Cell communication & regulation: a target for toxicants

Any sensitively regulated process is susceptible to toxicants

! REGULATIONS & SIGNALLING

Hierarchy

- systems: neuronal ←→ 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

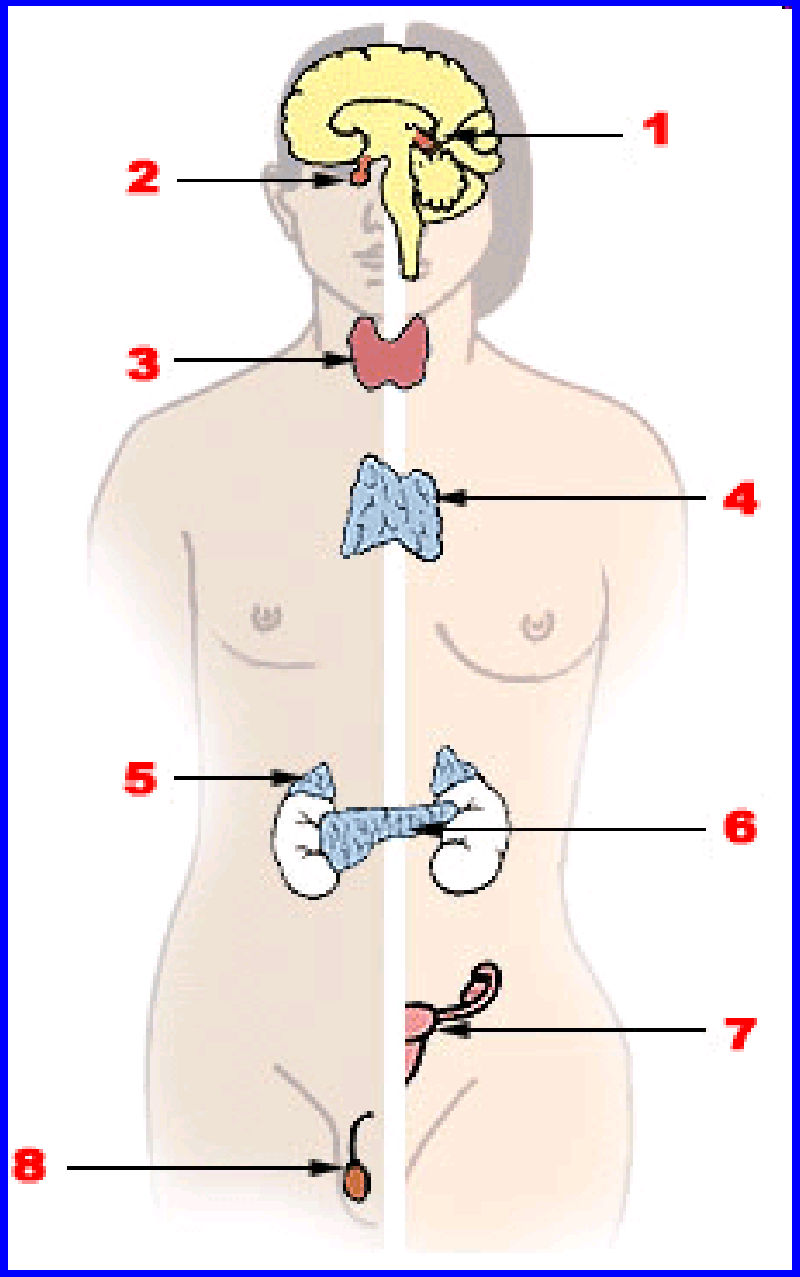
3. **Transport** of the hormone to the target cell(s)

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.

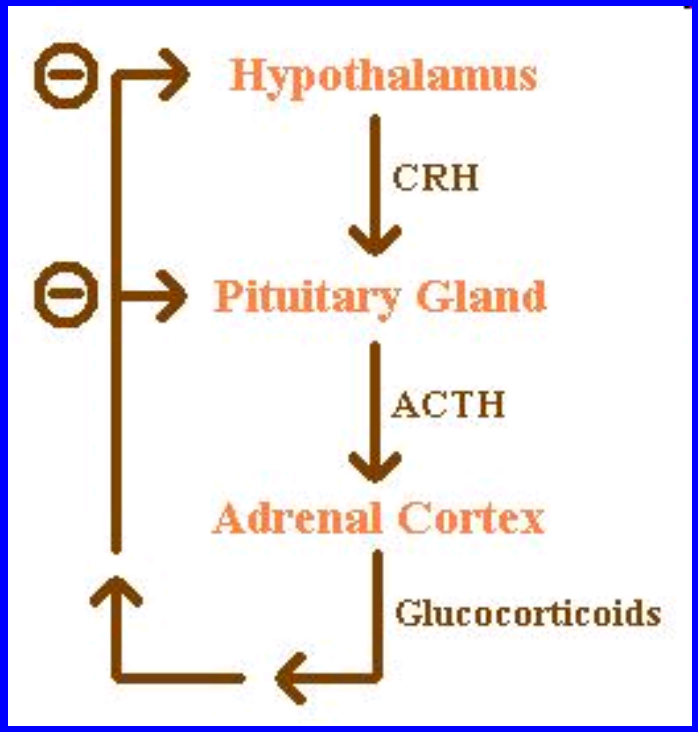
6. The reaction of the target cells is recognized by the original hormone-producing cells (**negative feedback loop**)

