

Cell communication & regulation: a target for toxicants

Any sensitively regulated process is susceptible to toxicants

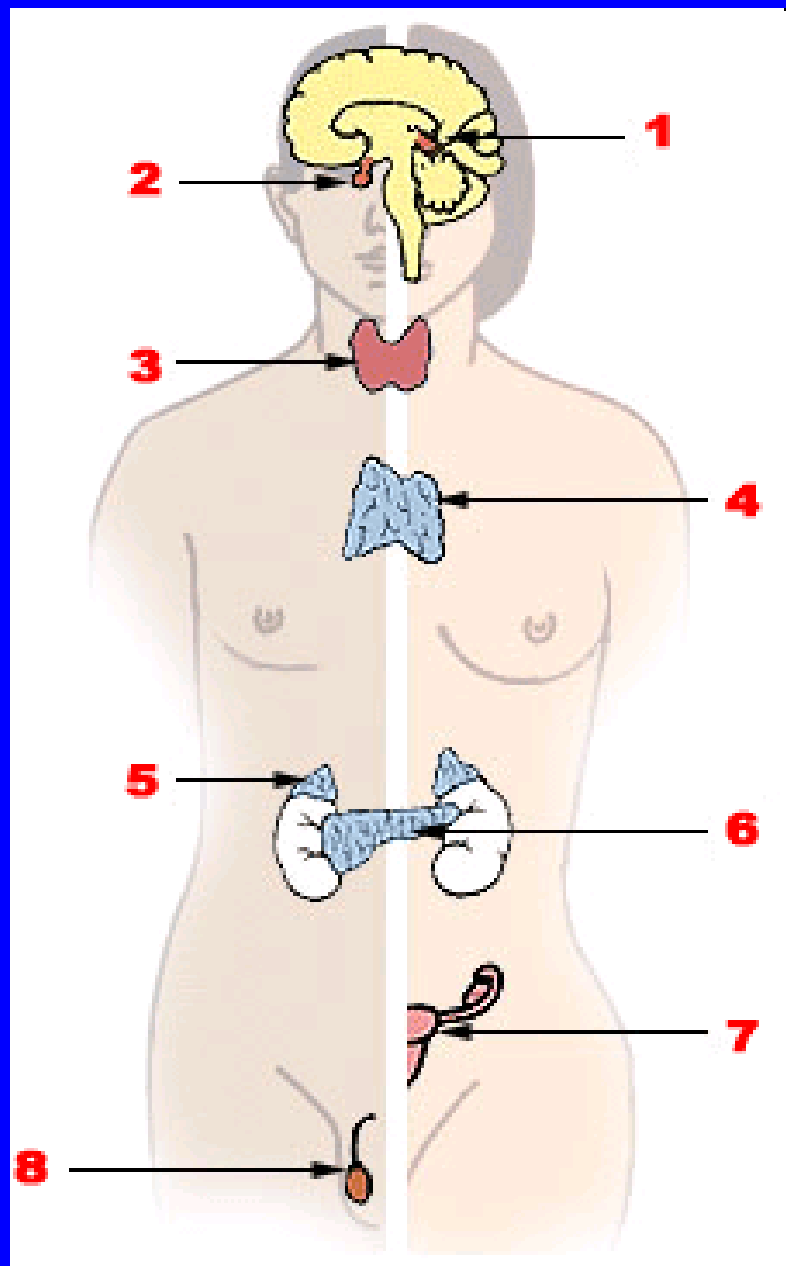
! REGULATIONS & SIGNALLING

Hierarchy

- systems: neuronal \leftrightarrow endocrine
- cell-to-cell
 - hormonal & neuronal signal transmission
 - contact channels
- intracellular signal transduction

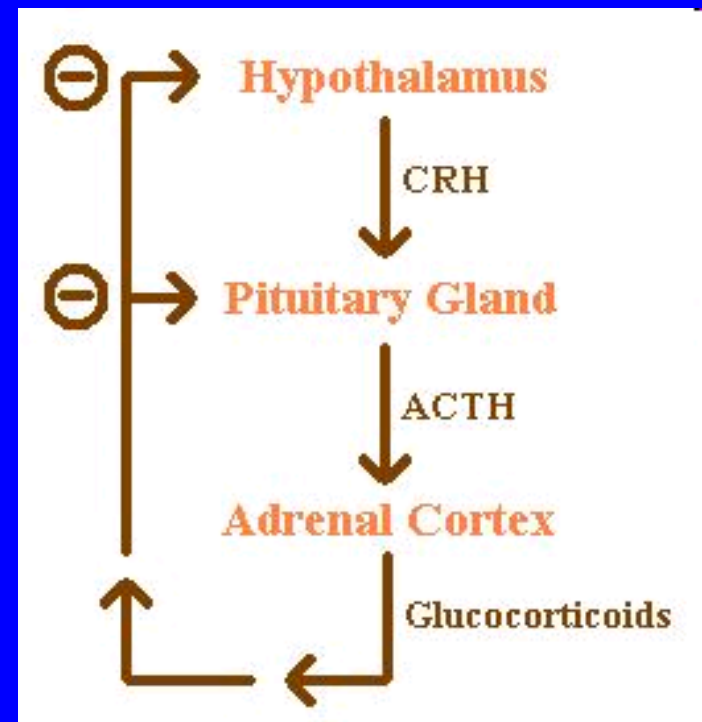
HORMONES - fate

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



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

HORMONES - actions and controls

- * 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

TOXICITY TO HORMONAL ACTION = ENDOCRINE DISRUPTION

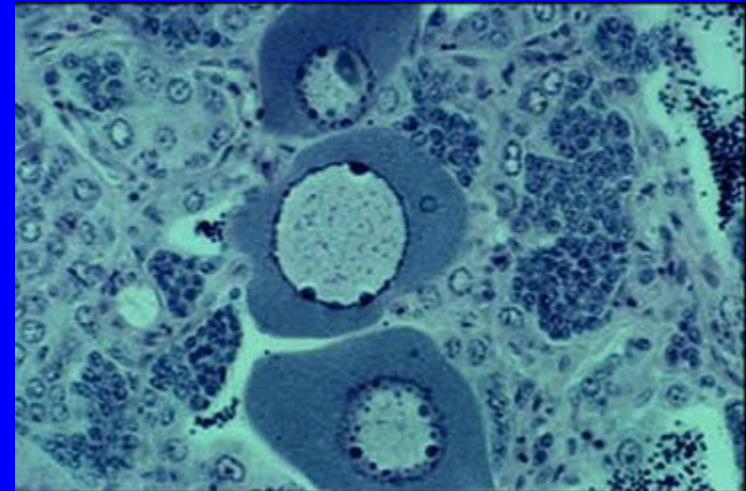
ED & EDCs - major problem in environmental toxicology

- Effects at all levels of hormonal action
(*synthesis, transport, action*)
- Multiple effects (! Not only „xenoestrogenicity“ & feminization)
(*immunotoxicity, reproduction ...*)

(WILL BE DISCUSSED FURTHER)

Intersex roach testis

containing both oocytes and spermatozoa,
caused by exposure to environmental oestrogens

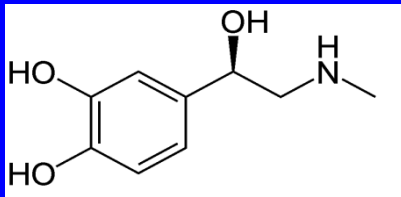


HORMONES - chemicals (vertebrates)

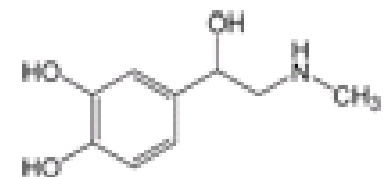
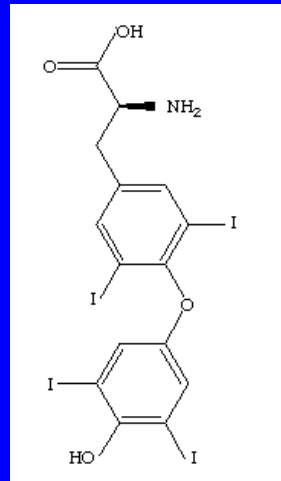
* Amine-derived hormones are derivatives of the amino acids tyrosine and tryptophan. Examples are catecholamines and thyroxine.

