Bi1100
Hormones – Cellular and Molecular Mechanisms

Syllabus

a) General function of hormones; hormone groups
b) Invertebrate hormones: Endocrine system of crustaceans and insects
c) Hypothalamic-hypophyseal system (hypothalamus, adenohypophysis, neurohypophysis) and hormonal function of the pineal gland
d) Thyroid gland and parathyroid glands; hormonal control of calcium level
e) Adrenal cortex and medulla; kidneys and water management
f) Pancreatic and gastrointestinal hormones
g) Ovaries, testes, hormonal control of the menstrual cycle and pregnancy
h) Eicosanoids and local hormones
i) Pheromones


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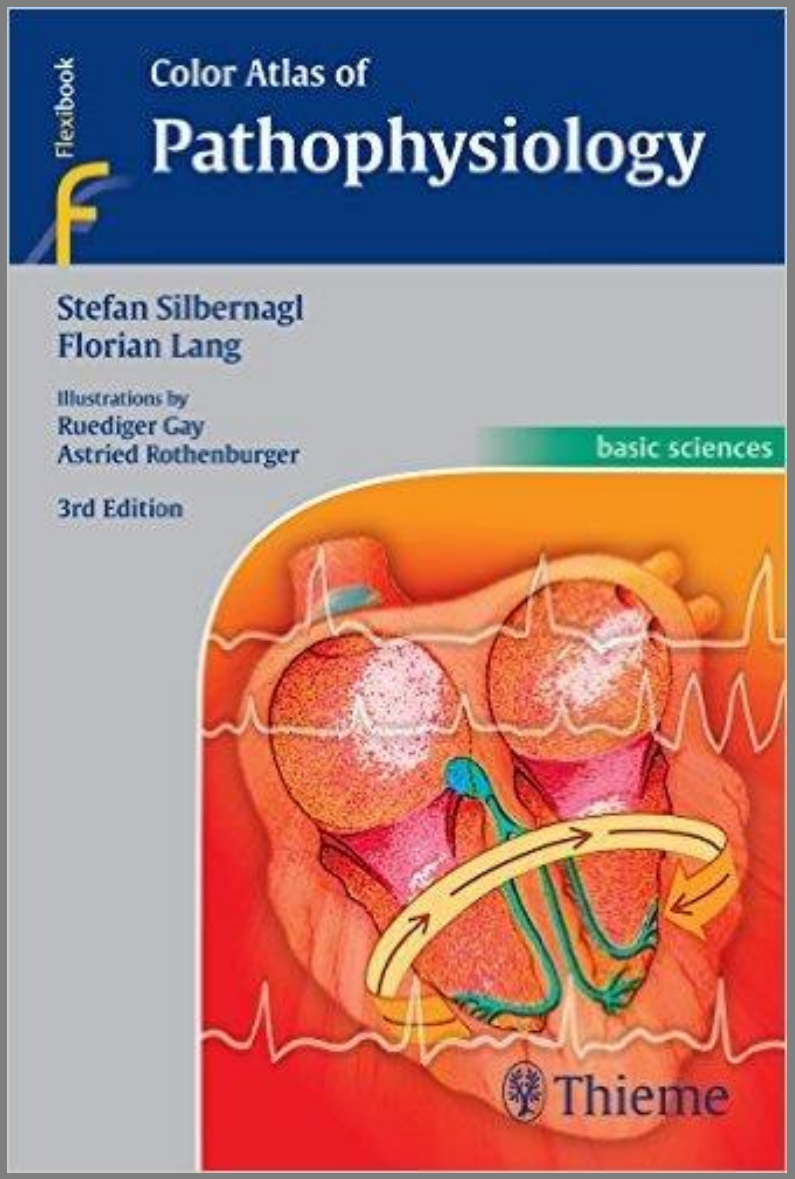
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Ernest Henry Starling (1866 - 1927)

- British physiologist who has been involved in describing of many basic physiological principles
- founder of endocrinology
- discovery of secretin, a substance that stimulates pancreatic secretion, and introduction of the term „**hormone**“ (1905)
- hormone = to set in motion (from Greek)

Endocrine system and hormonal action

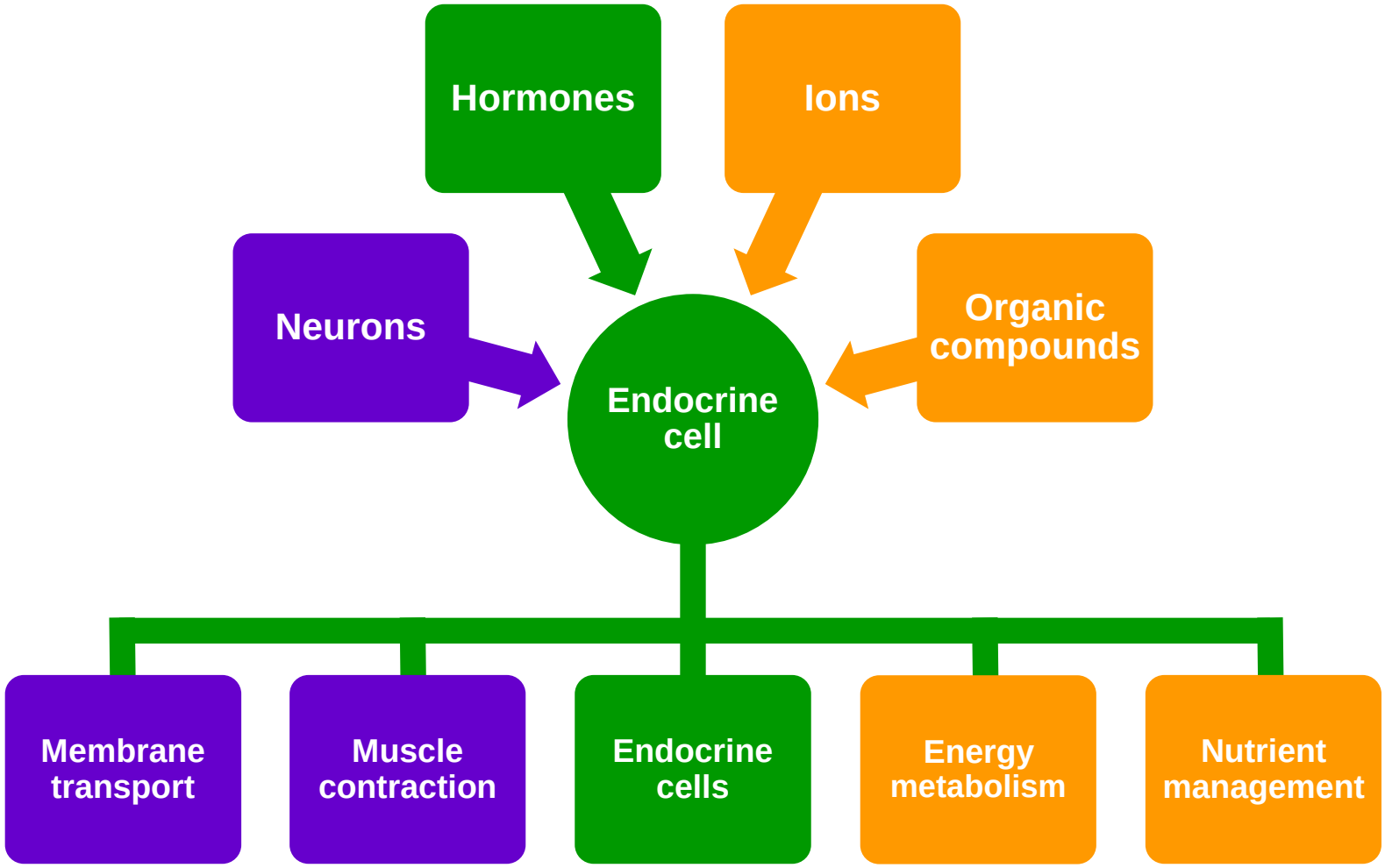
The endocrine system controls the individual functions of the body through hormones and maintains its internal balance (homeostasis).

- a hormone-producing cell affects another cell that responds to the hormone
- target cells need protein receptors to bind a hormone and respond
- by hormonal action we mean the processes that take place in the target cell when it receives a certain hormone through its receptors and responds to it
- the cell response depends not only on the properties of a received hormone, but also on the specific properties of the target cell itself; ie. the same hormone acts on different cells with different effects

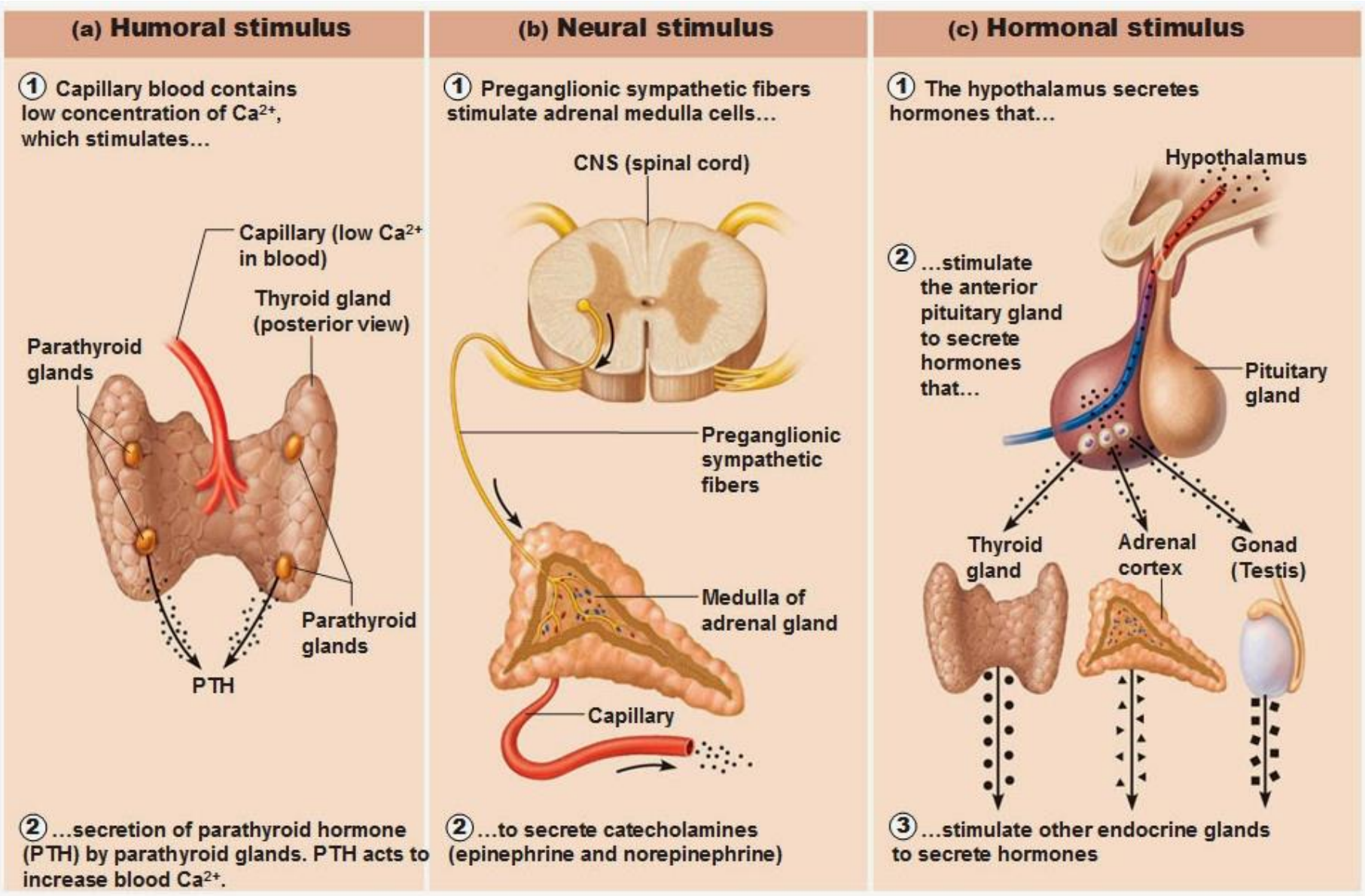
The result of the hormonal action is a specific response of the target cell.

