Centrum pro výzkum toxických látek v prostředí

# BIOMARKERS AND TOXICITY MECHANISMS

# 08 – Mechanisms

# Signalling and regulation

Luděk Bláha, PřF MU, RECETOX
www.recetox.cz

Tento projekt je spolufinancován Evropským sociálním fondem a státním rozpočtem České republiky.

EVROPSKÁ UNIE esf

MINISTERSTVO ŠKOLSTVÍ, MLÁDEŽE A TĚLOVÝCHOVY

OP Vzdělávání pro konkurenceschopnost

UNIVERSITAS MASARYKIANA BRUNENSIS

INVESTICE DO ROZVOJE VZDĚLÁVÁNÍ

# Cell communication & regulation: a target for toxicants

… especially sensitively regulated processes are highly susceptible to toxicants

→ toxicity to REGULATIONS & SIGNALLING

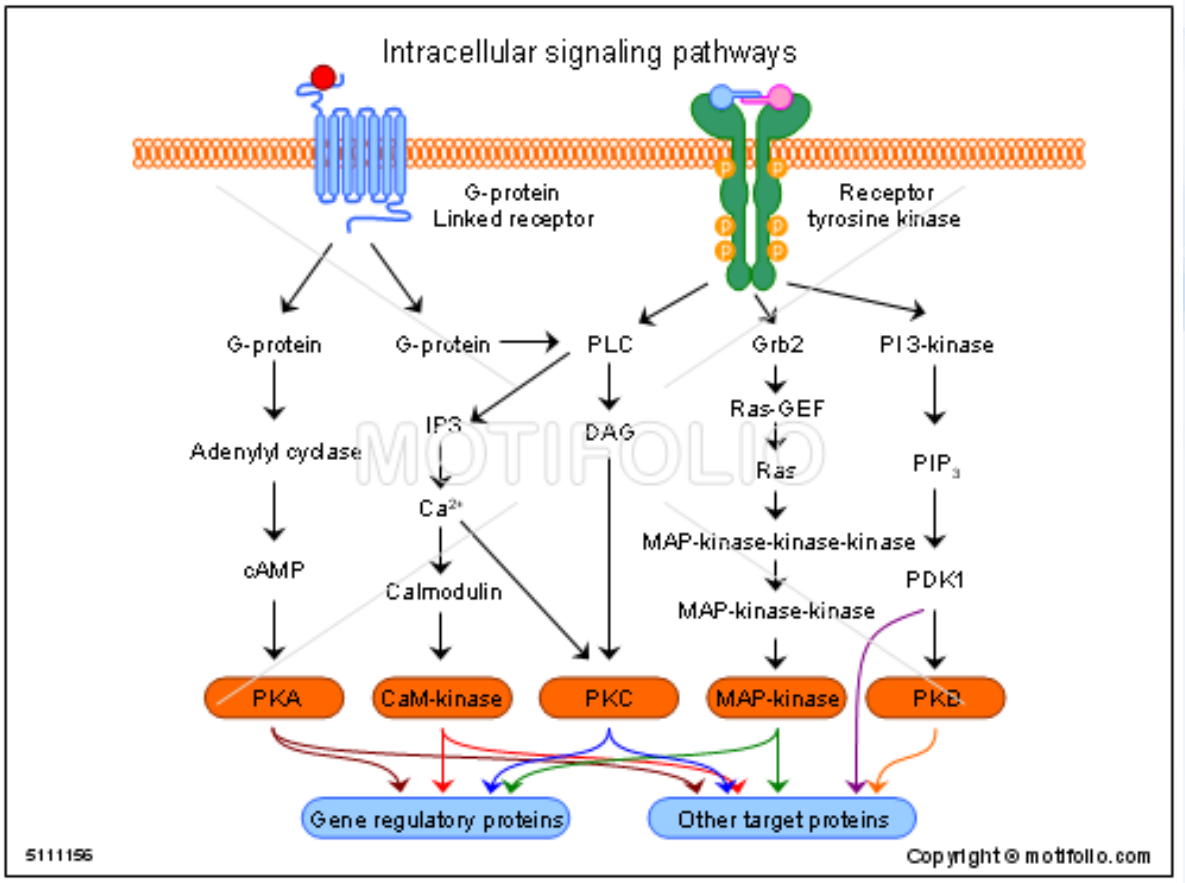
Hierarchy in signalling

- **systems**: neuronal ←→ endocrine

- **cell-to-cell**
  hormonal & neuronal signal transmission
  contact channels

- **intracellular** signal transduction

# INTRACELLULAR signals

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# Intracellular signal transduction: target of toxicants

- **Regulation of cell life = control of major cell functions**
  - metabolism
  - proliferation
  - differentiation
  - death (apoptosis)

- **Regulation controlled by complex signalling**
  - "network" of general pathways
  - similar in all cells / different cell-specific effects

# Intracellular signal transduction: target of toxicants

- **Consequences of signalling disruption**
  - unwanted changes in „homeostatic“ rates among proliferation / differentiation / apoptosis

→ cell transformation (carcinogenicity)
→ embryotoxicity
→ immunotoxicity
→ reproduction toxicity

*.... and other chronic types of toxicity*

# Signal transduction - principles

## Two major signalling processes

– **protein-(de)phosphorylation**

ProteinKinases - PKs, ProteinPhosphatases - PPases

- **secondary messengers**

cAMP / IP3, PIP2, DAG, Ca2+, AA

## Three major types of signalling

1: Membrane receptors (G-protein, kinases)

