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

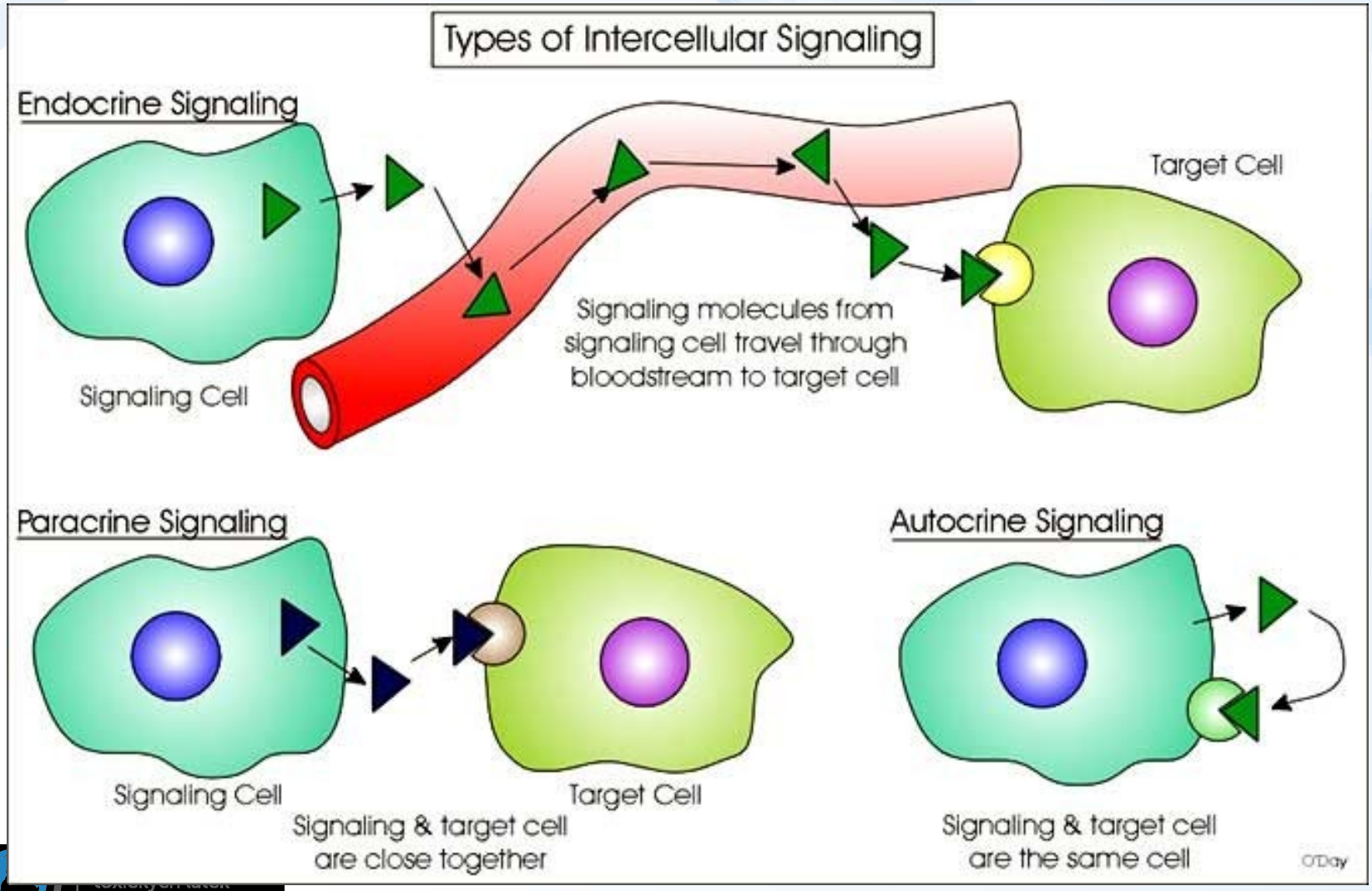
Hierarchy in signalling

- **systems**: neuronal ←→ endocrine

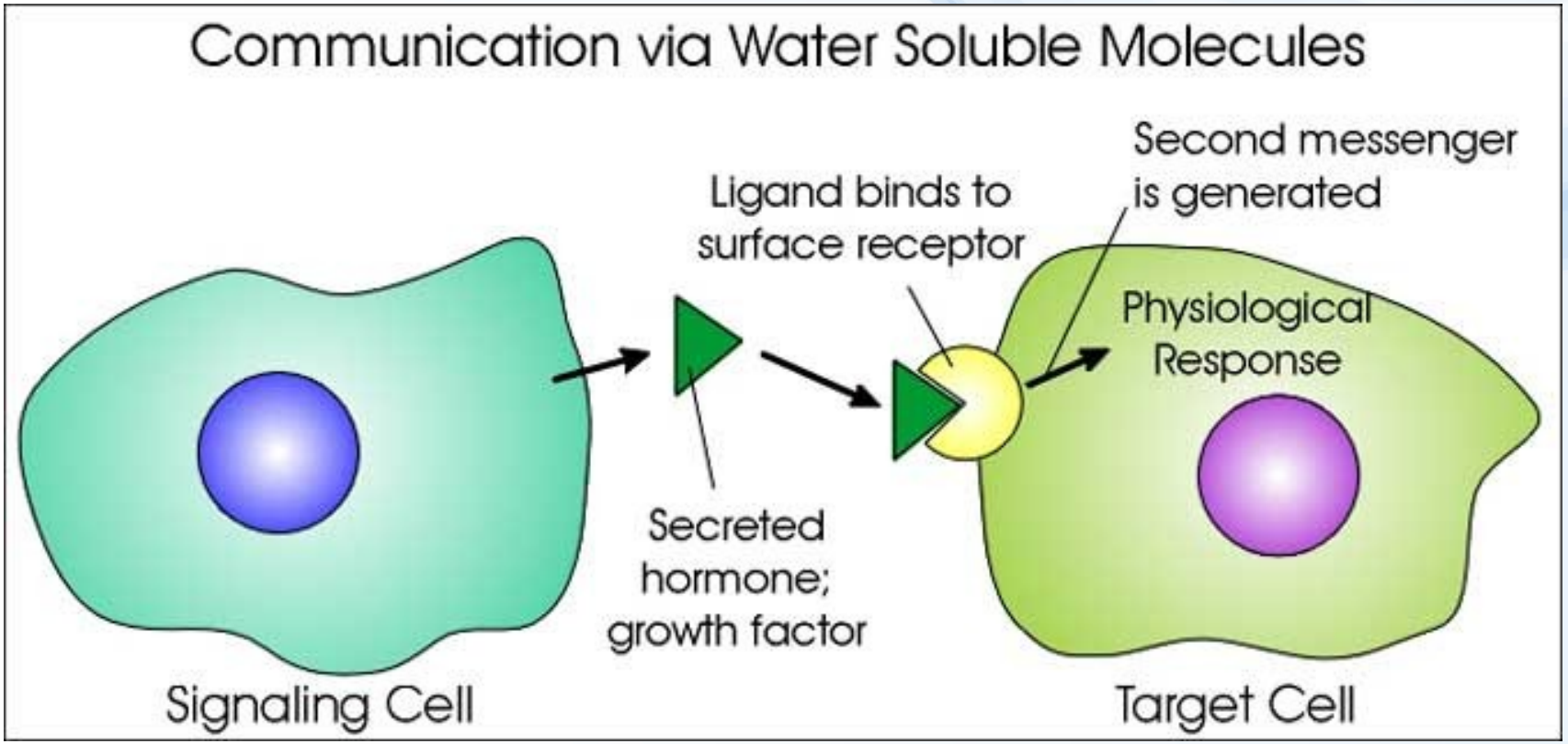
- **cell-to-cell**
  hormonal & neuronal signal transmission
  contact channels