- hormone production > secretion > storage and transport > receptor binding > signal transduction > effect on target cell > hormone degradation

Endocrine cell inputs and outputs



Endocrine cell inputs and outputs



Endocrine, nervous and neuroendocrine systems

- main animal communication and regulatory systems
- signal processing and responses to changes in the internal and external environment
- coordinate the functions of differentiated cells, tissues and organs

NS high speed

NS direct connection of two points through the nerve

NS electrochemical propagation (1/0)

ES large range

ES prolonged response

ES anatomically not restricted

ES chemical transfer of the signal (concentrations and receptors)

NES combines NS and ES characteristics

Endocrine, nervous and neuroendocrine systems

Nervous system

- somatic nerves
- autonomic nerves

- neurotransmitters
- neuromodulators

Neuroendocrine system

- neurons with large bodies (nucleus supraopticus and paraventriculus in the hypothalamus)
- neurons with small bodies in the hypothalamus producing releasing (liberins) and inhibitting (statins) hormones

- neuroendocrine character is typical also for adrenal medulla and glandula pinealis

Endocrine system

- endocrine glands
- endocrine cells diffused in tissues with primarily non-endocrine function

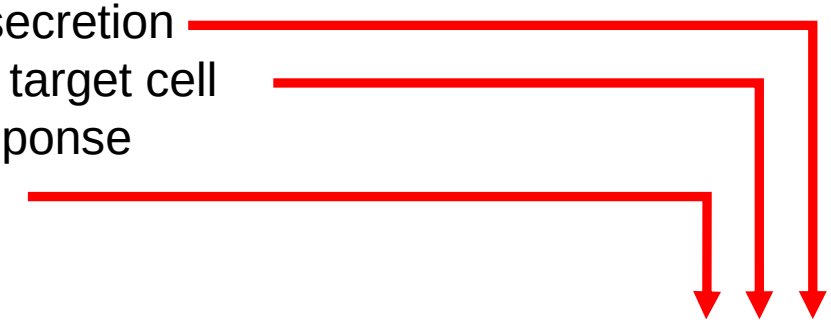
- hormone concentration in extracelullar space about 10^{-8} to 10^{-12} mol/l

Regulation of hormonal activity

Reception and signaling - if a biological need is detected, the endocrine system sends a signal to the target cells to ensure its satisfaction.

Key steps:

- receiving the stimulus
- hormone synthesis and secretion
- hormone transport to the target cell
- induction of a cellular response
- hormone degradation



The physiological effect of hormones depends on their concentration in the blood and extracellular fluids.

If the concentration of hormone is too high or low, various disorders and diseases can occur.

Regulation of hormonal activity

Production rate

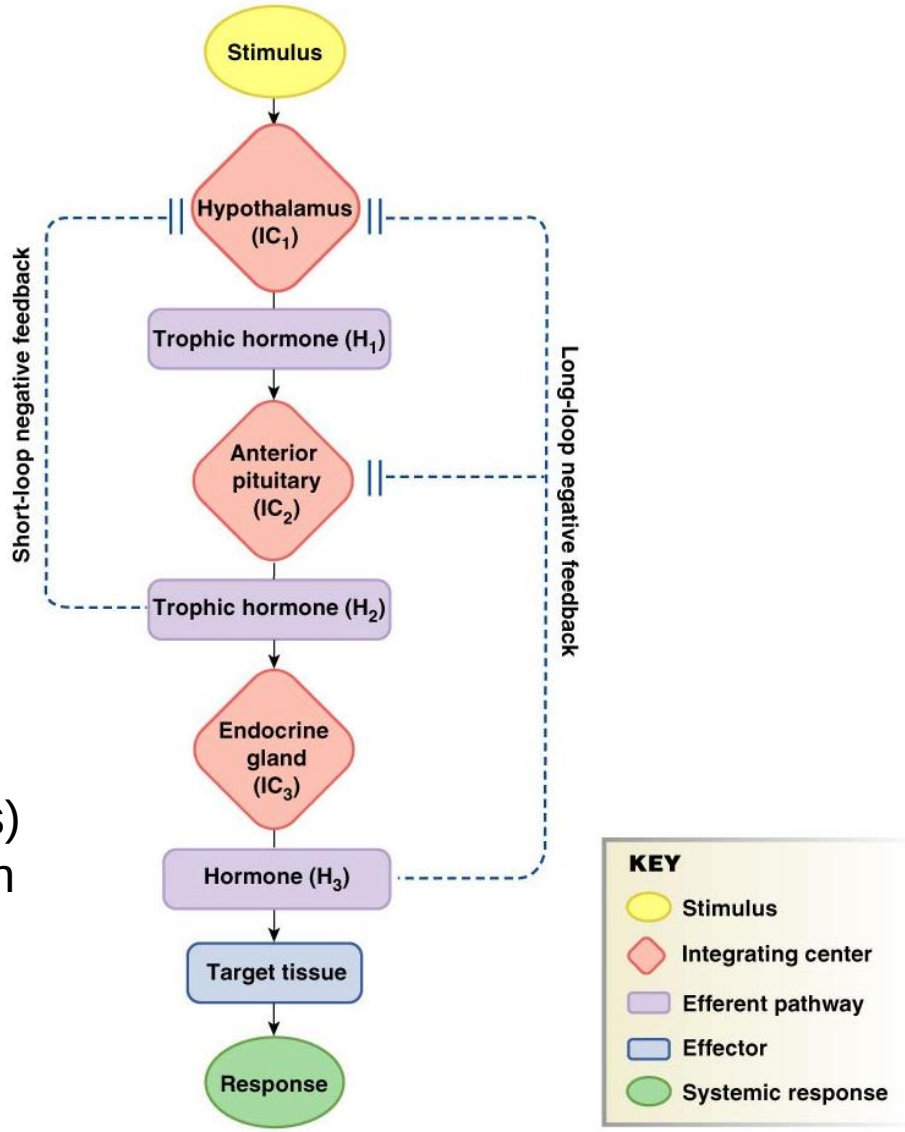
- main control step
- positive and negative feedback
- hypothalamic-hypophyseal axis

Transport rate

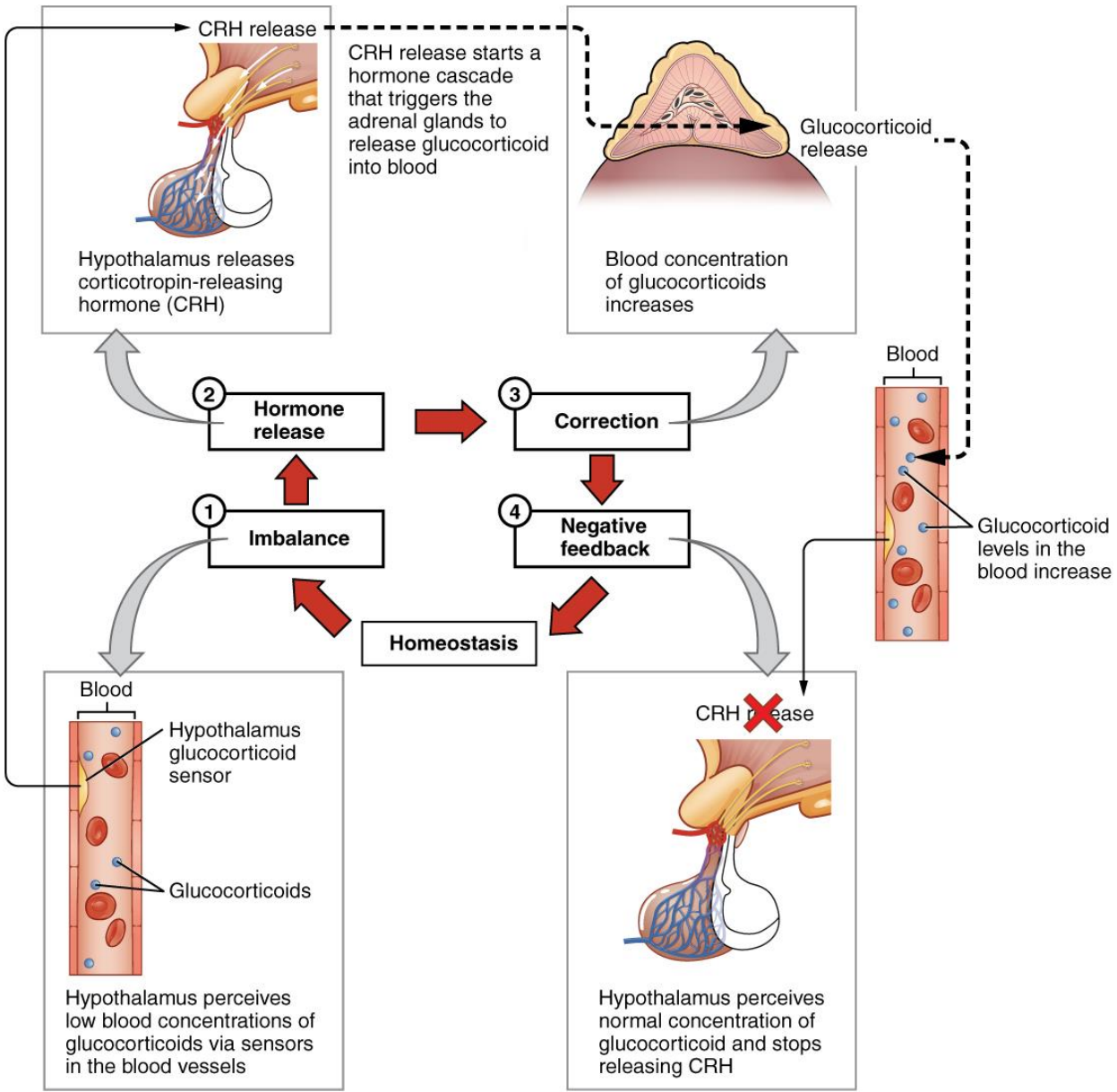
- blood flow regulation
- number of transporters