→ activation of protein kinase A (PKA):
major messenger: cAMP, **MAPKs**

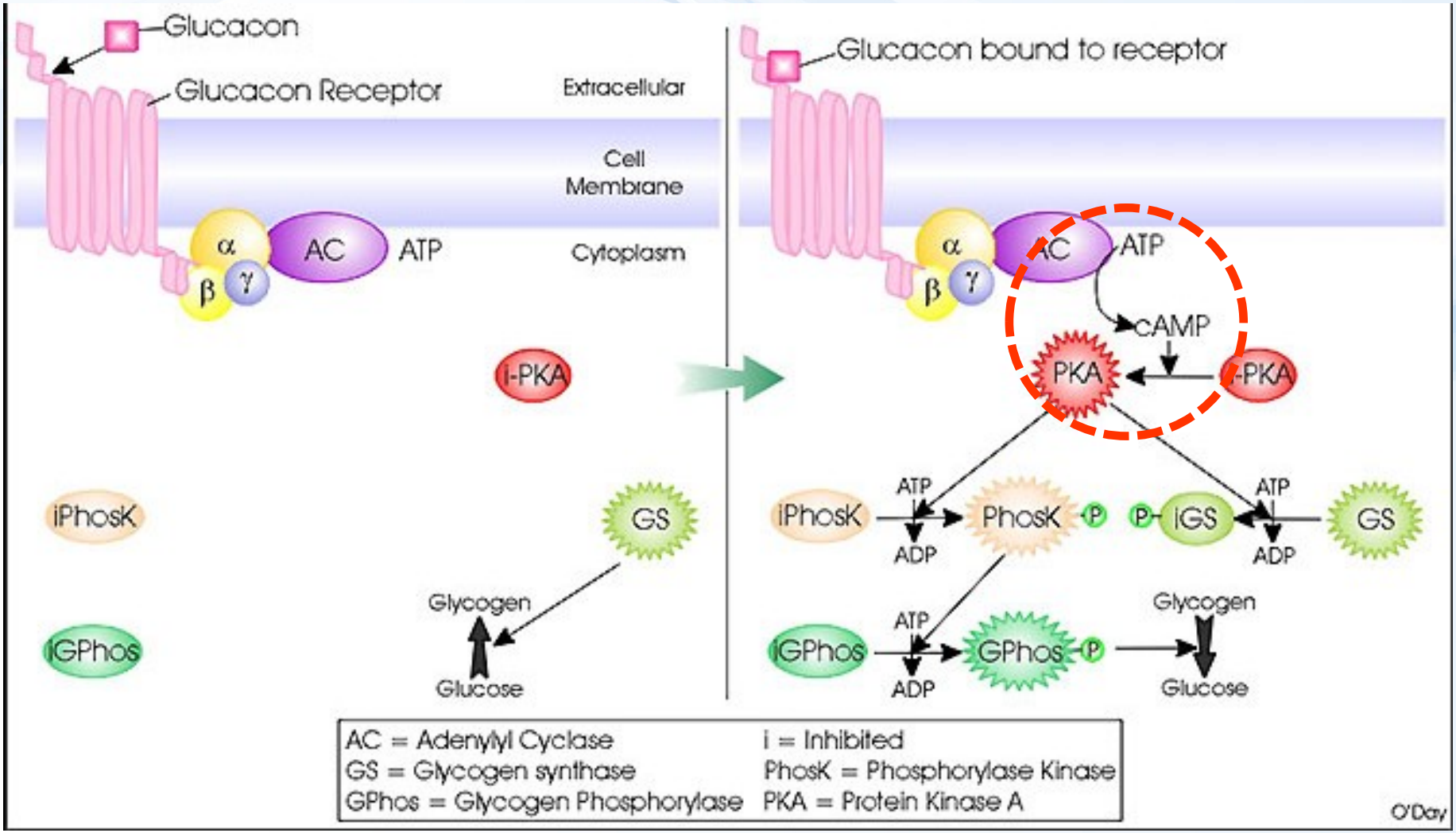
2: Membrane receptors

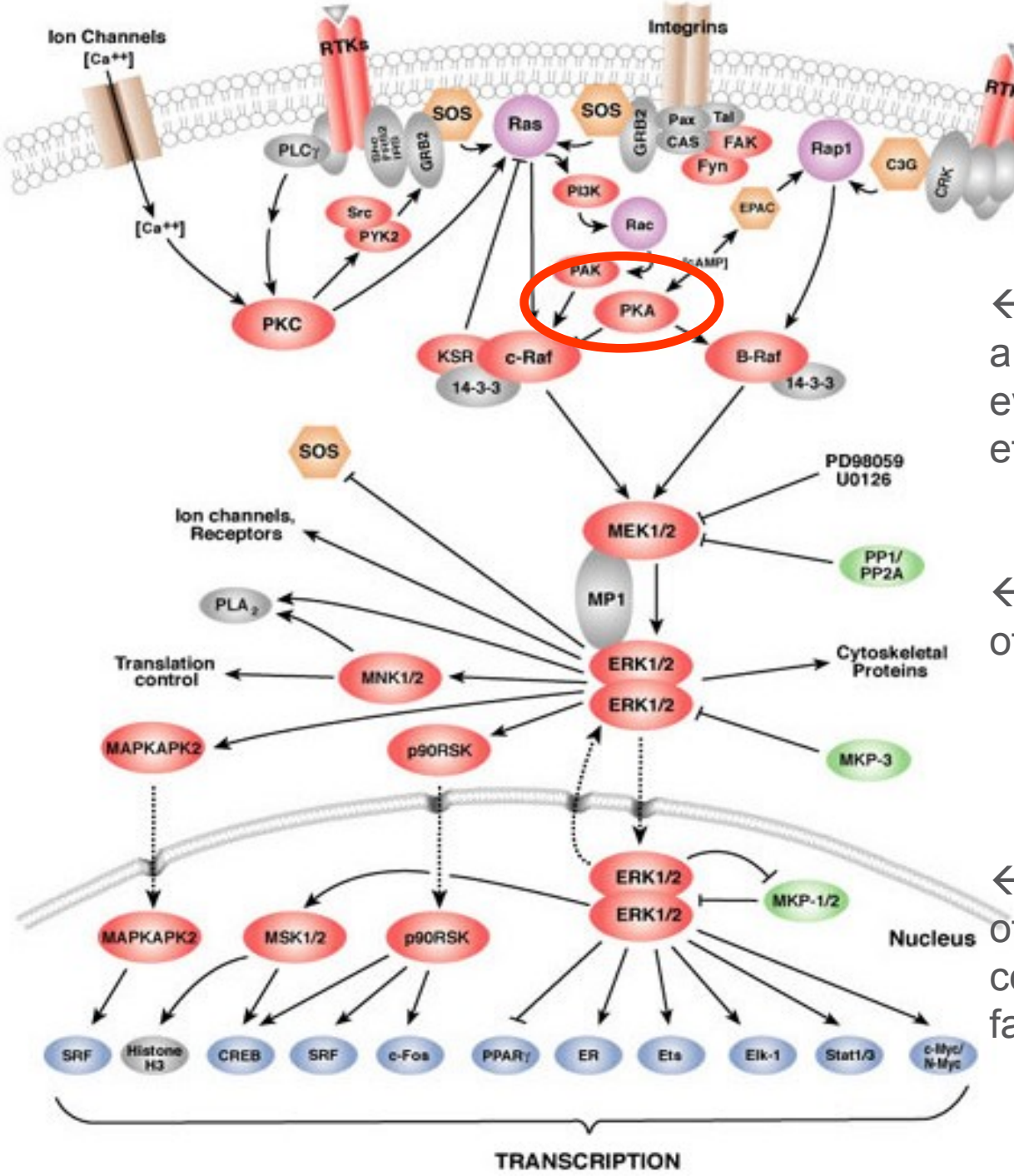
→ activation of membrane lipases → and later proteinkinase C
IP3, PIP2, DAG, Ca2+, AA

3: **Cytoplasmic (nuclear) receptors** (discussed in detail in other sections)

# Signalling mechanism 1

→ Activation of adenylate cyclase → cAMP → PKA



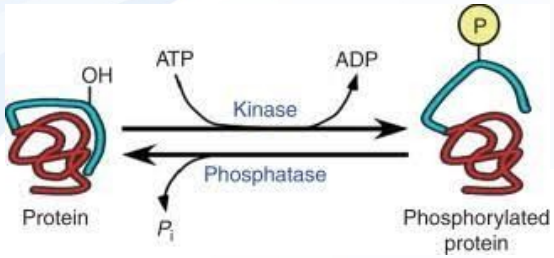


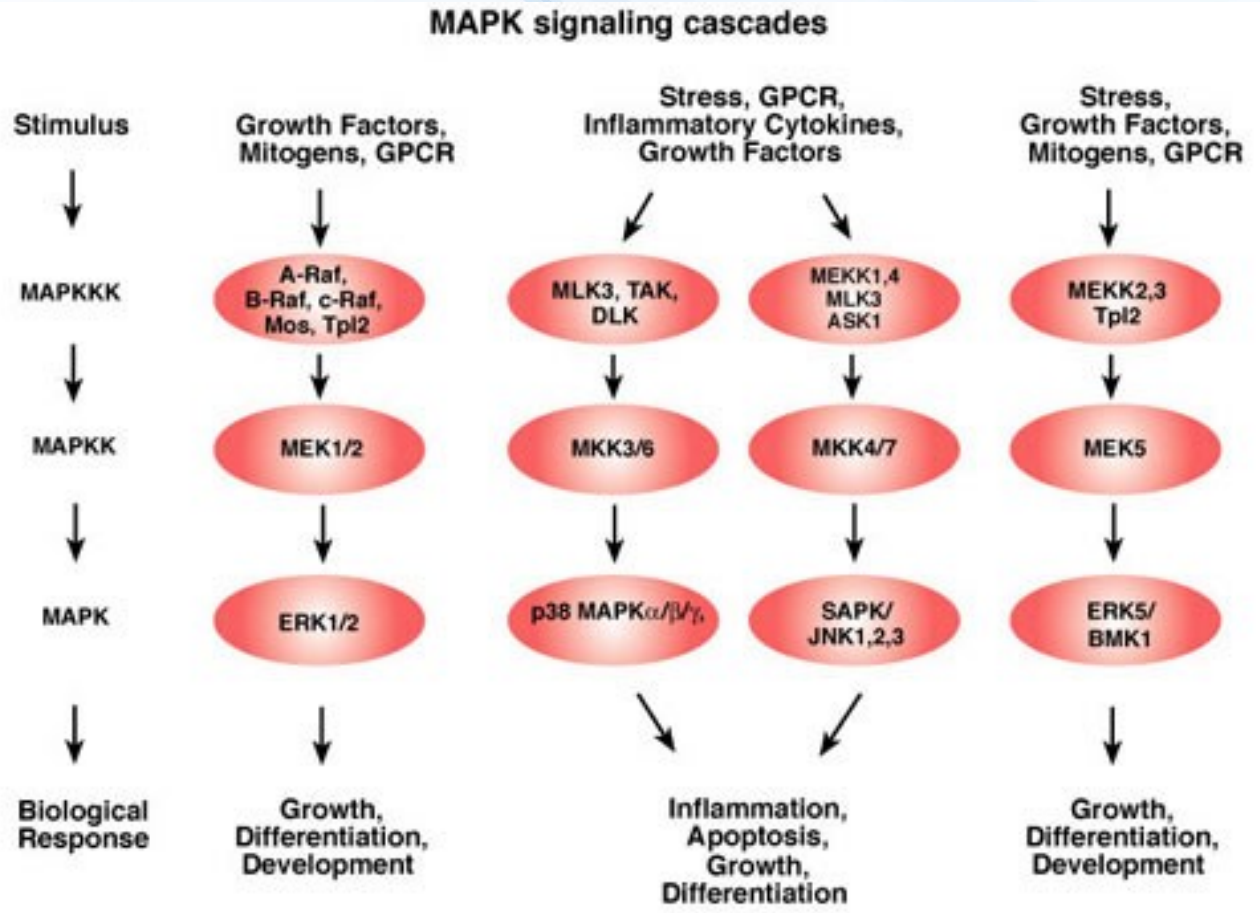

←PKA is central to a number of signalling events and following effects

←Including modulation of “MAPKs”

← Including modulation of Transcription (i.e. control of transcription factors)

# Mitogen Activated Protein Kinases (MAPKs) & dependent effects

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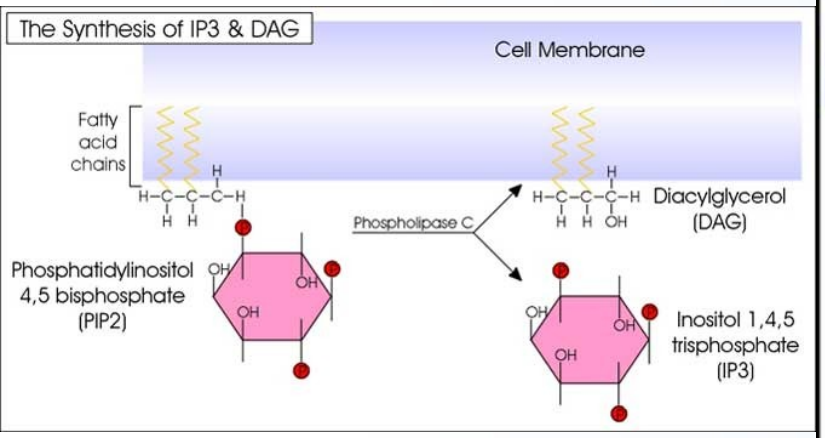
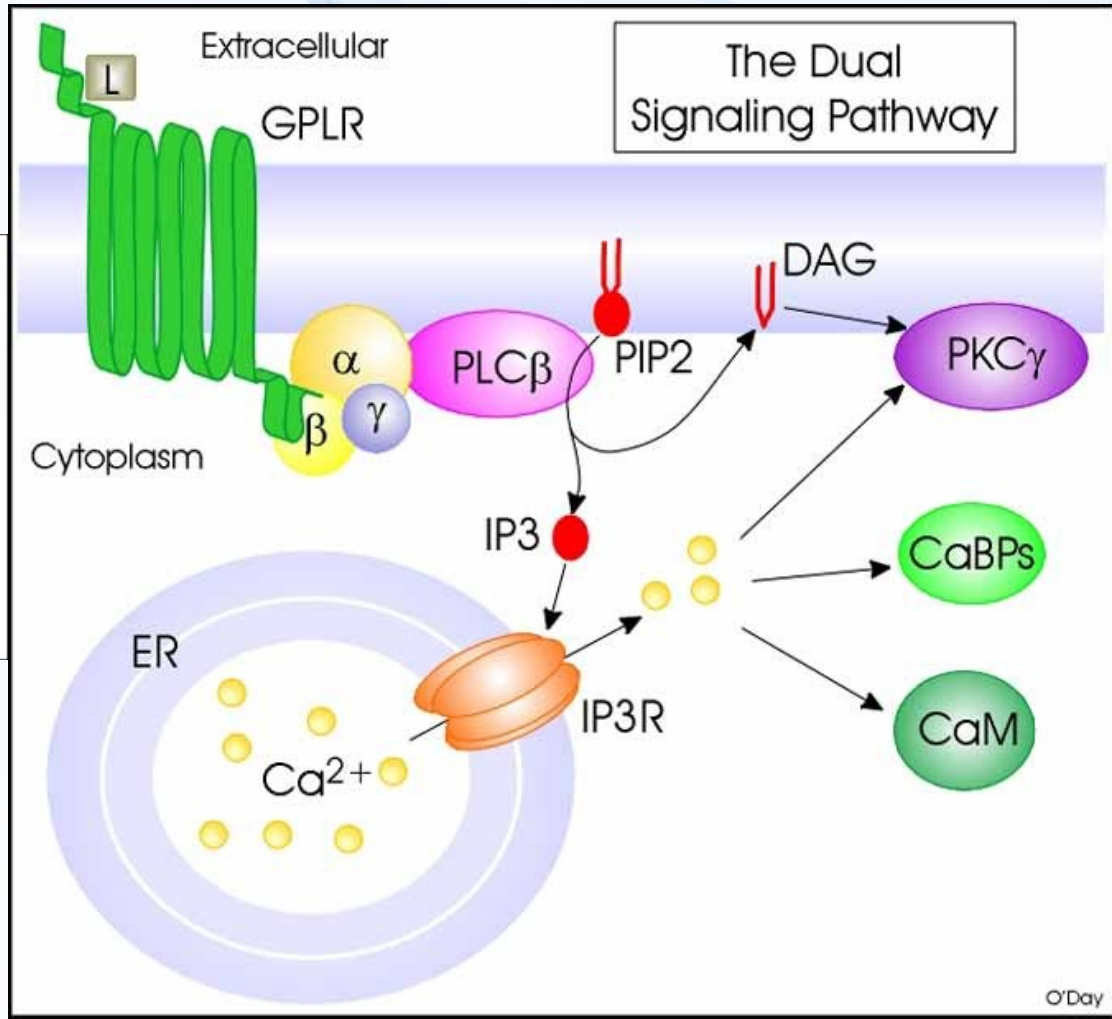
# Signalling mechanism 2

