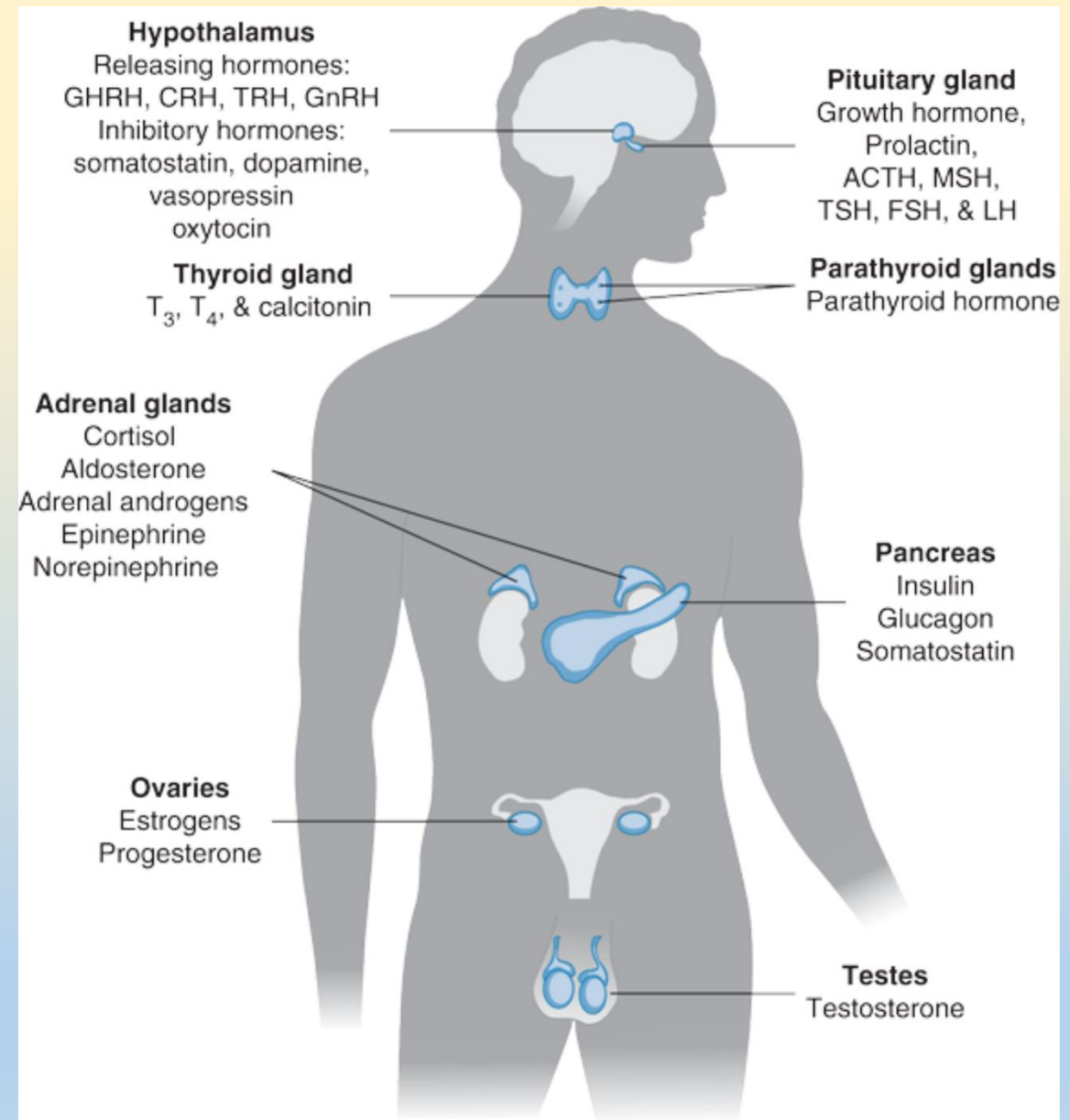


General principles of endocrine functions

M U N I
M E D

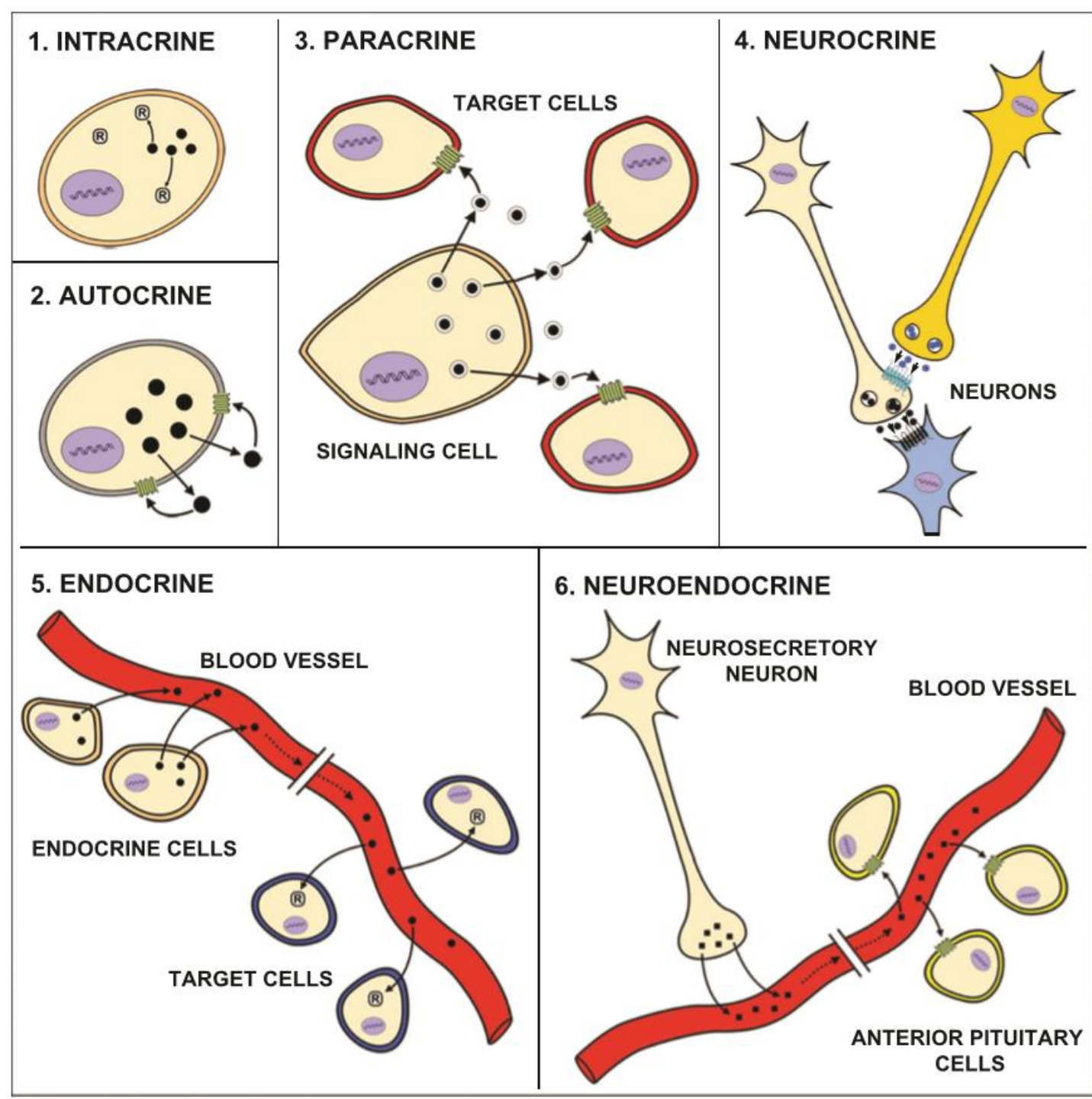
Hormones

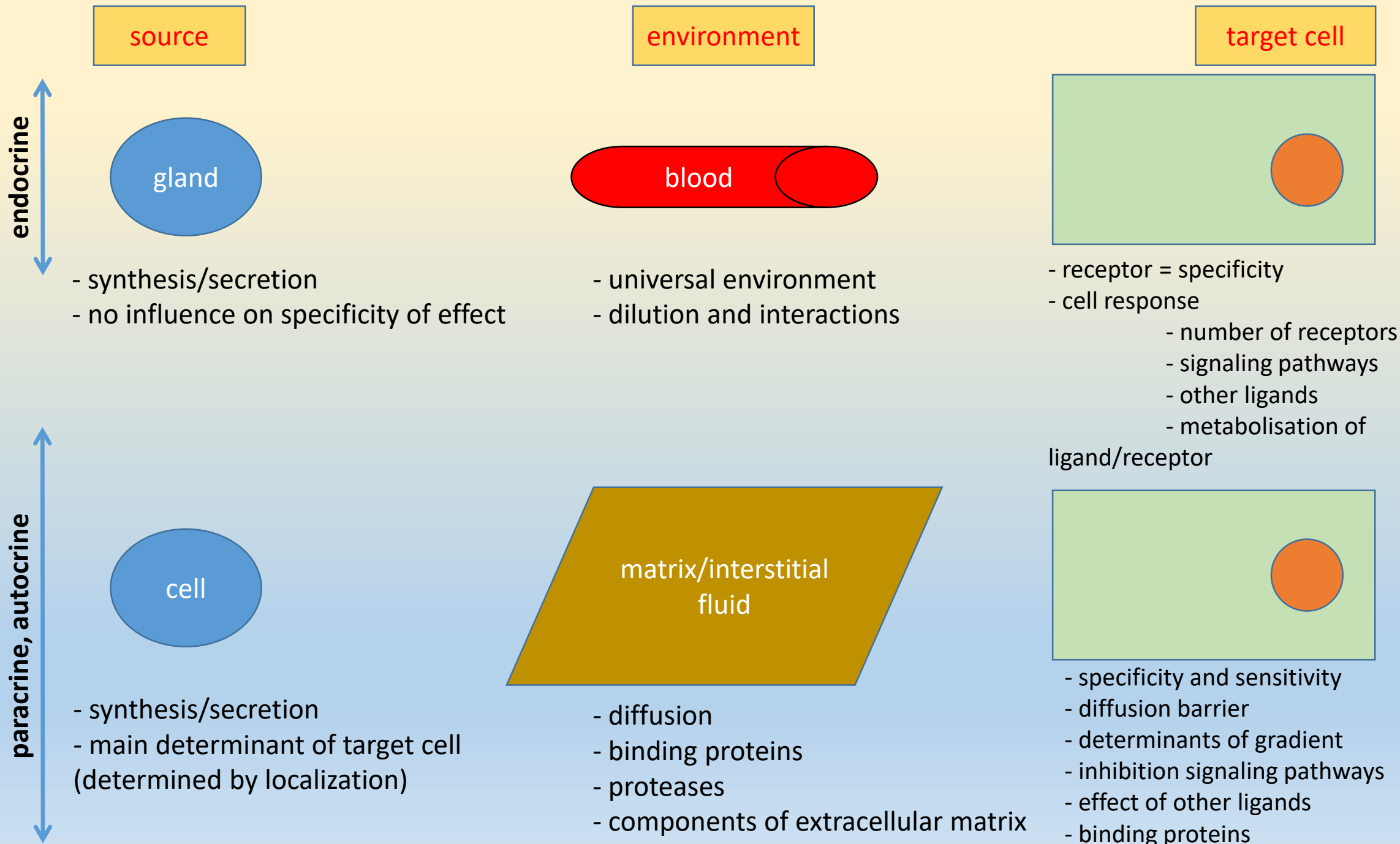
- Starling 1905 - *secretin*
- Definition?
- Glandotropic hormones
- Aglandotropic hormones



How do cells communicate?