Degradation rate

- degradation of biomolecules and their metabolism
- short vs. long half-life (seconds to hours)
- termination of secretion and degradation by the target organ
- removal through the kidneys and liver

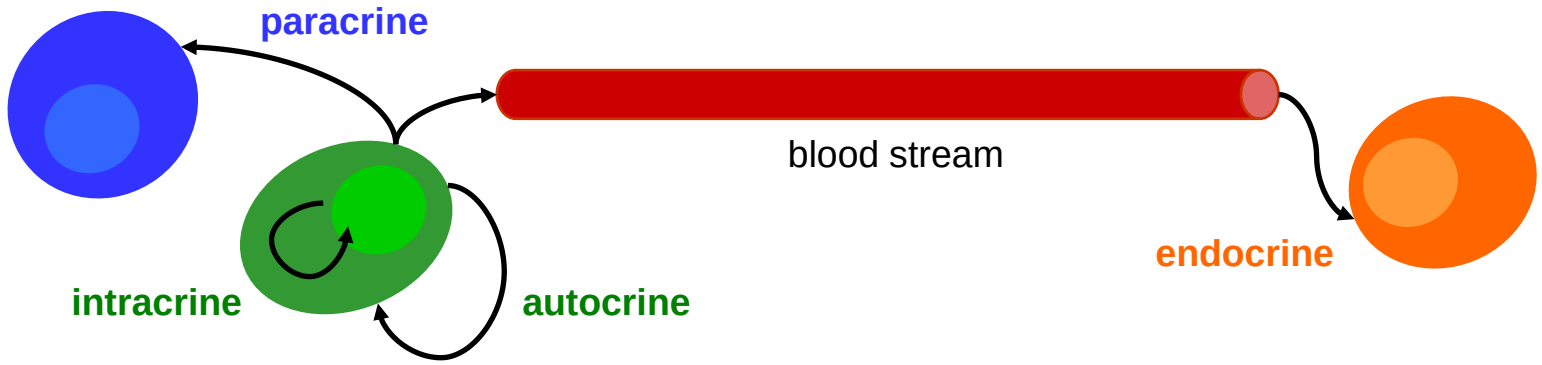


Regulation of hormonal activity



Hormonal signaling among cells

- **neurohormones** - released to circulatory system (synapses)
- **endocrine hormones** - circulatory system (classical hormones)
- **intracrine signals** - inside the cell that produces the hormone (angiotensin II)
- **autocrine secretion** - acts on the secretory cell itself (gastrin, cytokines)
- **paracrine secretion** - interstitium (short half-life)
- **exocrine secretion** - body cavities and out of the body (ectohormones)



Types of hormones according to the target cell distance:

- outside the organism (exocrine)
- distant (neurohormones and endocrine action)
- close (paracrine)
- the target is the source cell (autocrine and intracrine)

Hormonal signaling among cells

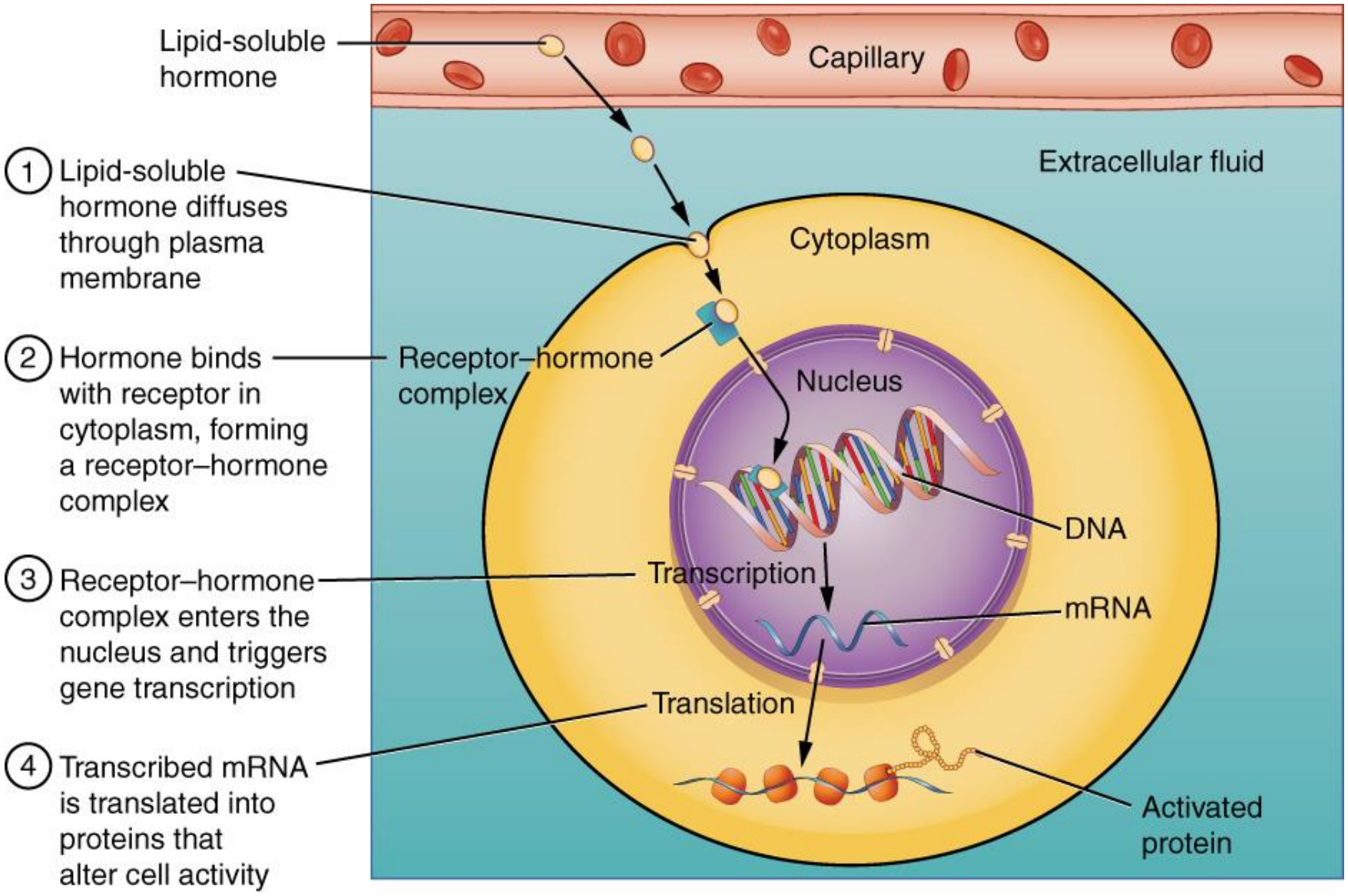
Most hormones circulate in body fluids and can come into contact with almost any cell in the body. However, they only affect **target cells** that have receptors for a particular hormone.

- hormones act as the **first messengers** (extracellular transmission)
- transported in the blood with or without binding to protein transporters
- fast non-genomic effect (activation of proteins) or slower gene response (control of transcription and increased expression of target genes)

1) Steroid (lipophilic, non-polar) hormones

2) Peptide/protein (hydrophilic, polar) hormones

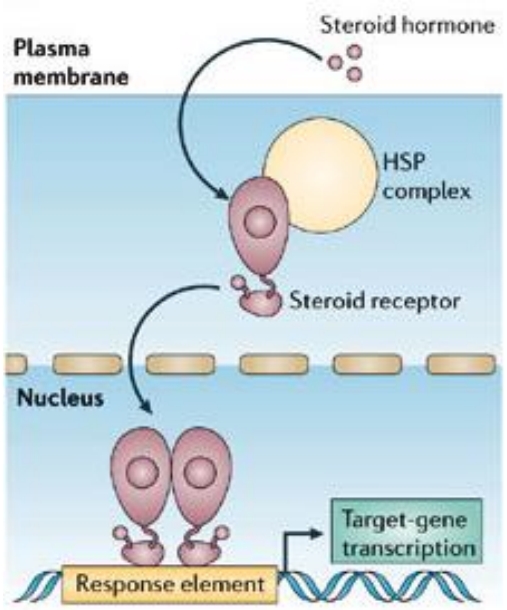
Steroid (lipophilic) hormones



Steroid (lipophilic) hormones

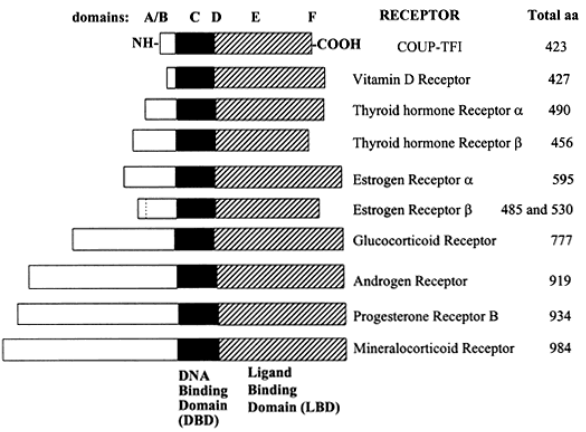
Mode of action:

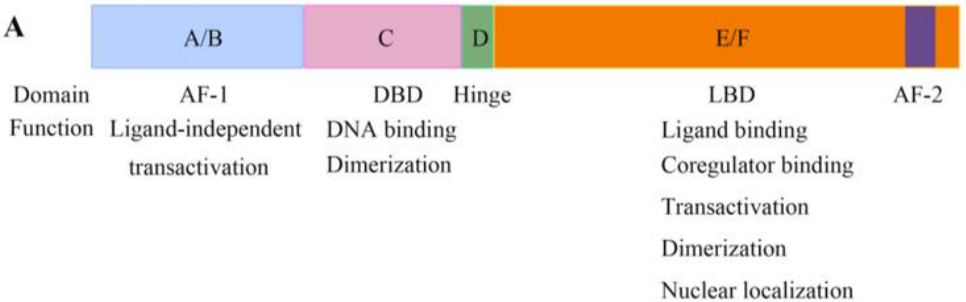
- they diffuse into the cells and enter the nucleus
- binding to a receptor (instead of heat shock proteins; HSP) and formation of complexes
- the complex (dimers/heterodimers) binds to DNA
- transcription of DNA into mRNA
- protein synthesis on ribosomes (translation)

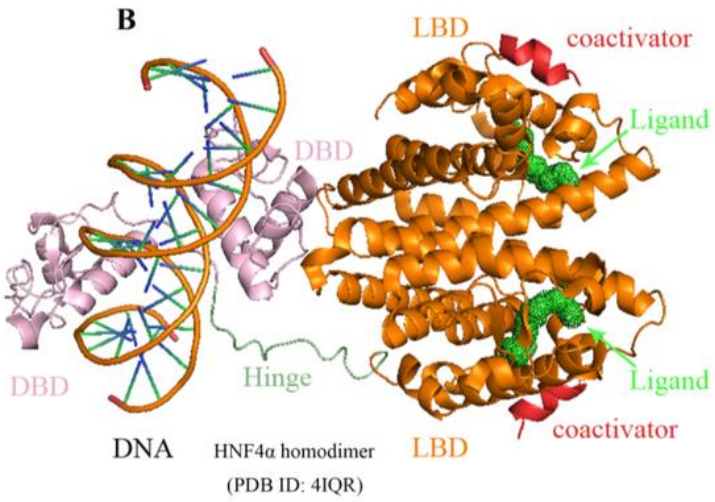


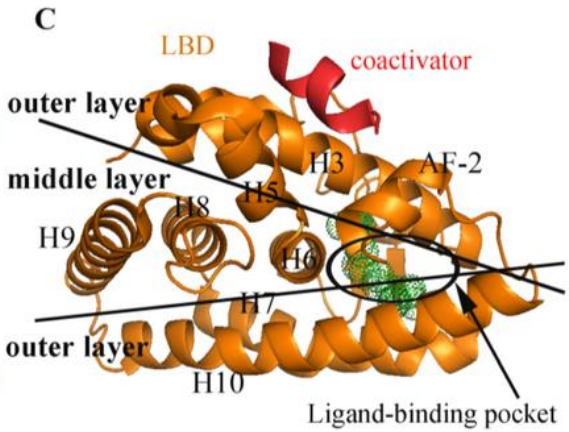
Steroid (lipophilic) hormones

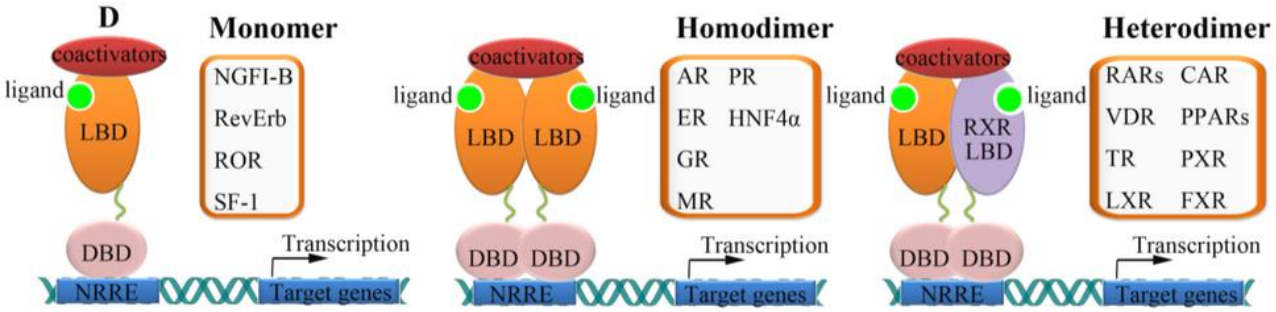
AR androgen receptor
ER estrogen receptor
PR progesterone receptor
GR glucocorticoid receptor
MR mineralcorticoid receptor
TR thyroidhormone receptor
RAR retinoicacid receptor
RXR retinoid X receptor
VDR vitamin D receptor