Activation of Phospholipase C

→ release of PIPs → DAG → PKC / arachidonic acid

+ IP3 → activation of $Ca^{2+}$ signalling

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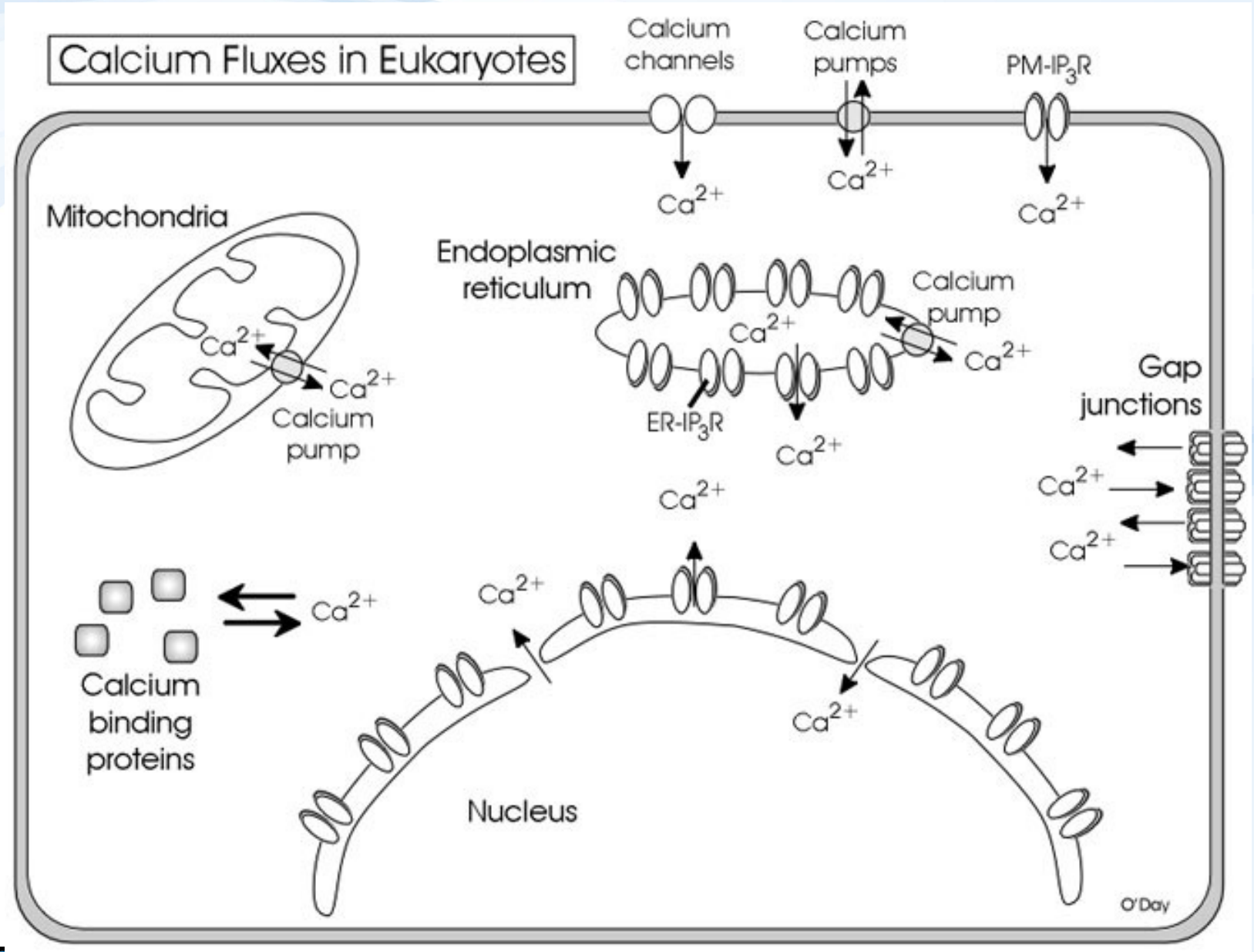
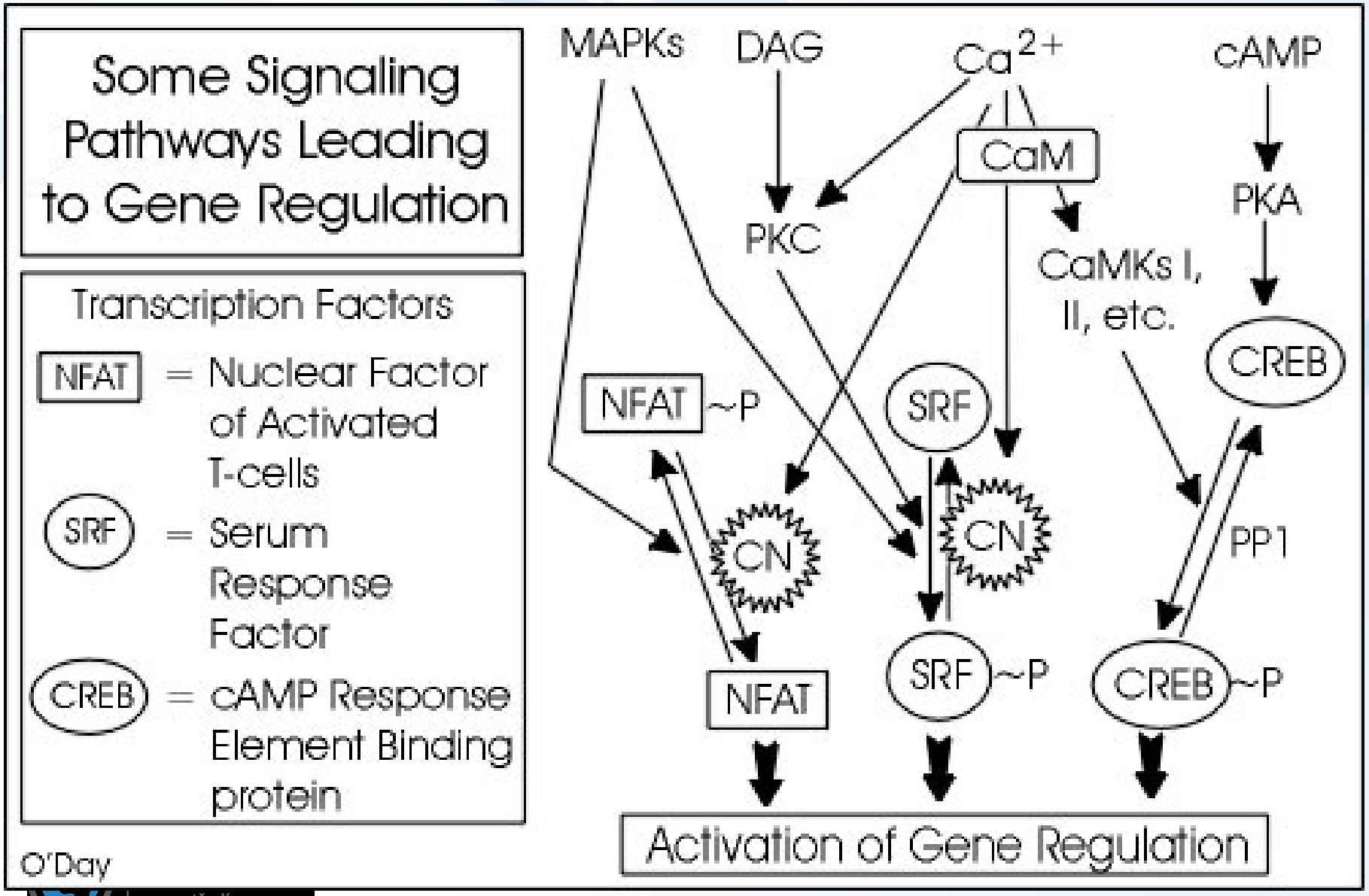
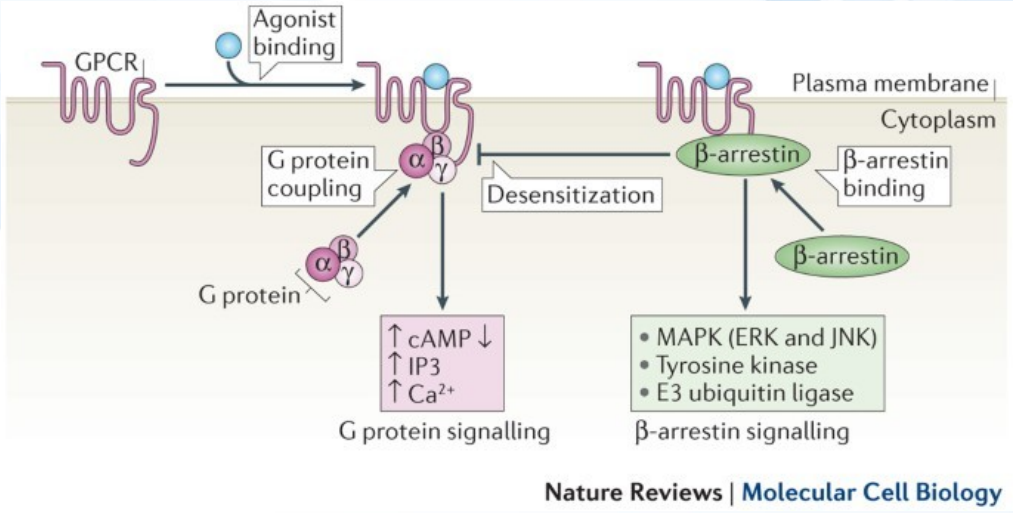