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

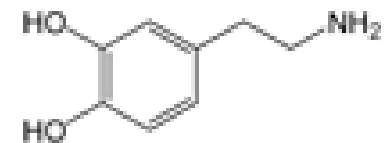
Adrenalin



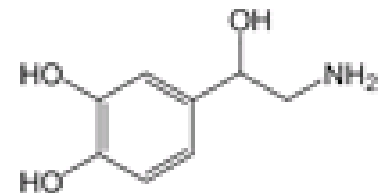
Thyroxin



Epinephrine



Dopamine



Norepinephrine

Further:

* Peptide hormones

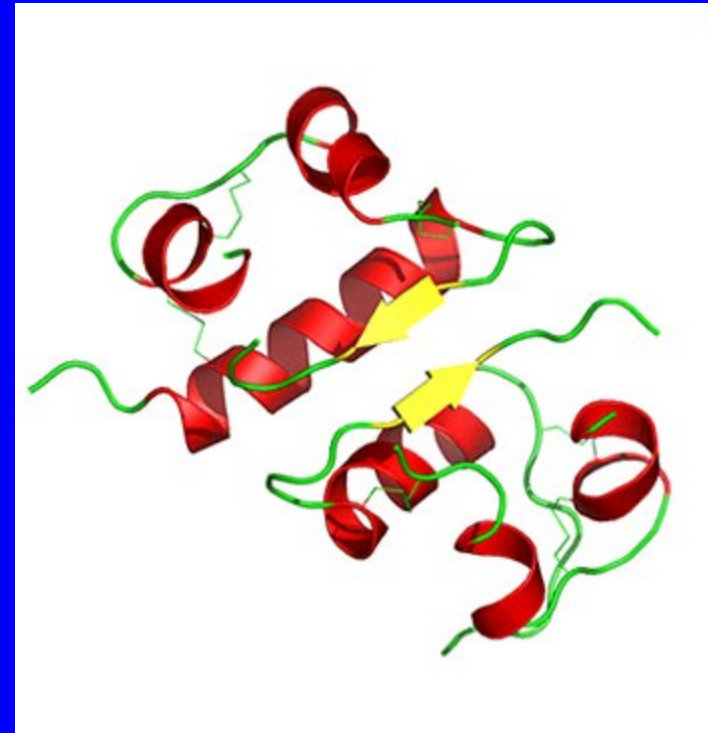
* Lipid and phospholipid-derived hormones

HORMONES - chemicals (vertebrates)

* Peptide hormones chains of amino acids. - small: TRH and vasopressin; proteins: insulin, growth hormone, luteinizing hormone, follicle-stimulating hormone and thyroid-stimulating hormone).

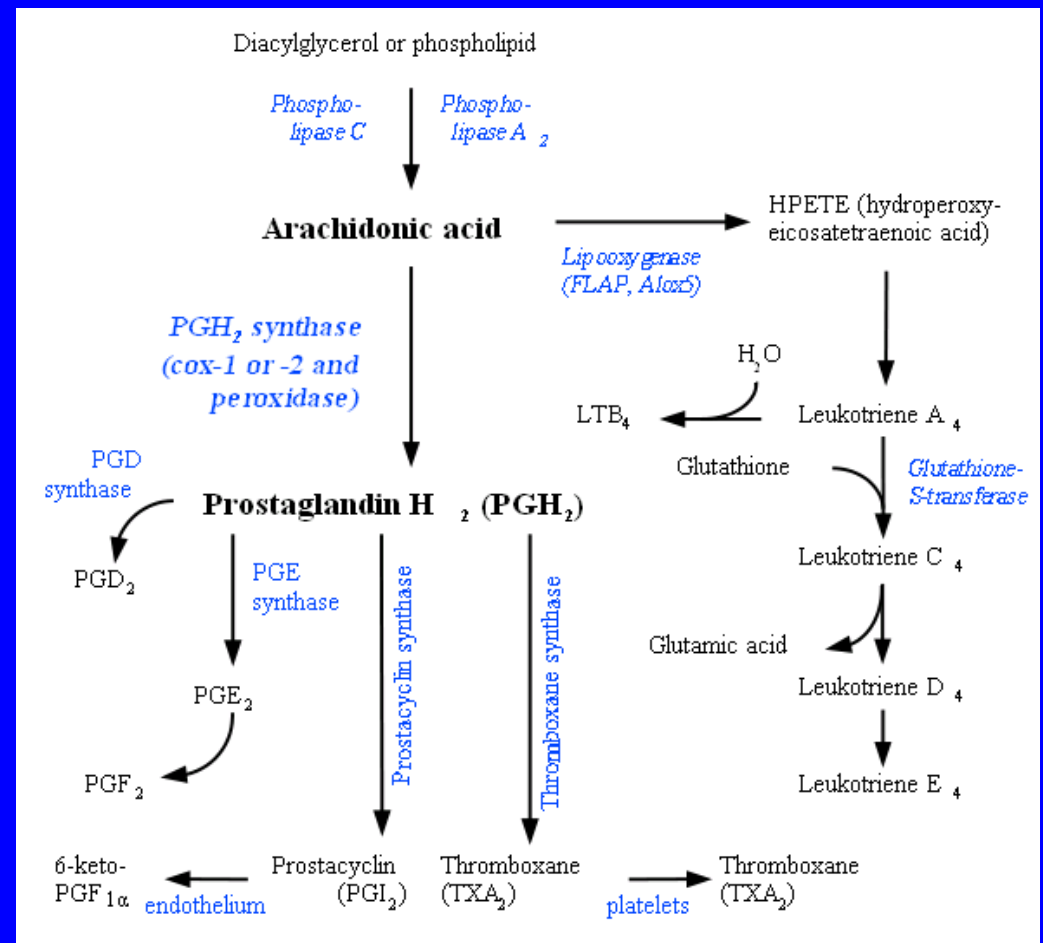
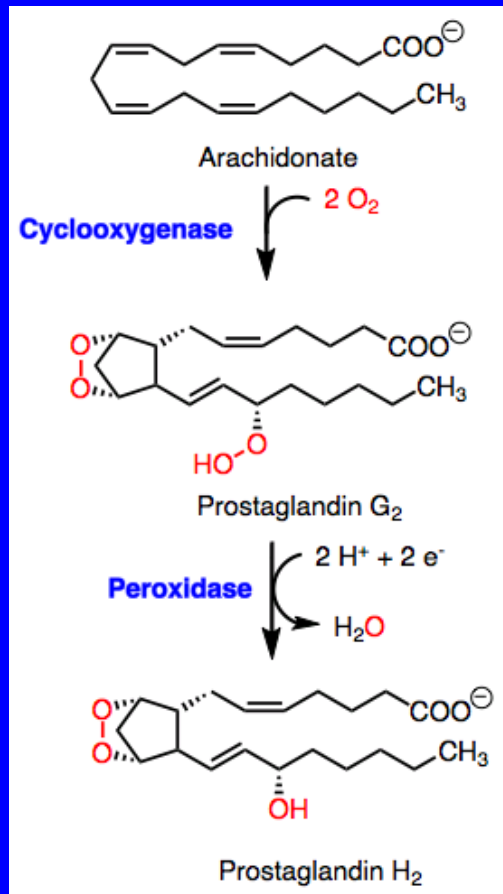
*Large molecules; receptors on surfaces of the cells
(Interactions with toxic chemicals less likely)*

Example - insulin



HORMONES - chemicals (vertebrates)