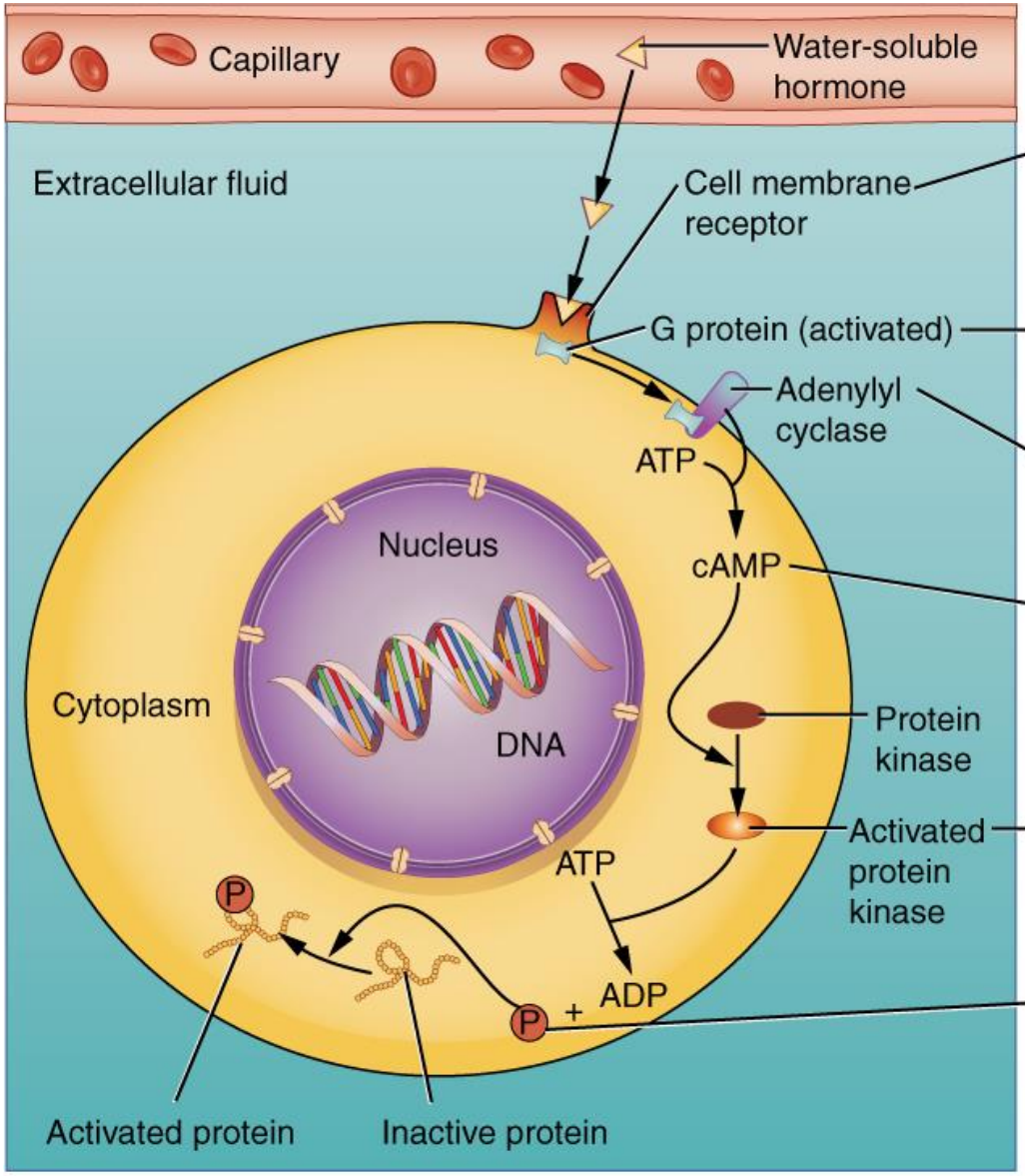






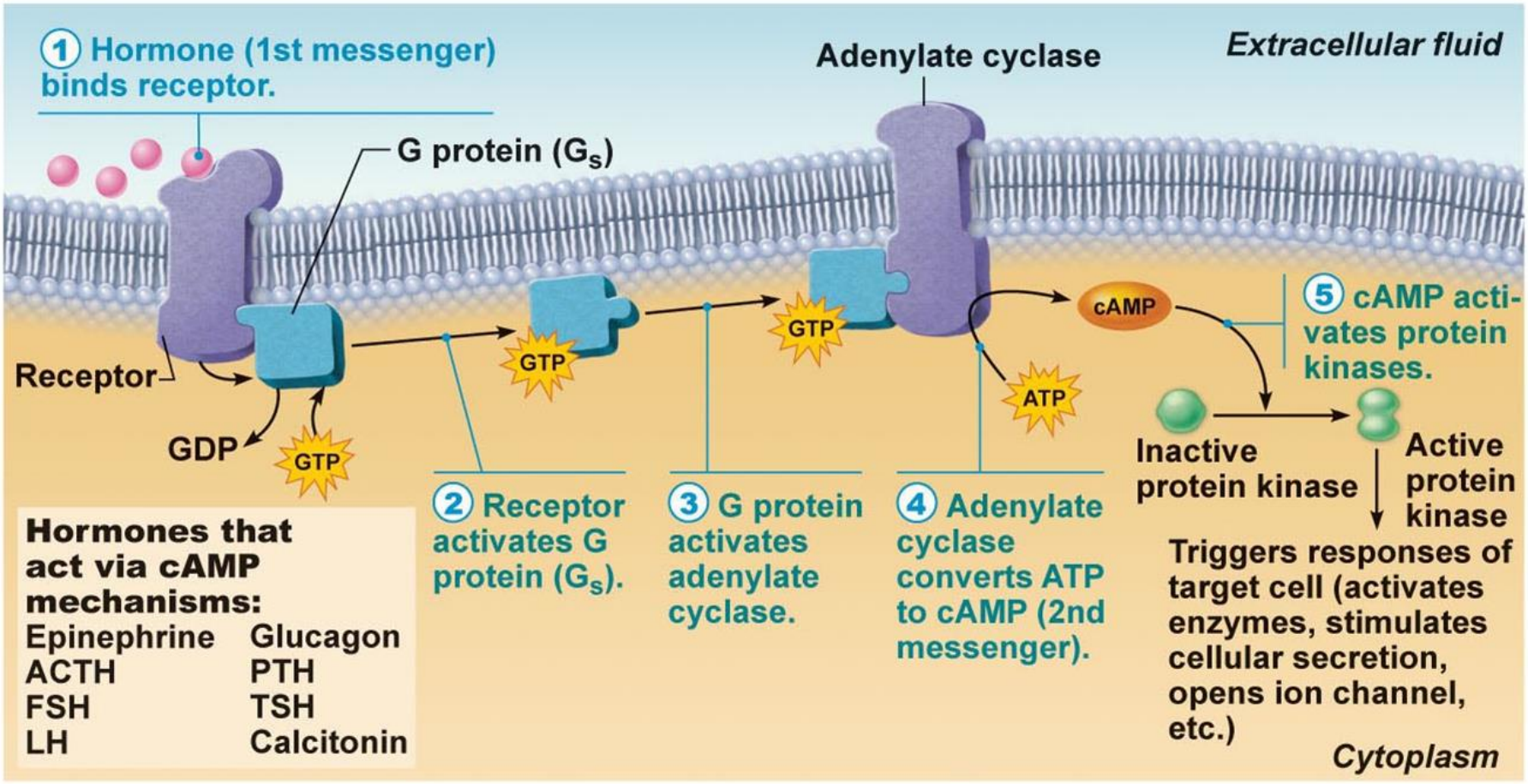


Peptide/protein (hydrophilic) hormones



1. Water-soluble hormones are membrane insoluble. They bind to membrane receptors.
2. The binding activates a G protein.
3. The activated G protein activates adenylyl cyclase.
4. Adenylyl cyclase catalyzes the conversion of ATP to cAMP, the secondary messenger in this pathway.
5. cAMP activates protein kinases.
6. Protein kinases phosphorylate proteins in the cytoplasm. This activates these proteins, allowing them to alter cell activity.

Peptide/protein (hydrophilic) hormones
second messenger cyclic AMP



- G protein (G_s) = stimulating
- c**A**MP dependent protein kinase (A-kinase;**PKA**)

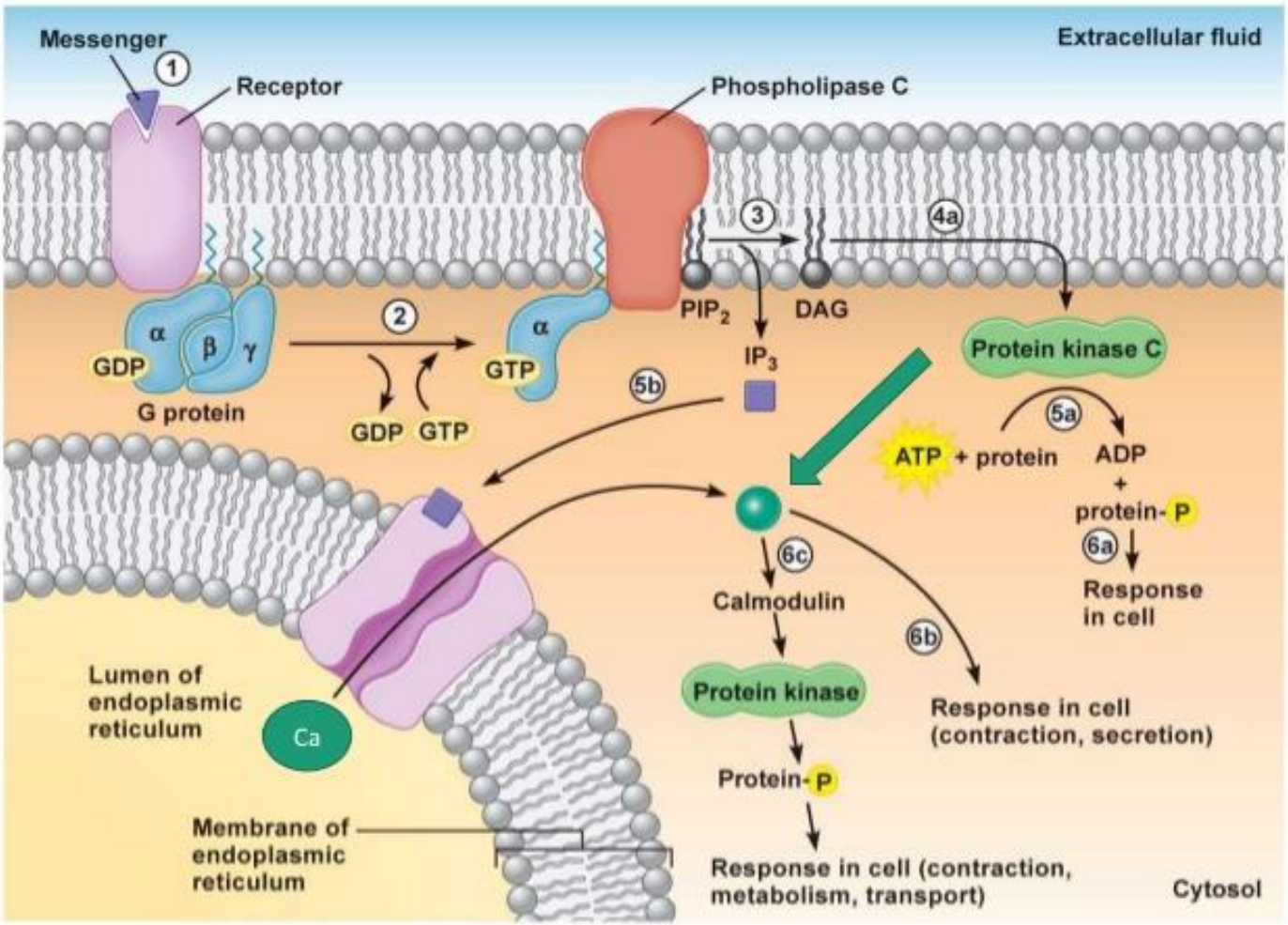
Peptide/protein (hydrophilic) hormones
second messenger cyclic AMP

Mode of action:

- hormone (first messenger) binds to a receptor in the membrane
- GDP is replaced by GTP
- G protein activation
- hydrolysis of GTP to GDP
- activation of **adenylate cyclase**
- G protein inactivation
- **cAMP** (second messenger) produced from ATP (regulation by phosphodiesterase, cAMP > 5'-AMP)
- activation of protein kinases (**PKA**) = receptors for cAMP
- phosphorylation of transcription factors (cAMP response element-binding protein, **CREB**)
- CREB together with co-activators stimulates transcription of target genes (cellular response)

Peptide/protein (hydrophilic) hormones

second messengers IP_3, DAG, and the third messenger Ca^{2+}



Peptide/protein (hydrophilic) hormones
second messengers IP_3, DAG, and the third messenger Ca^{2+}

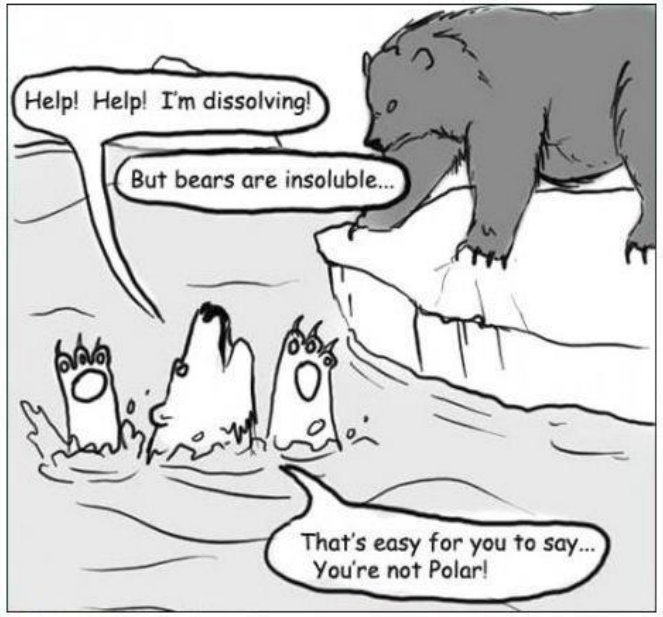
Mode of action:

- hormone (first messenger) binds to a receptor in the cellular membrane
- GDP is replaced by GTP
- G protein activation
- hydrolysis of GTP to GDP
- activation of **phospholipase C (PLC)**
- G protein inactivation
- phospholipase cleaves phosphatidylinositol-4,5-bis-phosphate $(PIP)_2$) to 1,2-diacylglycerol (**DAG**) and inositol 1,4,5-triphosphate (**IP_3**) = **second messengers**
- DAG activates protein kinase C (**PKC**) and IP_3 triggers the **Ca^{2+}** release (third messenger) from the endoplasmic reticulum
- Ca^{2+} directly activates the cellular response (opening of channels in the plasma membrane) or binds to calmodulin and activates protein kinases

Localisation of hormone receptors

Cell membrane

- for large polar molecules
- outer side of the cytoplasmic membrane
- all peptide hormones and some amino acid derivates (catecholamines and melatonin)