- **intracellular** signal transduction

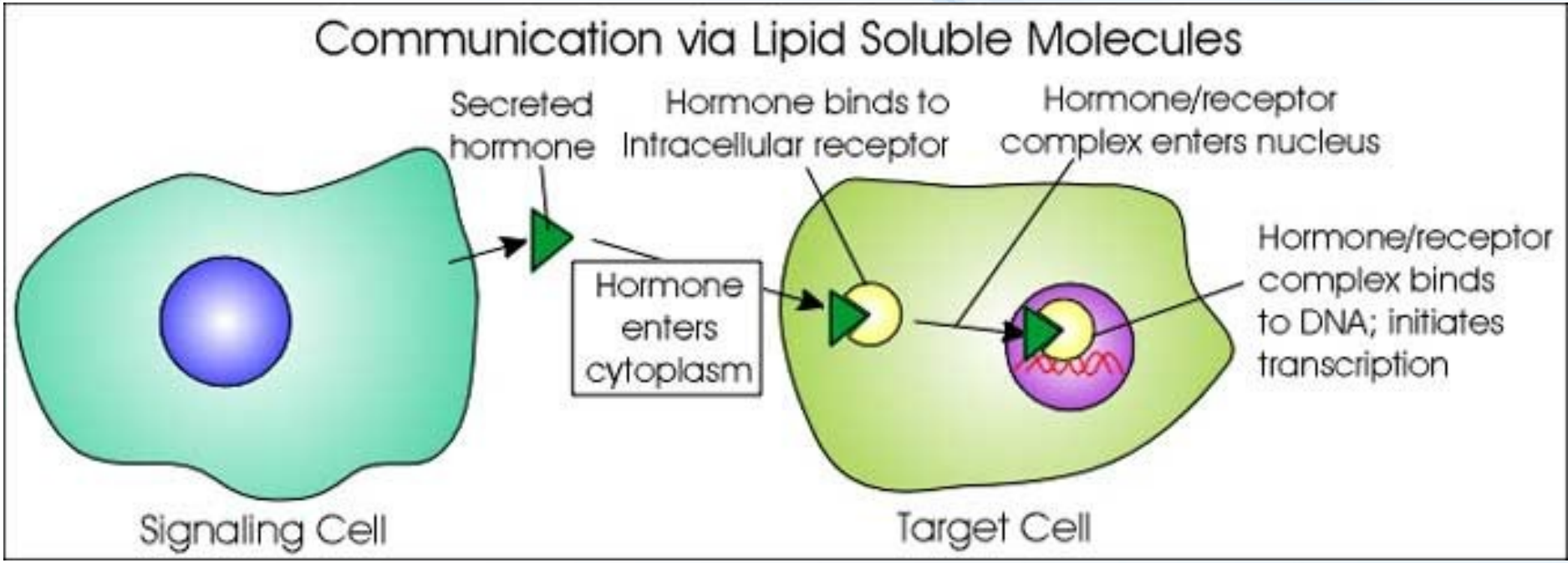
Cell communication & regulation: a target for toxicants



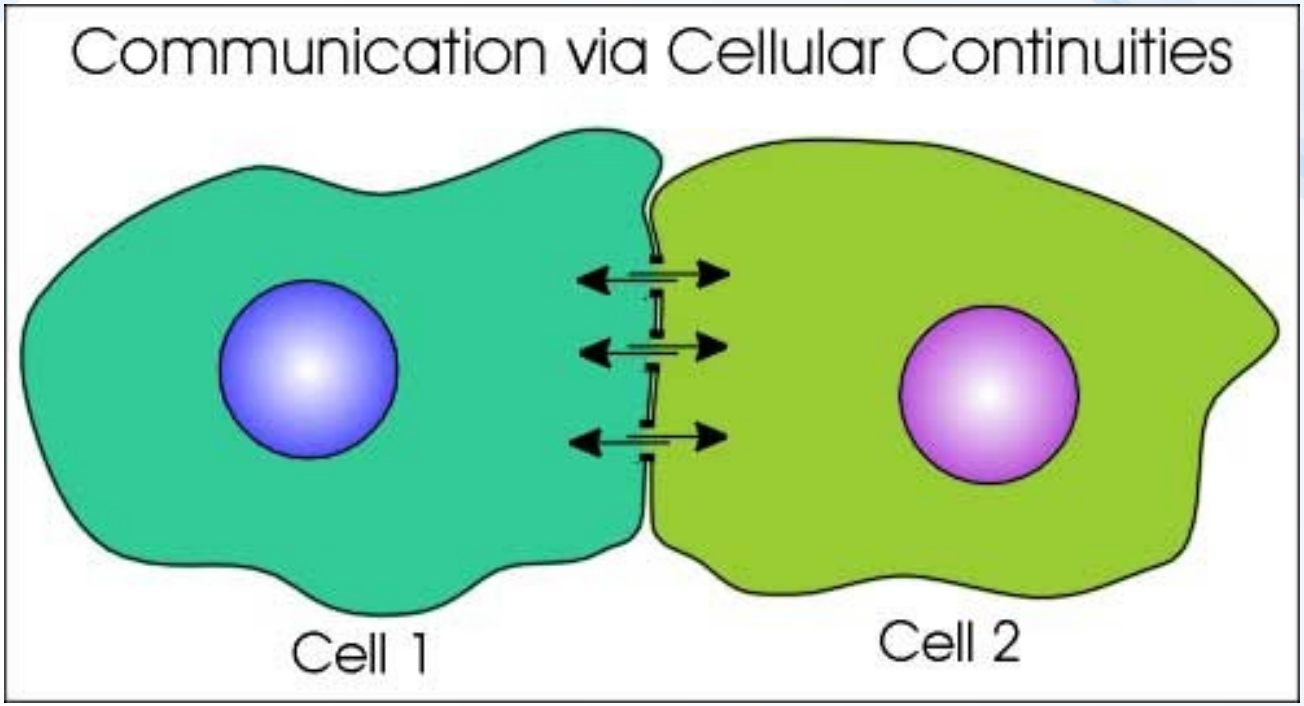
Cell communication (1)

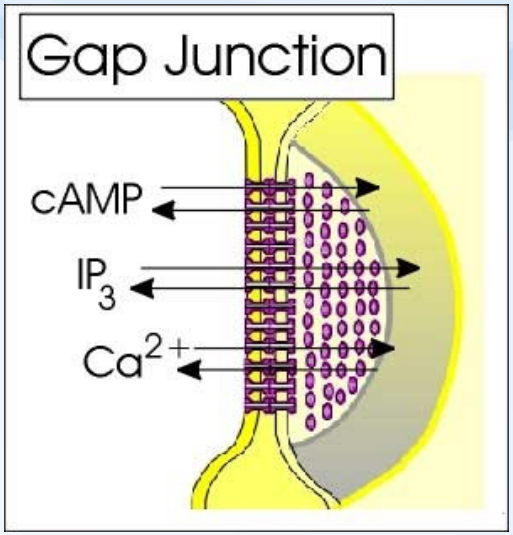


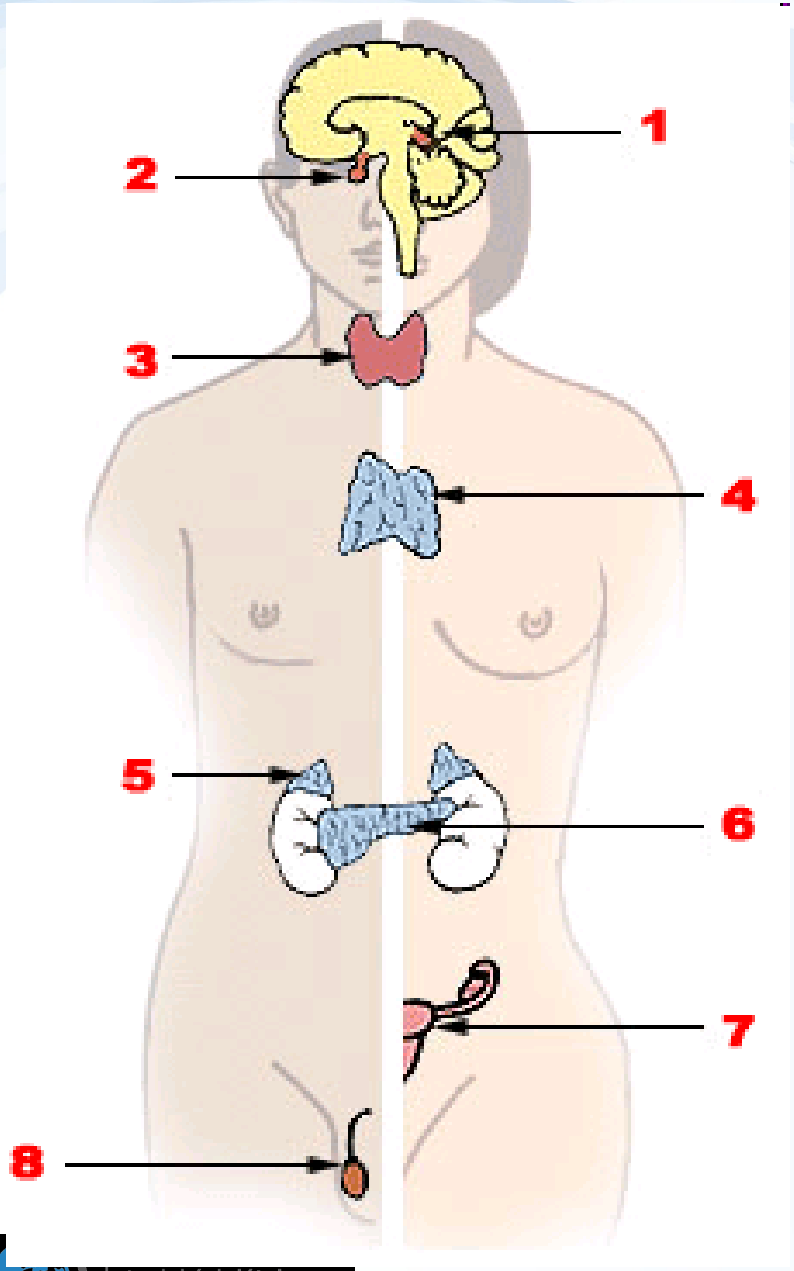
Cell communication (2)