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

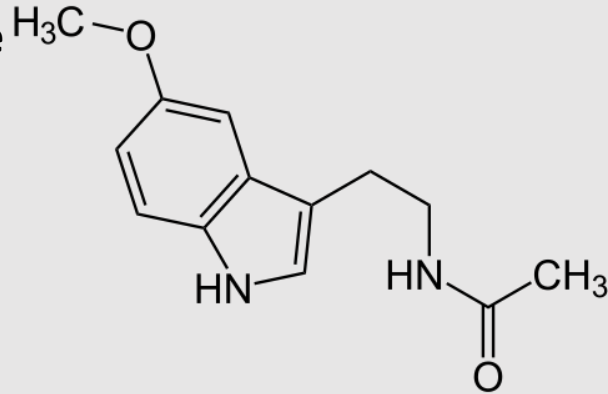




Chemical nature of hormones

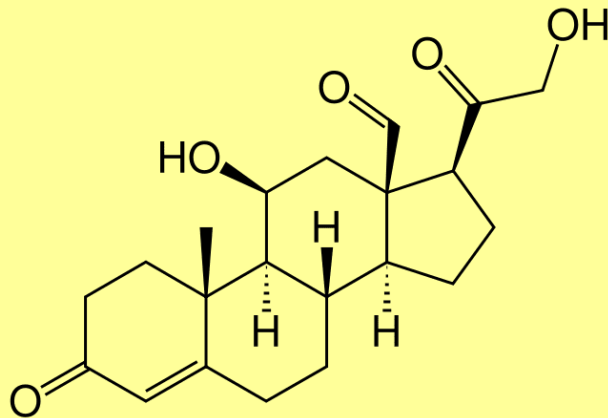
DERIVED FROM AMINOACIDS

- Adrenaline
- Noradrenaline
- Dopamine
- Melatonin
- T3/T4



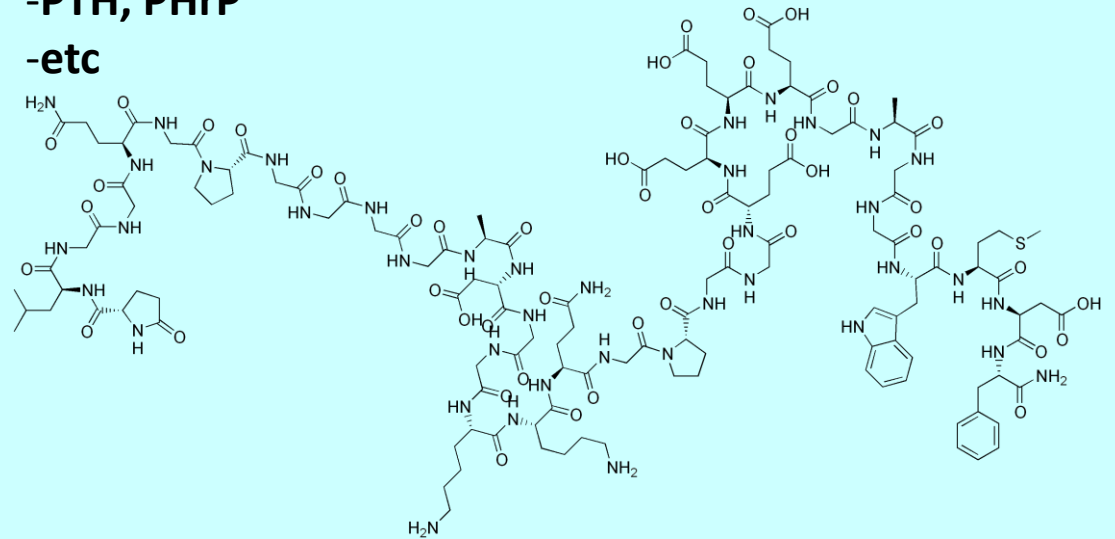
STEROID

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



PEPTIDES AND PROTEINS

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



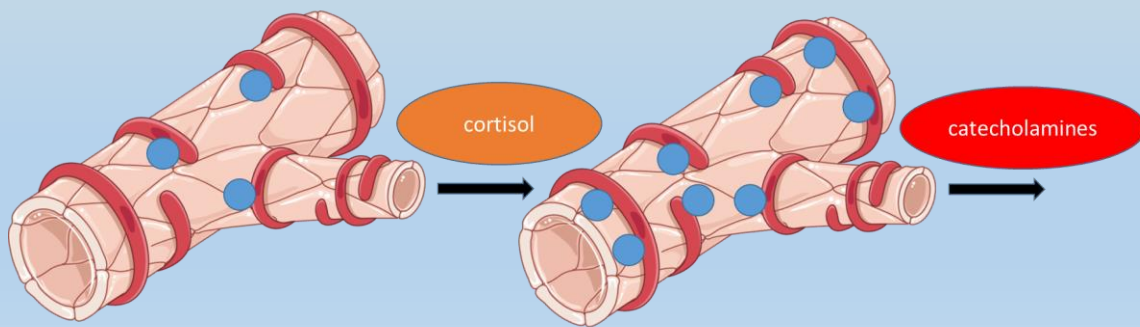
Chemical nature of hormones

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

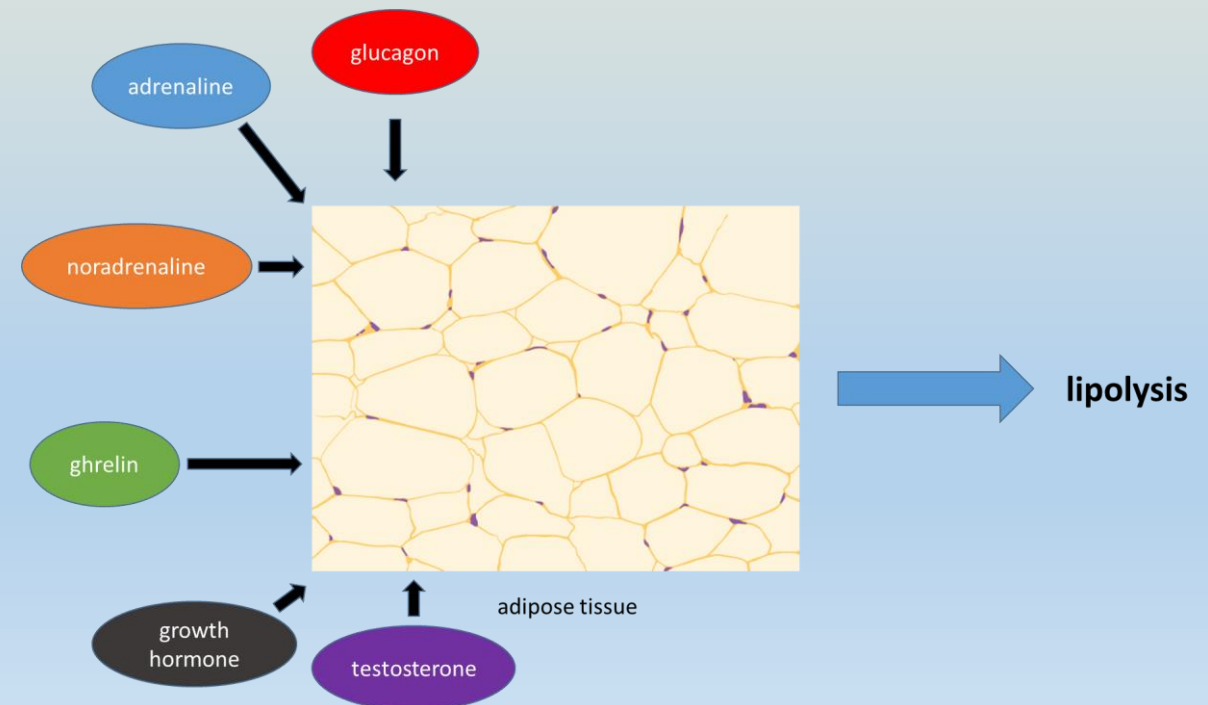
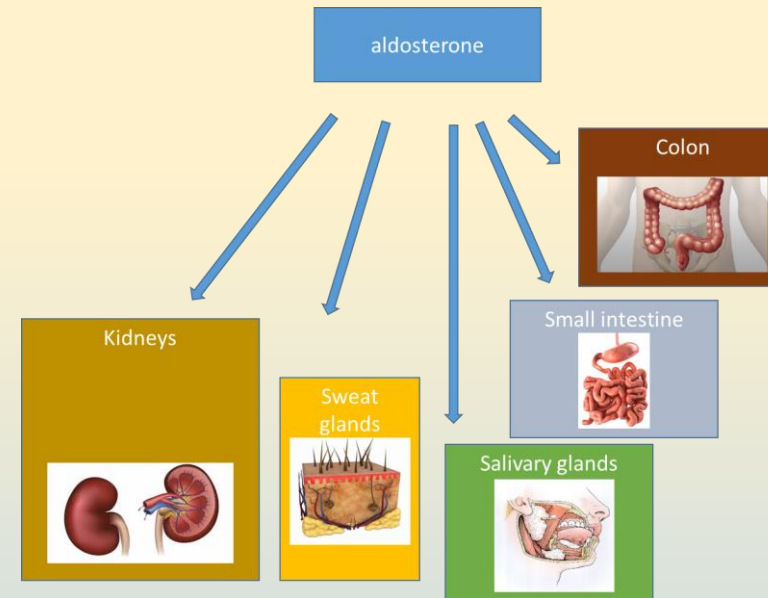
Hormones

- Pleiotropic effects
- Multiplicity
- Permissive effect



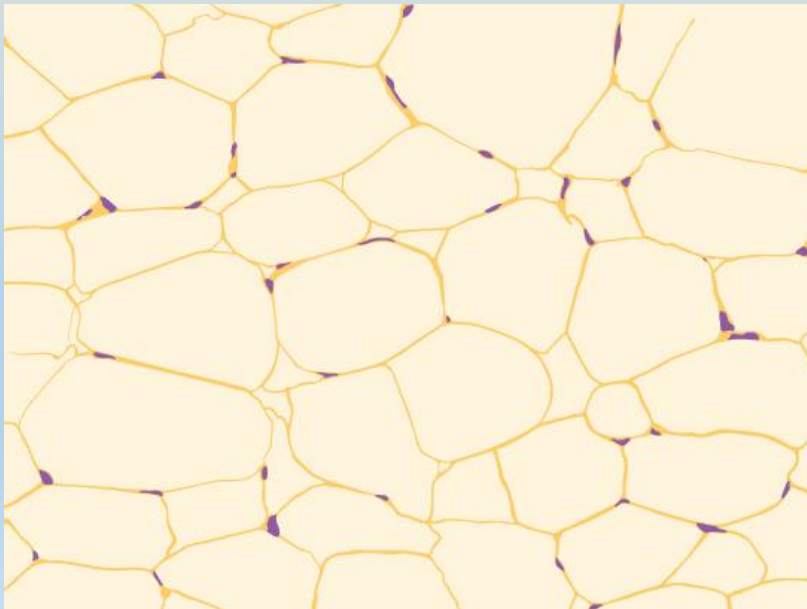
Arterioles – α_2 receptors

vasoconstriction

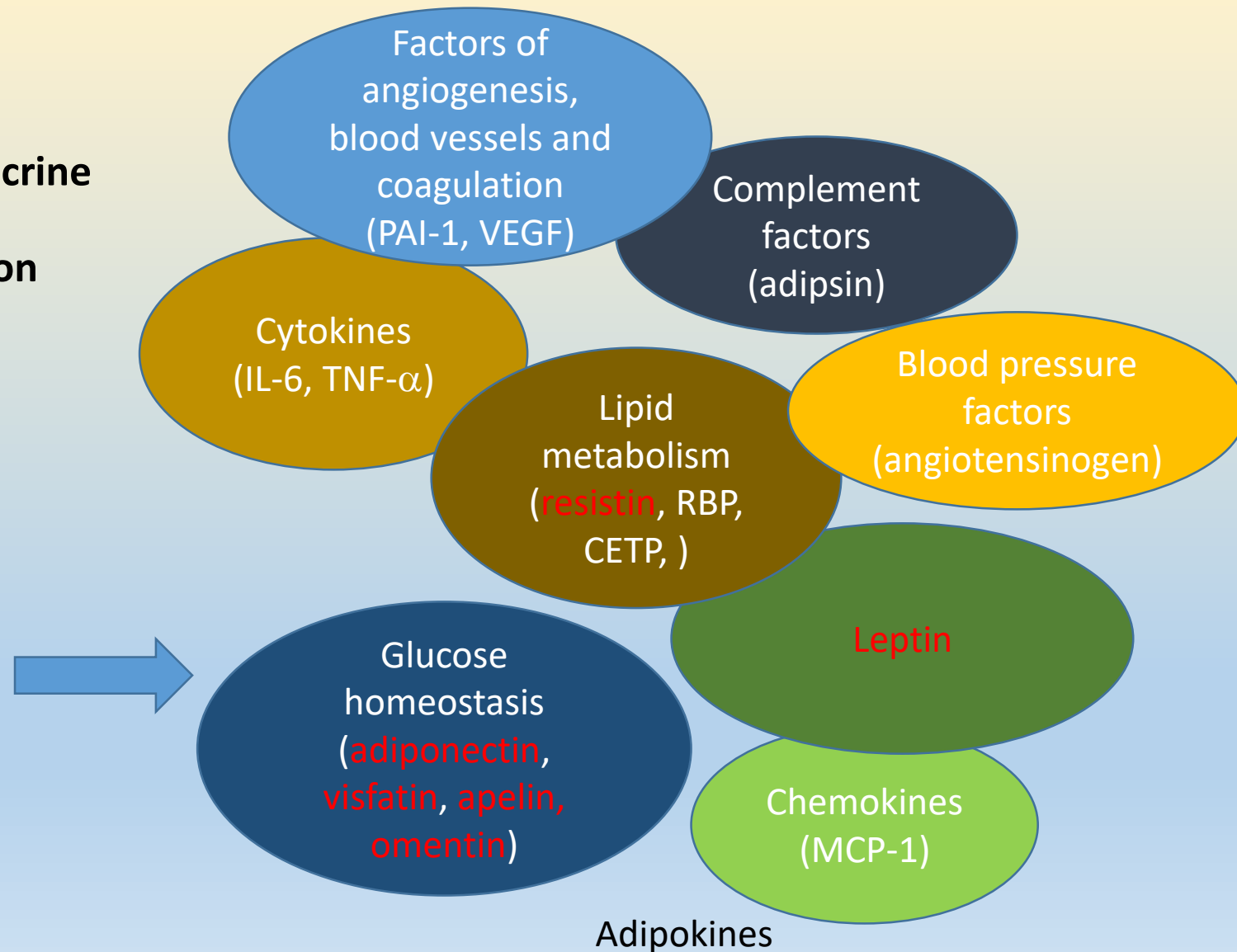


Endocrine organs

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



adipose tissue



Clinical aspects

- Production of hormones by tumors – PARANEOPLASTIC SYNDROMES

Lung tumors

- ADH (hyponatremia)
- ACTH (Cushing syndrome)
- PTHrP (hypercalcaemia)