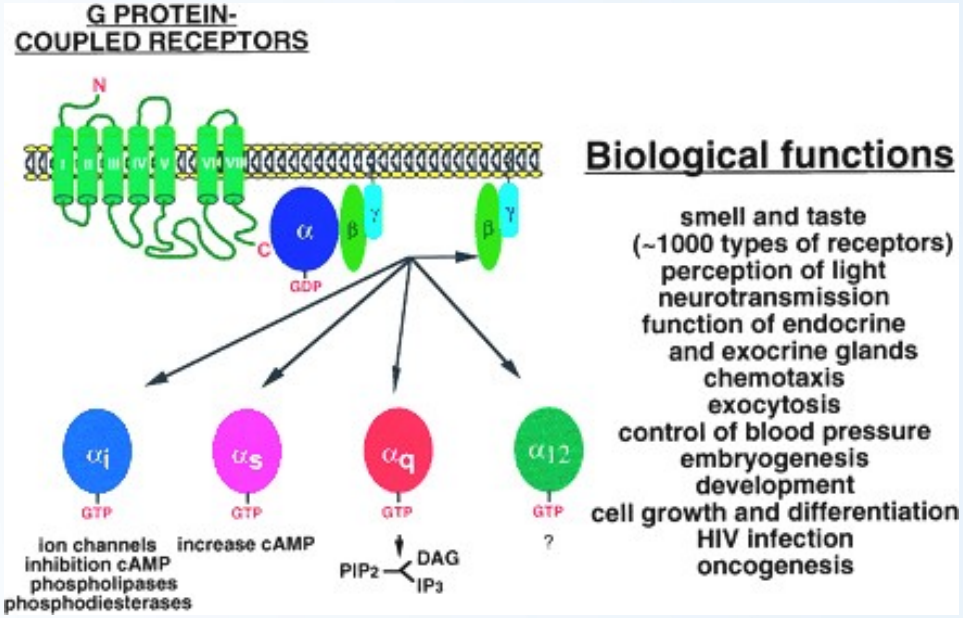
# Different signalling crosstalks → networks



# G-proteins & G-protein coupled receptors – GPCRs

**Involved in many functions → triggering multiple downstream events & networks**

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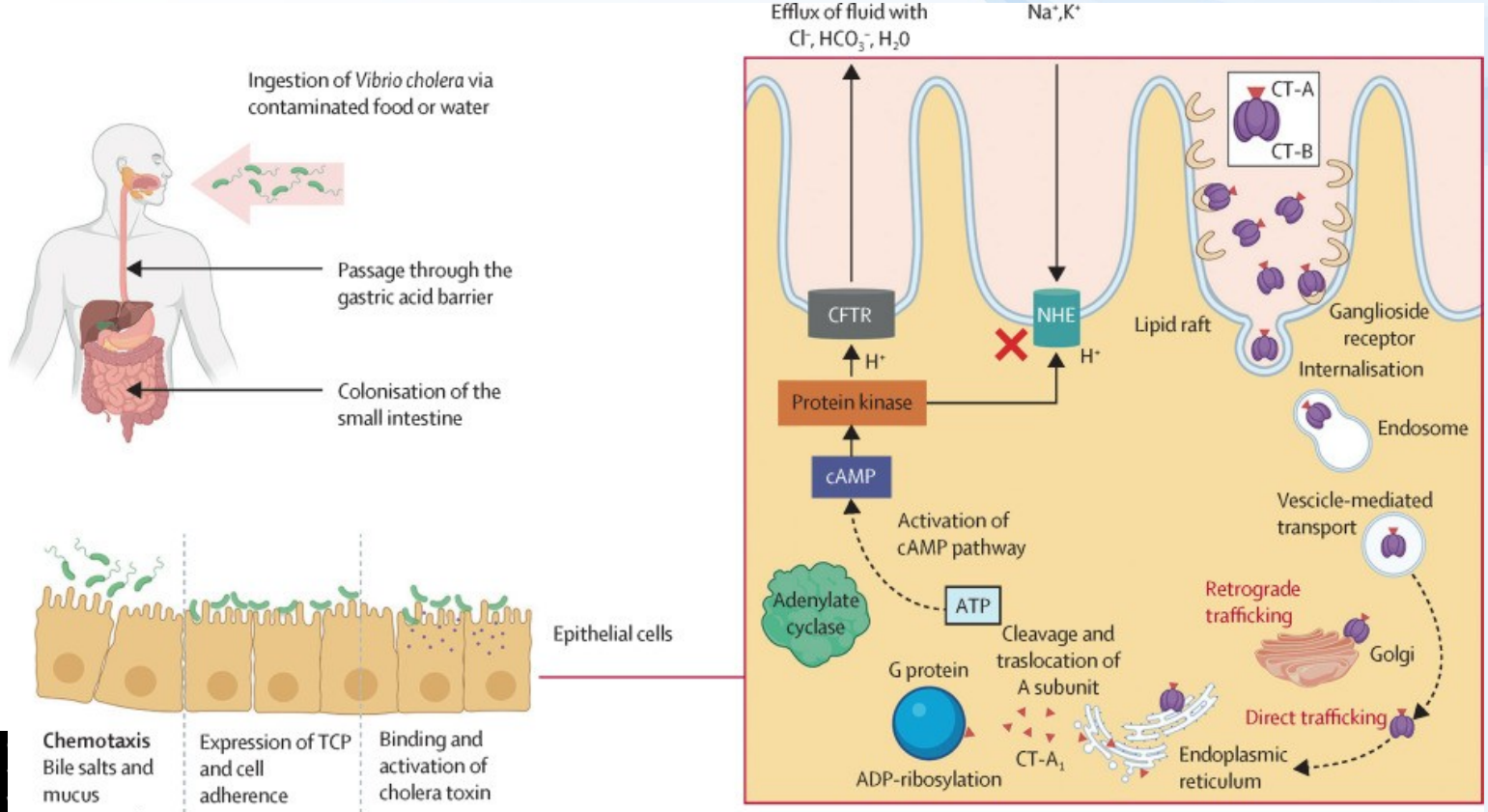
# Disruption of intracellular signaling - EXAMPLES

**Cholera toxin (from** *Vibrio cholerae* **)**

CT acts as **adenylate cyclase** enzyme

→ increasing cAMP levels

→ TOXICITY (diarrhea)



Environmental Science & Technology
DOI: 10.1021/acs.est.5b02049
Environ. Sci. Technol. 2015, 49, 12457−124