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

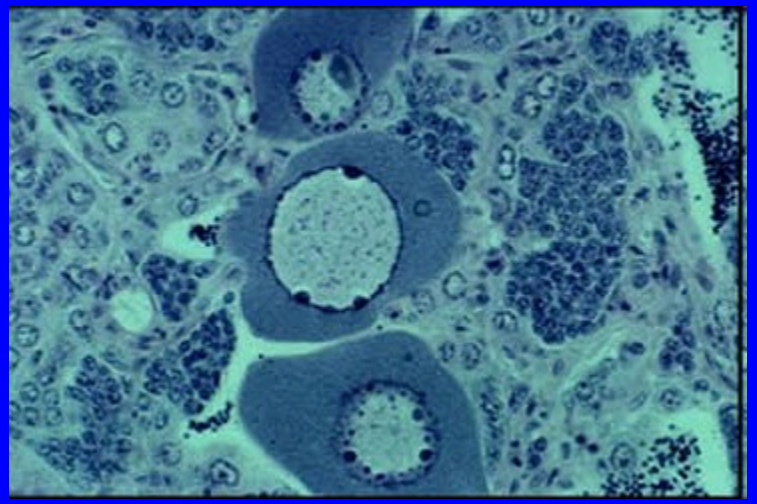
TOXICITY TO HORMONAL ACTION = ENDOCRINE DISRUPTION

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)



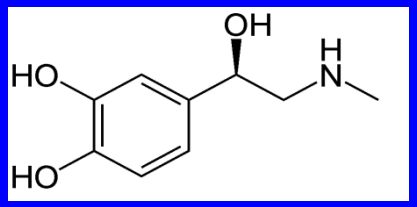
Intersex roach testis
containing both oocytes and spermatozoa,
caused by exposure to environmental oestrogens

HORMONES - chemicals (vertebrates)

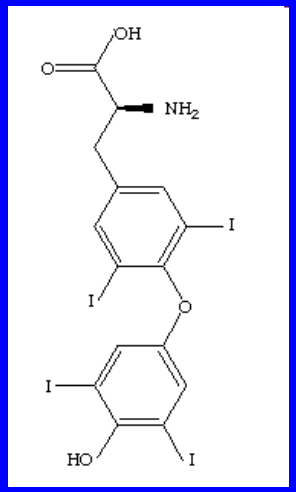
* **Amine-derived hormones** are derivatives of the amino acids tyrosine and tryptophan. Examples are catecholamines and thyroxine.

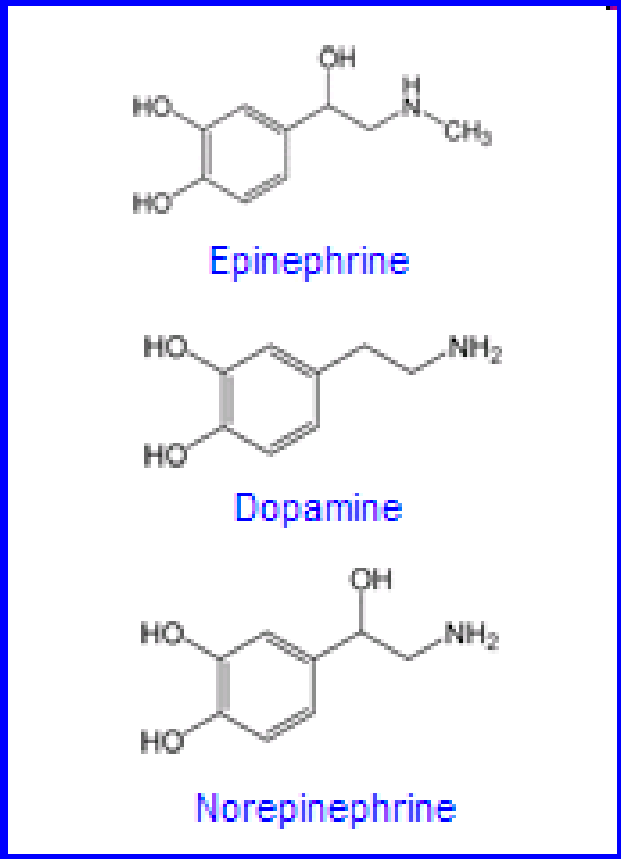
(small molecules - similar to organic toxicants - TOXIC EFFECTS)

Adrenalin



Thyroxin





Further:

* *Peptide hormones*
* *Lipid and phospholipid-derived hormones*

HORMONES - chemicals (vertebrates)

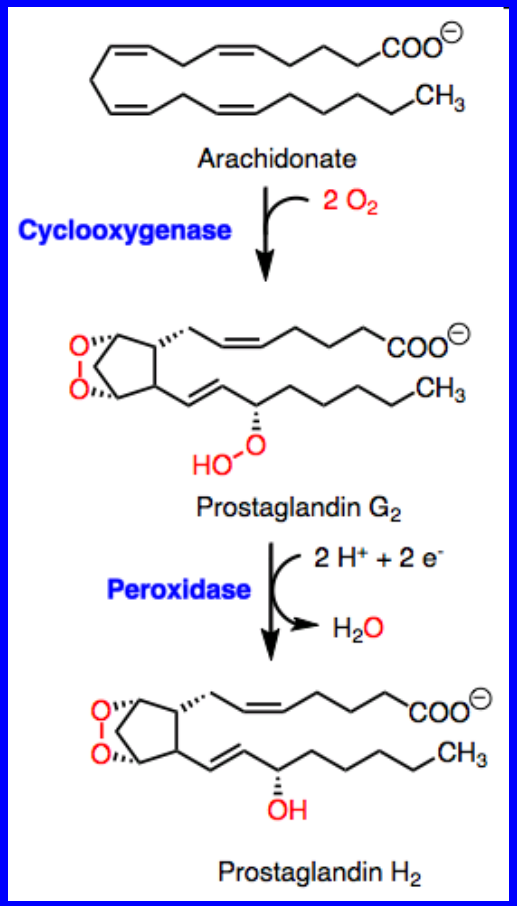
* **Peptide hormones** chains of amino acids. - small: TRH and vasopressin; proteins: insulin, growth hormone, luteinizing hormone, follicle-stimulating hormone and thyroid-stimulating hormone).