Liver and kidney tumors

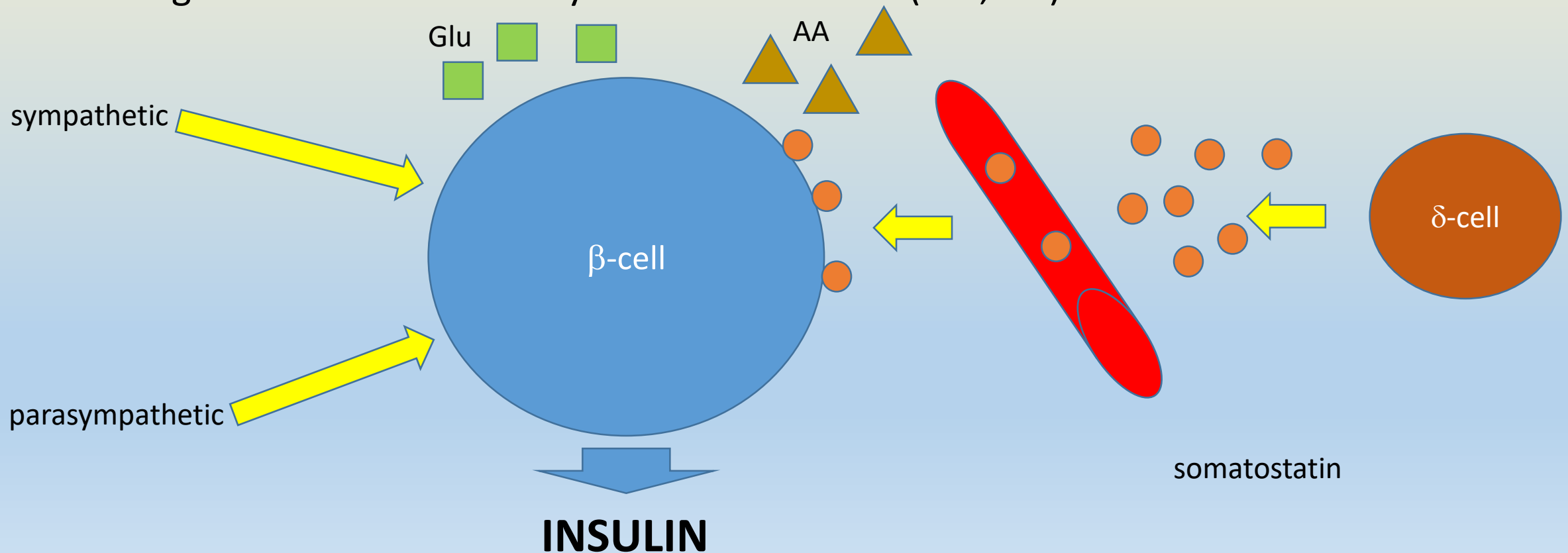
- erythropoietin
(polycythemia)

GIT tumors

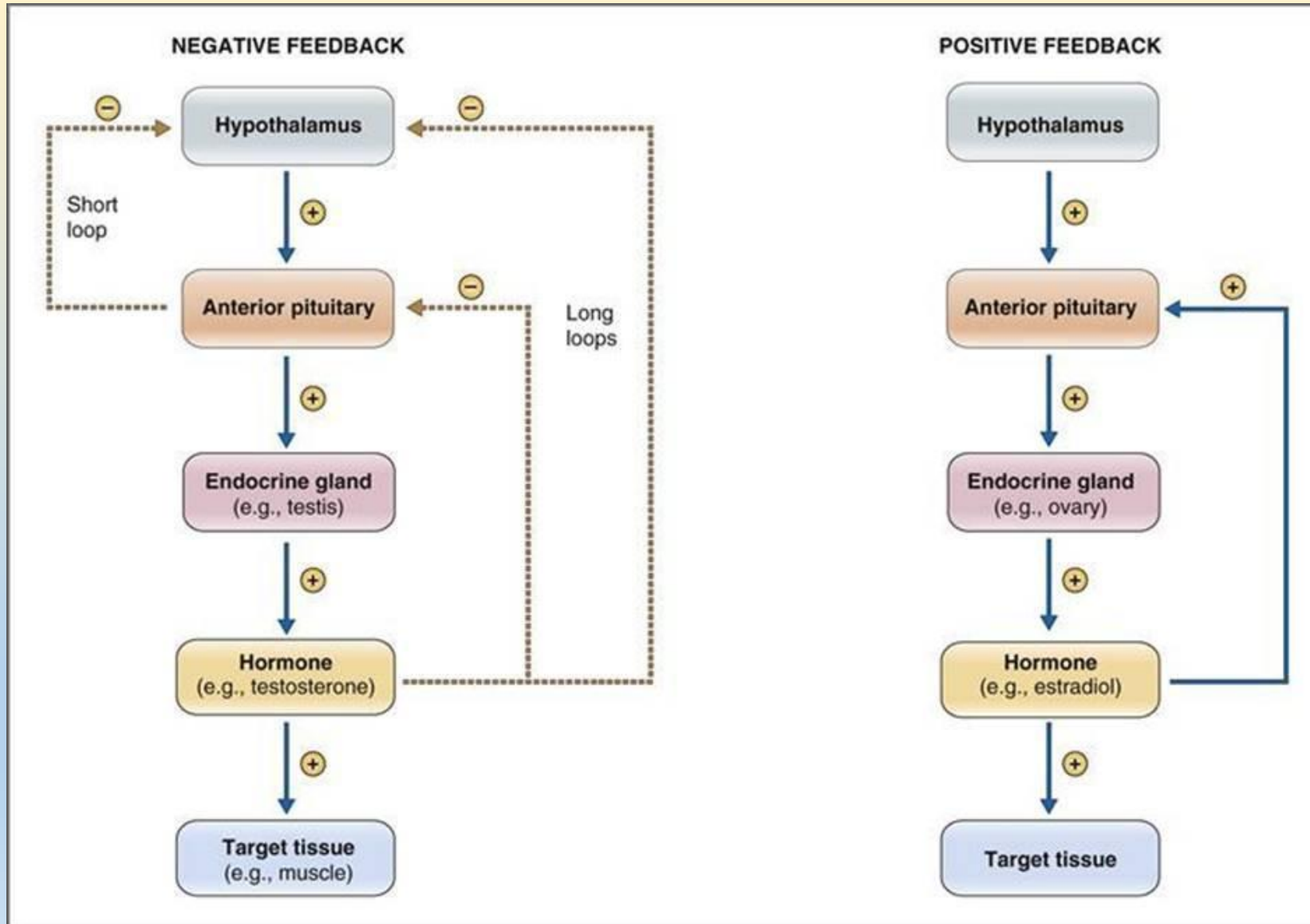
- ACTH (Cushing syndrome)

Secretion of hormones and its regulation

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

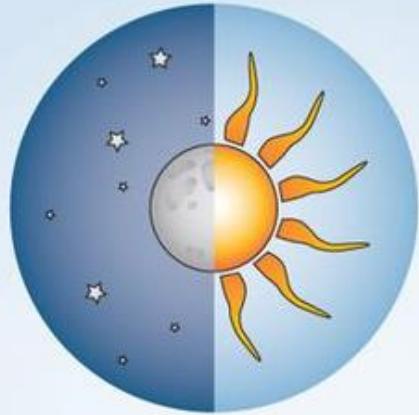


Hormone secretion is controlled by feedback system



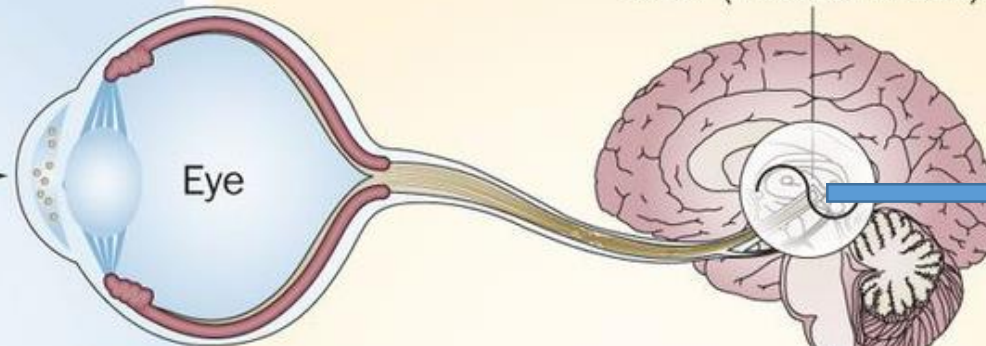
Cyclic changes in hormone secretion

External 24h light-dark cycle



Photic Zeitgeber

Endogenous circadian rhythm



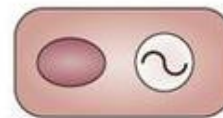
Entrainment

Synchronization

Peripheral oscillators



Cellular oscillators



SCN:

- Afferent – retina
- Efferent – hypothalamic nucleus

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

Neuronal/hormonal
= SNC-dependent

Satiety/fasting

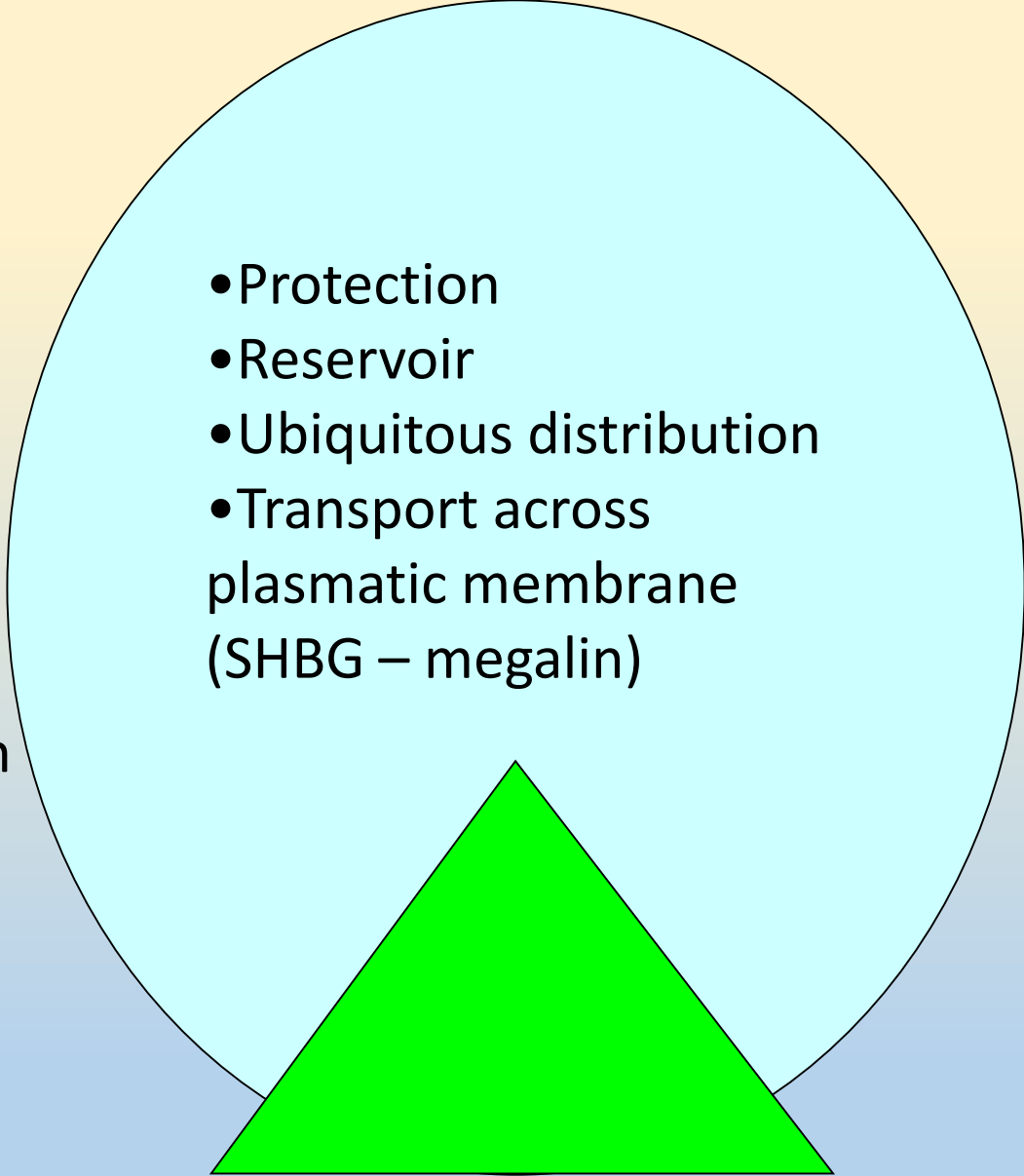
Body temperature

Nonphotic Zeitgeber

- Sleep-wake cycle
- Physical activity
- Social time
- Meals

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

PHASE I

- Hydroxylation, decarboxylation
- Oxidation, reduction

PHASE II

- Glucuronidation
- Sulphatation
- Methylation
- Conjugation with glutathione

metabolisation



Vascular system



bile

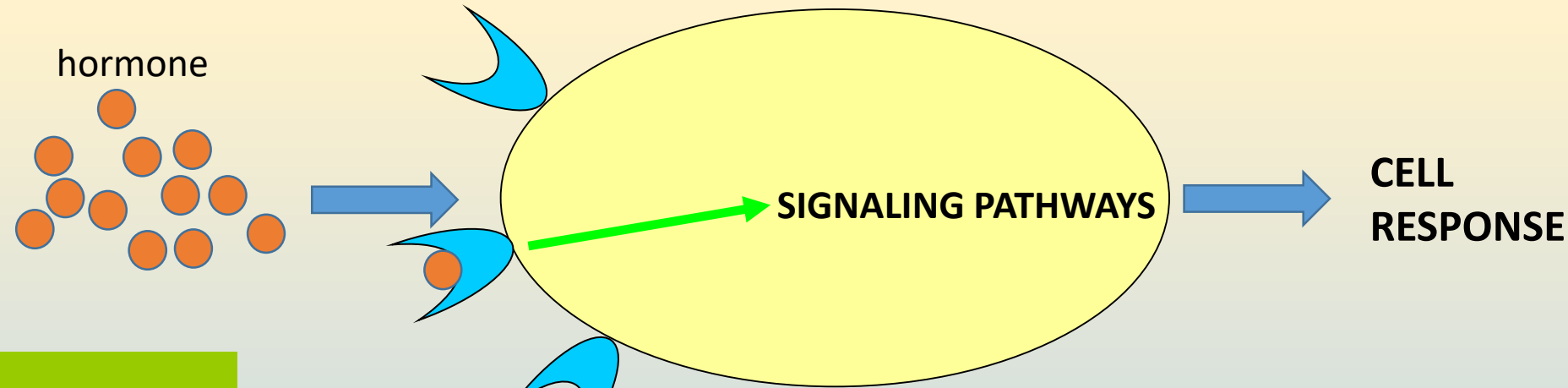


urine

elimination

Hormones and cell response

- Target cells
- Specificity
- High affinity
- Selectivity



MECHANISMS

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

Receptor binding

Signal amplification and transduction
effector molecules

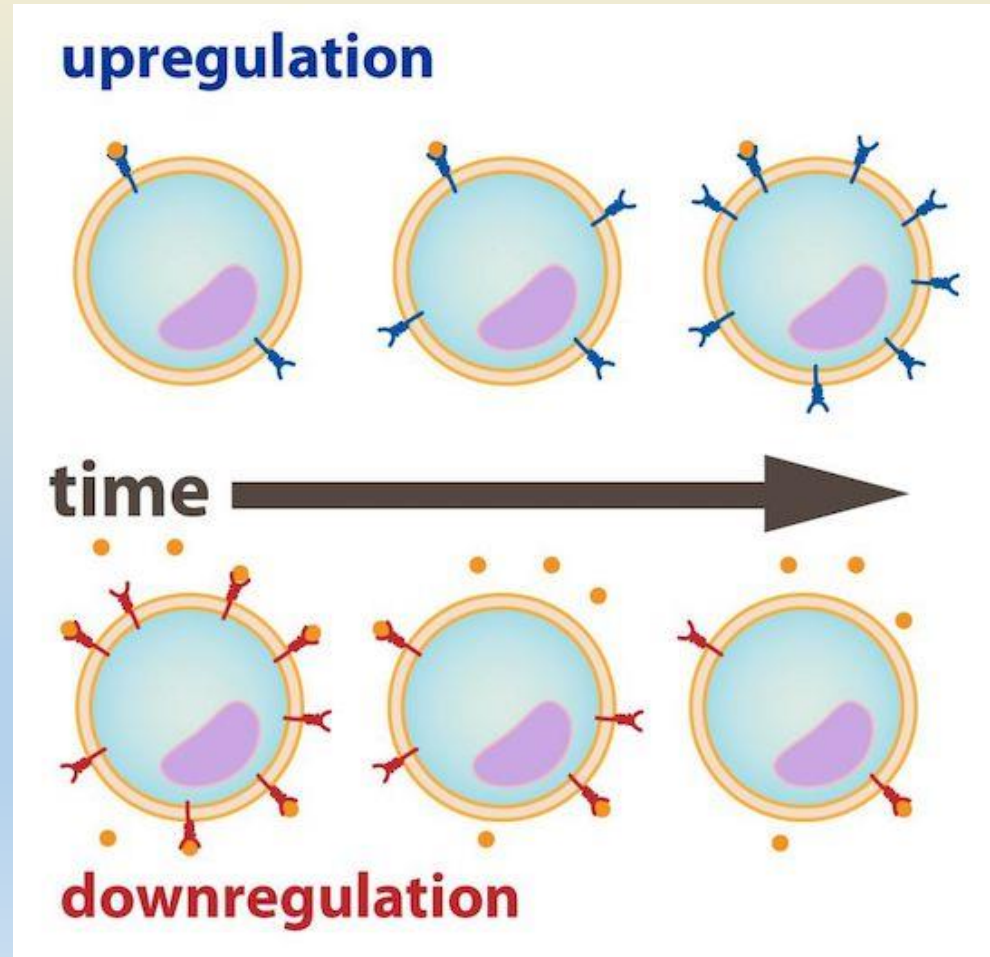
% of occupied receptors
conformation change

synergy
antagonism
possible loss of sensitivity
feedback-loop regulation

CELL RESPONSE IS MEDIATED BY RELEVANT RECEPTORS

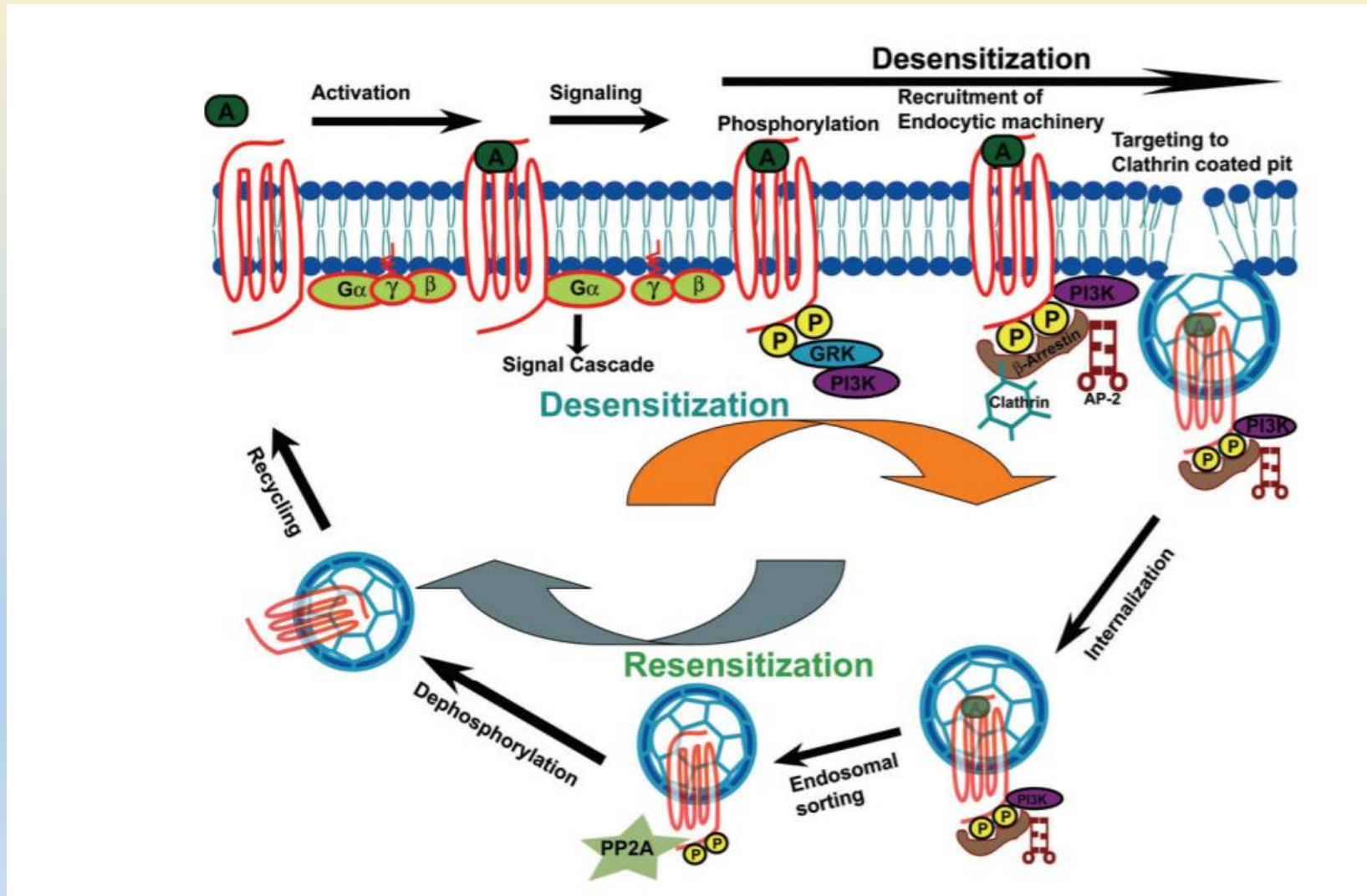
Regulation of cell response at receptor level

Downregulation versus upregulation

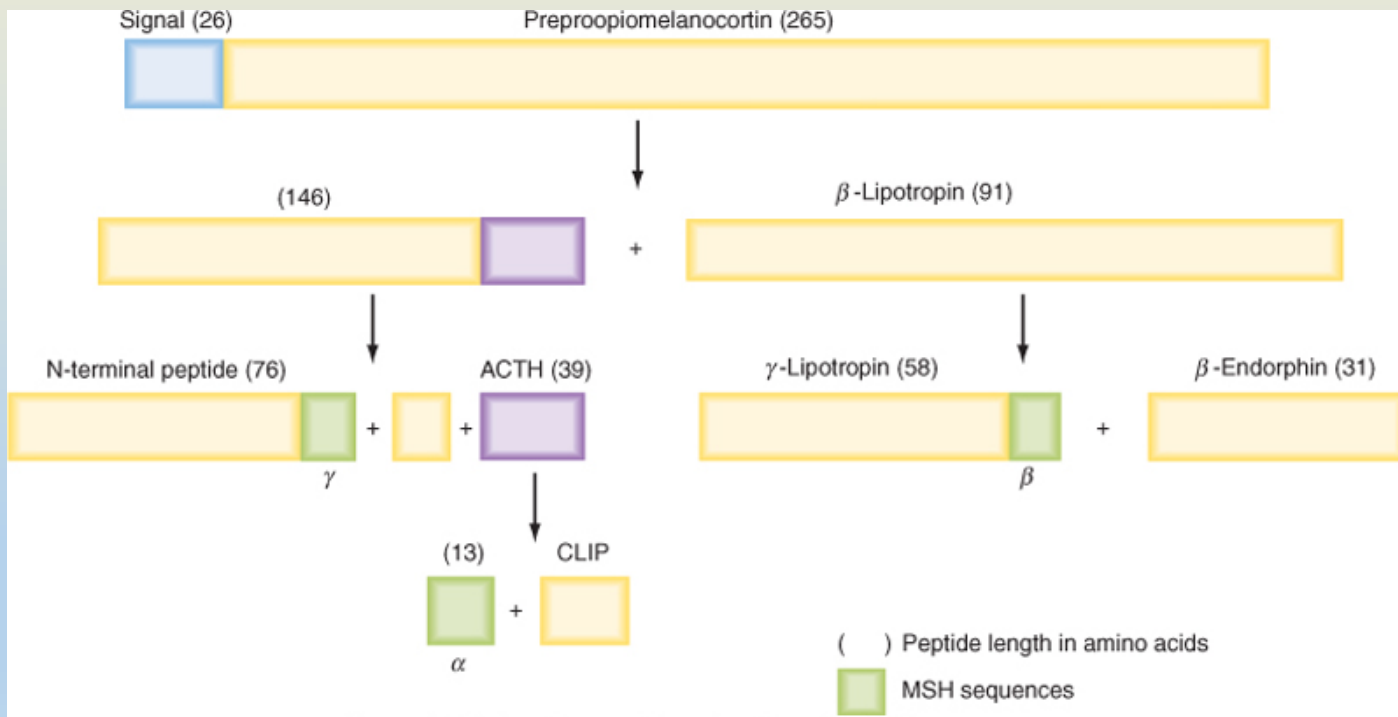


Regulation of cell response at receptor level

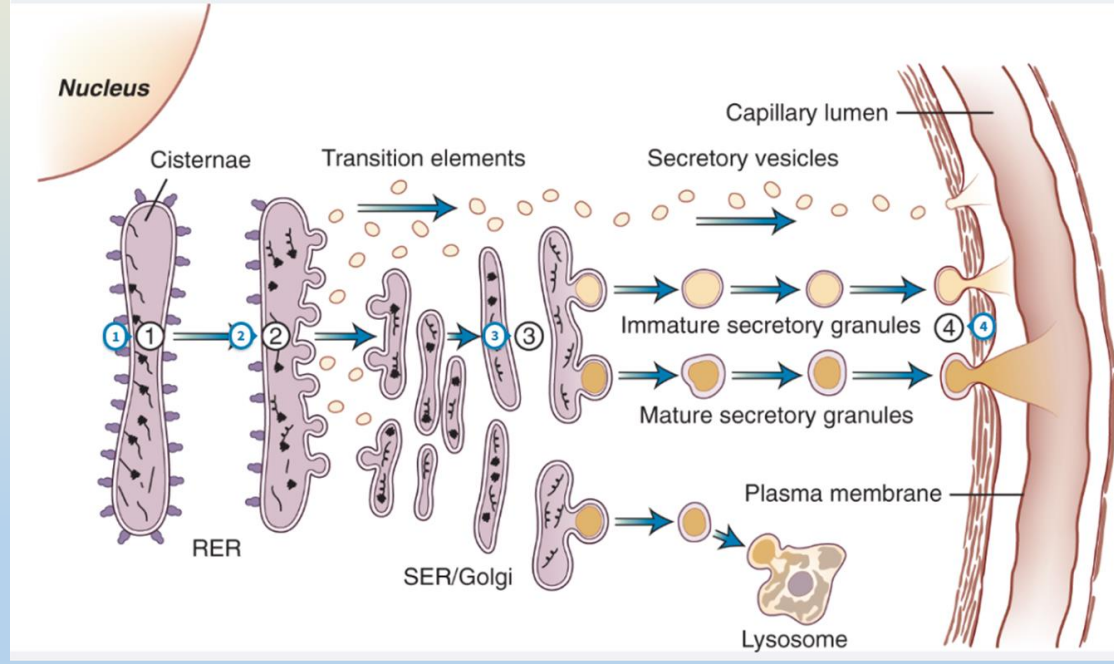
Homologous desensitization („with ligand“) X Heterologous desensitization („without ligand“)



Hormones – proteins and peptides



Koeppen & Stanton: Berne and Levy Physiology, 6th Edition.
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preprohormone – prohormone – hormone (+ fragments)

G protein-coupled receptors (GPCR)