# Immunomodulatory Potency of Microcystin, an Important Water-Polluting Cyanobacterial Toxin

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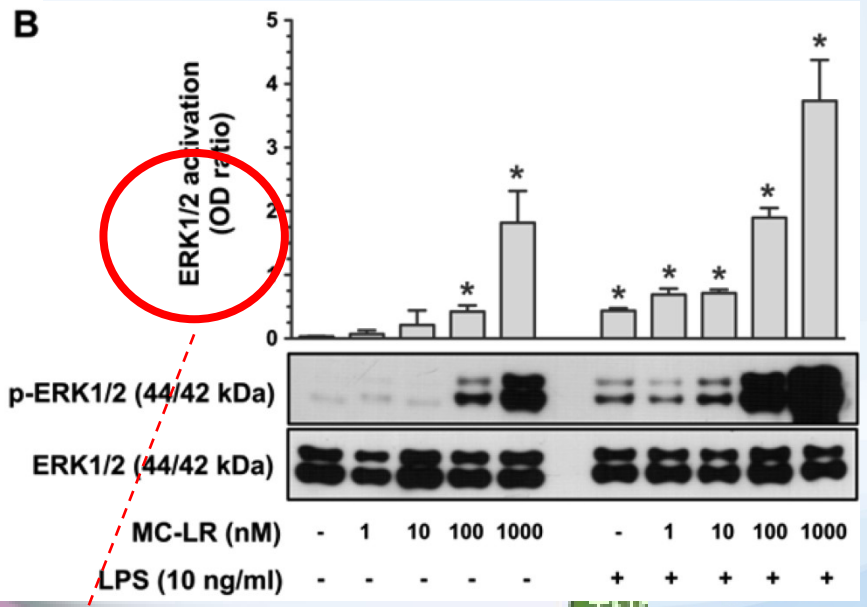
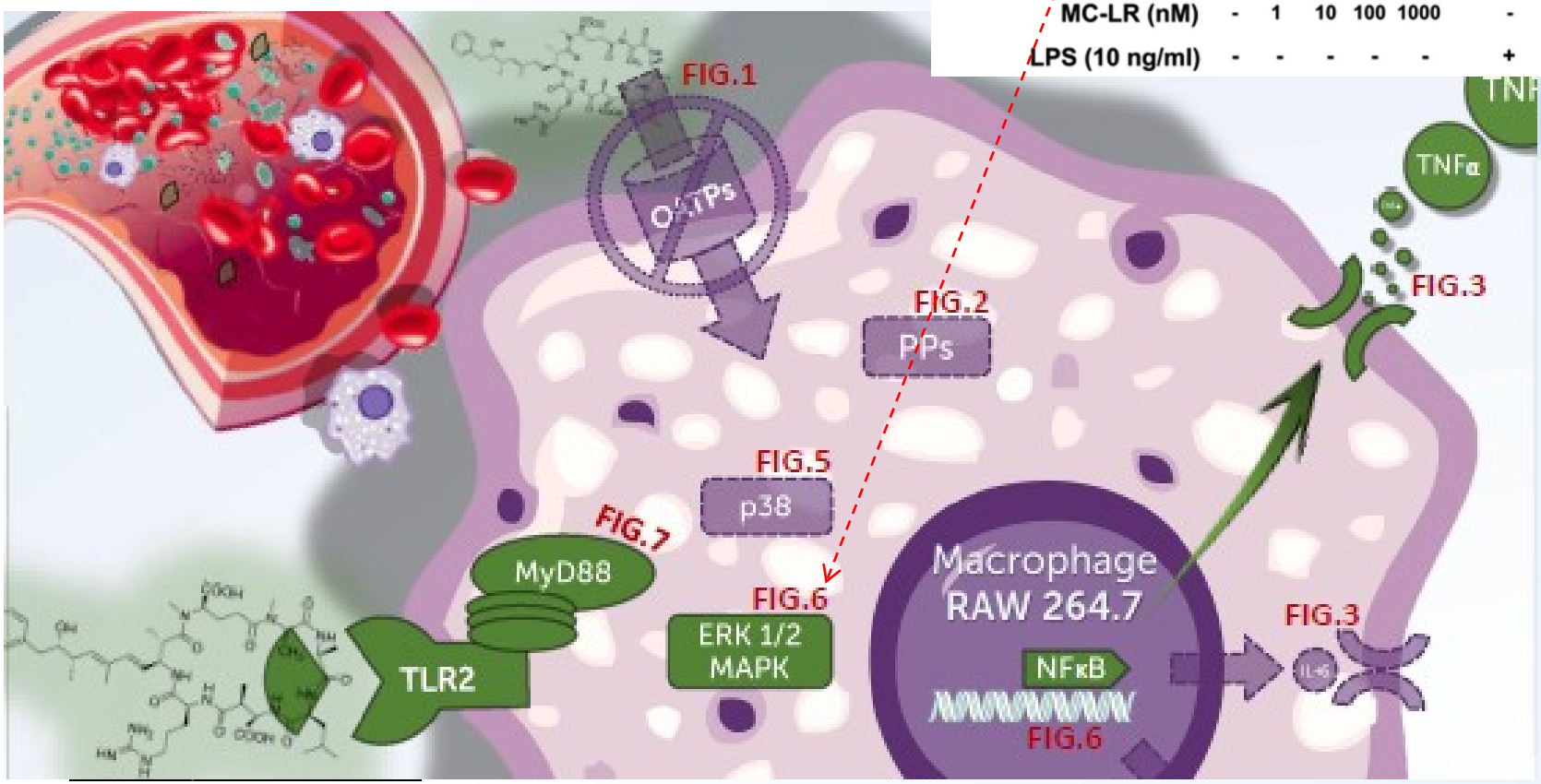
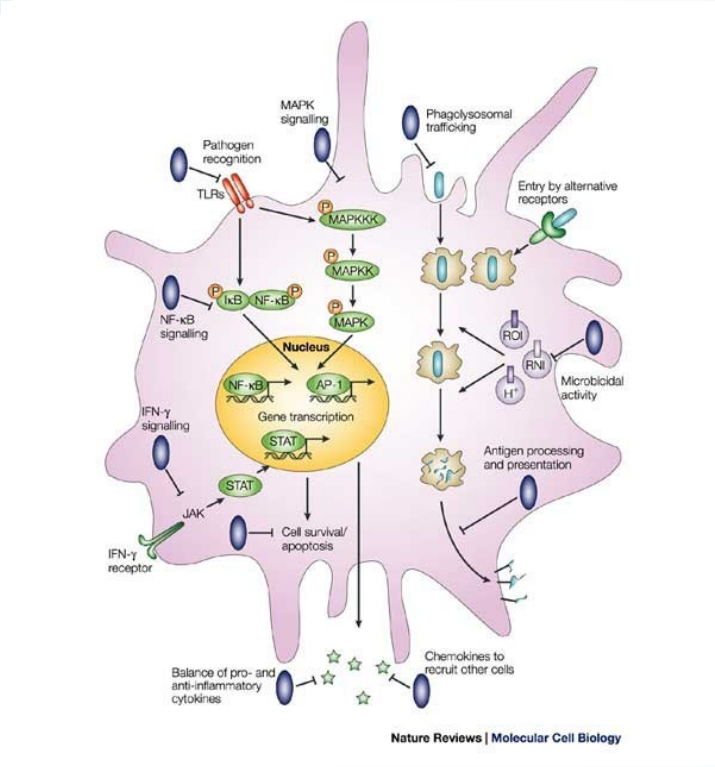
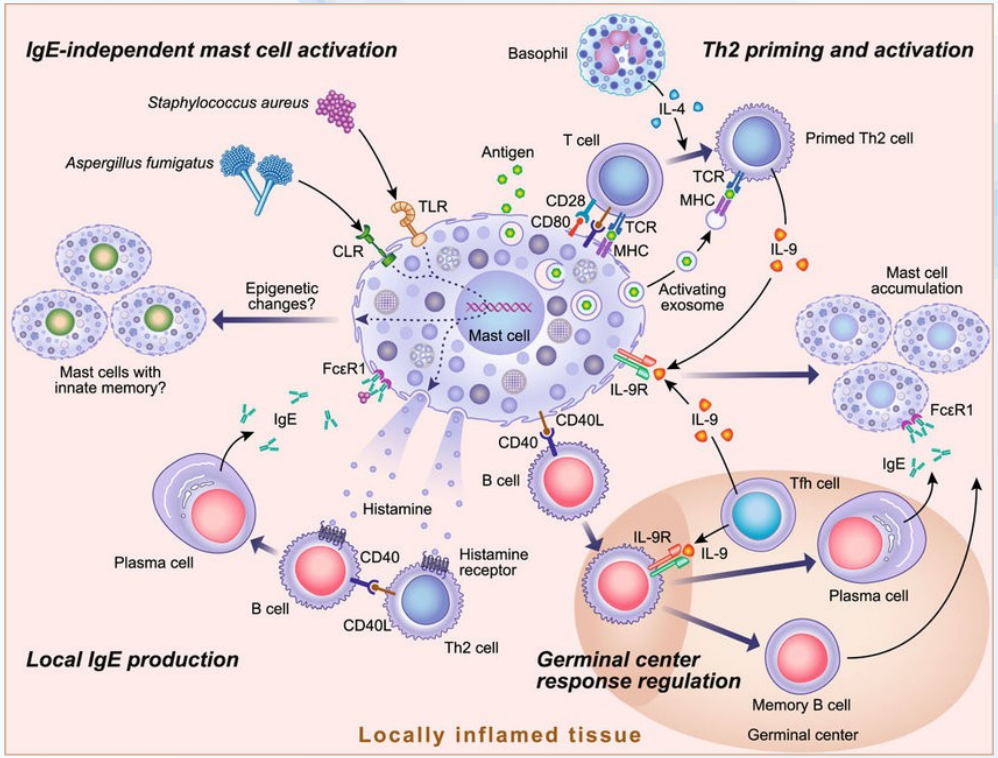