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



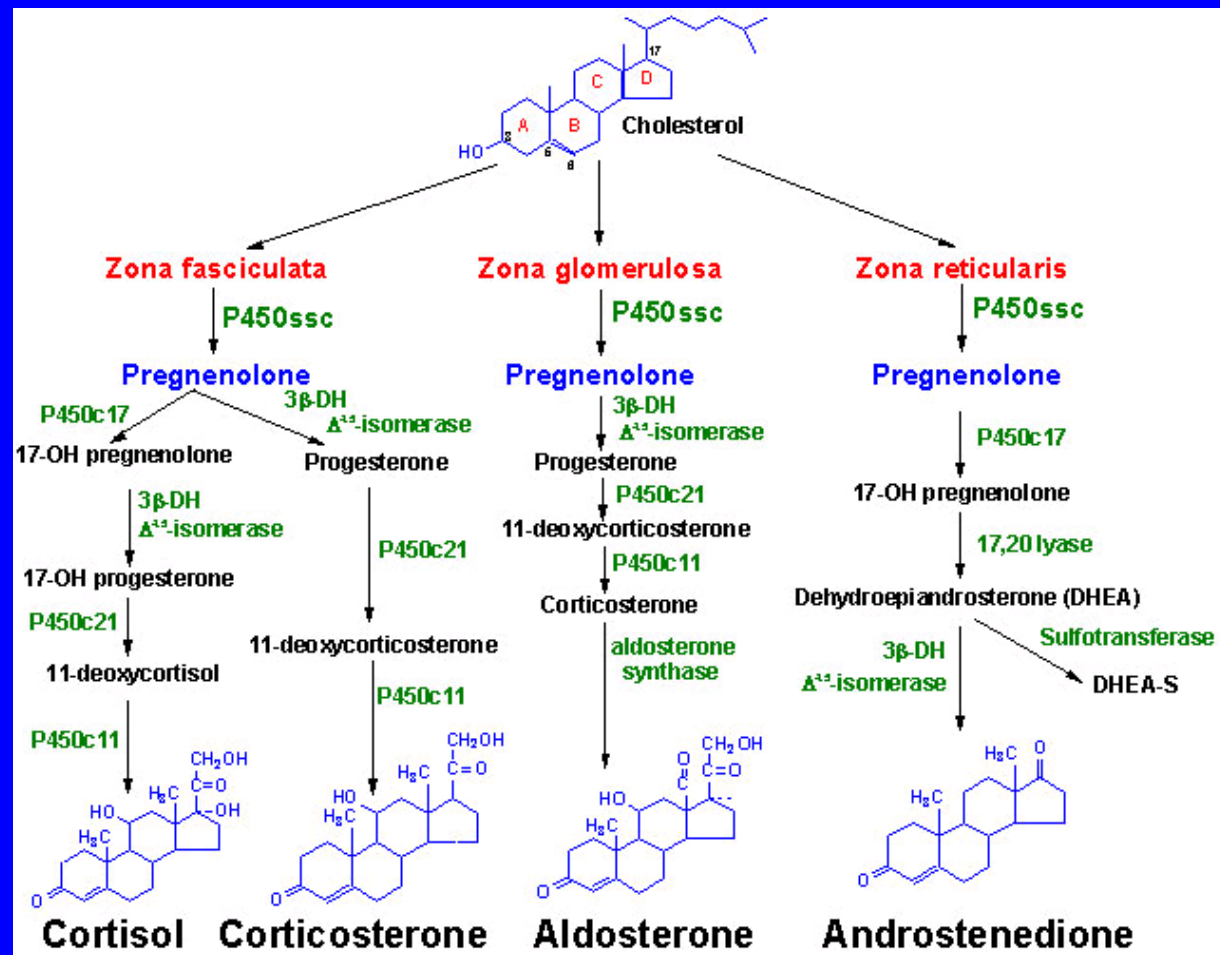
HORMONES - chemicals (vertebrates)

Lipid derived hormones (2)

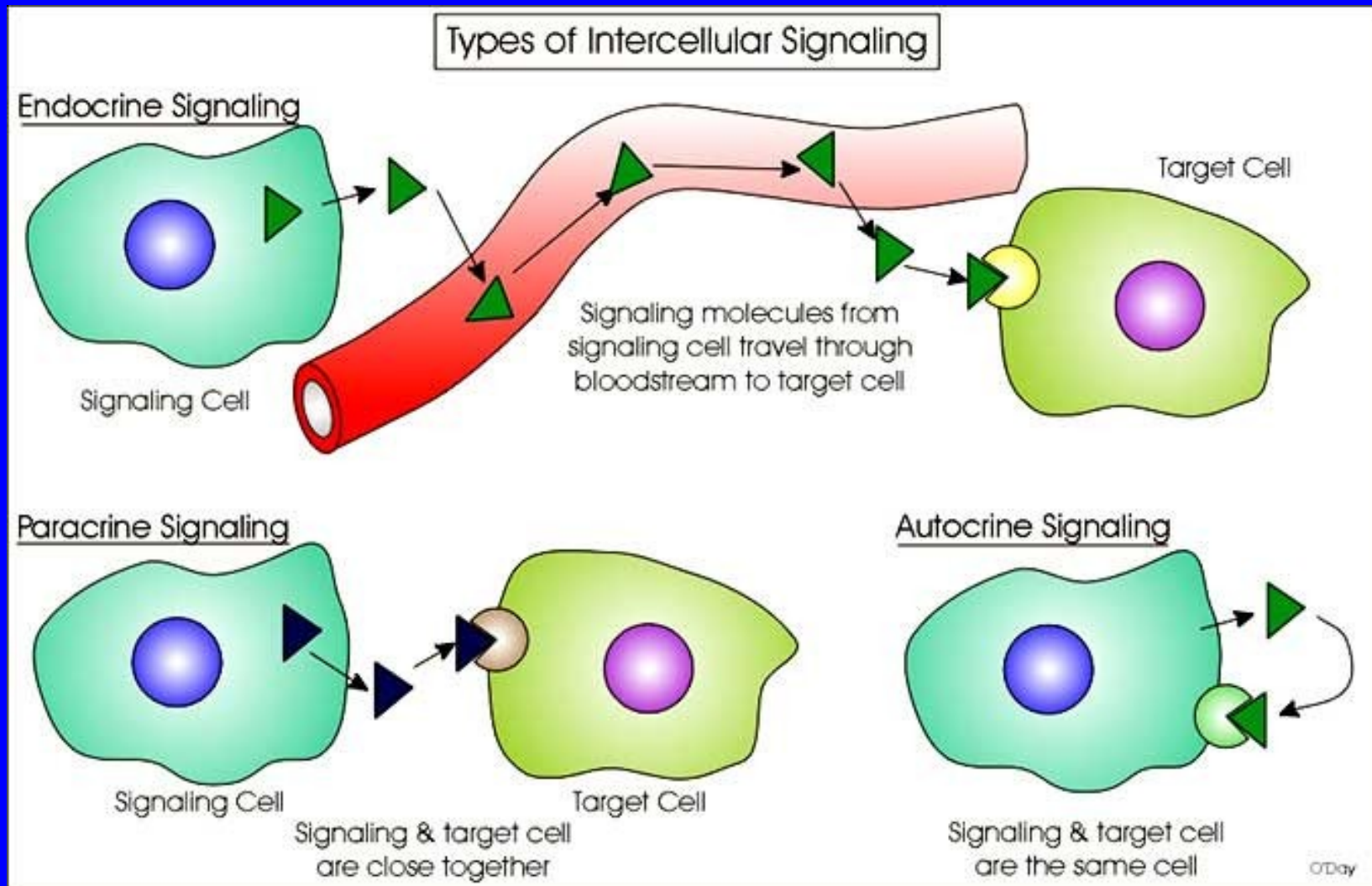
(small molecules - similar to organic toxicants - TOXIC EFFECTS)

- steroid hormones (from cholesterol)

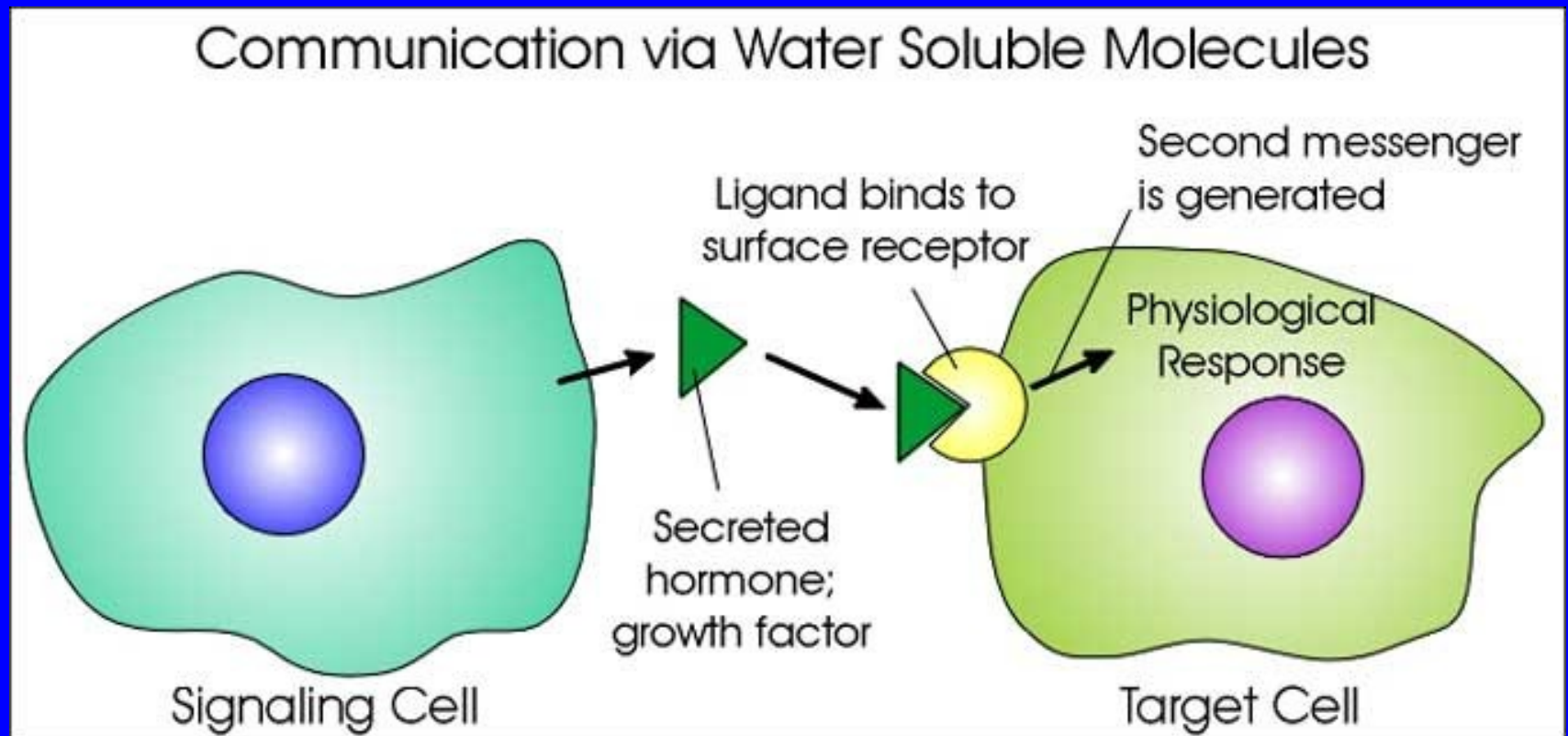
testosterone,
cortisol,
estradiol ...