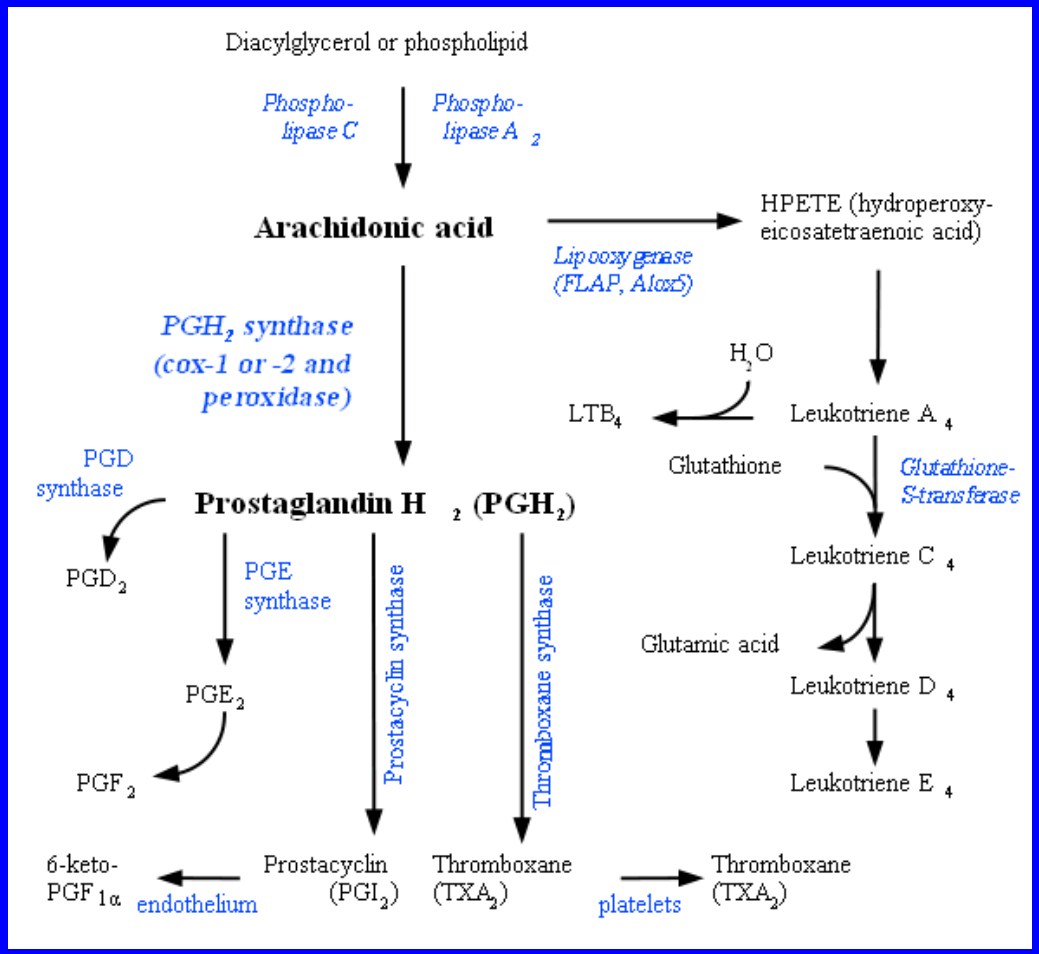
Large molecules; receptors on surfaces of the cells
*(Interactions with toxic chemicals **less likely**)*

Example - insulin

HORMONES - chemicals (vertebrates)

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





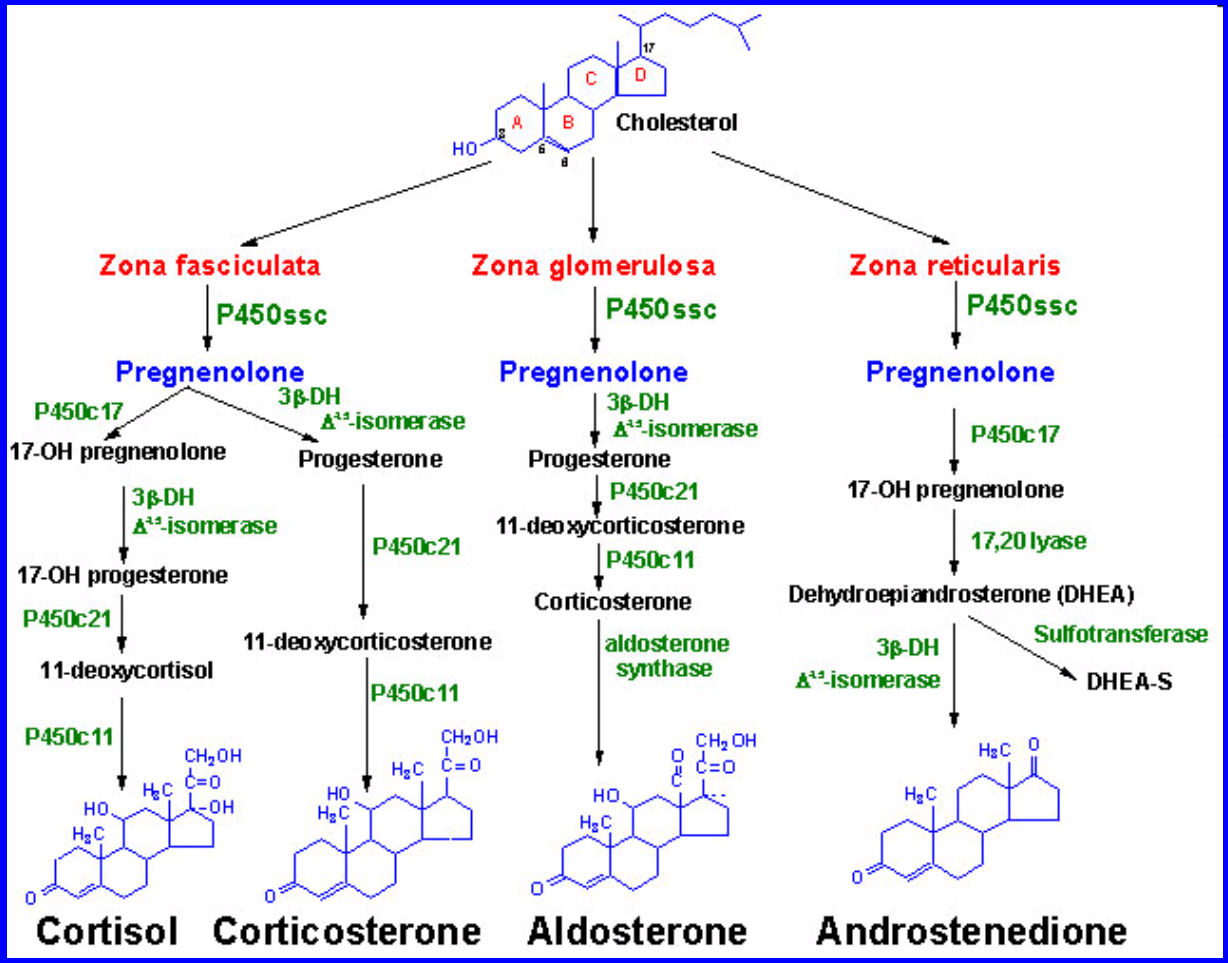
HORMONES - chemicals (vertebrates)