# **Example:** Lipopolysaccharides & exogenous agents inducing immune pathologies – allergies, auto-immune diseases

→ hyperactivation of intracellular signals → immunotoxicity

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# INTER-cellular signals

## Overview

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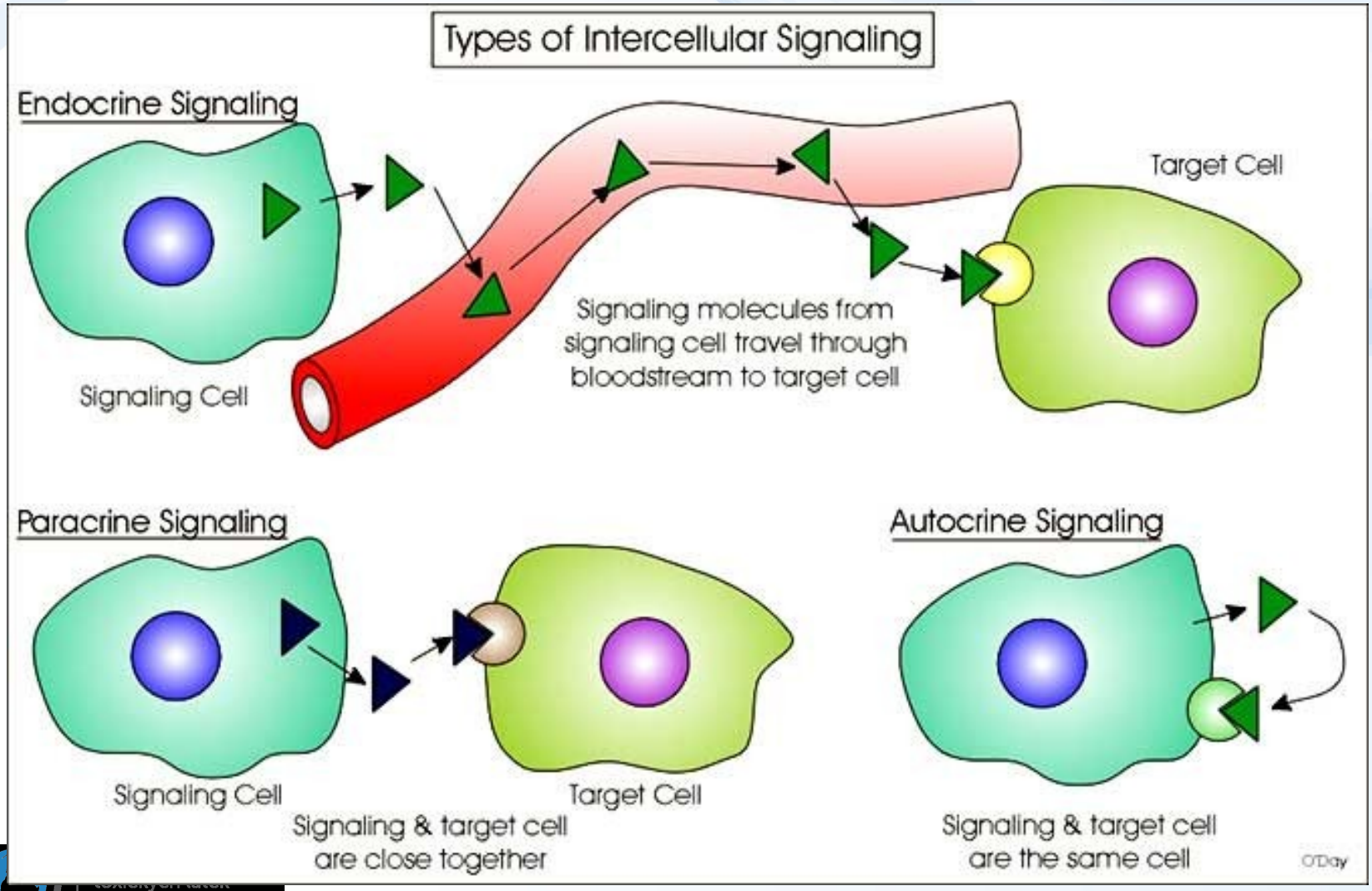
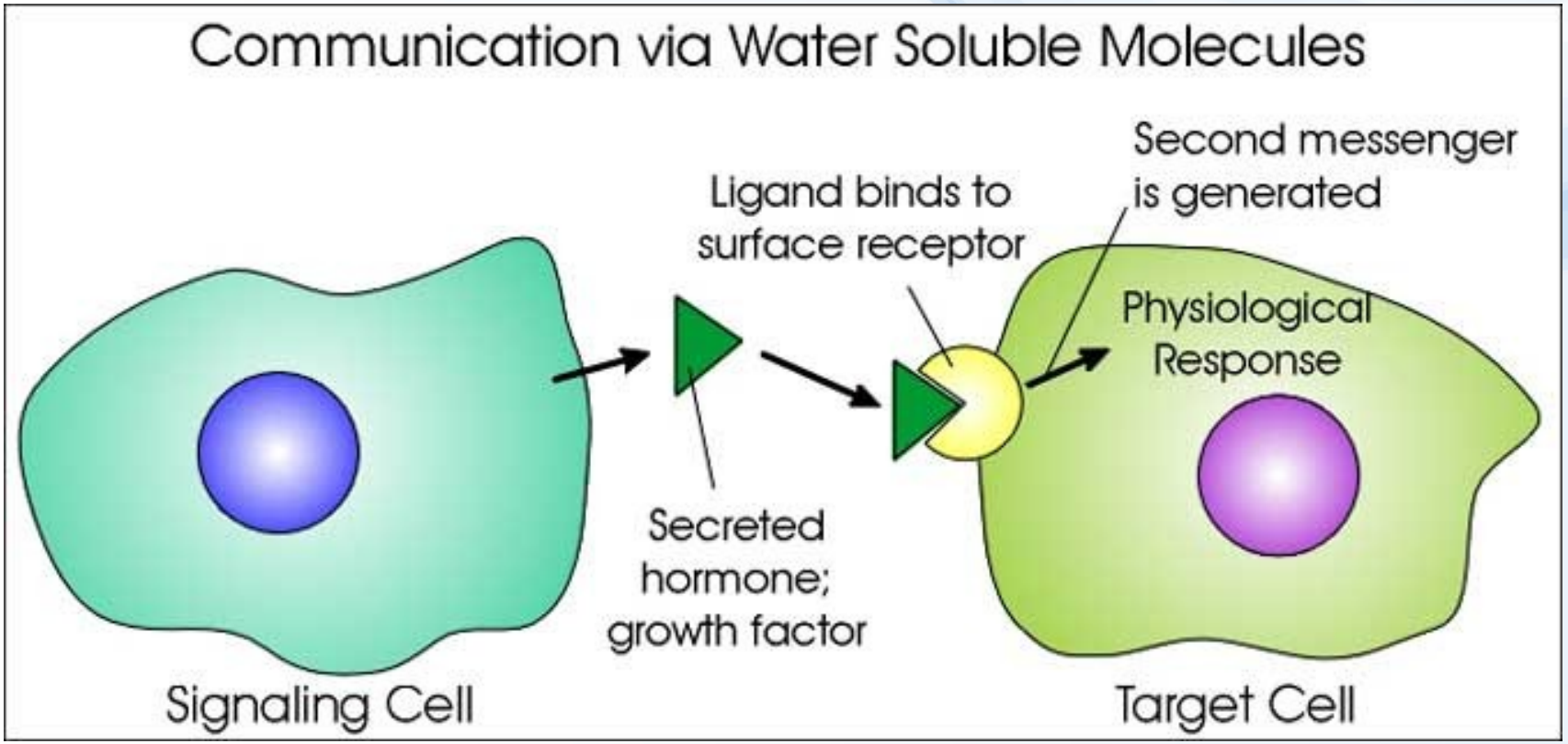
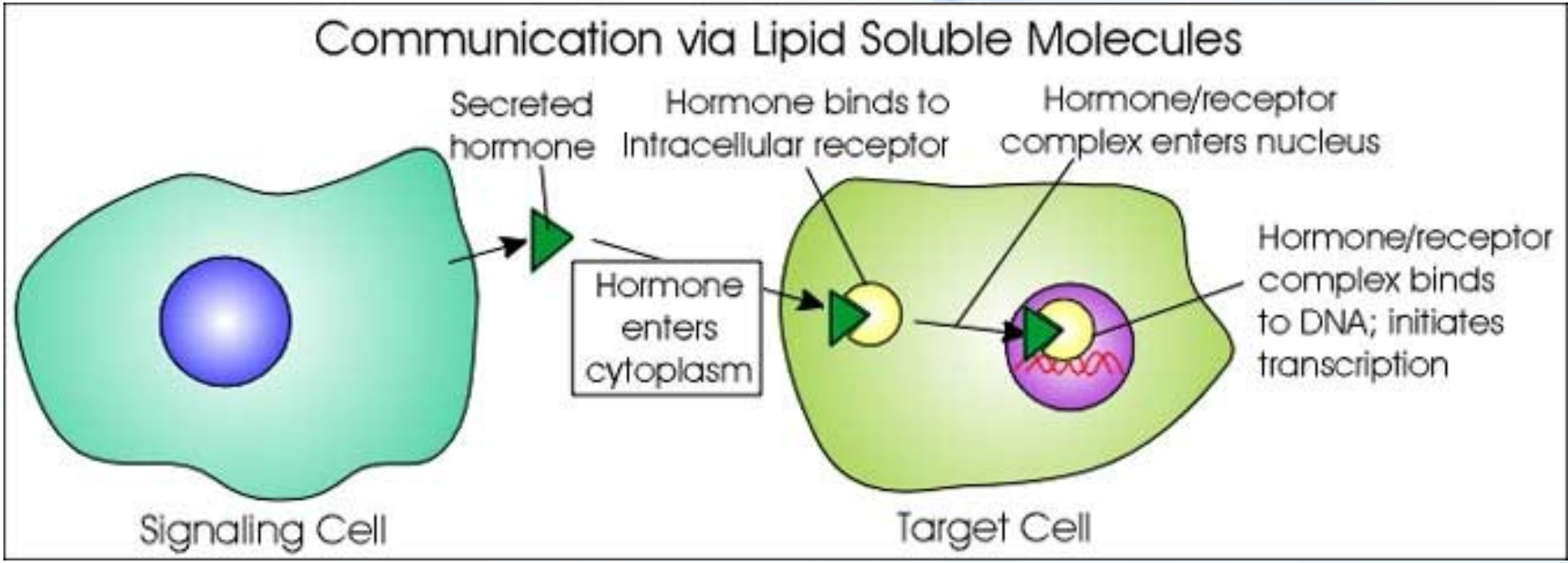
# Cell to cell communication & regulation: a target for toxicants



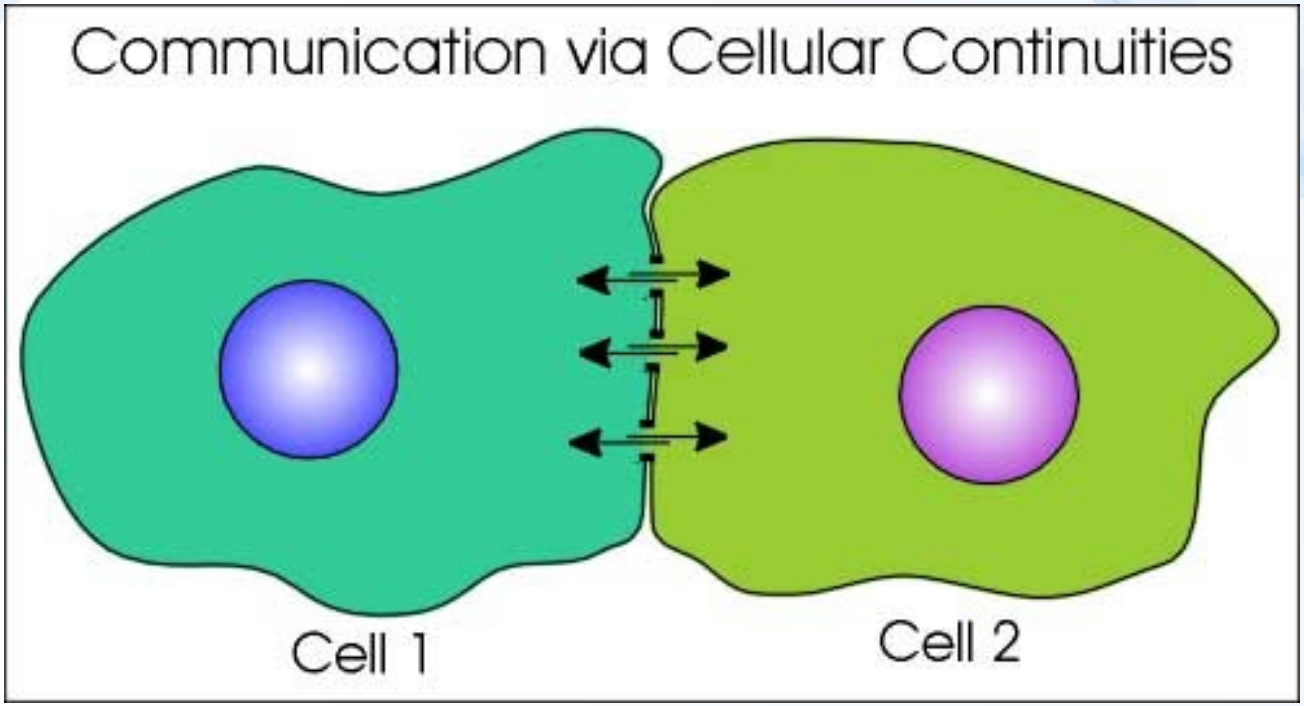
# Cell to cell communication (1)