Cell communication (3)

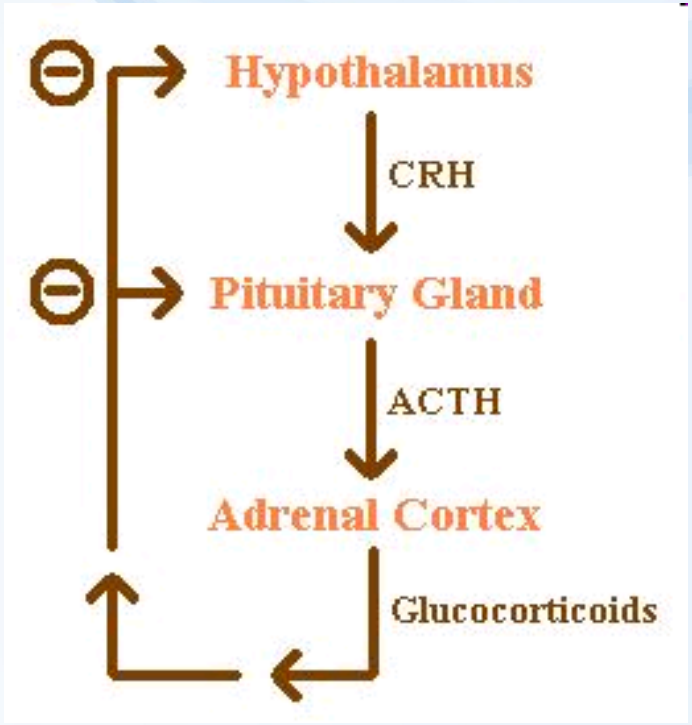






Endocrine system:

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.

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

Toxicity to hormone regulation = ENDOCRINE DISRUPTION

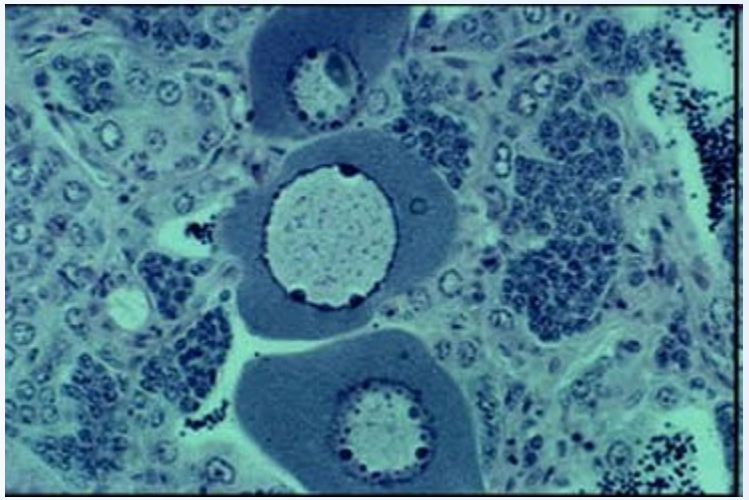
ED & EDCs (endocrine disrupting compounds)
= major problem in environmental toxicology

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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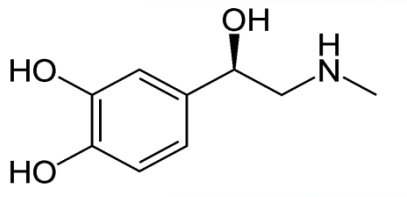
Types of hormones in vertebrates

Amine-derived hormones

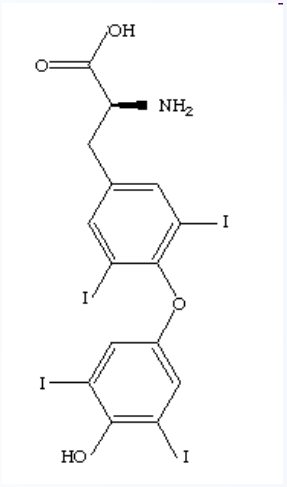
structure: derivatives of the amino acids tyrosine and tryptophan.
Examples - catecholamines and thyroxine.

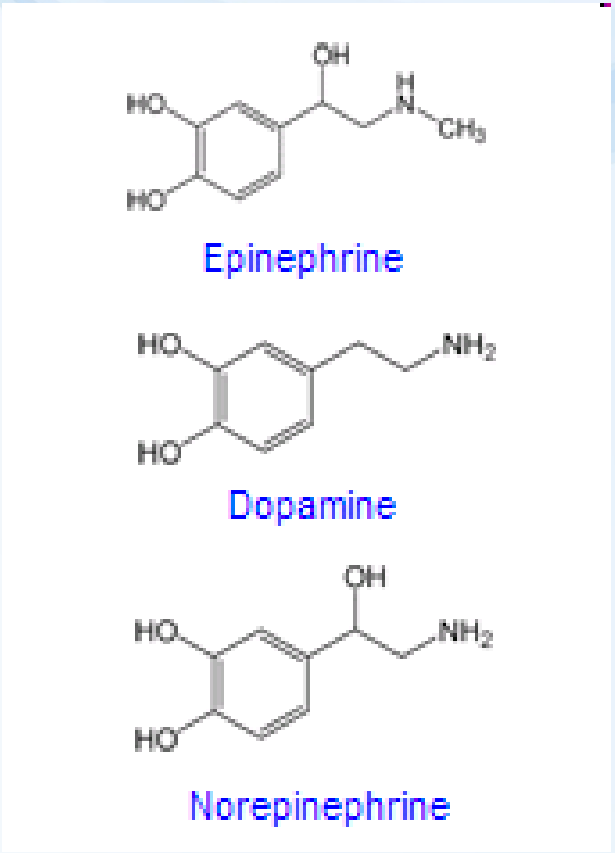
(small molecules - similar to organic toxicants → TOXIC EFFECTS)

Adrenalin



Thyroxin





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Types of hormones in vertebrates