Lipid derived hormones (2)

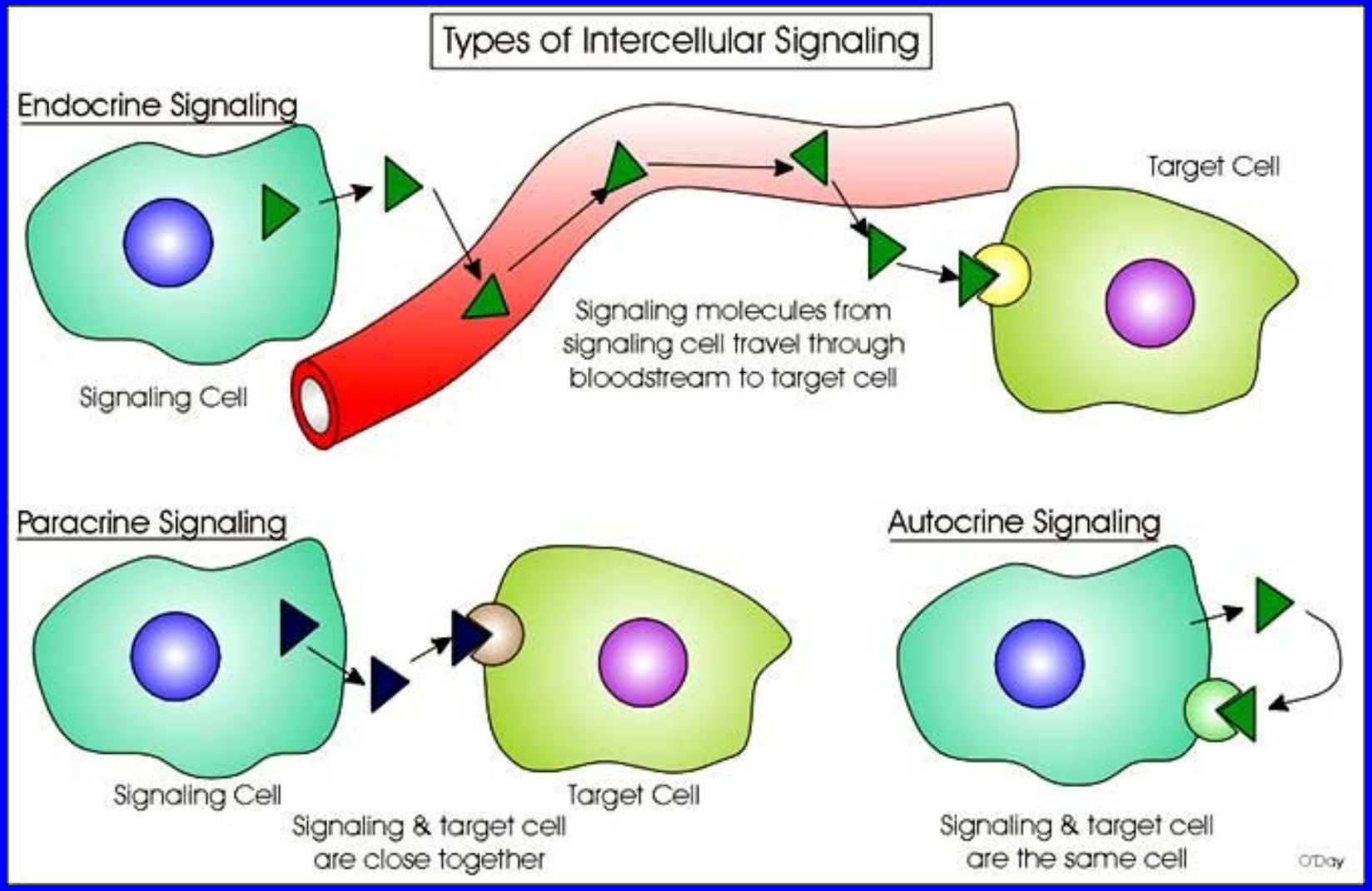
(small molecules - similar to organic toxicants - TOXIC EFFECTS)