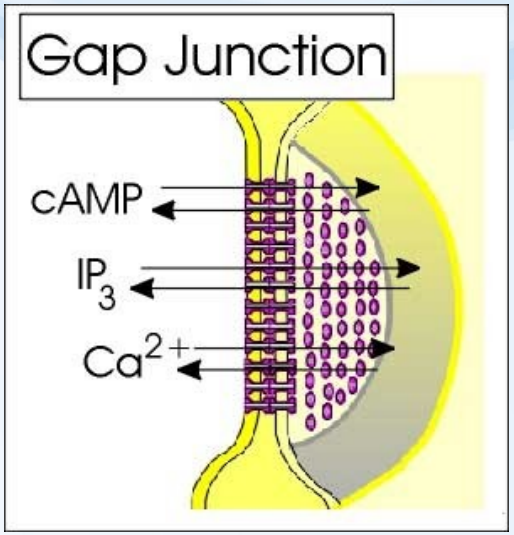


# Cell to cell communication (2)



# Cell to cell communication (3)

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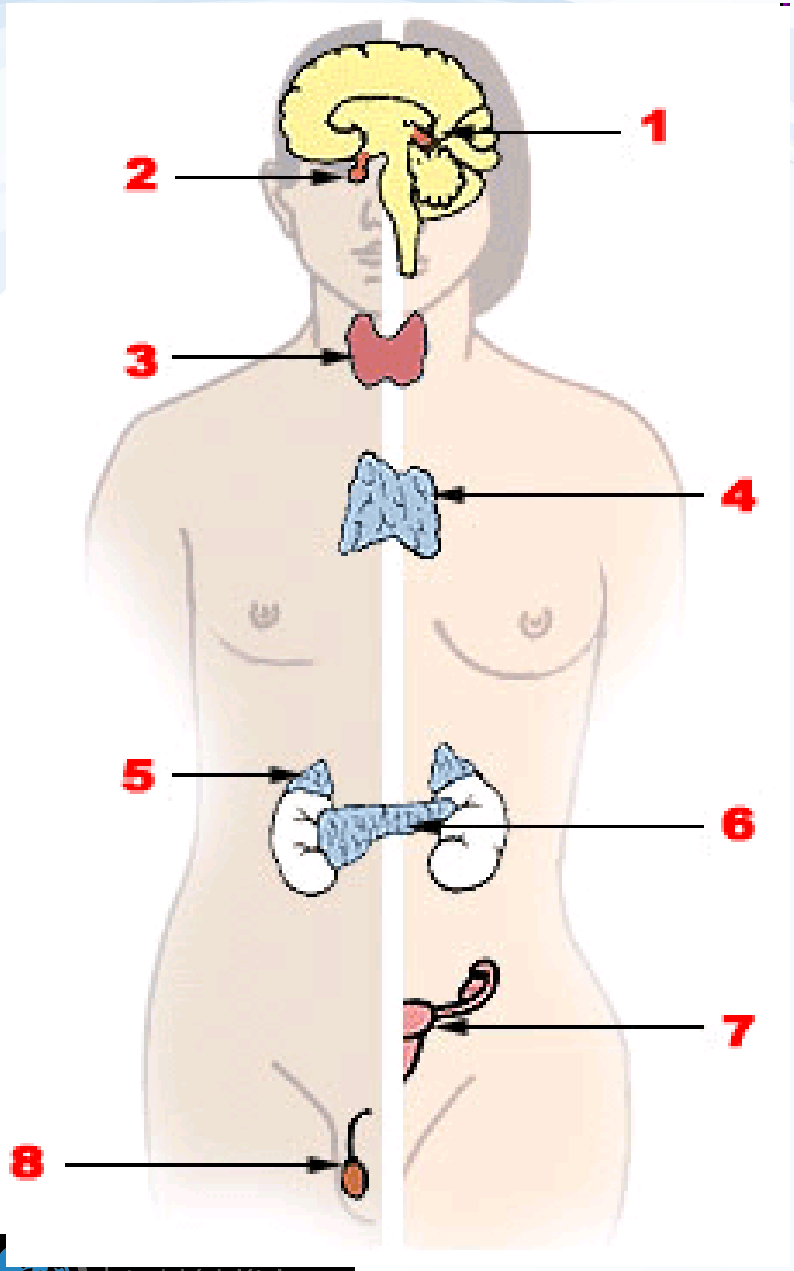
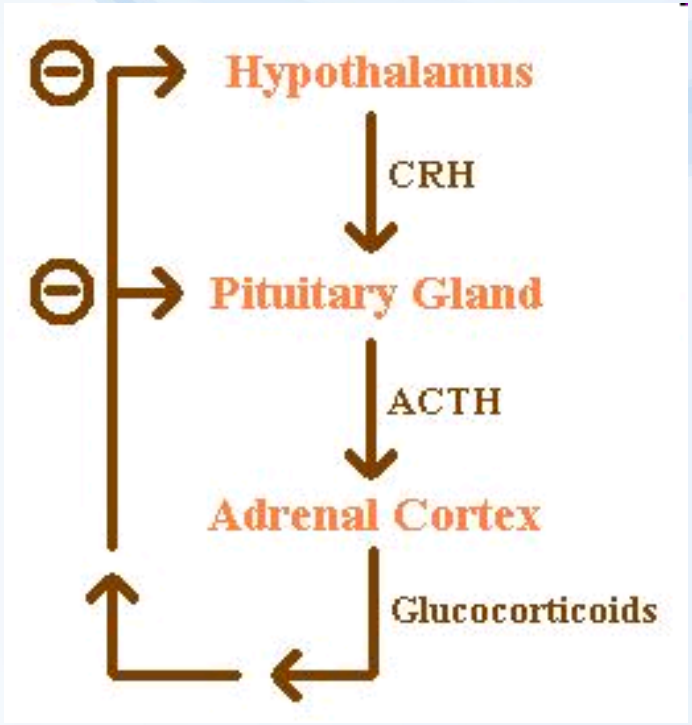
# INTER-cellular signals

## Hormones




**Endocrine system:**

1. Pineal gland, 2. Pituitary gland, 3. Thyroid gland, 4. Thymus, 5. Adrenal gland, 6. Pancreas, 7. Ovary, 8.Testis




**Example:** feedback loop

# FUNCTIONS OF HORMONES

* stimulation or inhibition of growth
* mood swings
* induction or suppression of apoptosis
  (programmed cell death)
* activation or inhibition of the immune system
* regulation of metabolism
* preparation for fighting, fleeing, mating …
* preparation for a new phase of life
  (puberty, caring for offspring, and menopause)
* control of the reproductive cycle
  …. etc.

Chemicals interfering with various hormonal functions
→ **diverse impacts (effects)**

# FATE OF HORMONES: target for toxicants

Toxic compounds can affect “hormone signalling” at various levels (**highligted**):

1. **Biosynthesis** of a particular hormone in a particular tissue

2. Storage and **secretion** of the hormone

3. **Transport** of the hormone to the target cell(s)

4. **Recognition of the hormone** by an associated cell membrane or intracellular receptor protein.

5. Relay and **amplification of the received hormonal signal** via a signal transduction process -> cellular response.

6. The reaction of the target cells is recognized by the original hormone-producing cells (**negative feedback loop**)

7. **Degradation and metabolism** of the hormone

More details will be discussed in the lectures dedicated to nuclear receptors

# Toxicity to hormone regulation = ENDOCRINE DISRUPTION

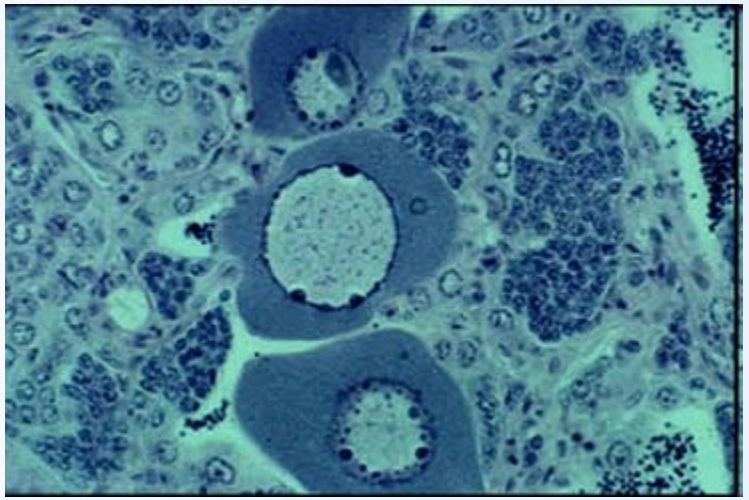
**ED & EDCs (endocrine disrupting compounds)**
= major problem in environmental toxicology

Effects at **all levels of hormonal action** have been demonstrated
→ *synthesis, transport, site of action ….*

- **Multiple effects** due to ED (! Not only „xenoestrogenicity“ & feminization)
→ *immunotoxicity, developmental toxicity*

*(ED - WILL ALSO BE DISCUSSED FURTHER)*

Example of ED - Intersex roach testis
containing both oocytes and spermatozoa,
caused by exposure to environmental oestrogens



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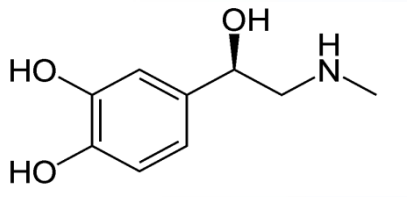
# Types of hormones in vertebrates

## Amine-derived hormones

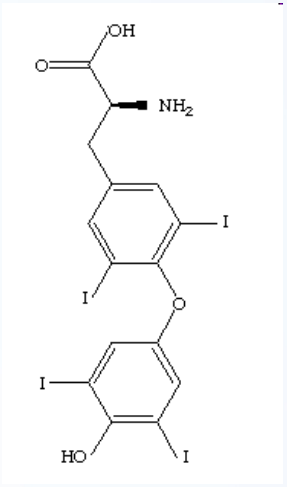
structure: derivatives of the amino acids tyrosine and tryptophan.
Examples - catecholamines and thyroxine.

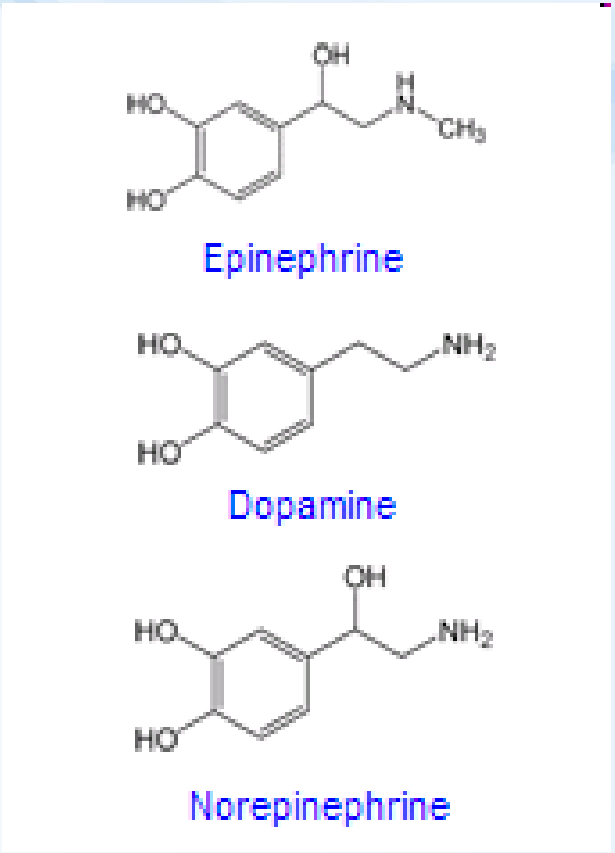
(small molecules - similar to organic toxicants → TOXIC EFFECTS)

Adrenalin




Thyroxin

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# Types of hormones in vertebrates

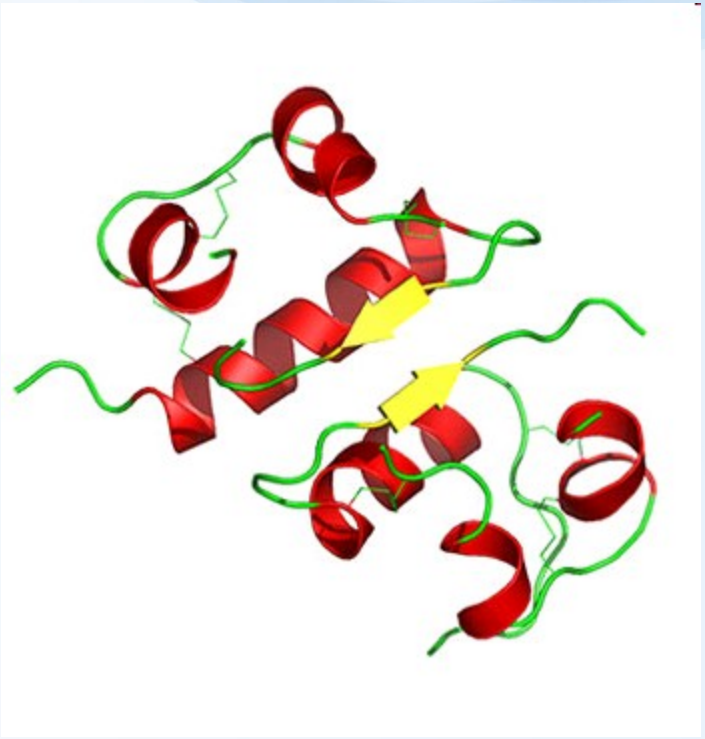
**Peptide hormones**

structure: chains of amino acids.