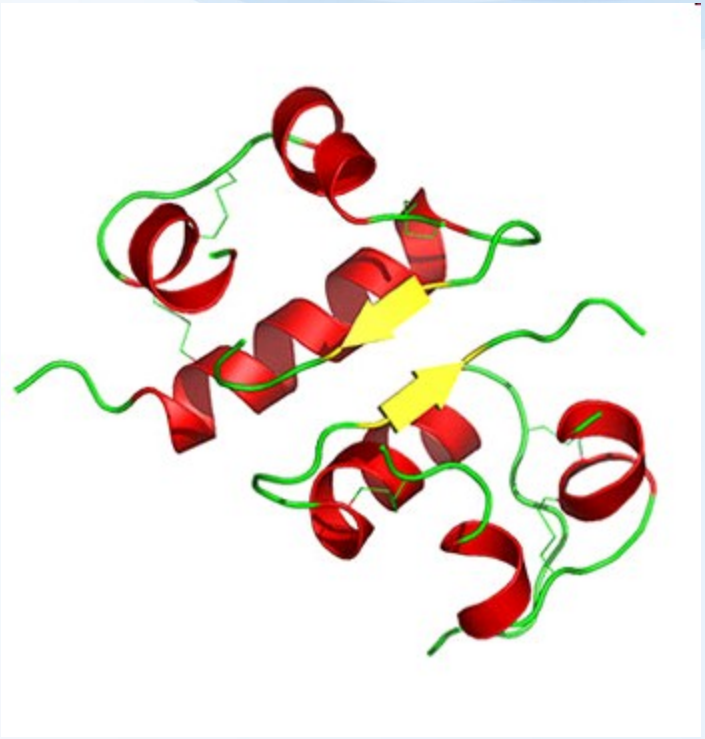
Peptide hormones

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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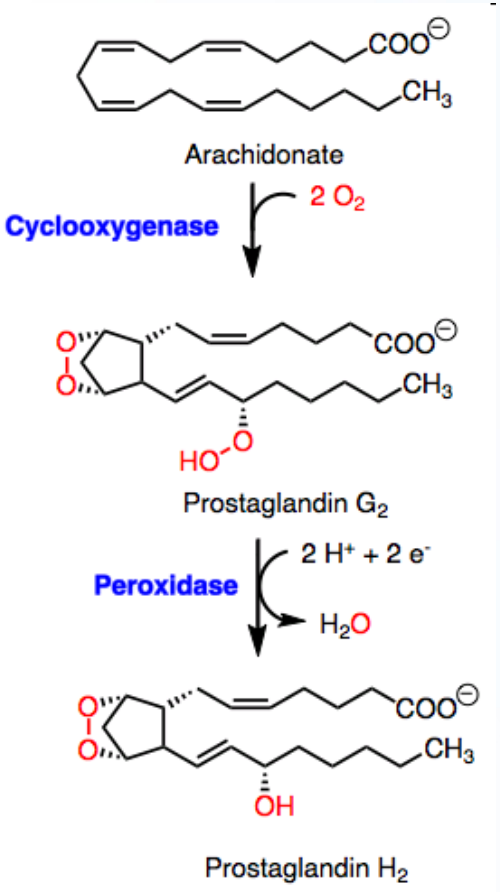
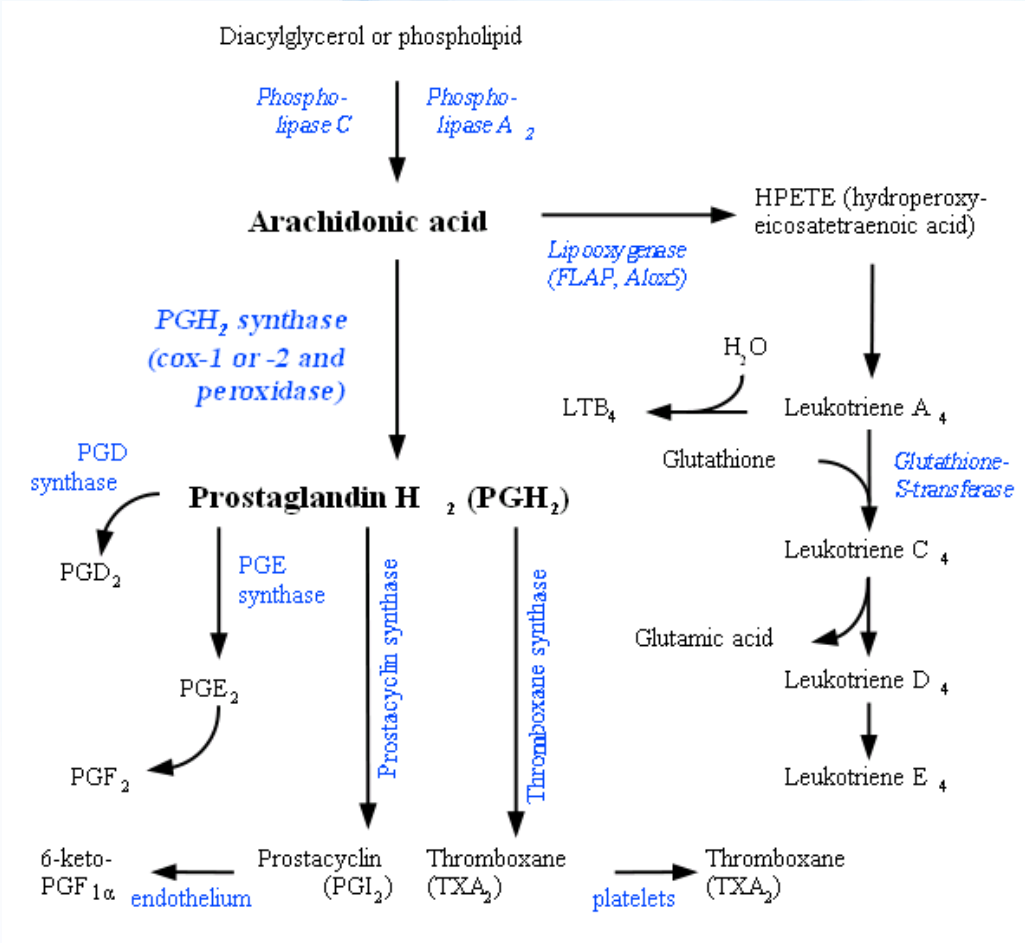
Types of hormones in vertebrates

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





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Types of hormones in vertebrates

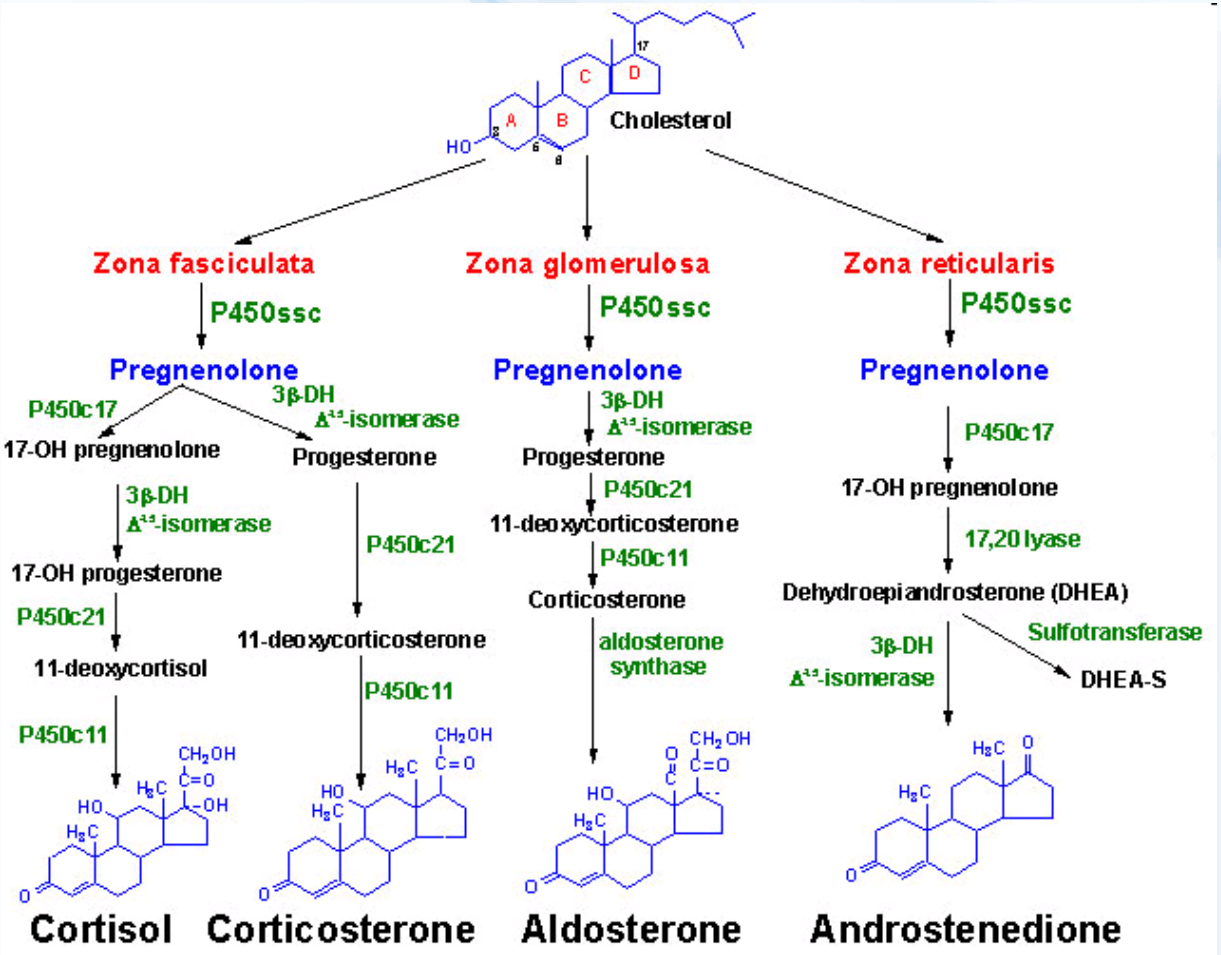
Lipid derived hormones 2 - steroid hormones

* Small molecules - similar to organic toxicants:

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

Derived
from cholesterol

Examples:
testosterone,
cortisol,
estradiol …



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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