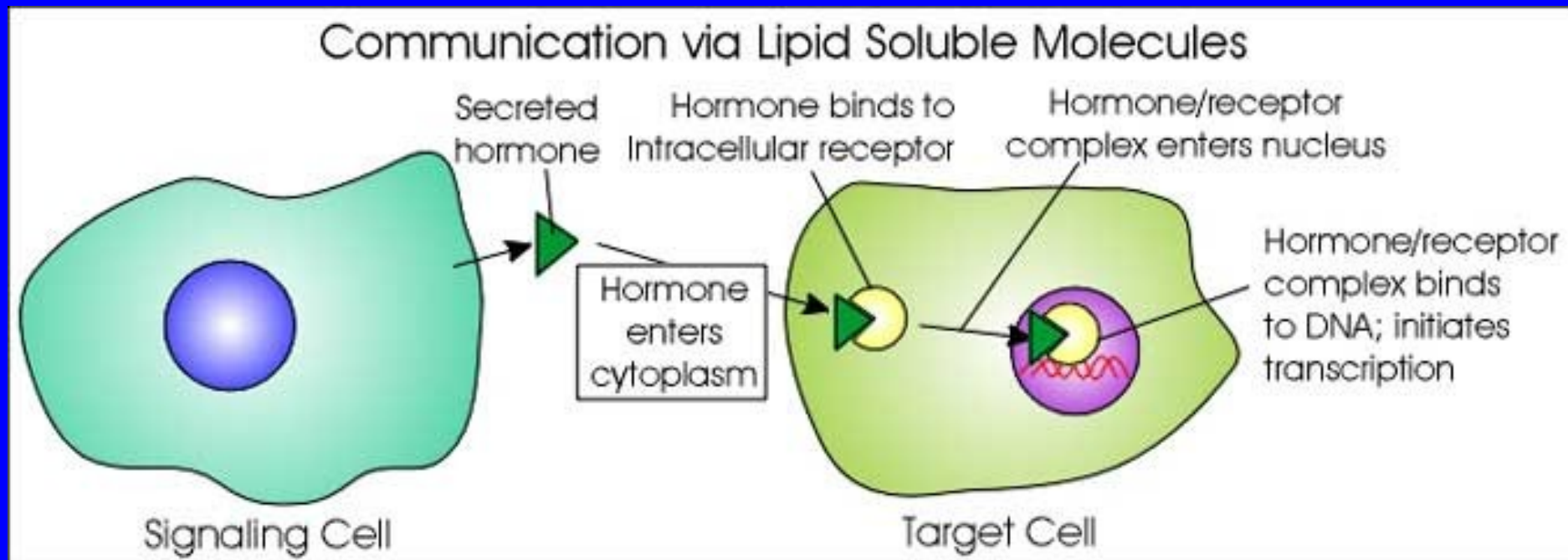
Cell communication & regulation: a target for toxicants



Cell communication (1)

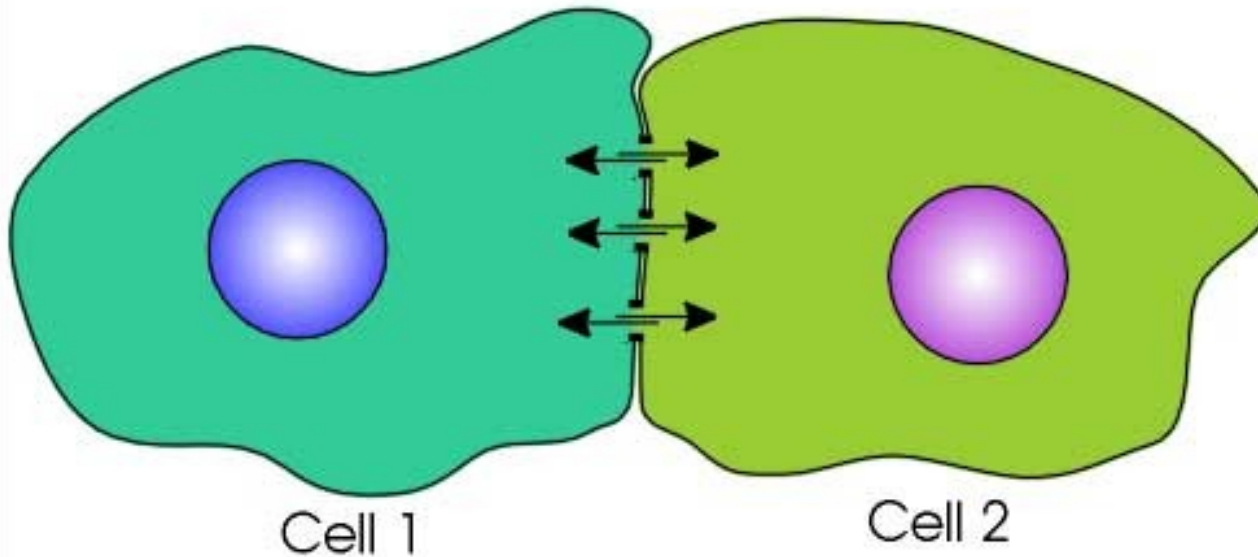


Cell communication (2)

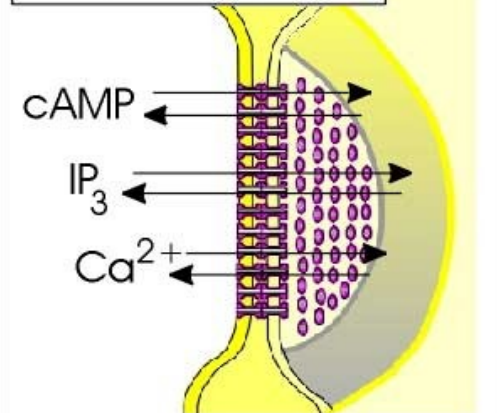


Cell communication (3)

Communication via Cellular Continuities



Gap Junction



Signal transduction - target of toxicants

- **Regulation of cell life / death (apoptosis)**
 - metabolism
 - proliferation
 - differentiation
 - death (apoptosis)

- **Signalling**
 - "network" of general pathways
 - similar in all cells / different cell-specific effects

Signalling disruption

- **Consequences of signalling disruption**
 - unwanted changes in proliferation / differentiation / apoptosis
 - > cell transformation (carcinogenicity)
 - > embryotoxicity
 - > immunotoxicity
 - > reproduction toxicity
 - *other chronic types of toxicity*

Signal transduction - principles

: major processes

– protein-(de)phosphorylation (**PKinases, PPases**)

- secondary messengers (cAMP / IP3, PIP2, DAG, Ca²⁺, AA)

1: Membrane receptors (G-protein, kinases)

