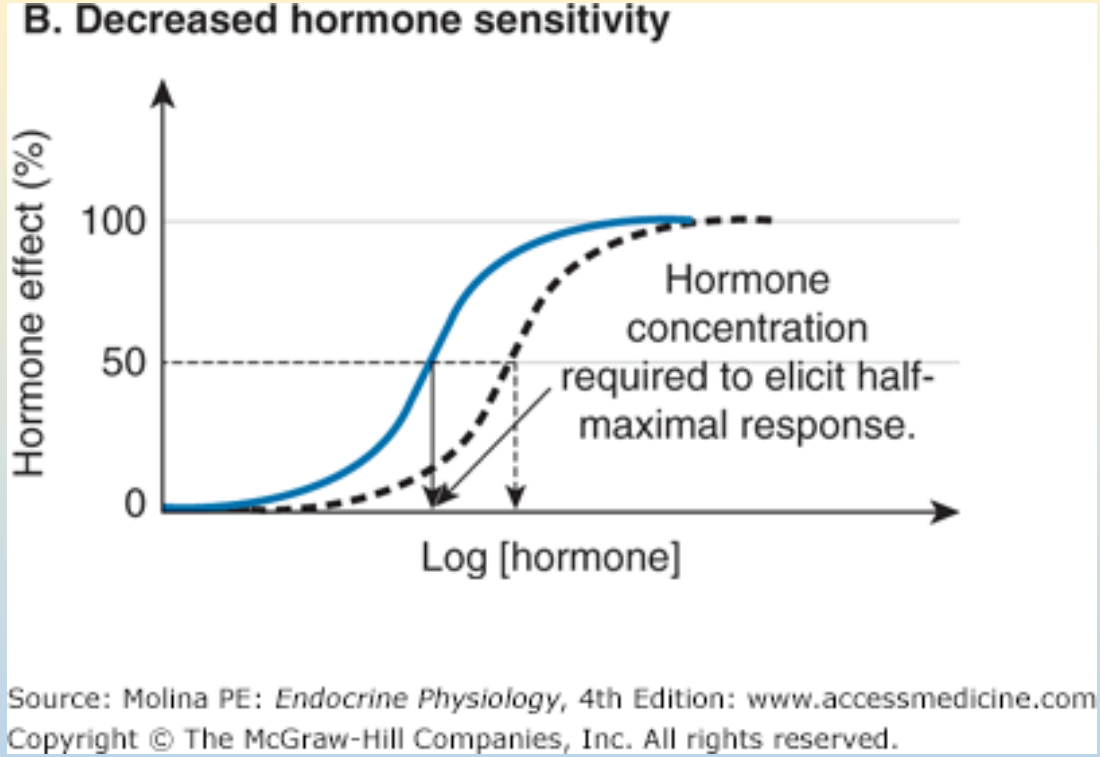
- Hormone overproduction
- Hormone underproduction
- Changes in sensitivity of target tissues and/or change in cell response
- Higher rate of inactivation or degradation of hormones
- Insufficient production or higher degradation of transport proteins
- Changes of transport hormones production during physiological conditions (pregnancy)

Clinical aspects



Source: Molina PE: *Endocrine Physiology*, 4th Edition: www.accessmedicine.com

- **Decreased number of receptors**
- **Decreased concentration of hormone-activating enzyme(s)**
- **Increased concentration of non-competitive inhibitor**
- **Decreased number of target cells**



Source: Molina PE: *Endocrine Physiology*, 4th Edition: www.accessmedicine.com

- **Decreased affinity of hormone to receptor**
- **Decreased number of receptors**
- **Increased rate of hormone degradation**
- **Increased concentration of antagonists/competitive inhibitors**