- steroid hormones
(from cholesterol)

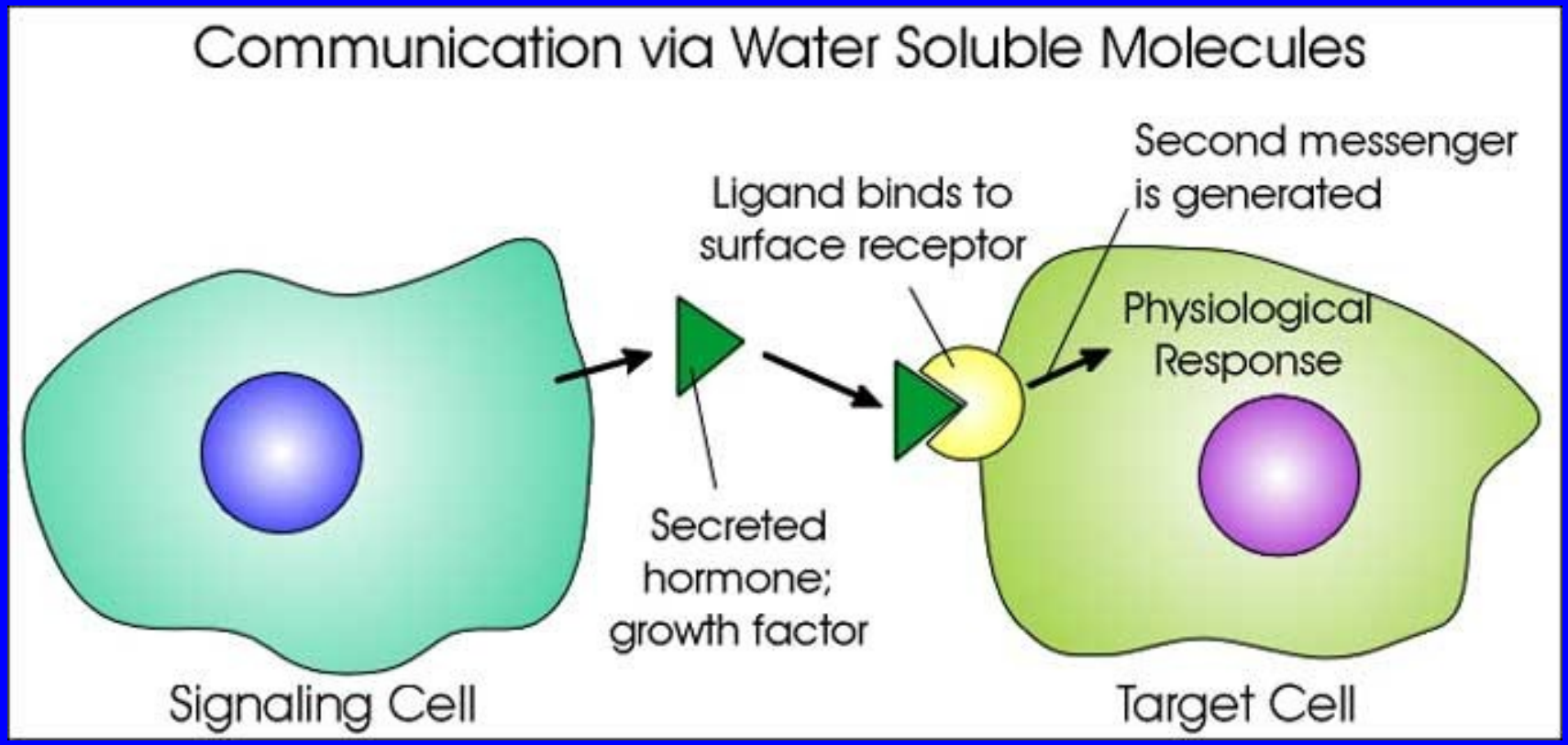
testosterone,
cortisol,
estradiol …



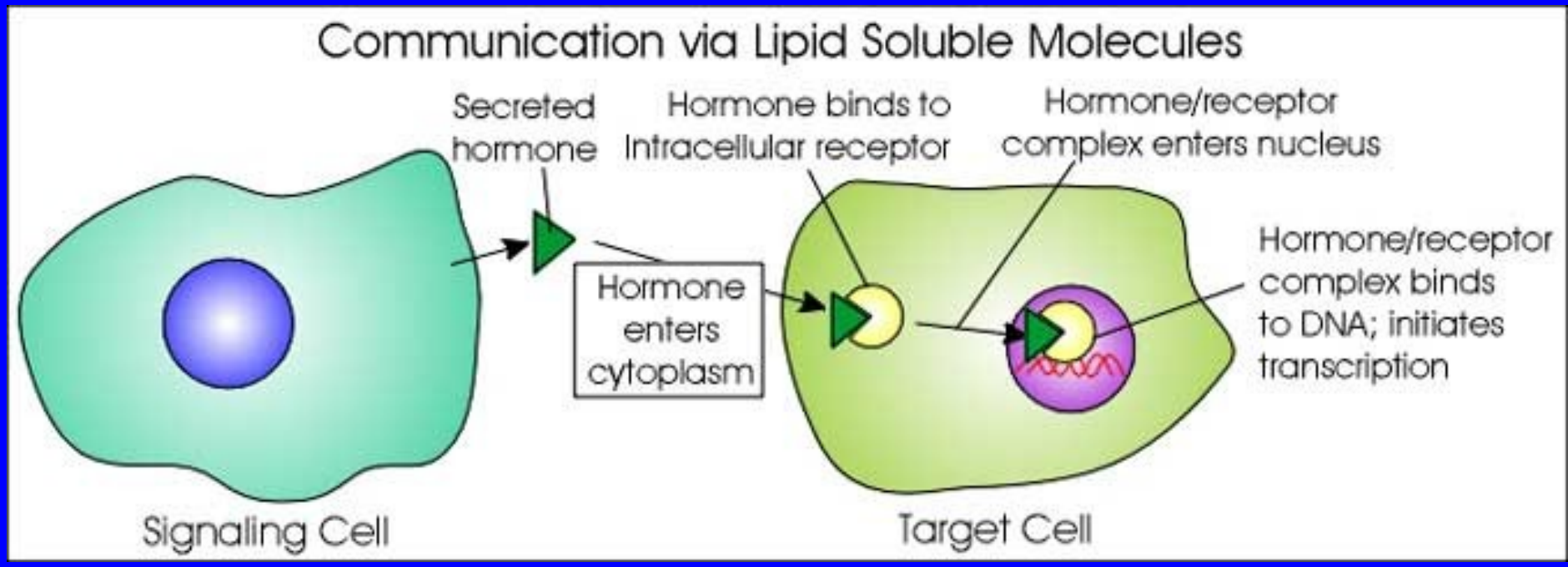
Cell communication & regulation: a target for toxicants