-> **PKA activation:** cAMP

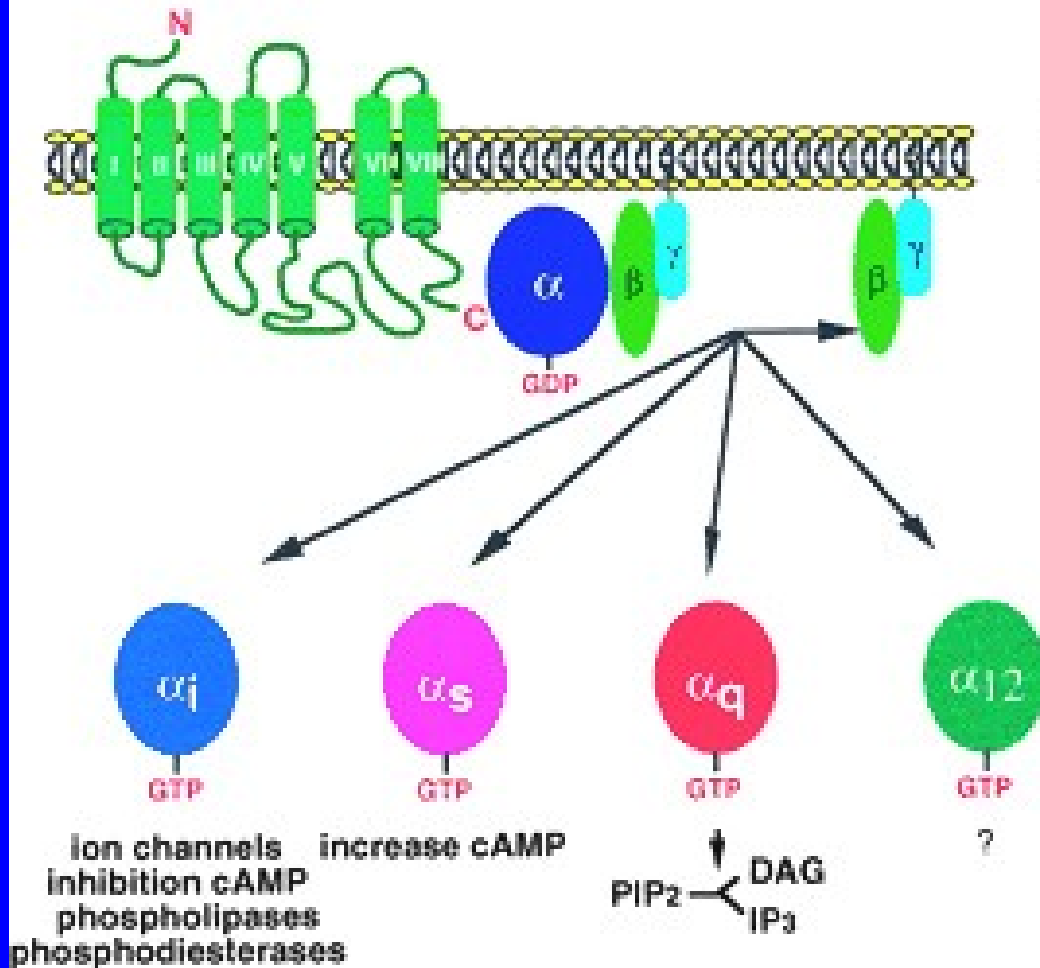
2: Membrane receptors -> PLC / PKC activation

-> **PKC activation:** IP3, PIP2, DAG, Ca²⁺, AA

3: Cytoplasmic (nuclear) receptors

Membrane receptors (PKs): G-proteins (GPCRs)