Intracellular

- all non-polar and small polar molecules
- in the cytoplasm (steroid h.), nucleus (thyroid h.), mitochondria
- all steroid hormones and some amino acid derivates (thyroid hormones)

Types of hormones

- **according to the place of their synthesis:**

1) Neuroendocrine (neurosecretory) system

- neurohormones / blood system x neurotransmitters / synapses (i.e. they are neuroparacrine)
- neurotransmitters are often hormones
- large spatial and temporal area of effect compared to neurotransmitters
- slower transport compared to neurotransmitters

2) Endocrine system

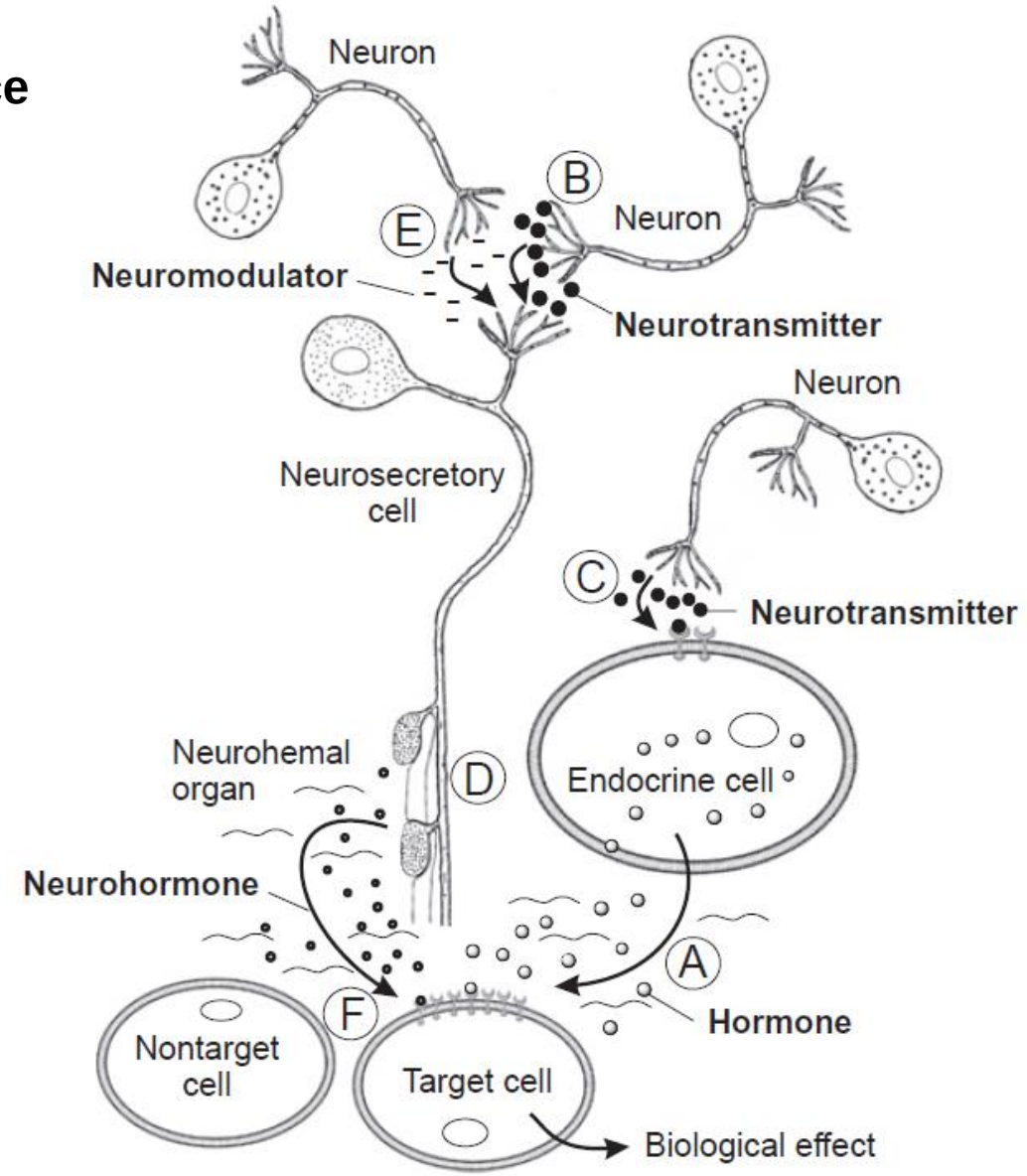
- specialized and clearly distinguishable secretory cells
- secretion directly into the blood typically via fenestrated capillaries

3) Tissues and organs

- tissue hormones
- cells scattered in the tissue; they are not localised in the specialized endocrine organs
- adipose tissue, intestine, stomach, kidneys, heart and more

Types of hormones

- **according to the place of their synthesis:**



Types of hormones

- **according to the structure:**

1) derived from amino acids
(hormones of adrenal medulla)

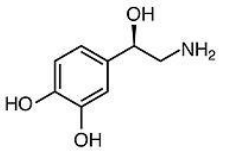
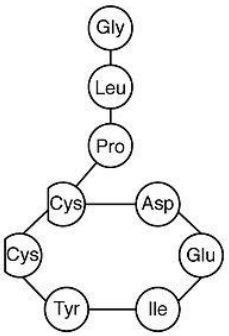
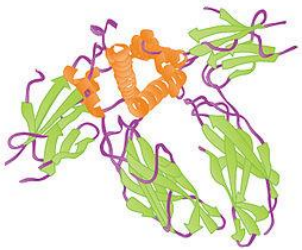
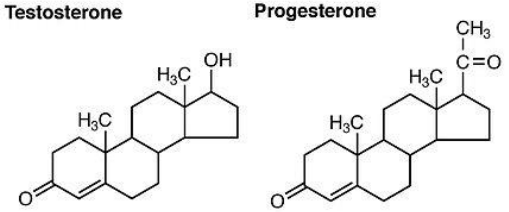
2) peptide hormones
(neurohypophyseal hormones)

3) protein hormones
(> 50 AA; somatotropin)

4) steroids
(hormones of adrenal cortex, gonads)

5) eicosanoids
(fatty acid derivatives; local hormones)

6) less common structures
(insect terpenoids)

Hormone Class	Components	Example(s)
Amine Hormone	Amino acids with modified groups (e.g. norepinephrine's carboxyl group is replaced with a benzene ring)	**Norepinephrine** 
Peptide Hormone	Short chains of linked amino acids	**Oxytocin** 
Protein Hormone	Long chains of linked amino acids	**Human Growth Hormone** 
Steroid Hormones	Derived from the lipid cholesterol	**Testosterone** **Progesterone** 

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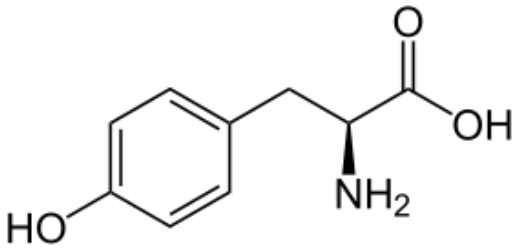
Hormones derived from AA

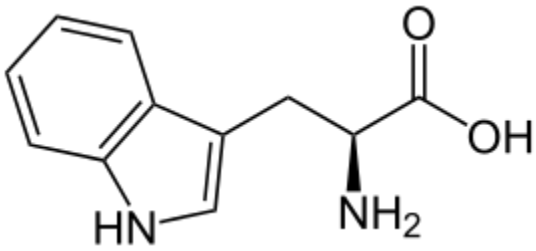
Tyrosine

- thyroid hormones (thyroxine)
- catecholamines produced in the adrenal medulla (adrenaline and noradrenaline)