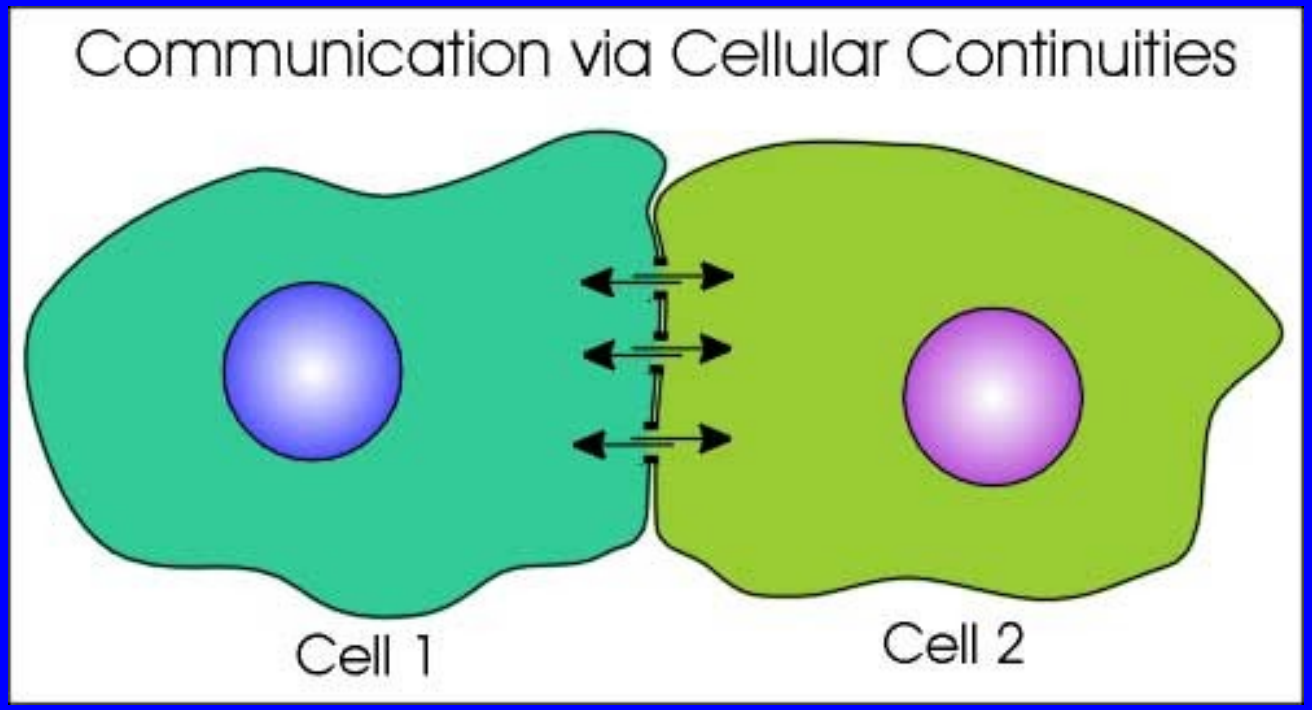
Cell communication (1)

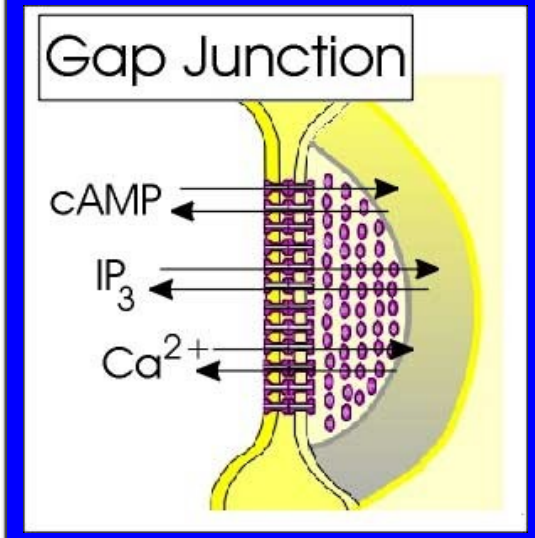


Cell communication (2)



Cell communication (3)





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)