G PROTEIN- COUPLED RECEPTORS

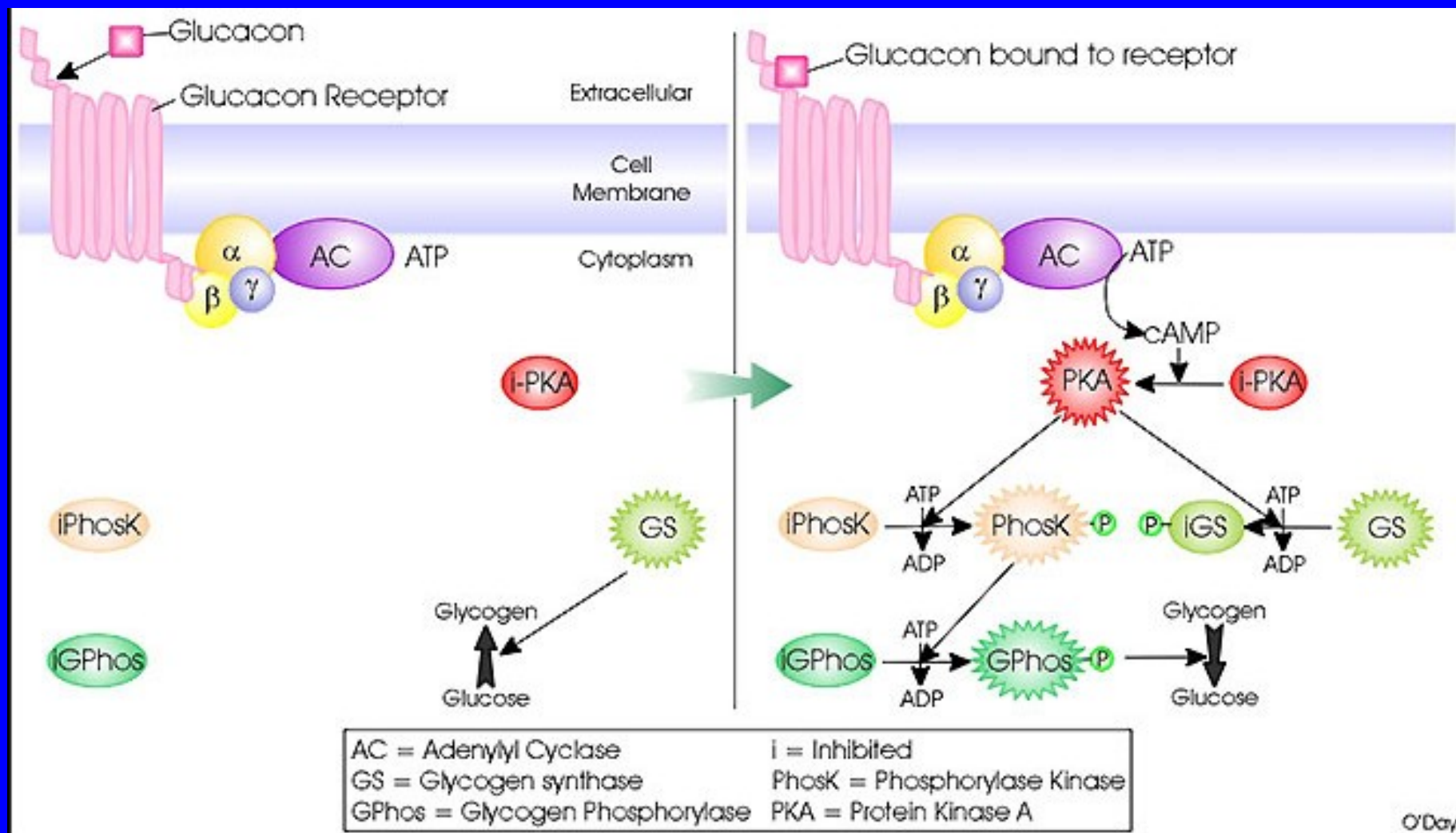


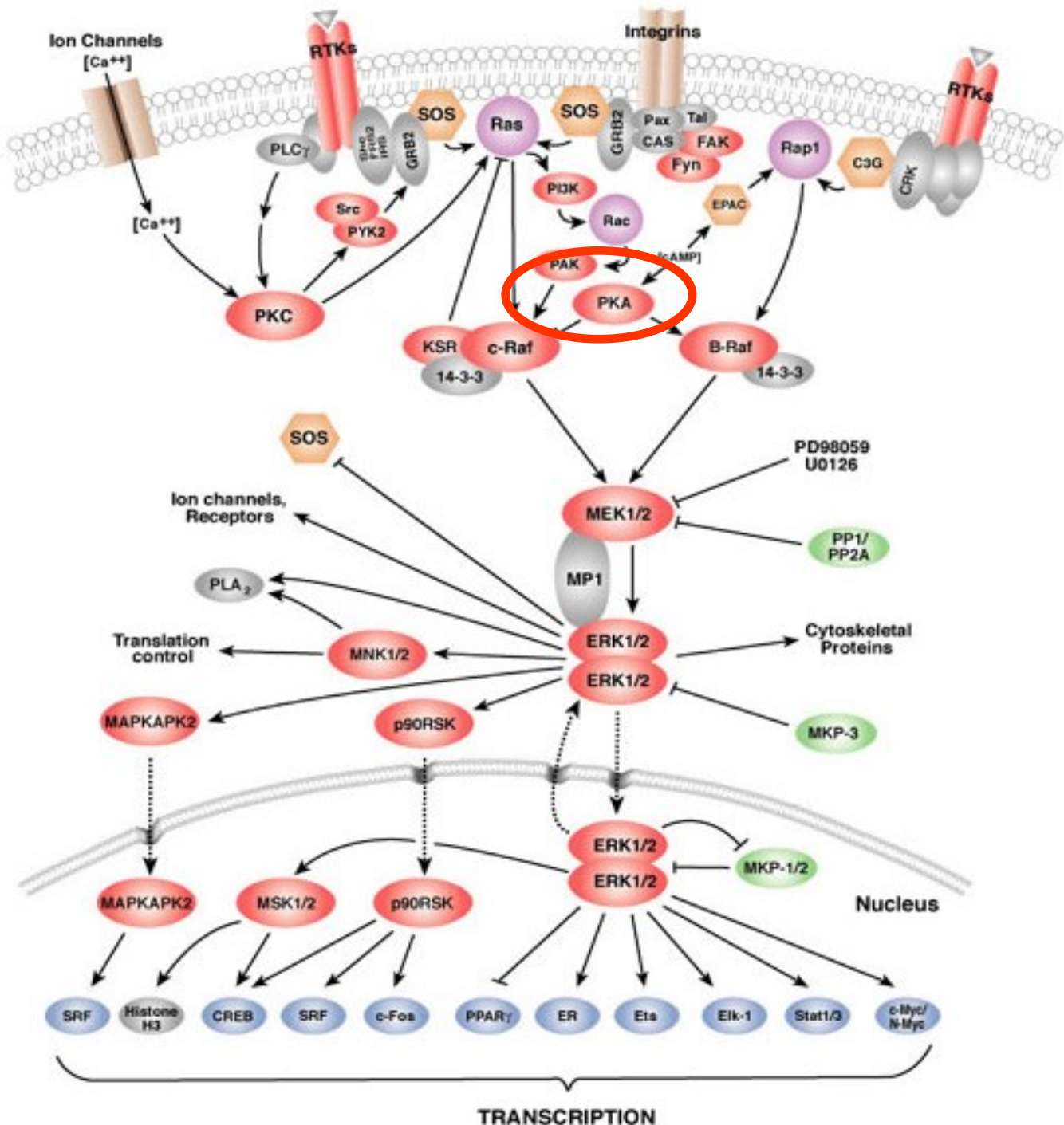
Biological functions

smell and taste
 (~1000 types of receptors)
 perception of light
 neurotransmission
 function of endocrine
 and exocrine glands
 chemotaxis
 exocytosis
 control of blood pressure
 embryogenesis
 development
 cell growth and differentiation
 HIV infection
 oncogenesis

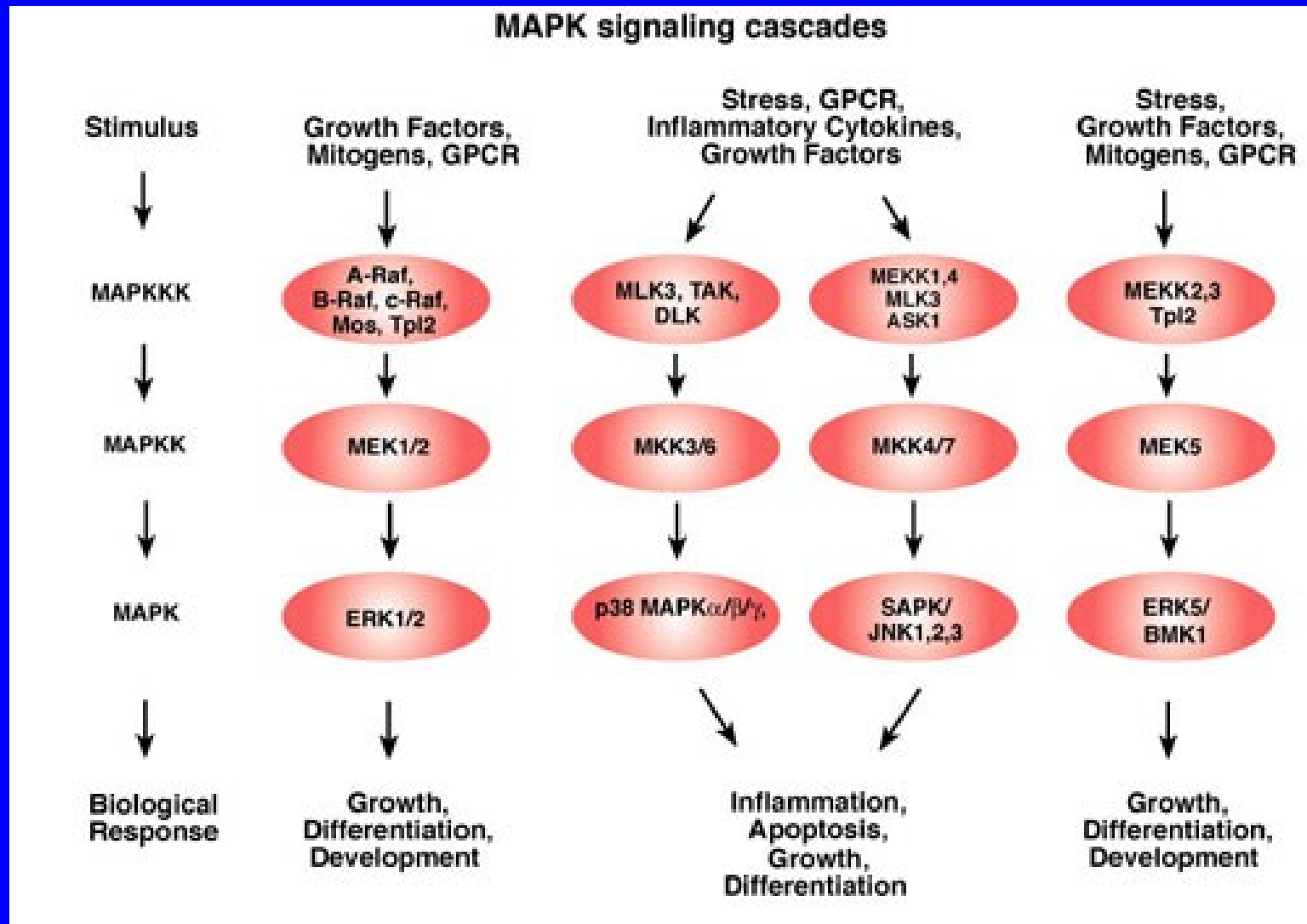
1: Membrane receptors (PKs)