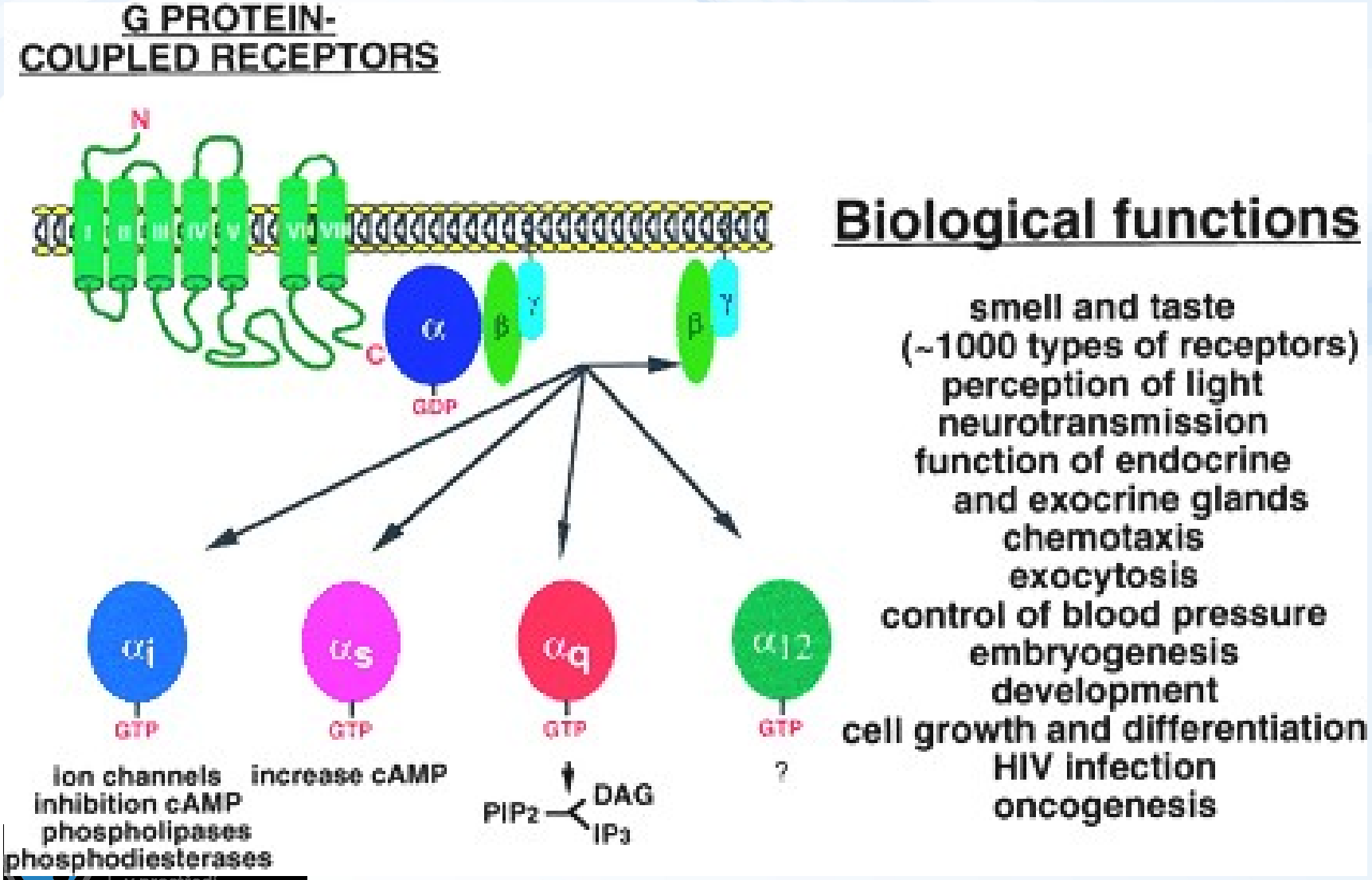
2: Membrane receptors

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

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

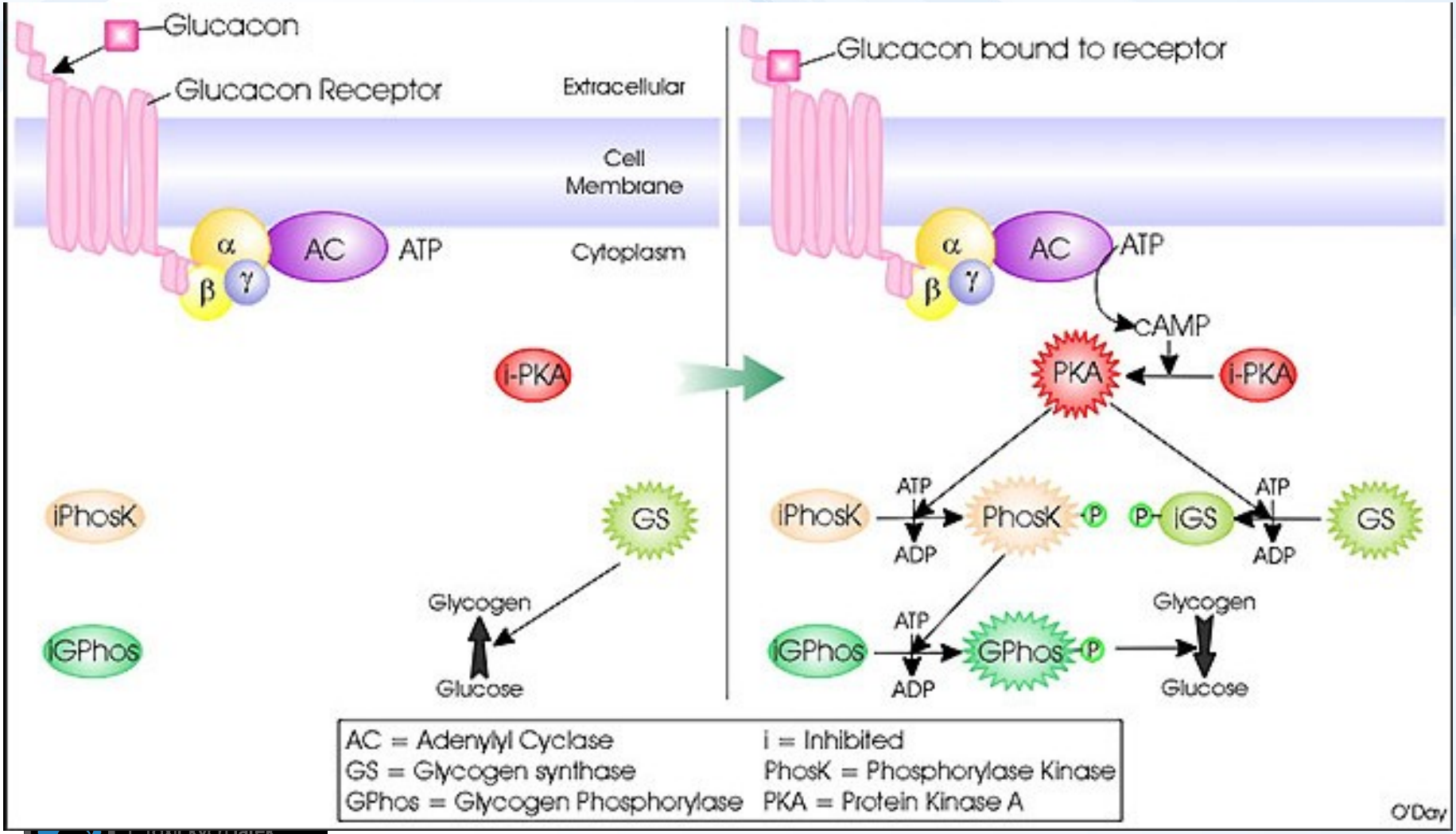
Membrane receptors acting as ProteinKinases