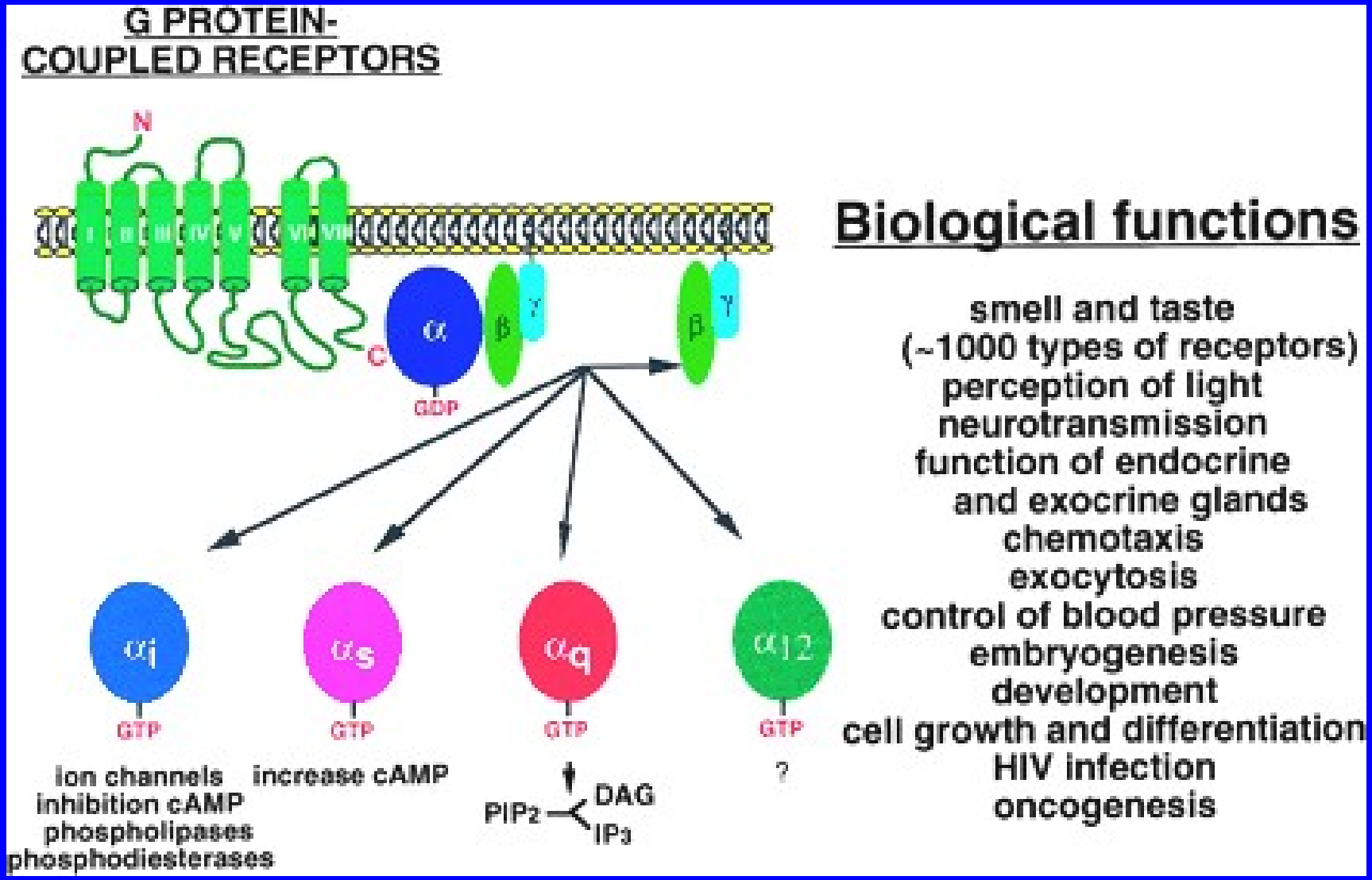
-> PKA activation: cAMP

2: Membrane receptors -> PLC / PKC activation

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