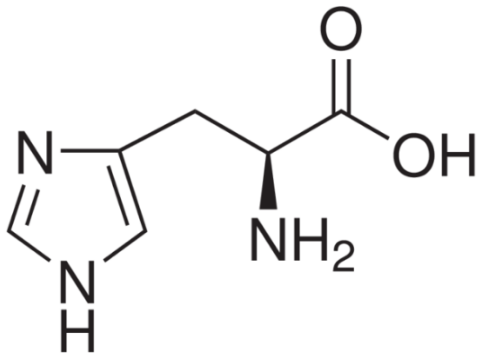
Tryptophan

- serotonin and melatonin precursor



Histidine

- histamine synthesis



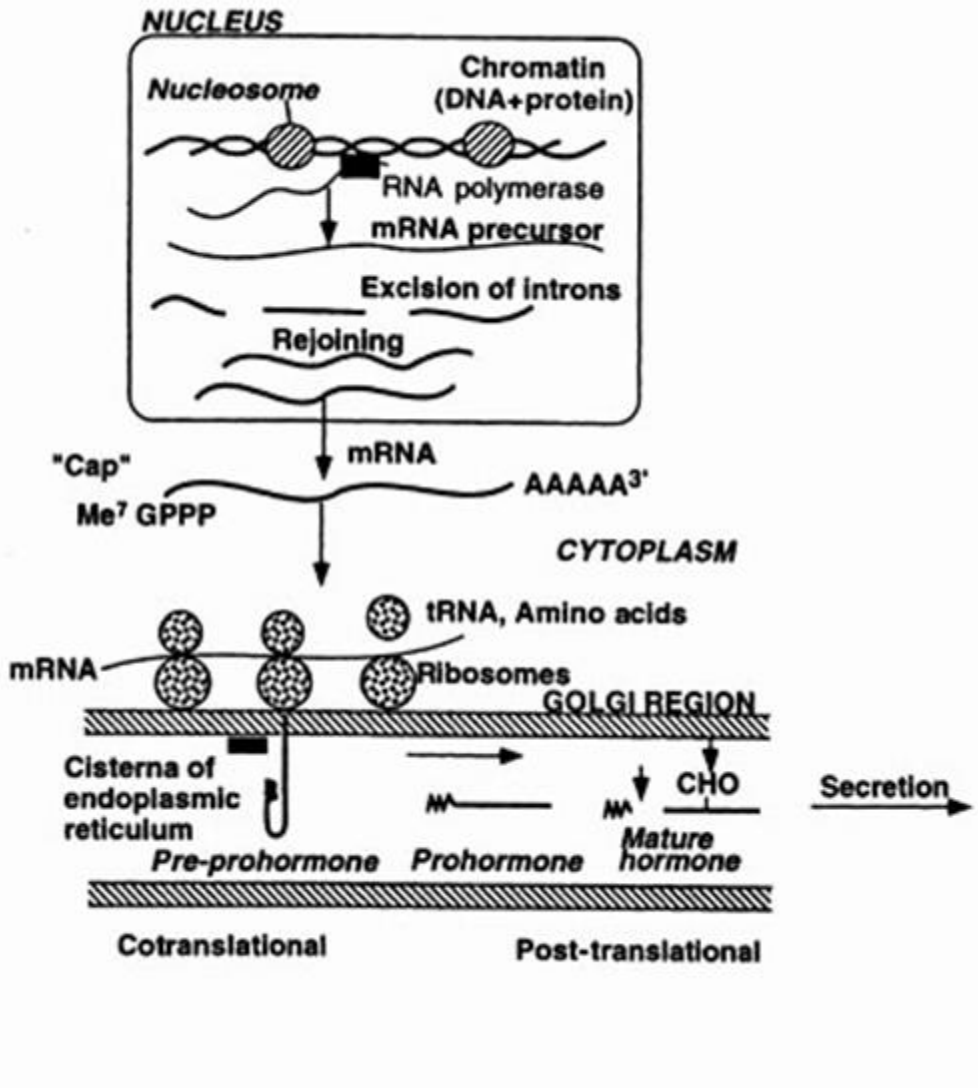
Peptide and protein hormones

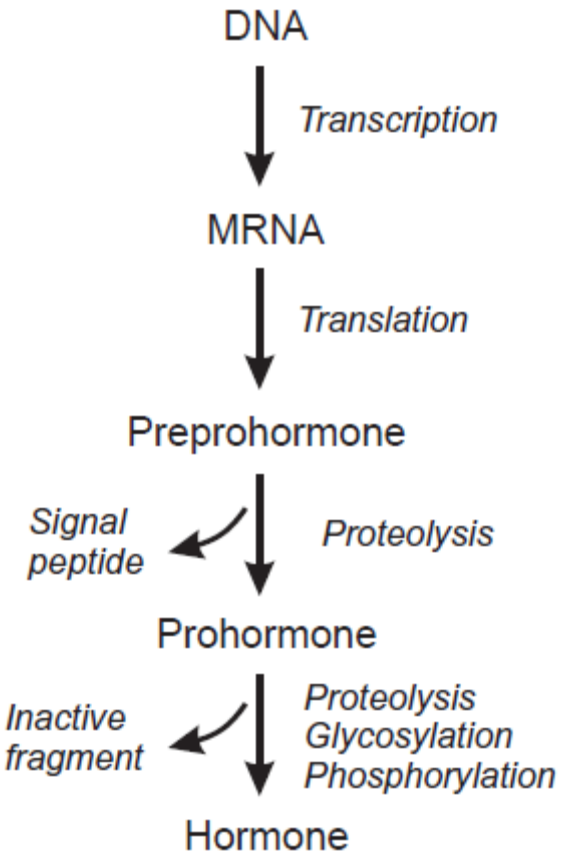
- the largest group of hormones
- three to hundreds of AA in the chain
- often produced as larger precursors, which are subsequently proteolytically cleaved to the active hormone
- **soluble in water**

Synthesis:

- specific gene > transcription into mRNA > translation into the precursor (**preprohormone**) > posttranslational modification in the endoplasmic reticulum > cleavage of the signal sequence (hydrophobic AA) in the Golgi apparatus (**prohormone**) > proteolytic cleavage to **active hormone** (convertases) and its storage in secretory vesicles > transport of the vesicles to the plasma membrane > exocytosis and secretion into the blood stream
- alternatively, the secretion of prohormone and its activation in the circulation (e.g. angiotensin secreted by liver cells and activated in the blood by enzymes from kidneys and lungs)

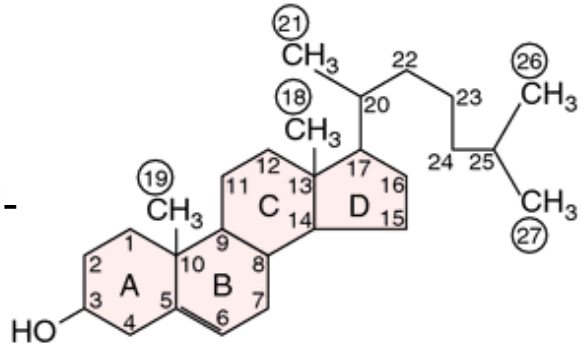
Peptide and protein hormones

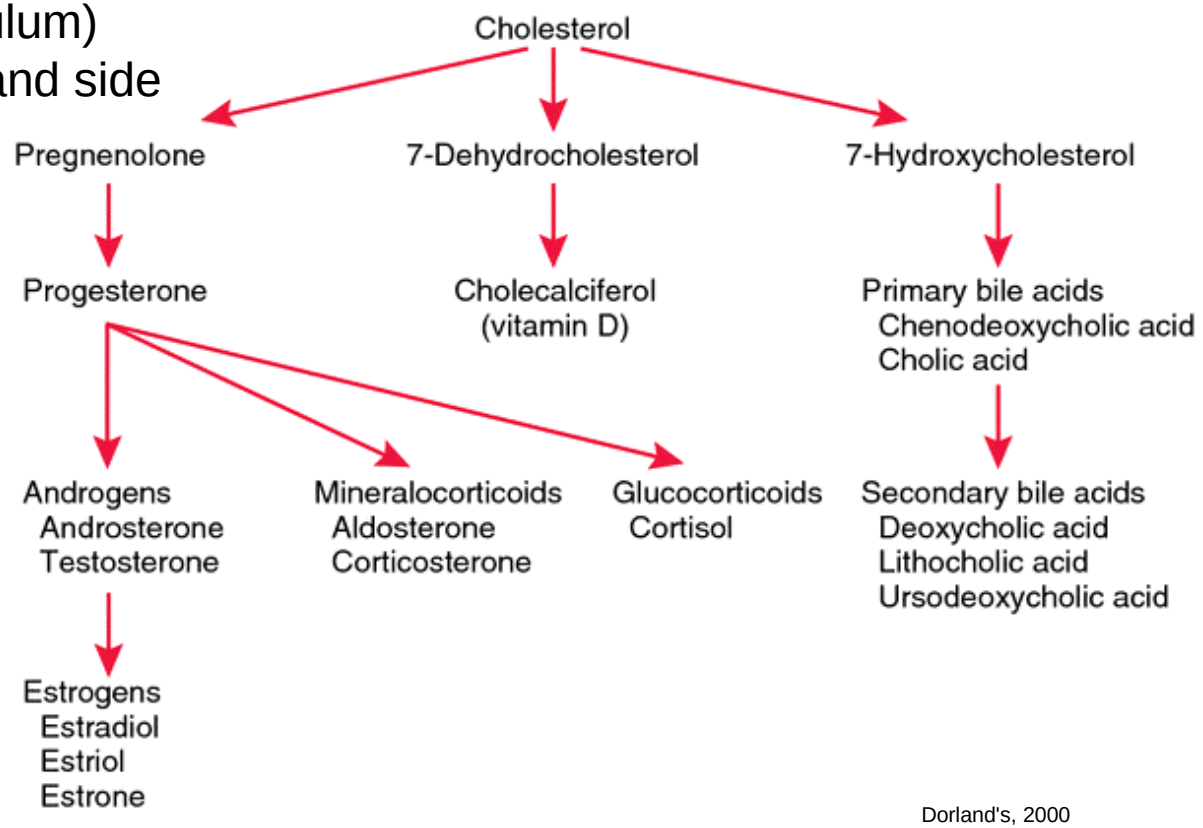




Steroids

- derived from cholesterol
- synthesis in the liver (~ 20%) and the glands producing steroid hormones
- citrate from mitochondria + ATP + acetyl-CoA > farnesyl diphosphate > cholesterol
  (cytosol + endoplasmic reticulum)
- differences in ring structure and side chains
- **soluble in lipids**





Dorland's, 2000

Steroids

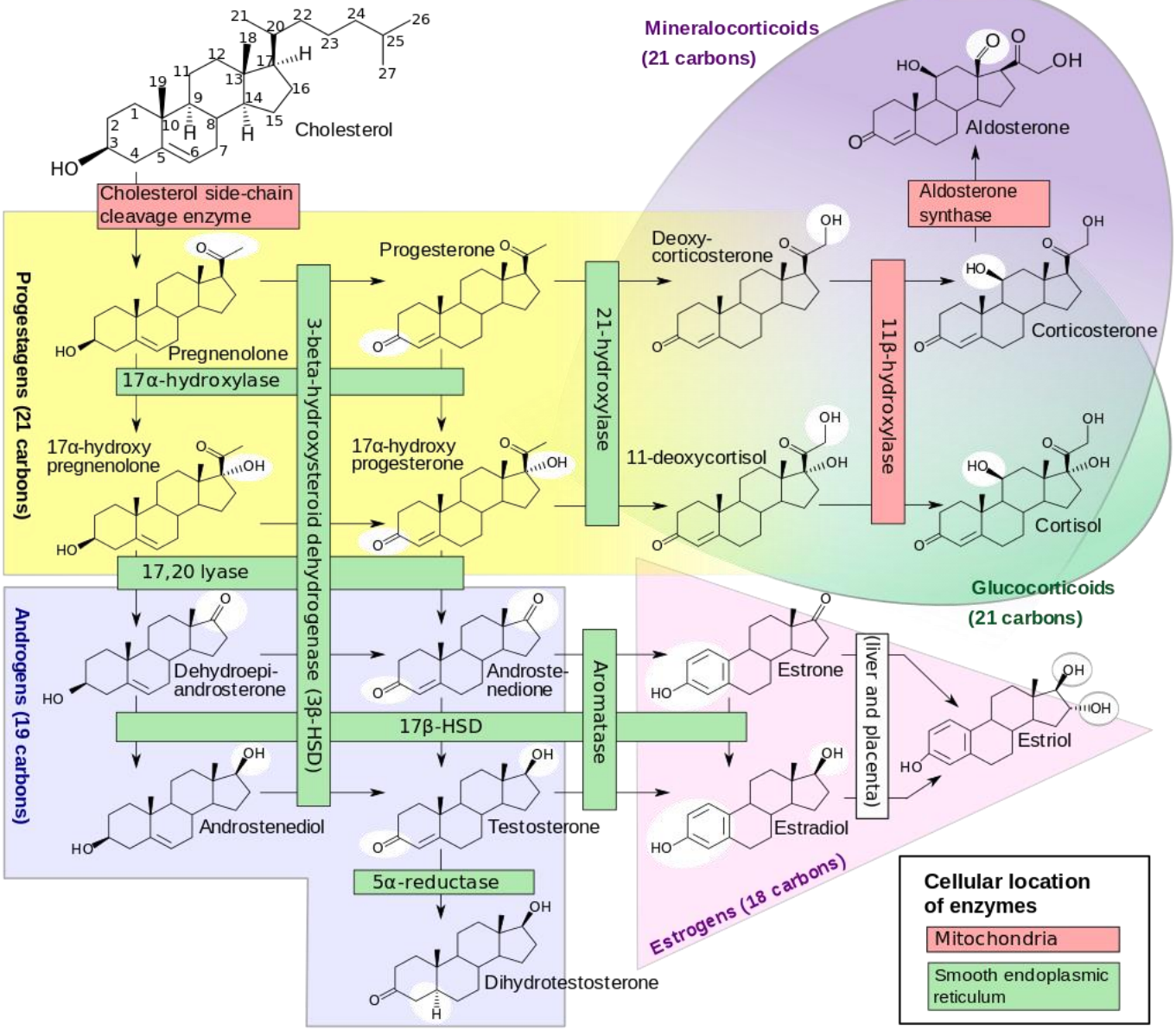
Synthesis:

- cholesterol pool, intracellular acetate synthesis, extracellular lipoproteins
- enzymes in mitochondria and smooth endoplasmic reticulum
- the transport of free cholesterol from cytoplasm to mitochondria is the limiting step
- Steroidogenic Acute Regulatory Protein (StAR, STARD1)
- **side-chain cleavage enzyme** / desmolase / $P450_{SCC}$ / CYP11A1
- steroids are not stored in cells, but released immediately after their synthesis
- permeate cell membranes
- in some cases, the conversion to an active form takes place in the target cell (e.g. androgen secreted in gonads is converted to estrogen in the brain)
- 1,25-dihydroxyvitamin D_3 (calcitriol; cholesterol-derived; synthesis in the kidneys is stimulated by parathyroid hormone)

Transport:

- insoluble in water > complexes with specific globulins
- corticosteroids-binding (cortisol) globulin, sex steroids (testosterone and estradiol) –binding globulin

Steroids - synthesis



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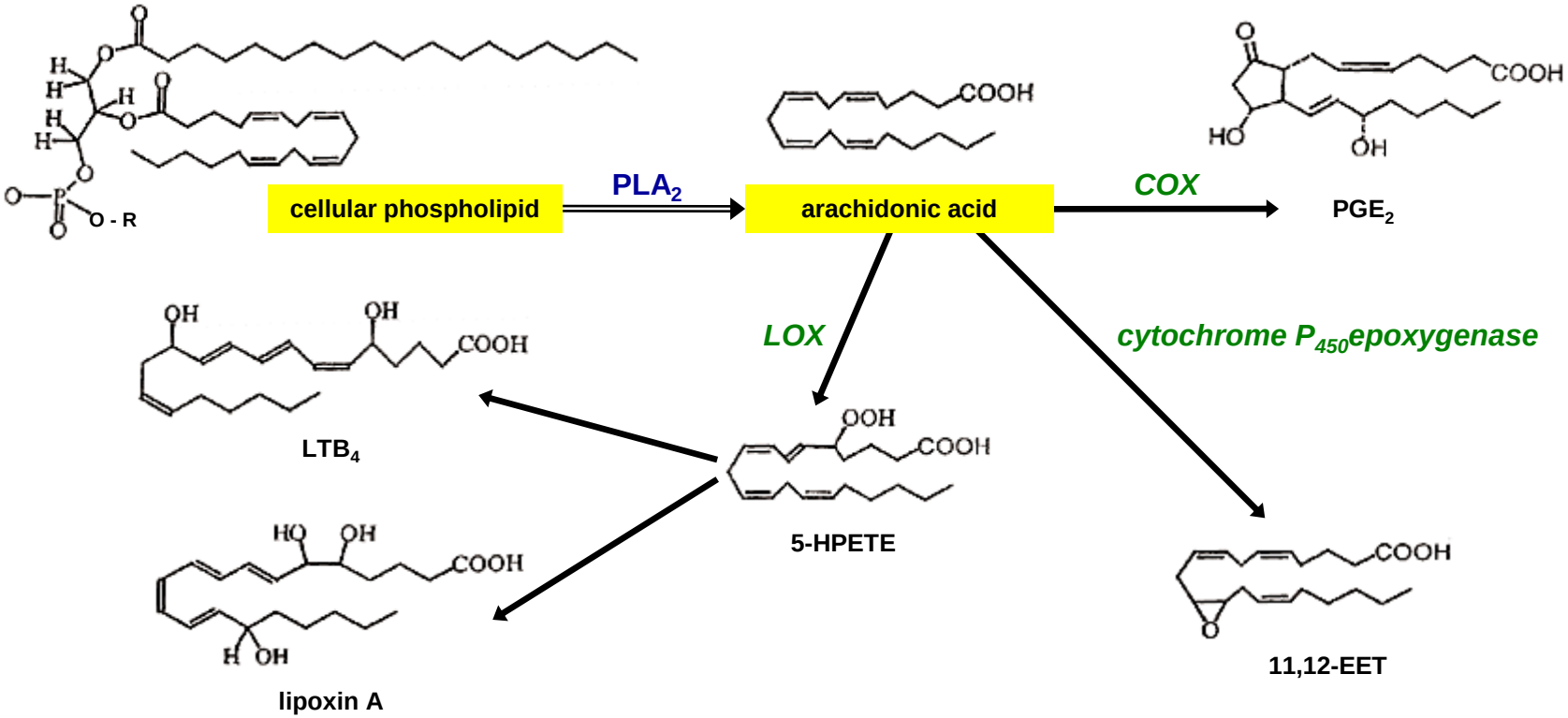
Eicosanoids

- derived from polyunsaturated fatty acids (PUFAs)
- **arachidonic acid** (AA; 20: 4n-6), eicosapentaenoic (EPA; 20: 5n-3) and dihomo-γ-linolenic acid (DGLA; 20: 3n-6)
- source of PUFAs are the membrane lipids - phospholipase A_2
- expression of cyclooxygenases (COX), lipoxygenases (LOX) and other enzymes that control eicosanoid synthesis



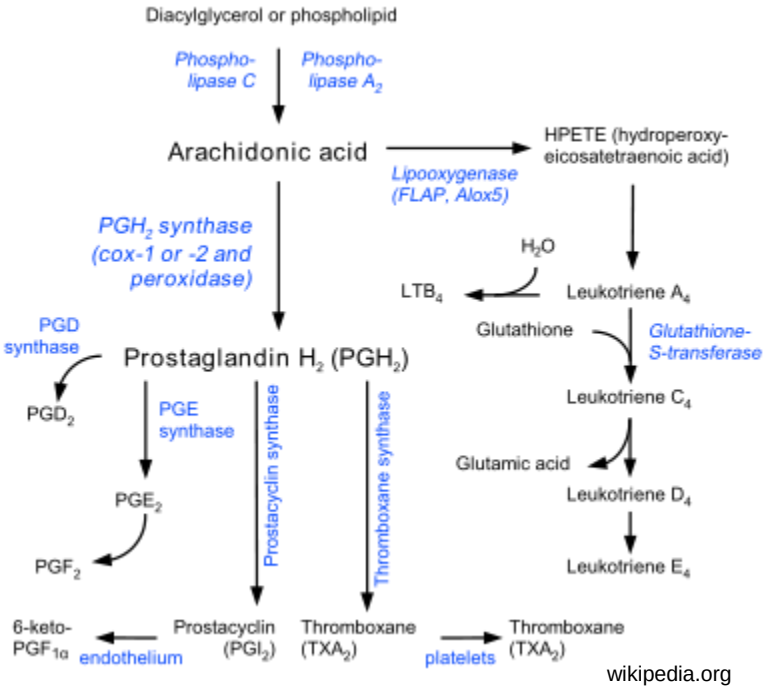
Eicosanoids

Classical eicosanoids (vertebrates, invertebrates)**:**

- prostanoids (prostaglandins, prostacyclins, thromboxanes) and leukotrienes

Non-classical eicosanoids (mammals)**:**

- hepoxilins, lipoxins, epi-lipoxins, epoxyeicosatriene acids, isoprostanes



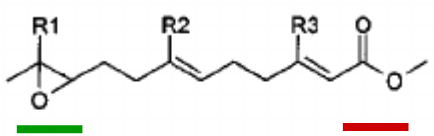
- eicosanoids are not stored in the cells; synthetised if necessary
- rapid metabolic inactivation; typically active for only few seconds

Terpenoids

- biosynthesis similar to the cholesterol production in animals
- takes place in cytosol and endoplasmic reticulum
- citrate, acetyl-CoA, ATP, mevalonate… farnesyl diphosphate > diphosphatase > farnesol > NAD+ dependentdehydrogenase > pharnesoic acid > methylation (pharnesoic acid methyl transferase) and epoxidation (P450 dependent methyl transferase)
- in the structure contain epoxy and methyl ester group

- freely pass through the membranes
- they are not stored in cells
- transported in binding with lipophorins

Insect Juvenile Hormones



JH O : R1 = Et , R2 = Et , R3 = Et

JH I : R1 = Et , R2 = Et , R3 = Me

JH II : R1 = Et , R2 = Me , R3 = Me

JH III : R1 = Me , R2 = Me , R3 = Me

Summary of hormone types and their basic properties

	soluble in lipids		insoluble in lipids	
	STEROIDS	**THYROID HORMONES**	**PEPTIDES AND PROTEINS**	**CATECHOLAMINS**
Type of secretion	diffusion	diffusion	exocytosis	exocytosis
Binding to a carrier protein	Yes	Yes	Rarely	No
Half-life in plasma	hours	days	minutes	seconds
Time constant of effect	hours to days	days	minutes to hours	seconds or less
Receptor localization	cytosolic or nuclear	nuclear	on the plasma membrane	on the plasma membrane