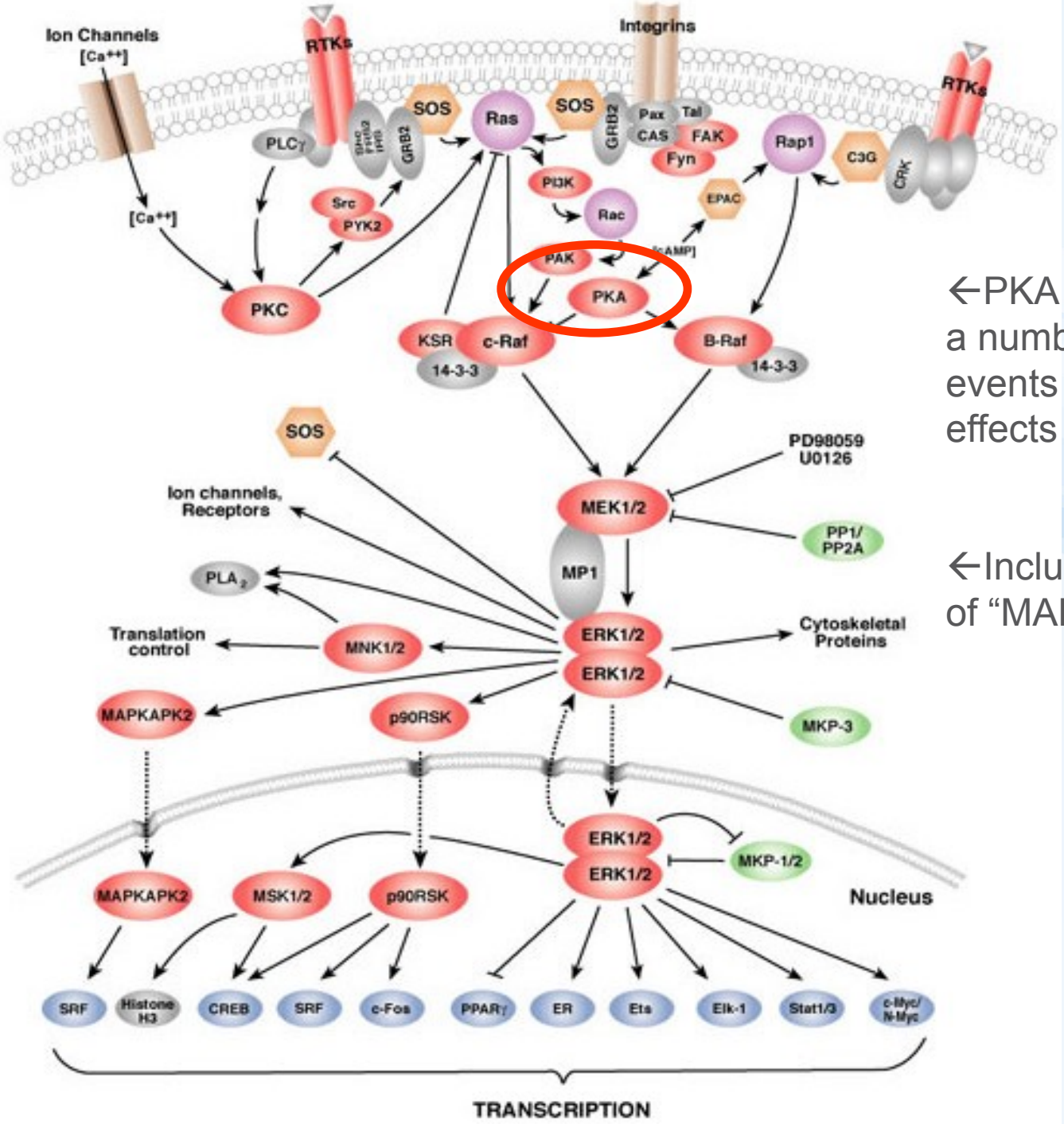
G-proteins & G-protein coupled receptors - GPCRs



Signalling mechanism 1

→ Activation of adenylate cyclase → cAMP → PKA

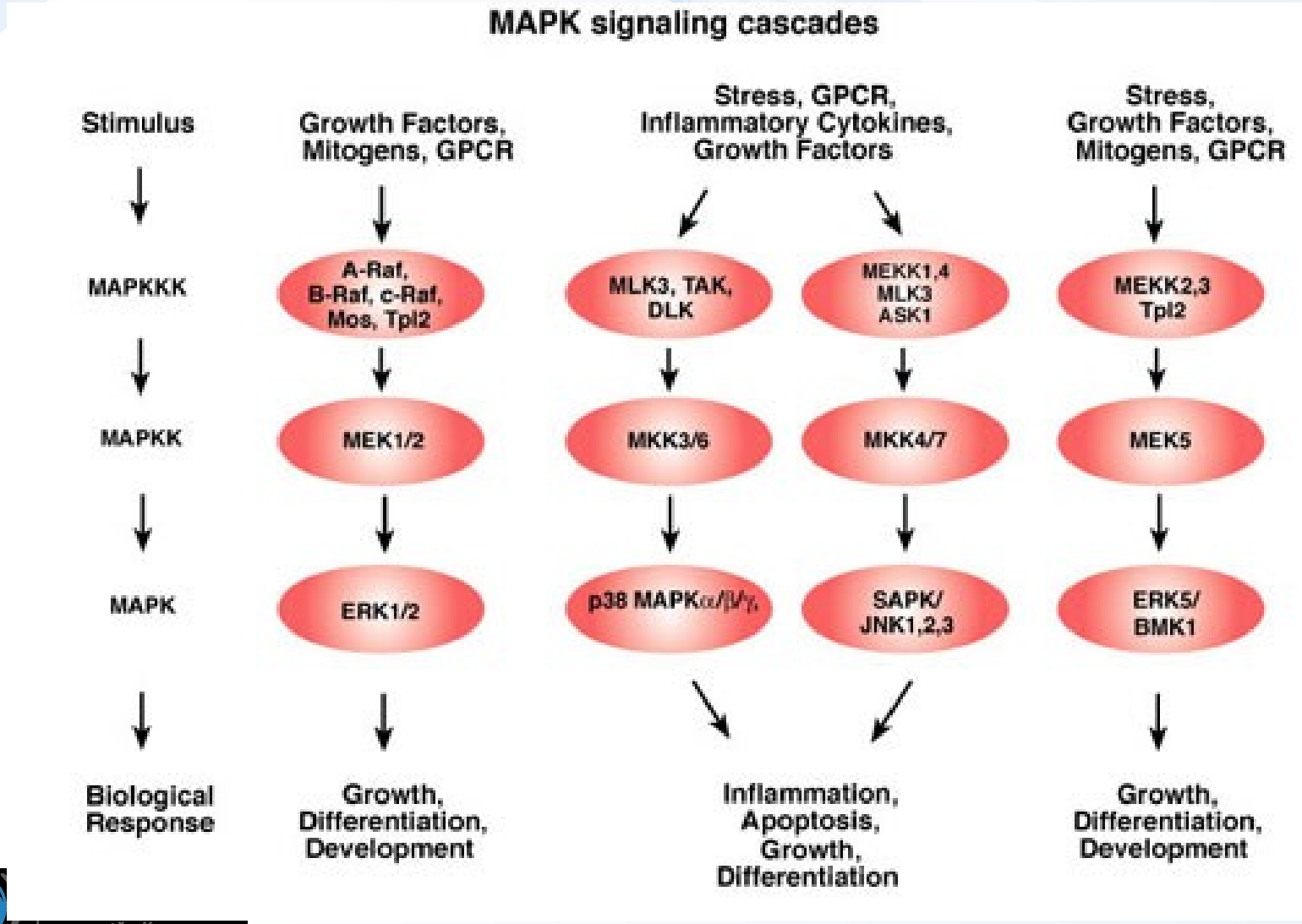




←PKA is central to a number of signalling events and following effects

←Including modulation of “MAPKs”