- small peptides: TRH and vasopressin;
- large proteins: insulin, growth hormone, luteinizing hormone, follicle-stimulating hormone and thyroid-stimulating hormone etc.

*Large molecules;*
*receptors on surfaces of the cells*
*(Interactions with toxic chemicals **less likely**)*

Example - insulin



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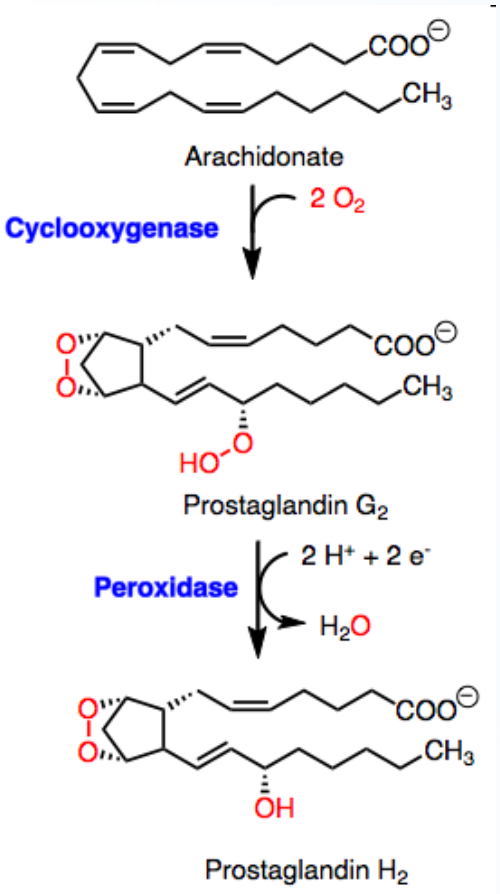
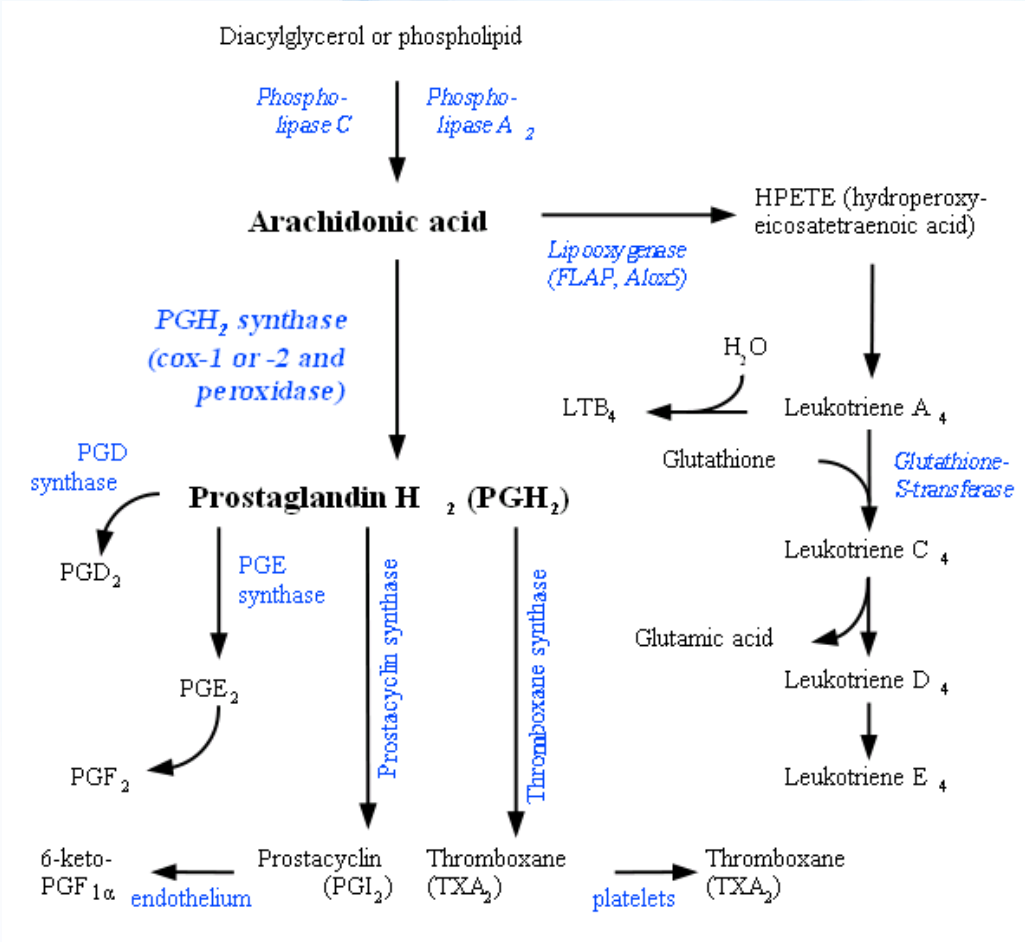
# Types of hormones (signal molecules) in vertebrates

## **Lipid derived "hormones" (1) -** from linoleic acid, arachidonic acid **- prostaglandins**




v prostředí

# Types of hormones in vertebrates

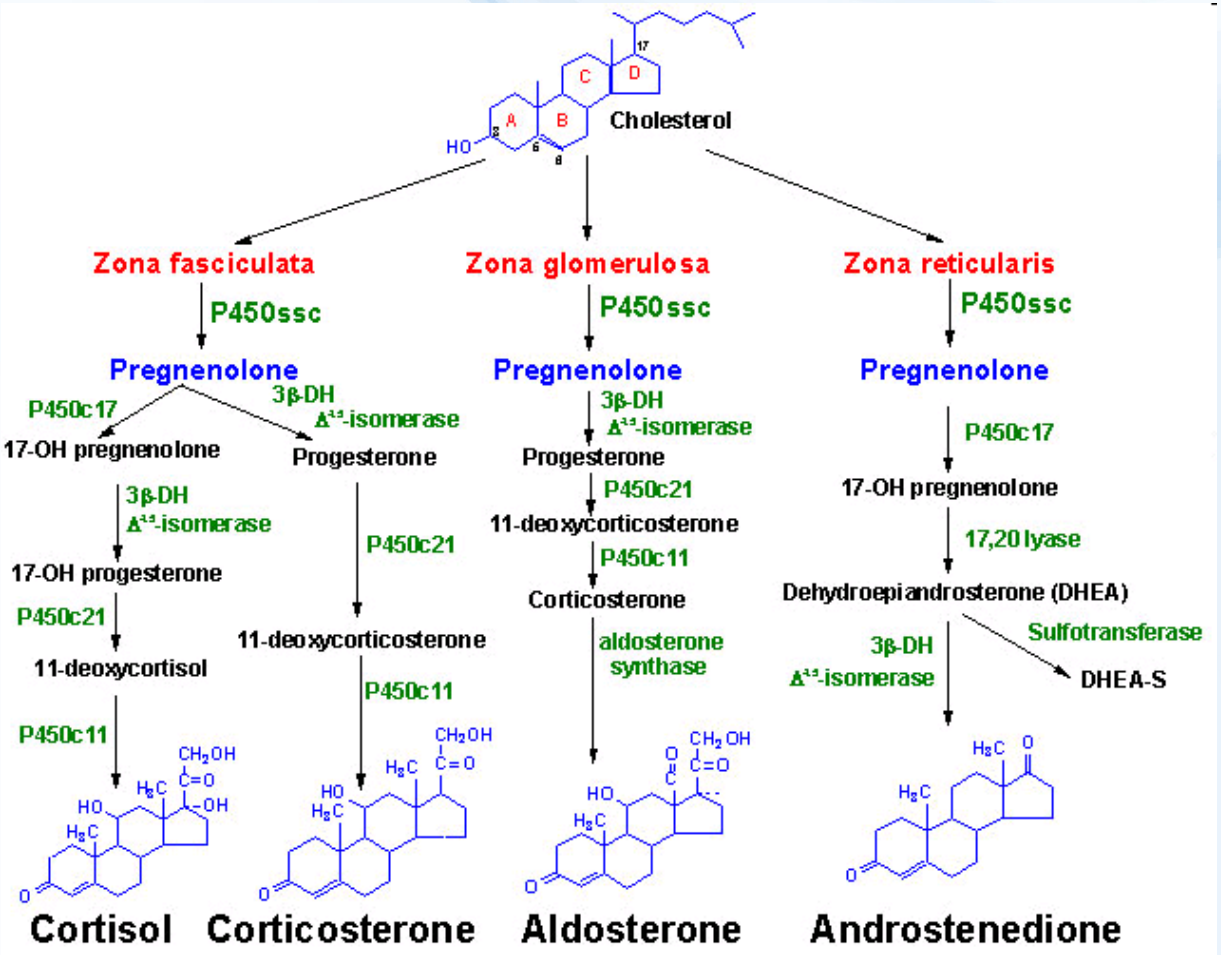
## Lipid derived hormones 2 - steroid hormones

* Small molecules - similar to organic toxicants:

→ several compounds **interfere with steroid hormones → toxicity !!!**

Derived
from cholesterol

Examples:
testosterone,
cortisol,
estradiol …

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