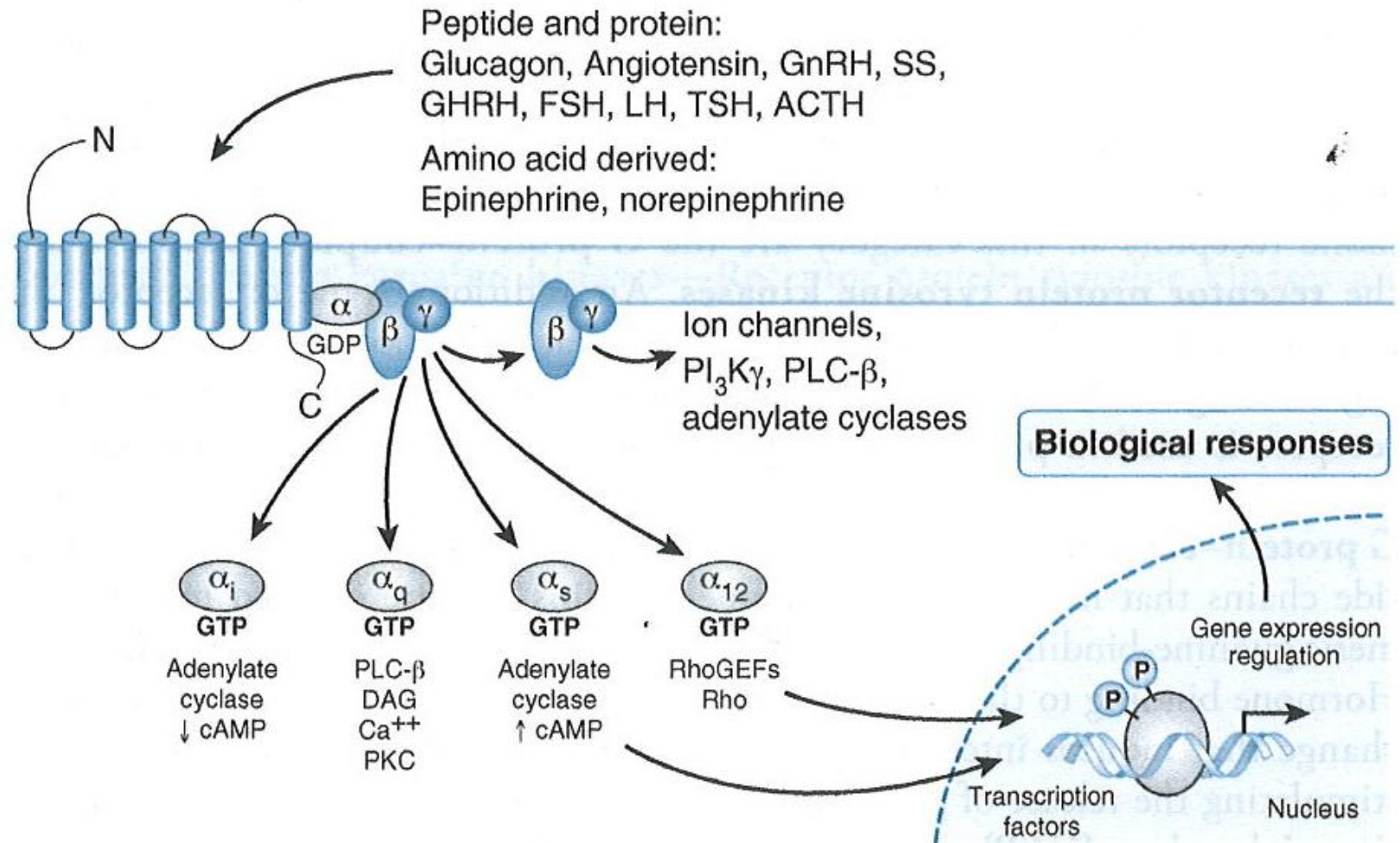
$G_s - G_{s'}$, G_{olf}

G_i

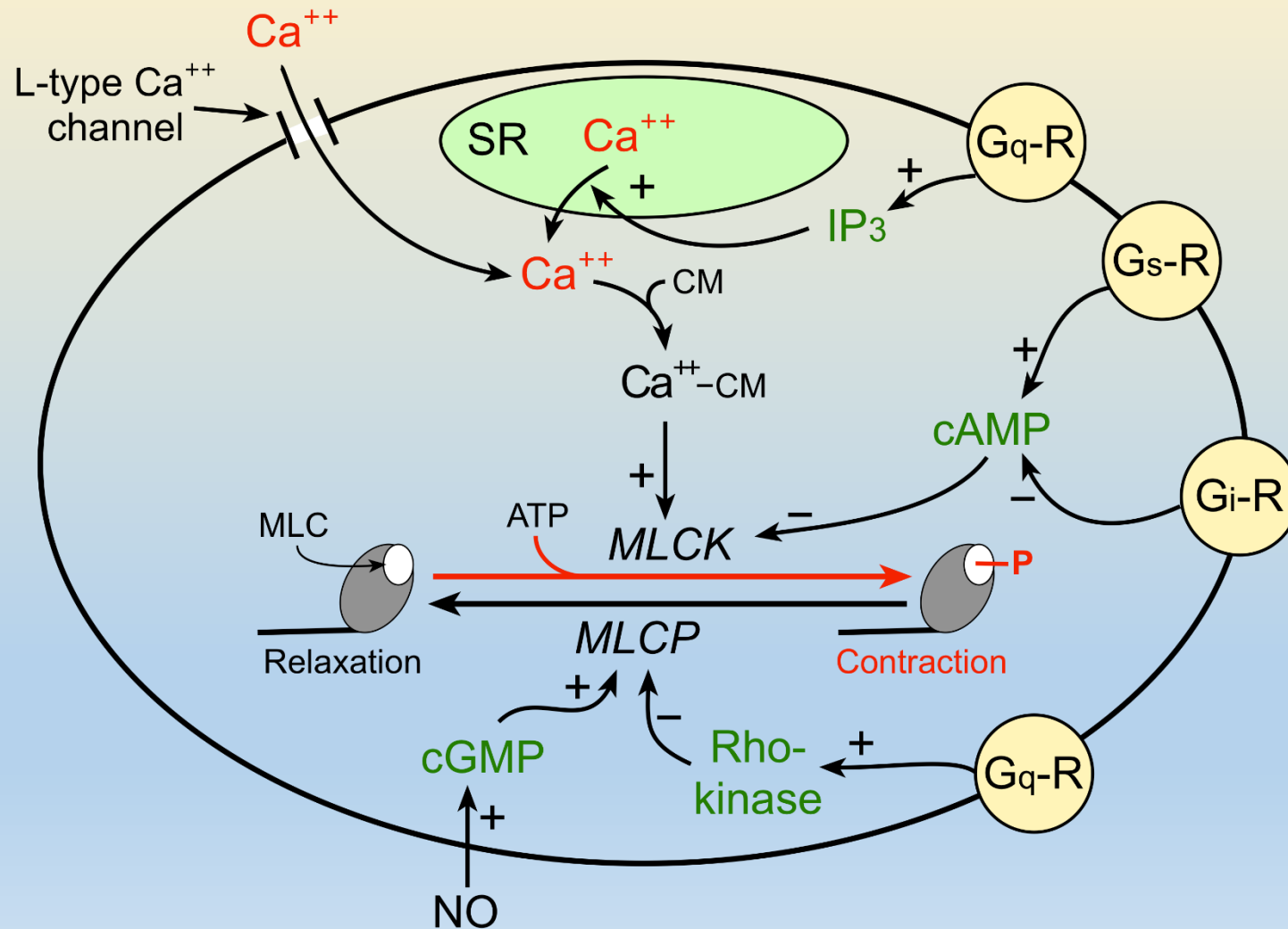
- G_0 (2, brain)
- G_t (2, photorec. – cAMP-PDE)
- G_z (inhibition of K^+ channels)

$G_{q/11}$

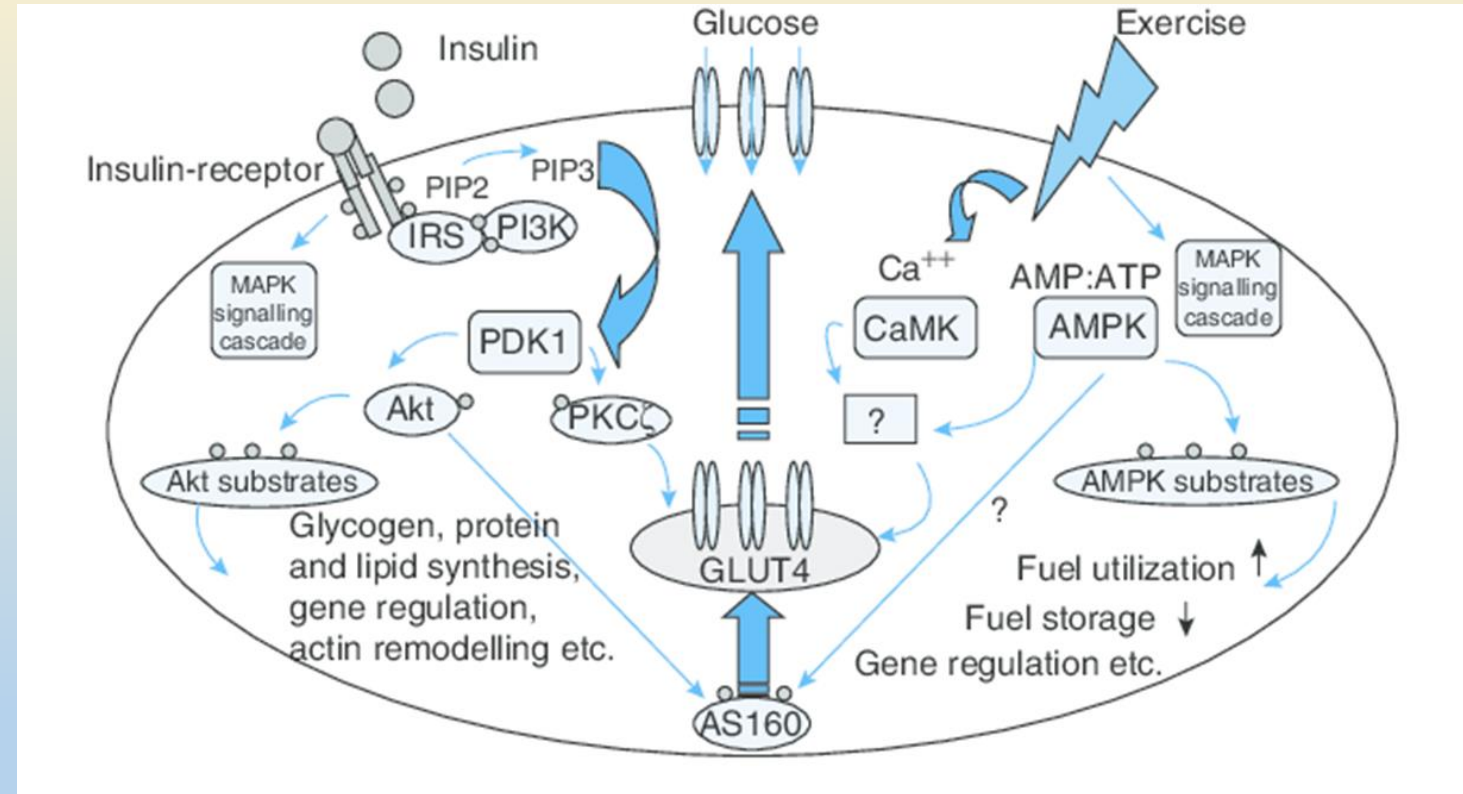
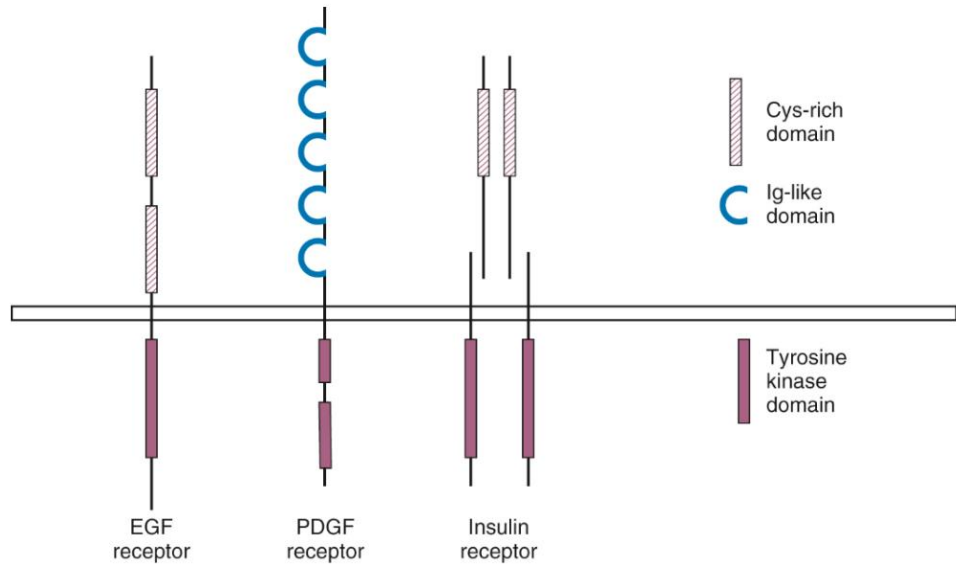
$G_{12/13}$