-> Adenylate cyclase -> cAMP -> PKA – modulation





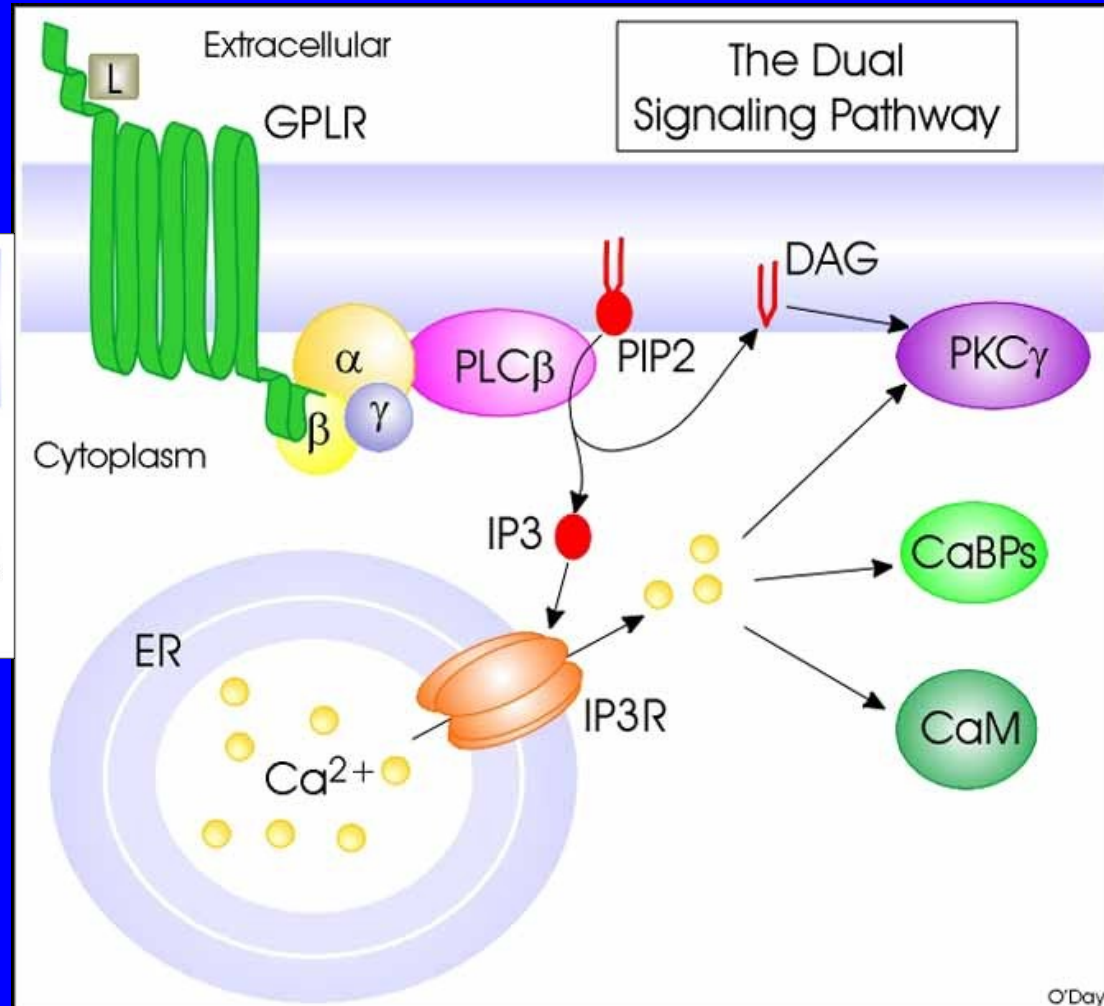
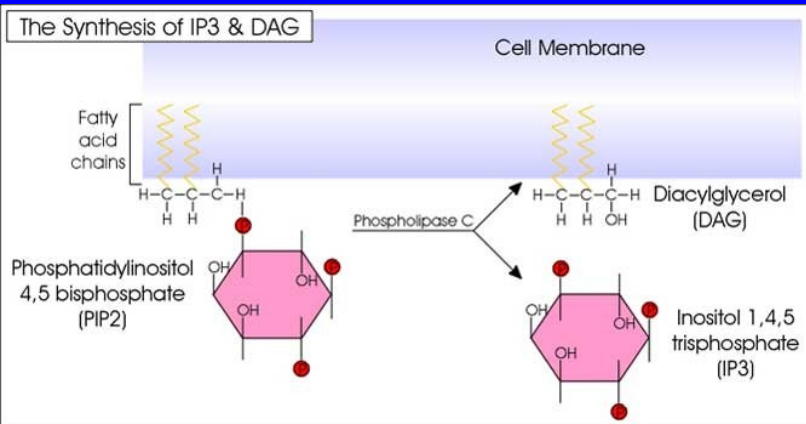
(!!!) Mitogen Activated Protein Kinases (MAPK) – dependent effects



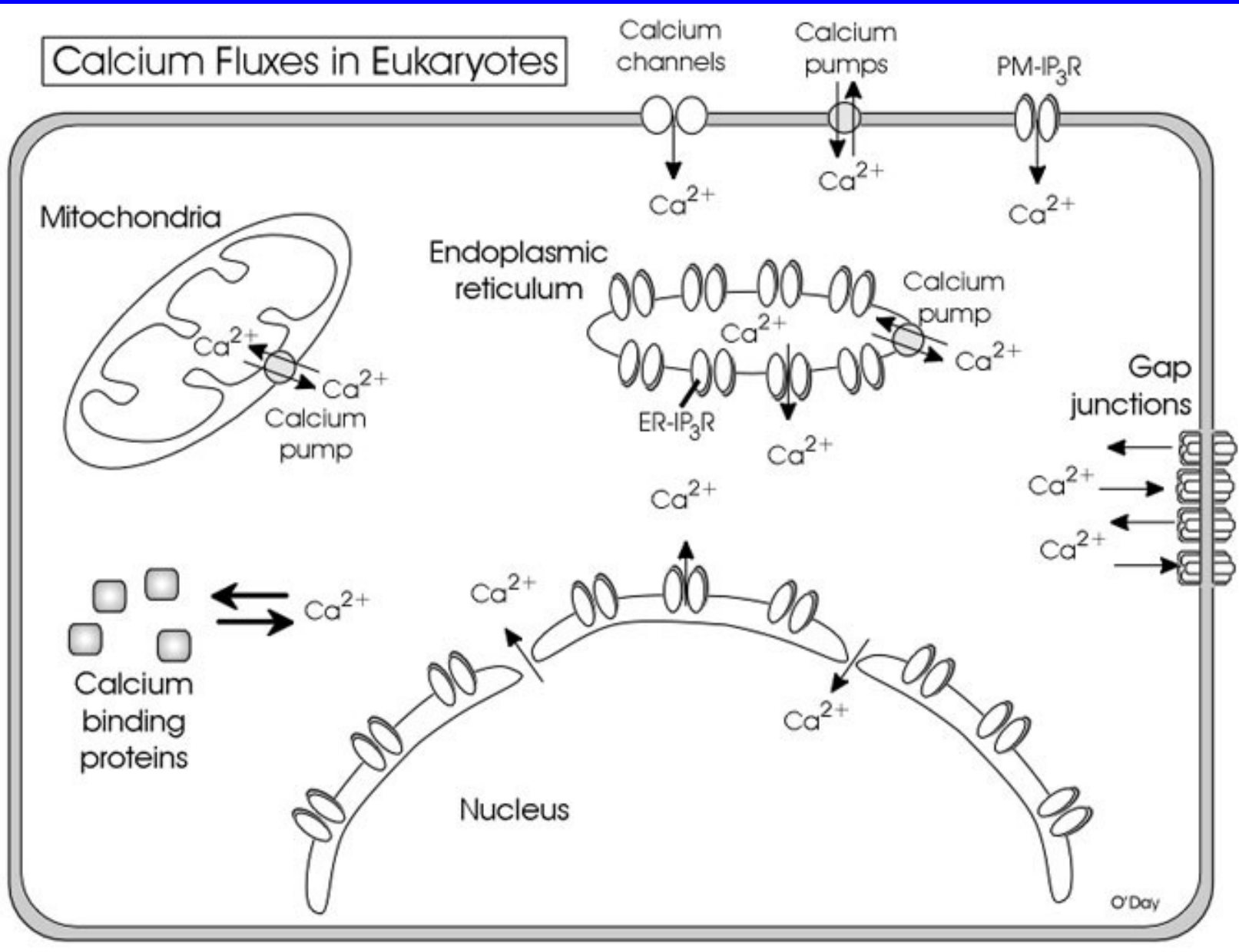
2: Membrane receptors

-> Phospholipase C:

PIPs -> DAG -> PKC / arachidonic acid
+ IP3 -> Ca²⁺



Calcium Fluxes in Eukaryotes

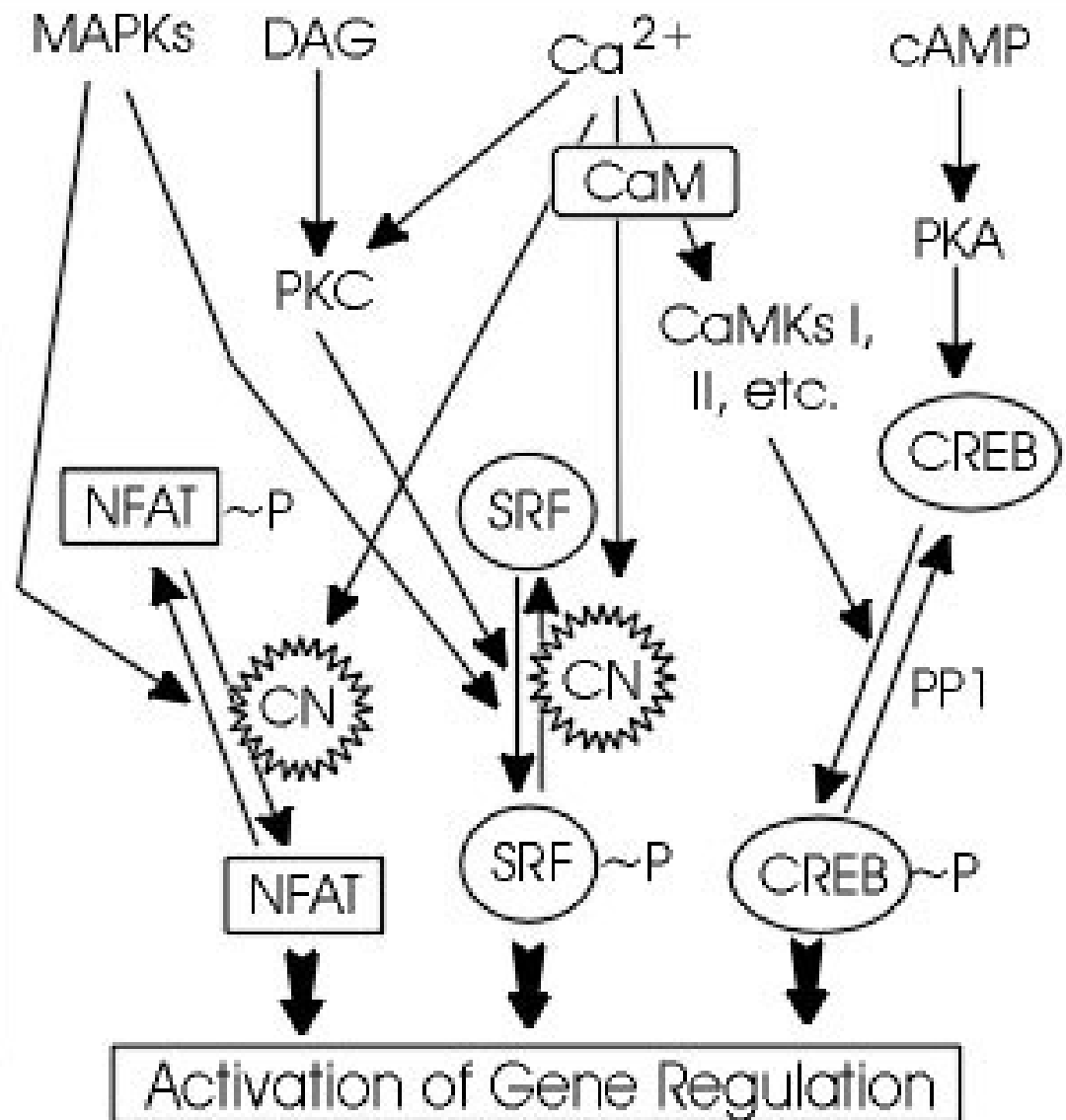


Signalling crosstalk

Some Signaling Pathways Leading to Gene Regulation

Transcription Factors

- NFAT** = Nuclear Factor of Activated T-cells
- SRF** = Serum Response Factor
- CREB** = cAMP Response Element Binding protein

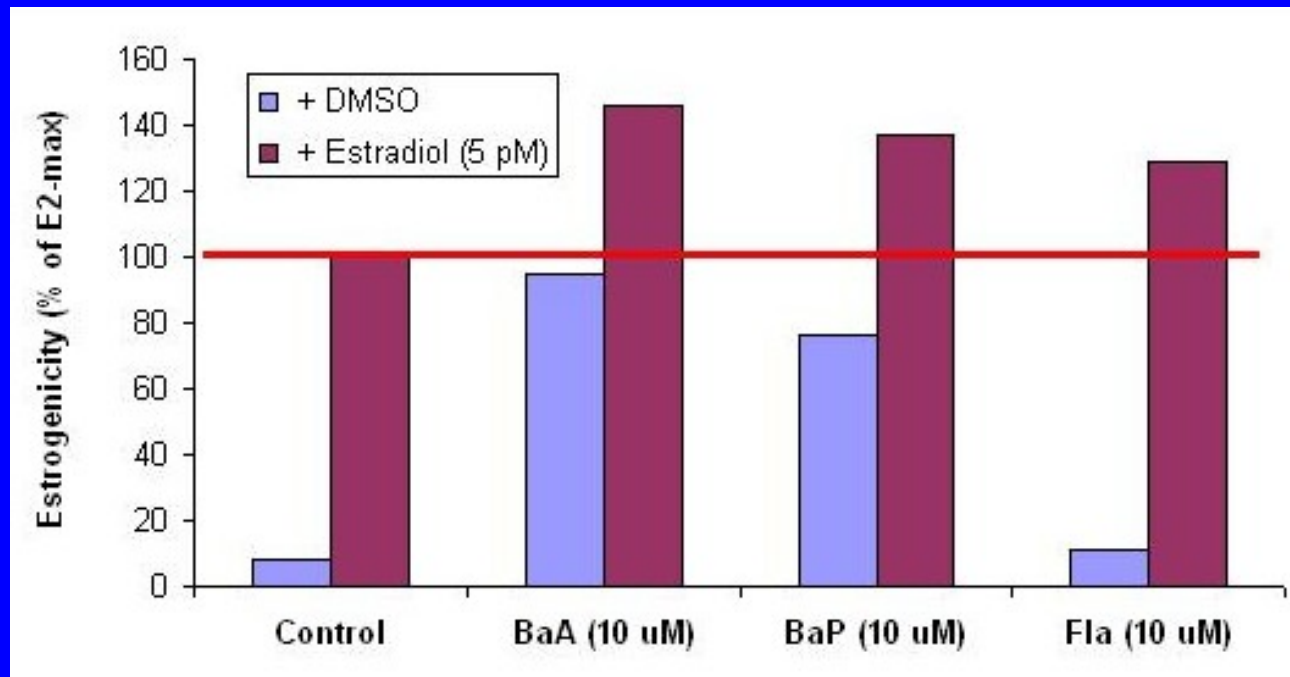


Examples

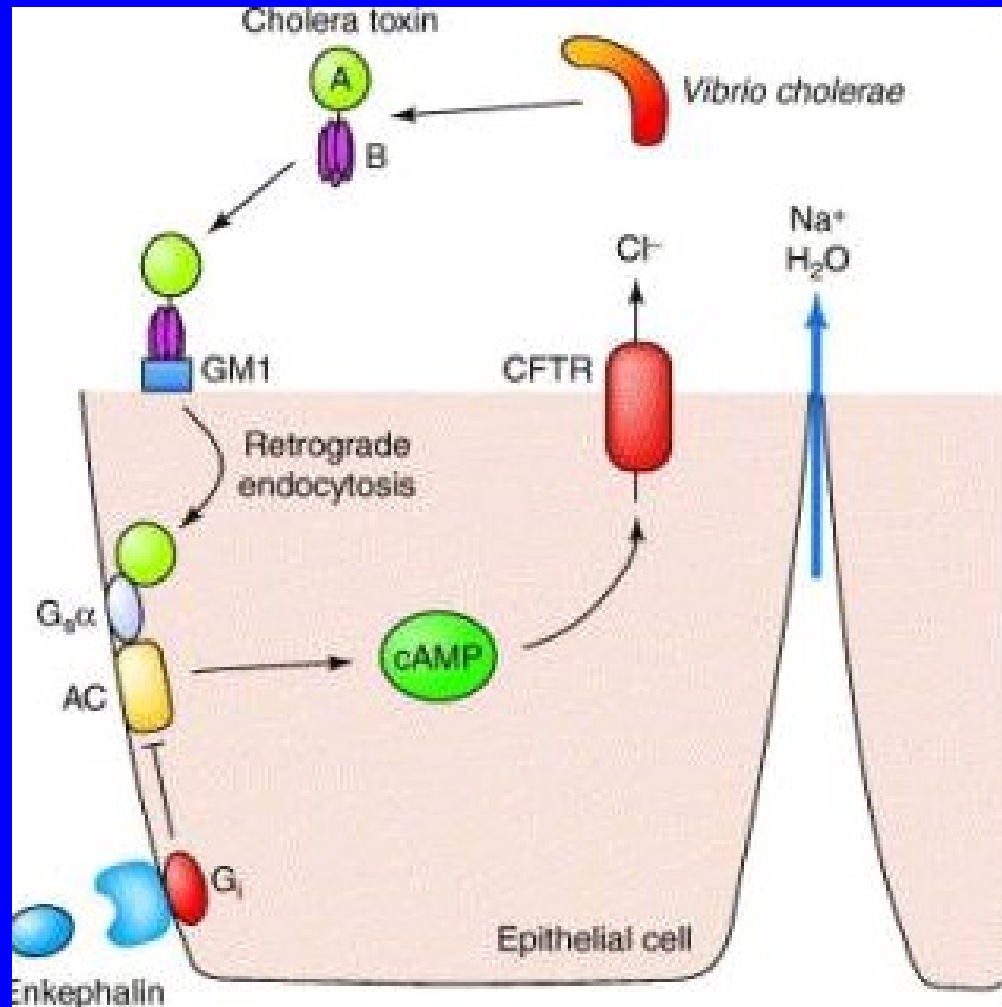
ER-independent estrogenicity (PAHs)

modulation of PKs/PPases: phosphorylation
-> activation of ER-dependent genes

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



Cholera toxin - activation of adenylate cyclase



Lipopolysaccharide (bacteria) - immunotoxicity