Mitogen Activated Protein Kinases (MAPKs) & dependent effects



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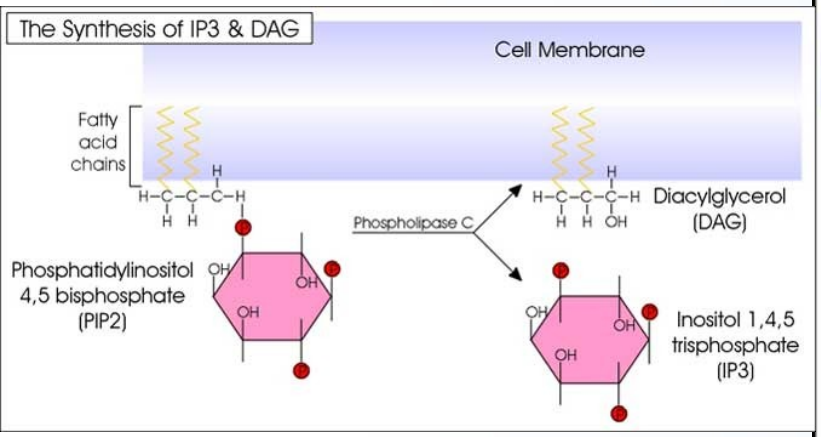
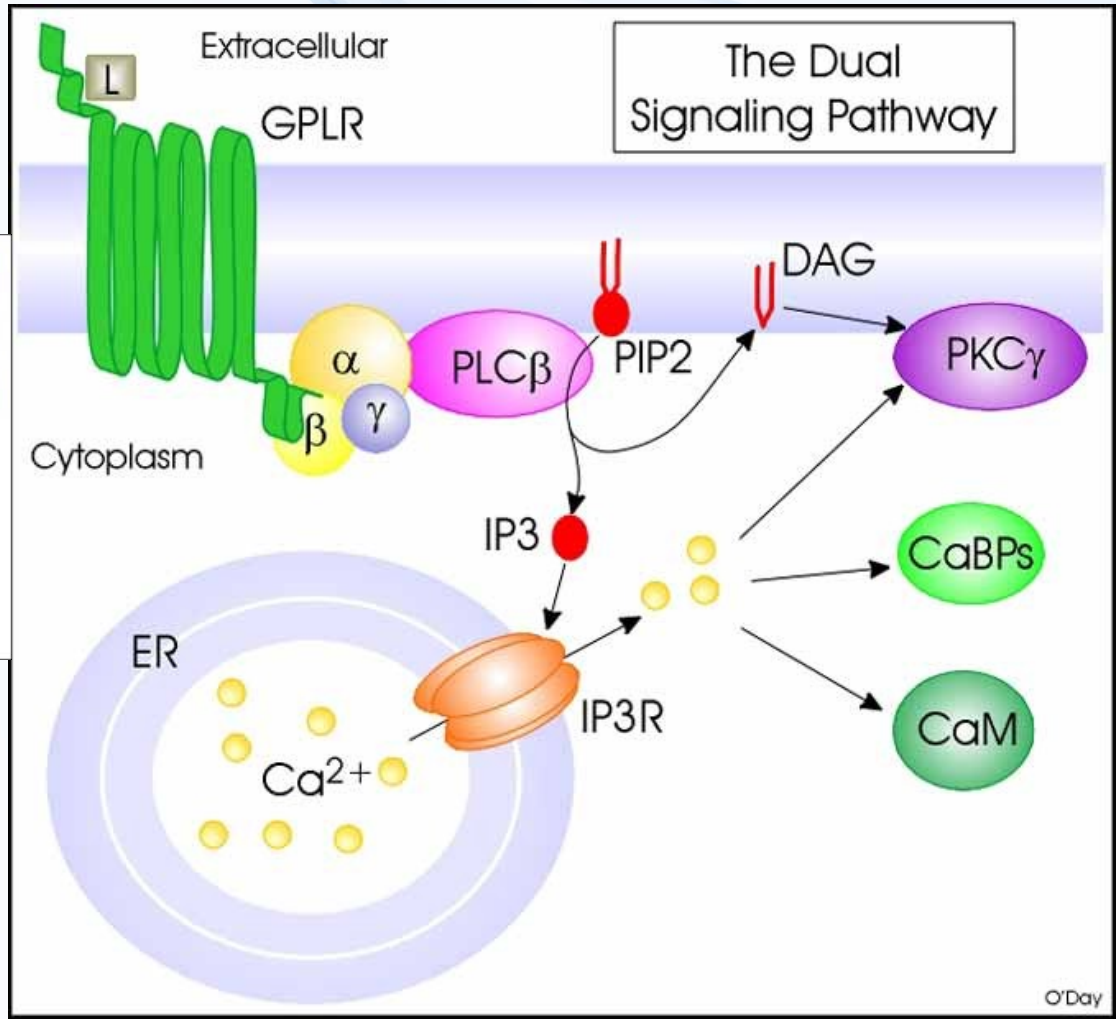
Signalling mechanism 2

Activation of Phospholipase C

→ release of PIPs → DAG → PKC / arachidonic acid

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





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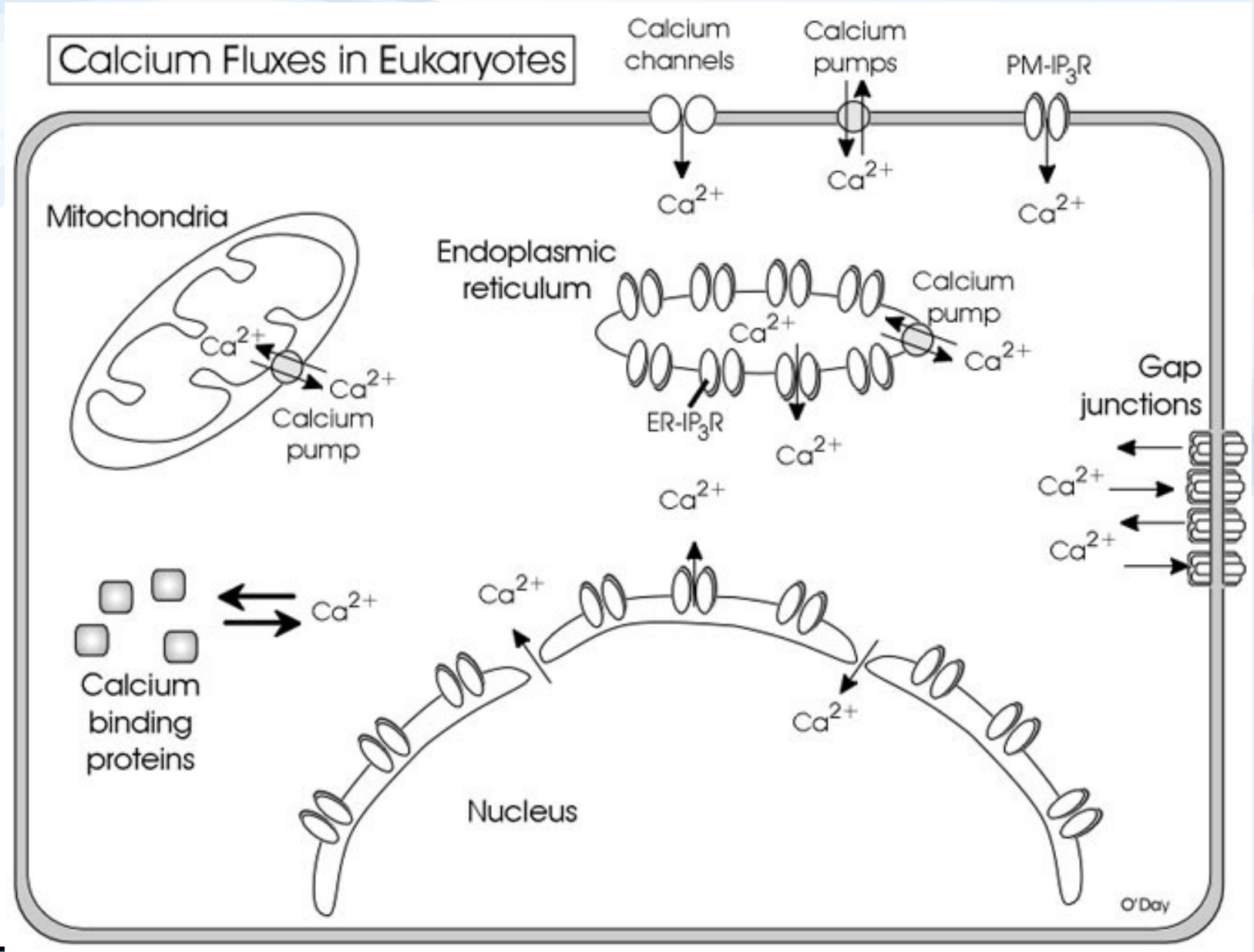
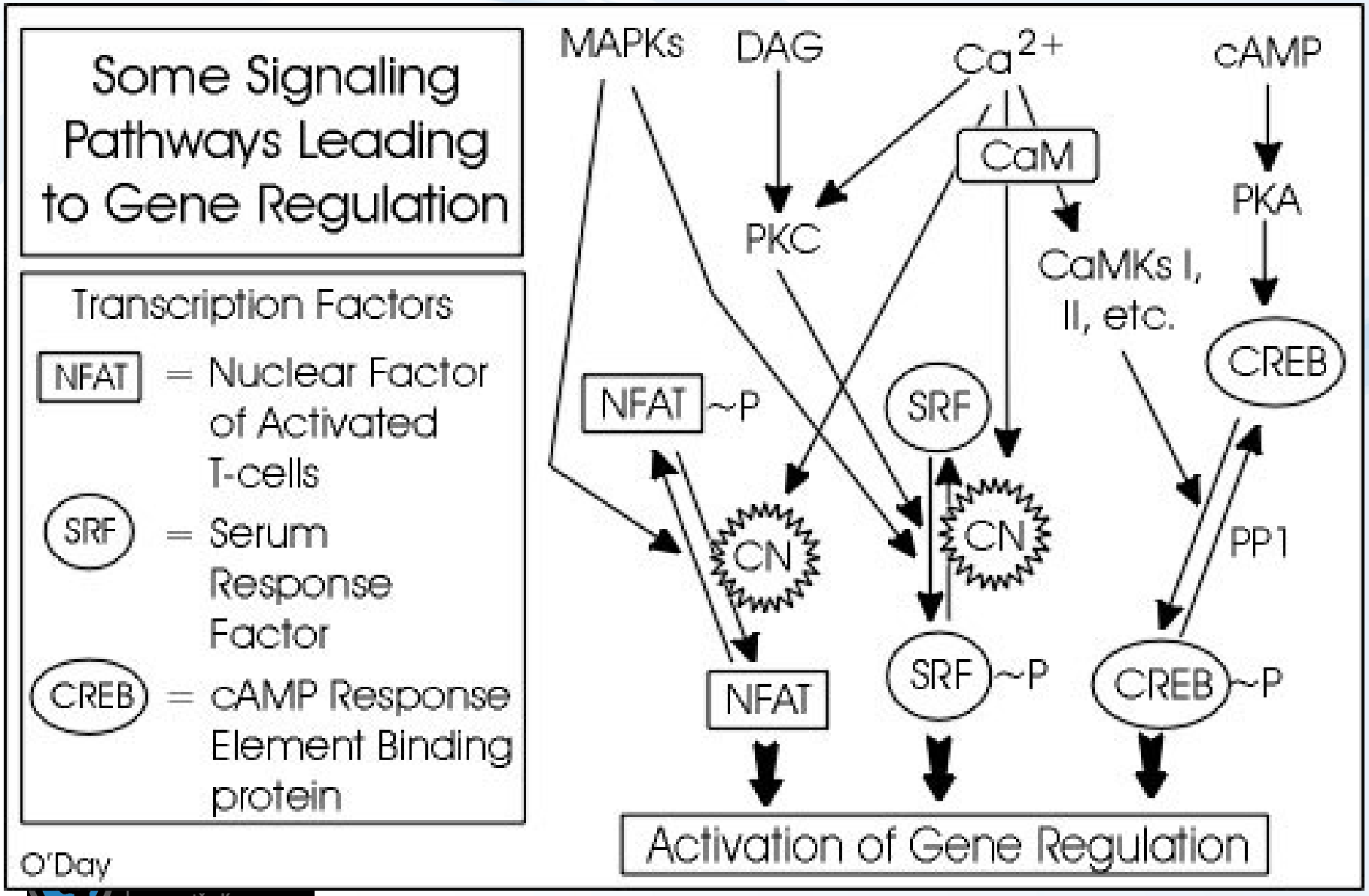