Example – G-protein coupled receptors and smooth muscle



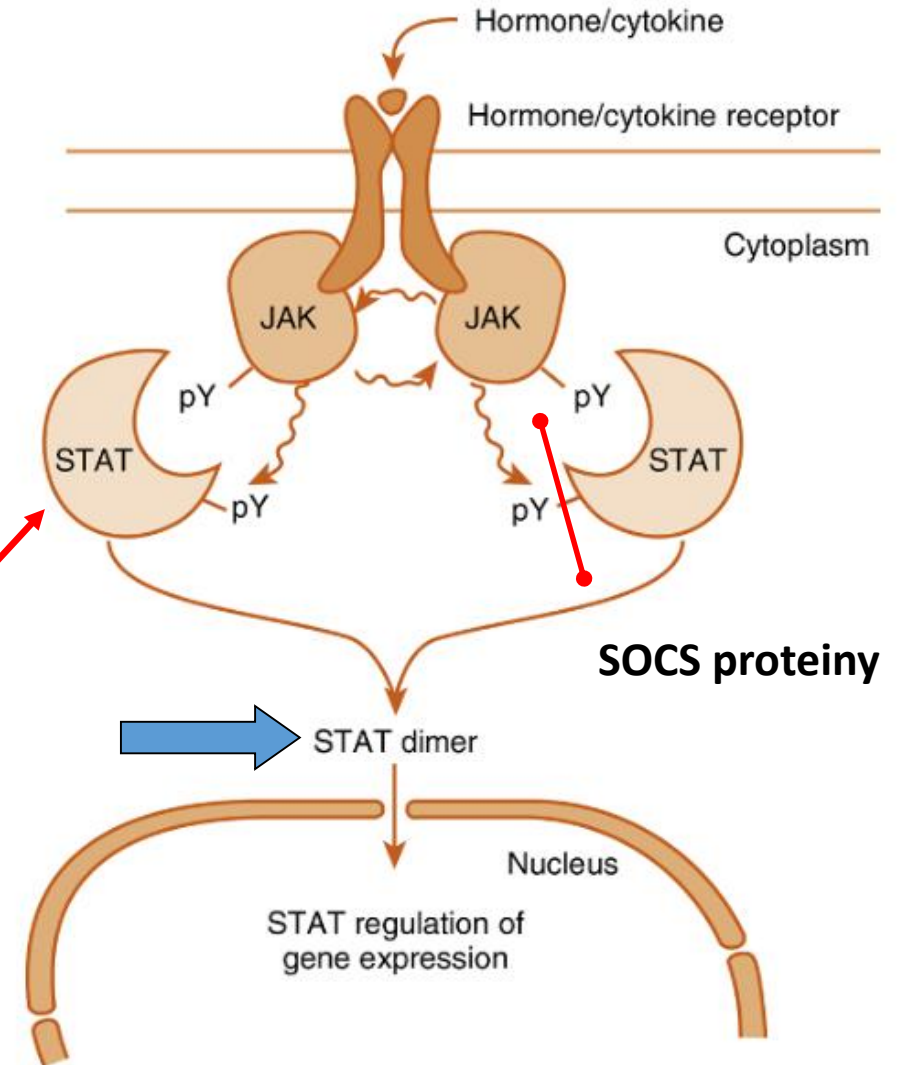
Receptor tyrosinkinases



Receptors associated with cytosolic TK

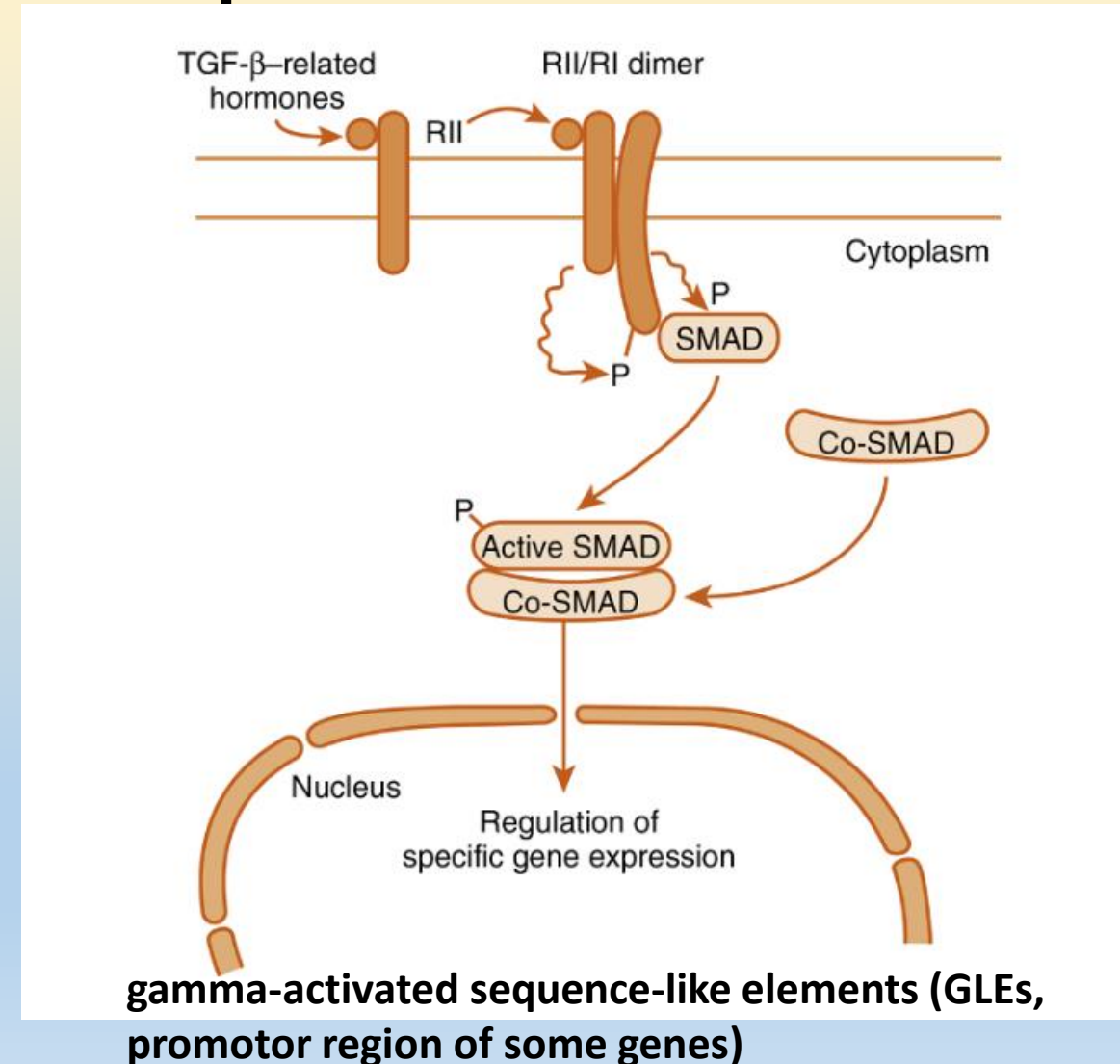
- GH
- Prolactin
- Leptin
- erythropoietin

signal transducers and activators of transcription



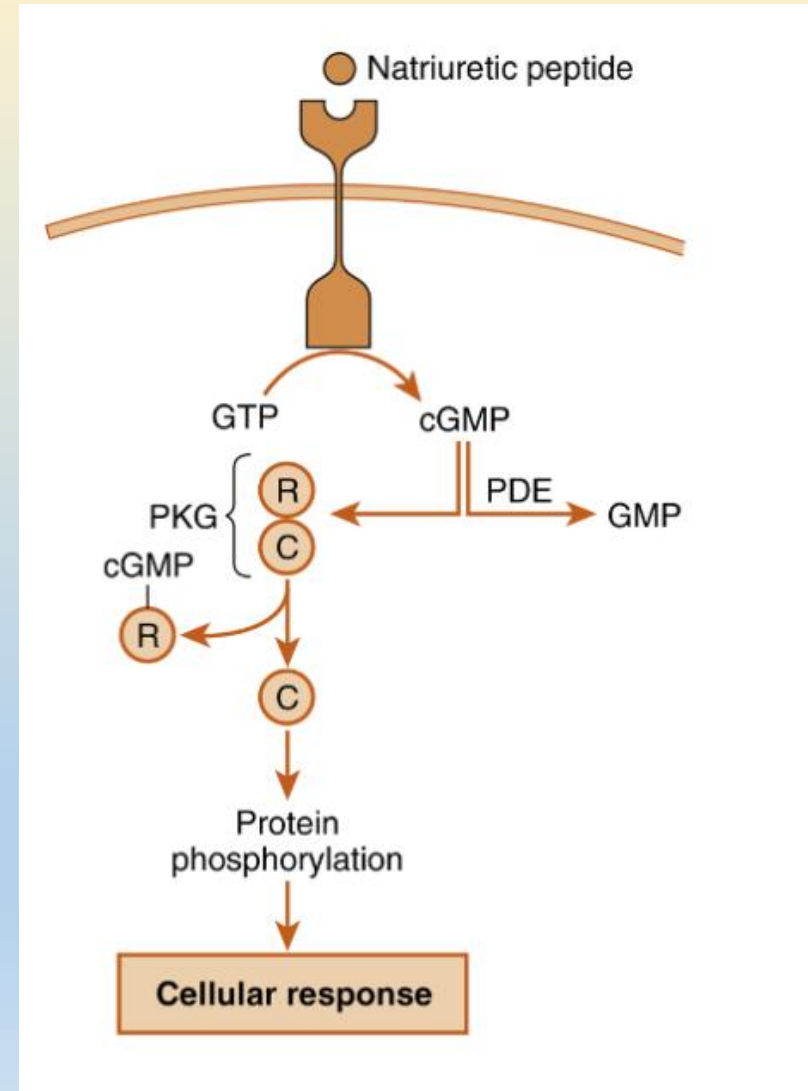
Receptor serine/threonine protein kinases

- Anti-Müllerian hormone
- inhibitin
- SMAD = „latent transcription factors“



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 IP₃

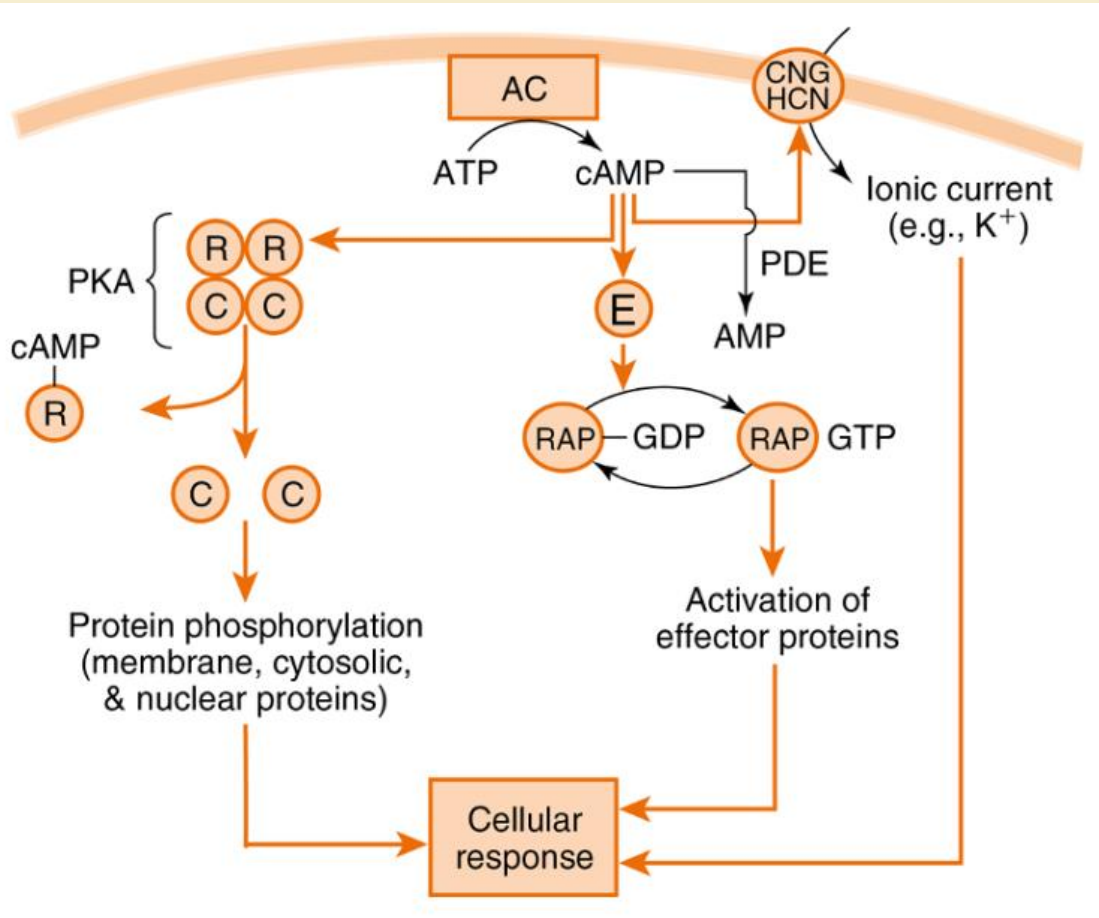
- PIP₂ – phospholipase C system

• Ca²⁺

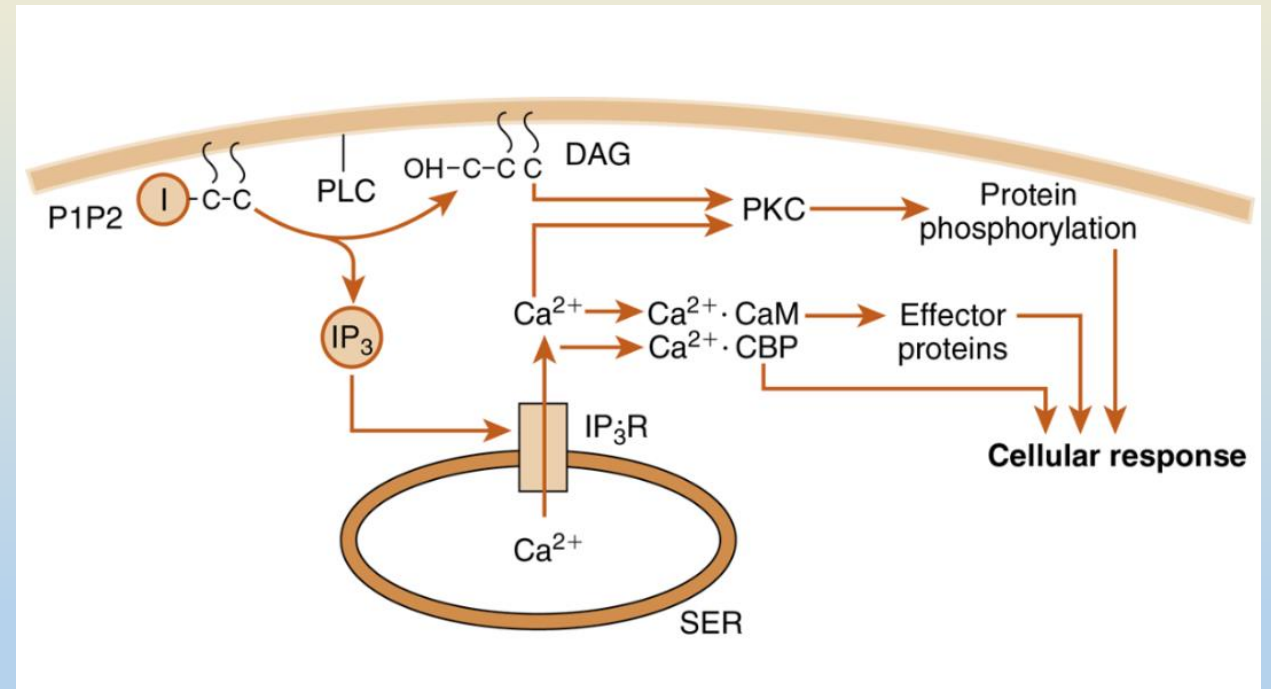
- Ca²⁺/Ca²⁺- calmodulin

EXTRACELLULAR SIGNAL MUST BE CONVERTED TO INTRACELLULAR RESPONSE

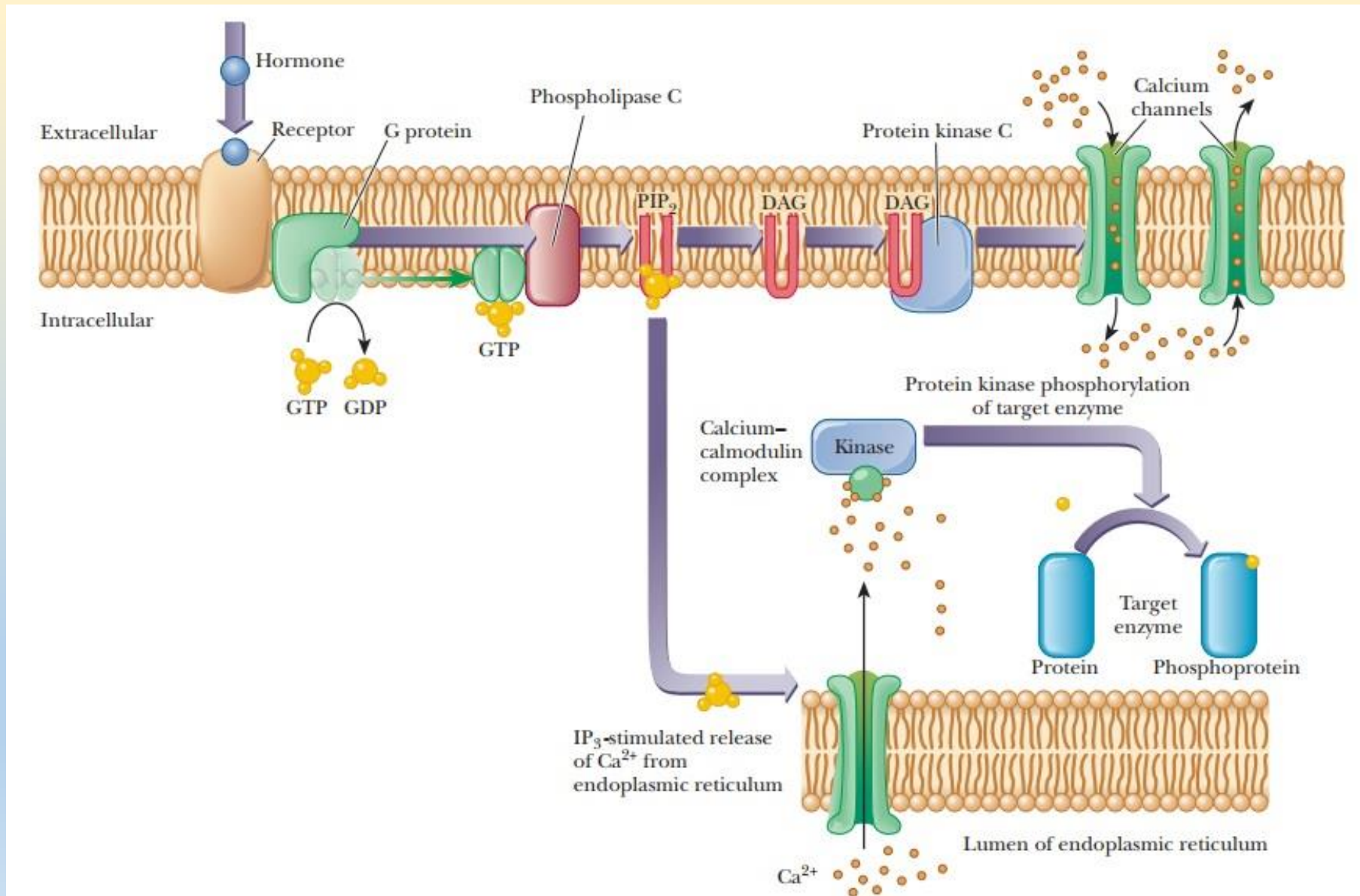
AC – cAMP system



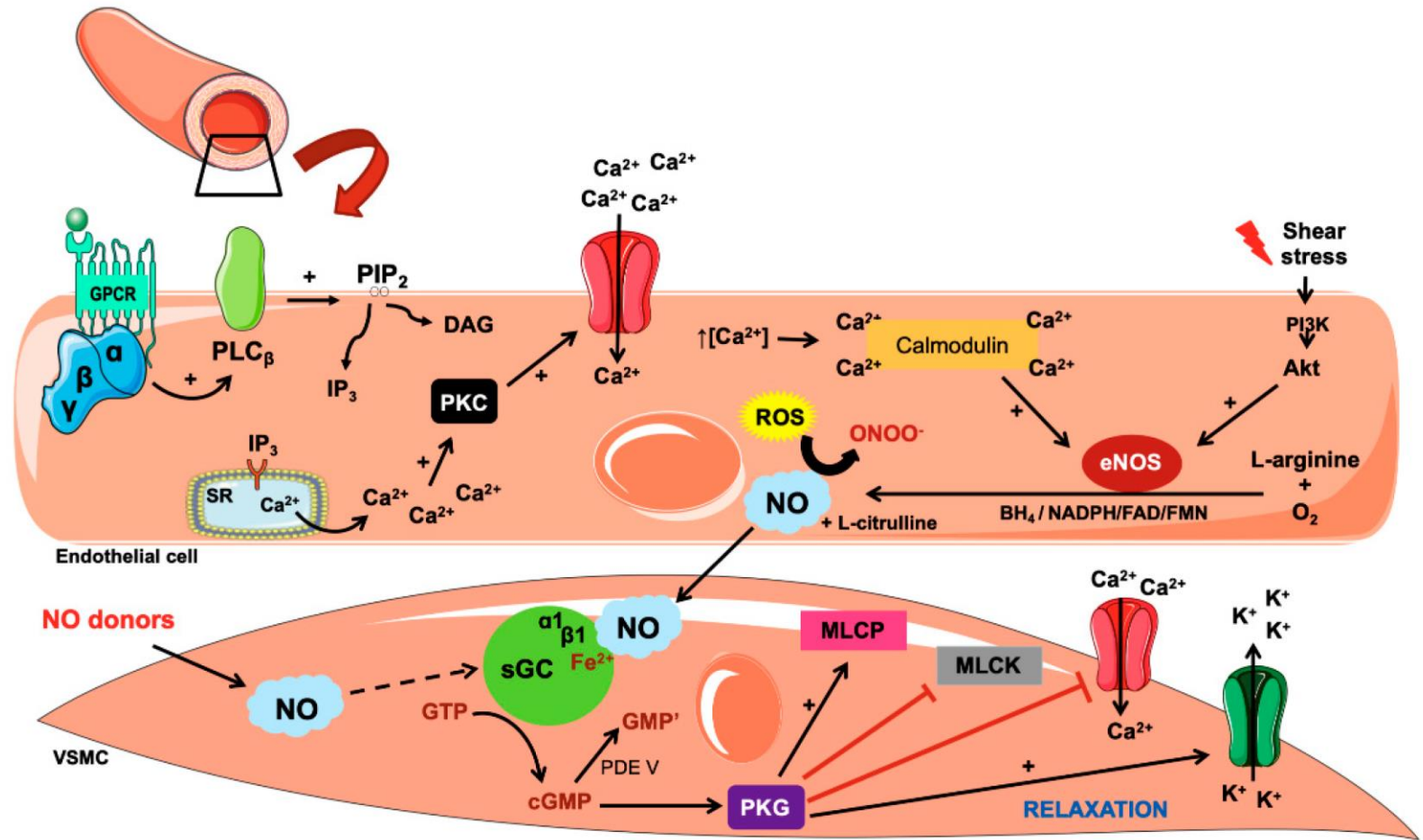
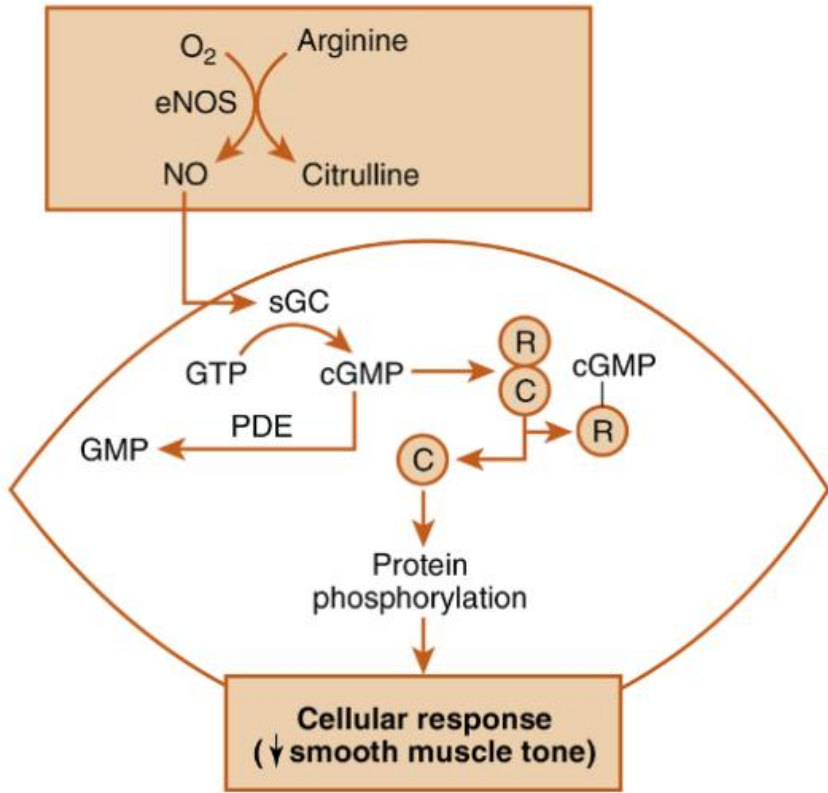
PLC - DAG and IP₃ system



Ca²⁺ - calmodulin system



NO as a signalling molecule - cGMP



Clinical aspects

- Syndromes of resistance to hormones (i.e. IR, IGF-1, TR β)
- Syndromes caused by CPCR and G proteins mutations
 - ADH – nephrogenic diabetes insipidus
 - ACTH – familiar ACTH resistance
 - GnRH – hypogonadotropic hypogonadism
 - FSH – hypergonadotropic ovarian dysgenesis
 - LH – male pseudohermaphroditism
 - Melanocortin 4 – obesity
 - PTH/PTHrP – Blomstrand lethal chondrodysplasia

Hormones acting through nuclear receptors

HORMONES

- Thyroid hormones – TR α / β
 - Estrogens – ER α / β
 - Testosterone - AR
 - Progesterone - PR
 - Aldosterone - MR
 - Cortisol - GR
- ← heterodimers
- 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
-