Different “types” of signalling crosstalk and form networks

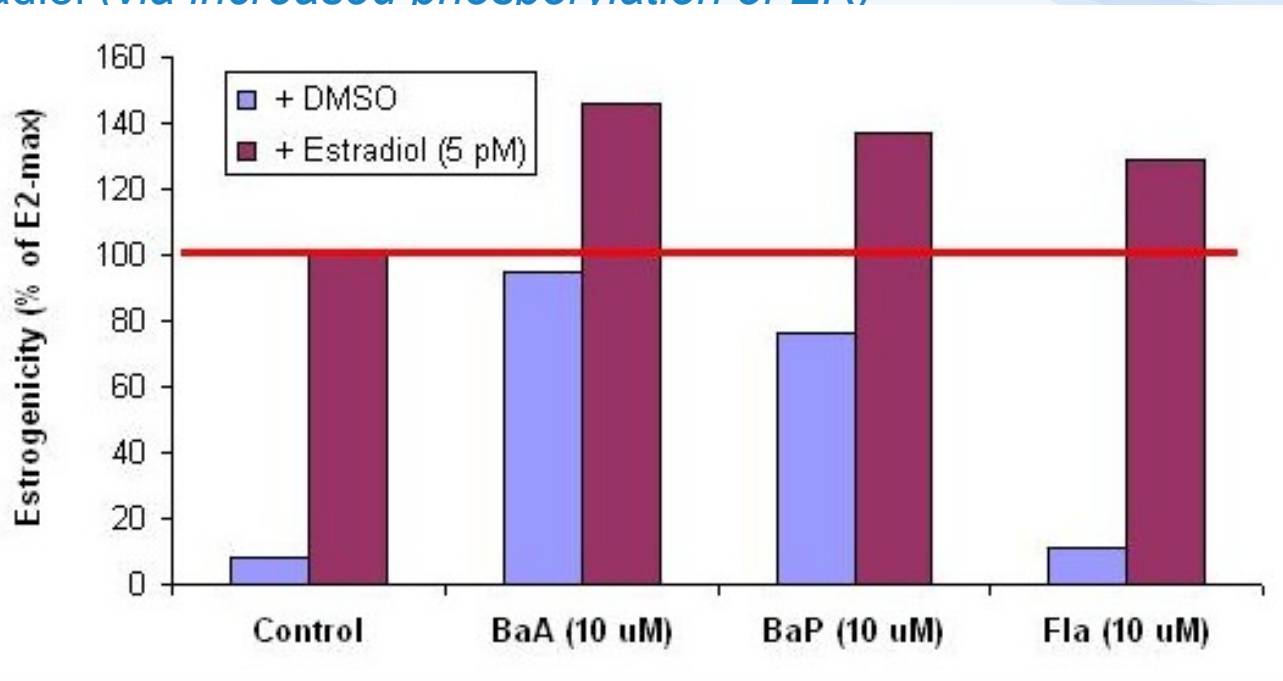


Examples

Estrogenicity of PAHs independent on activation of estrogen receptor

PAHs →modulation of PKs/PPases: phosphorylation events
→ ligand independent activation of ER

PAHs significantly potentiate the effect
of 17β-estradiol (*via increased phosporylation of ER*)



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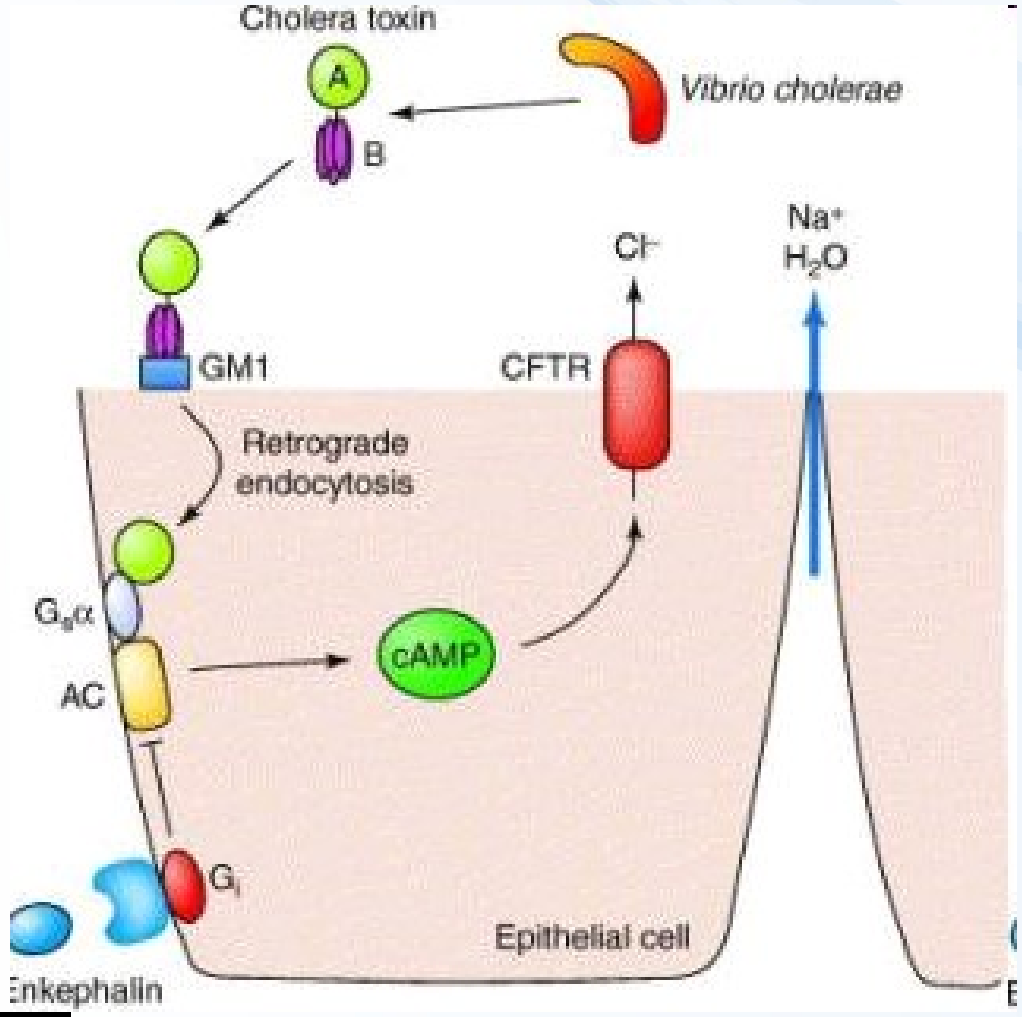
Vondráček et al. 2002 Toxicol Sci 70(2) 193

Example - cholera toxin:

CT acts as adenylate cyclase

→ increasing cAMP levels → TOXICITY



Example: Lipopolysaccharides (LPS) from cell walls

→ hyperactivation of intracellular signals → immunotoxicity