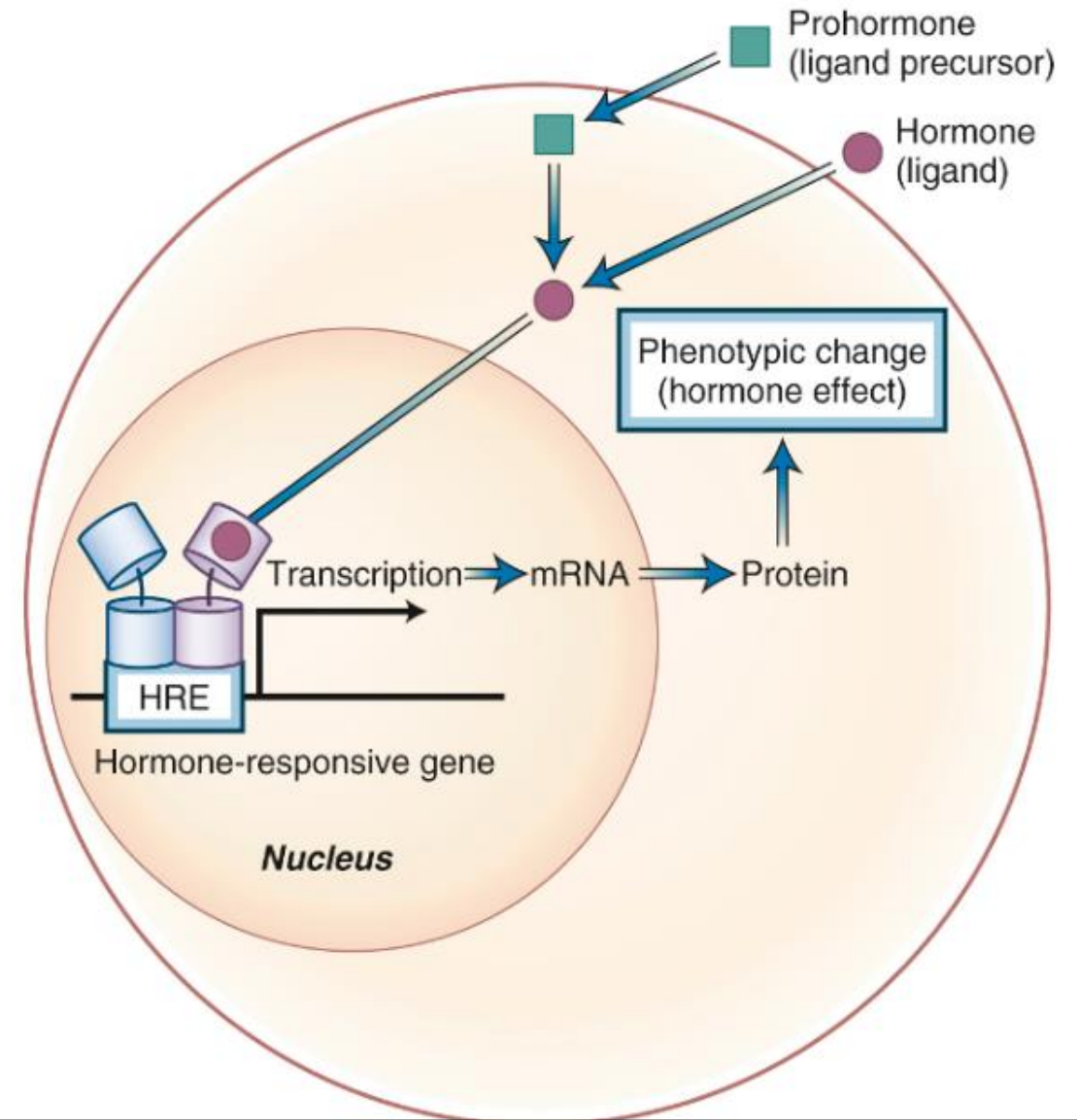
Explanation of some effects and pathologies

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

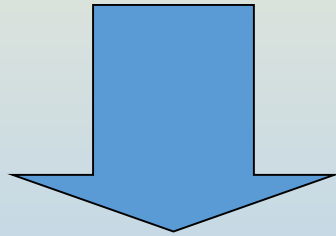
WHY ONLY NUCLEAR RECEPTORS?

- Synthesis in cytoplasm
- Stay until ligand binding or until transport to nucleus

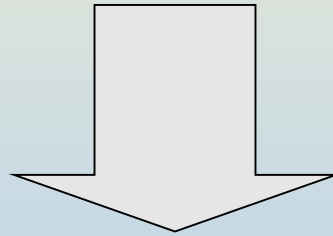


- Regulation mechanism – modification, count of receptors
- Important parameter – selectivity of target cells
- Tissue-specific factors, coactivators and corepressors

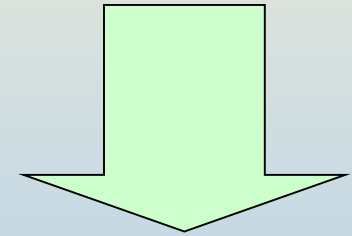
Nuclear receptors



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

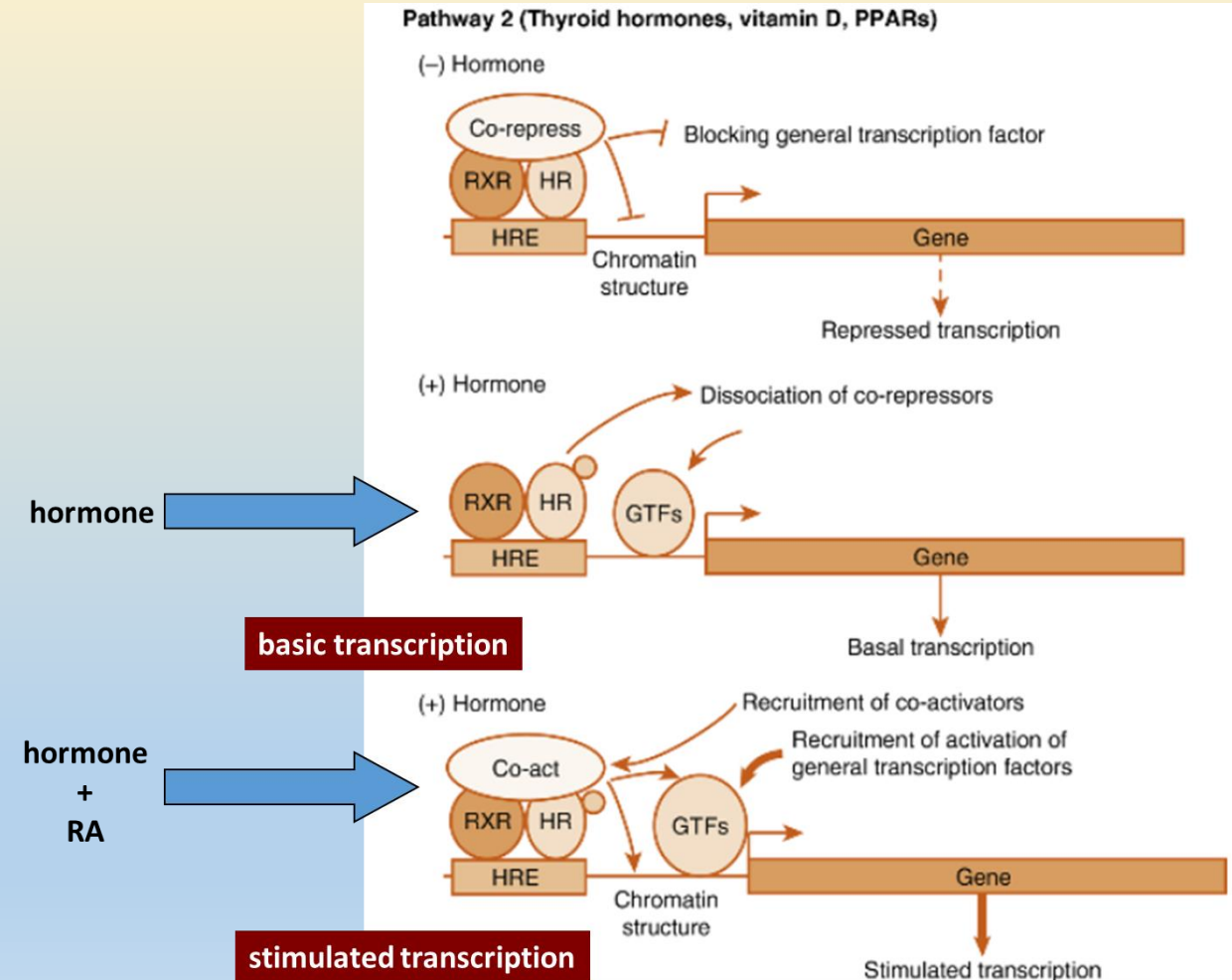
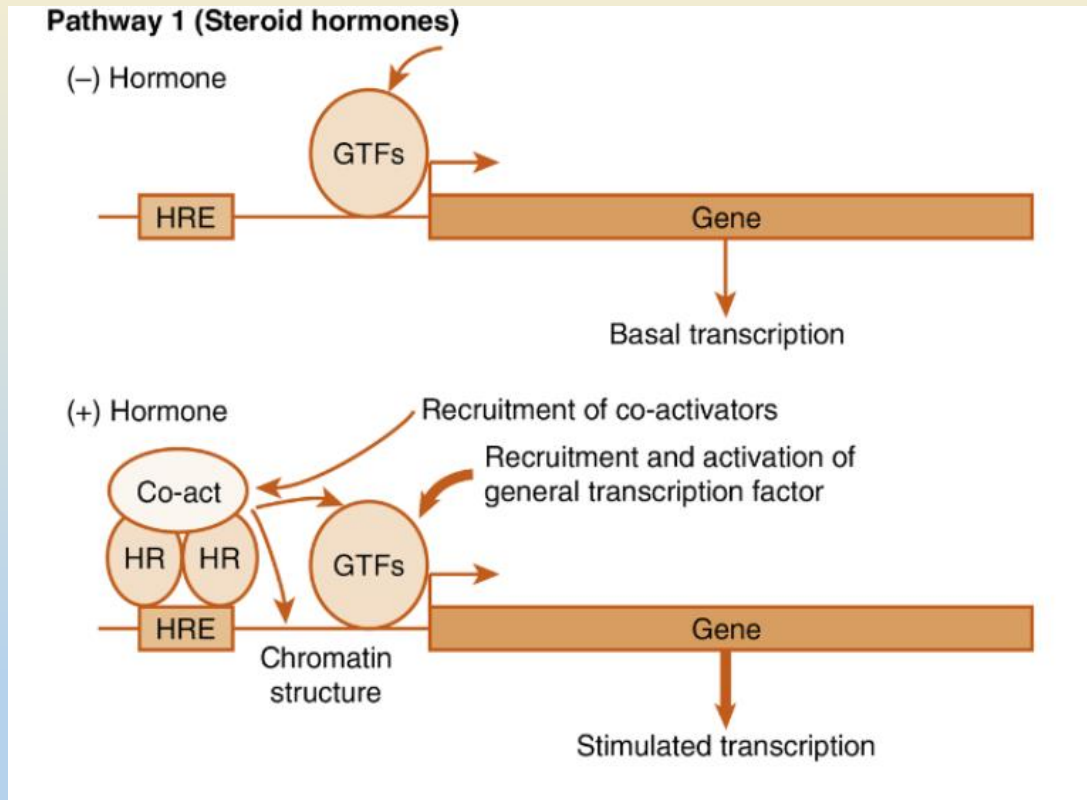


- DNA binding (zinc fingers)
- Dimerisation
- ERE, PRE, GRE, MRE, ARE



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

Example – steroid hormones X thyroid hormones



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)

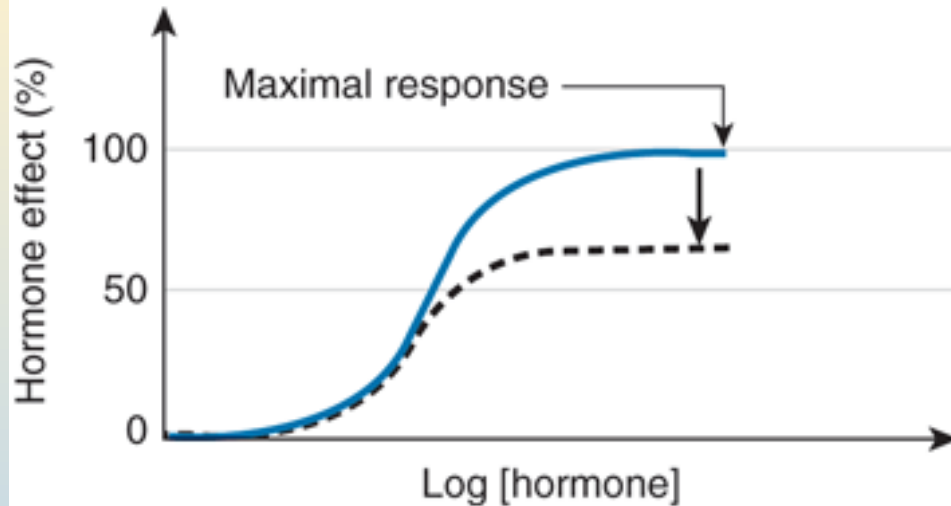
Inner enzymatic activity and its regulation

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)

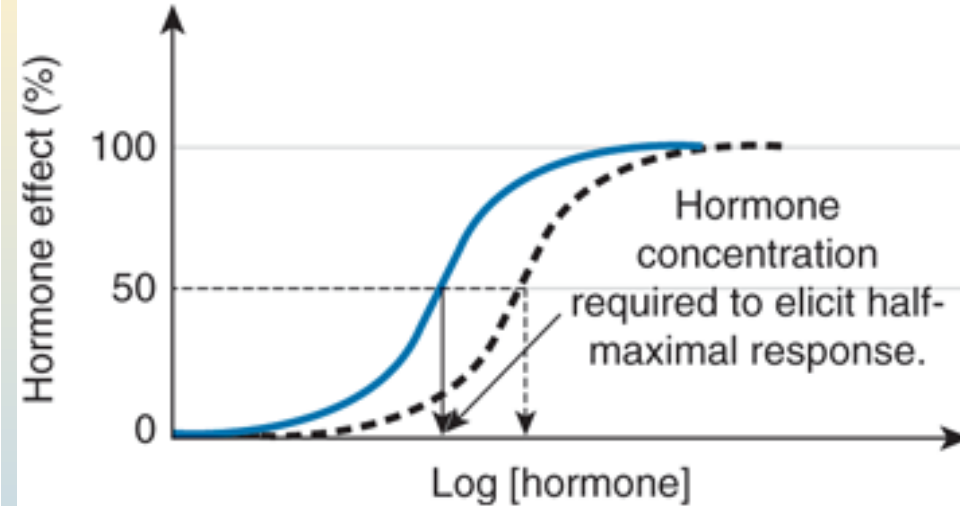
Clinical aspects

A. Decreased hormone responsiveness



Source: Molina PE: *Endocrine Physiology*, 4th Edition: www.accessmedicine.com
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B. Decreased hormone sensitivity



Source: Molina PE: *Endocrine Physiology*, 4th Edition: www.accessmedicine.com
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- Decreased number of receptors
- Decreased concentration of hormone-activating enzyme(s)
- Increased concentration of non-competitive inhibitor
- Decreased number of target cells

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