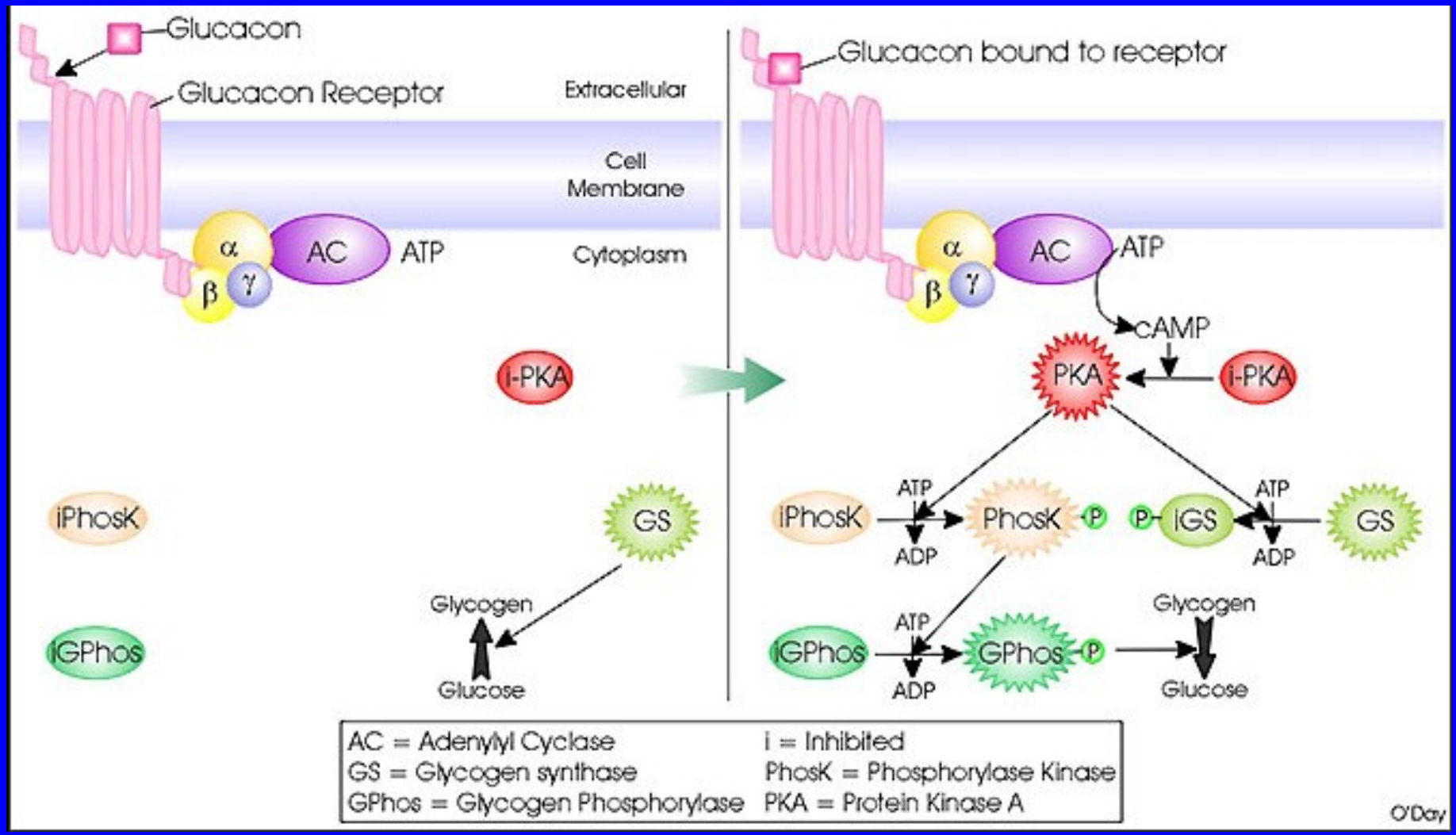
3: Cytoplasmic (nuclear) receptors

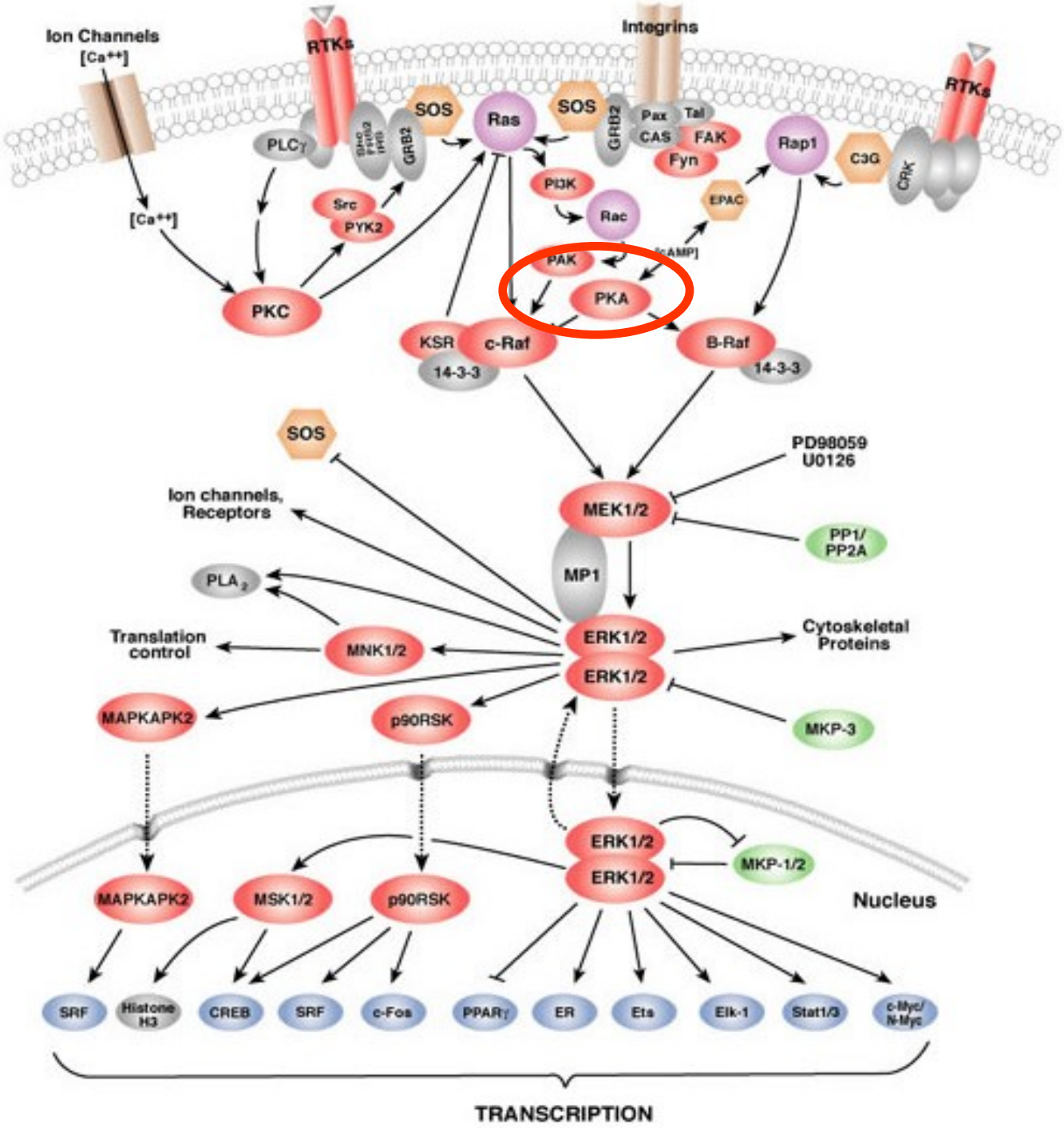
Membrane receptors (PKs): G-proteins (GPCRs)



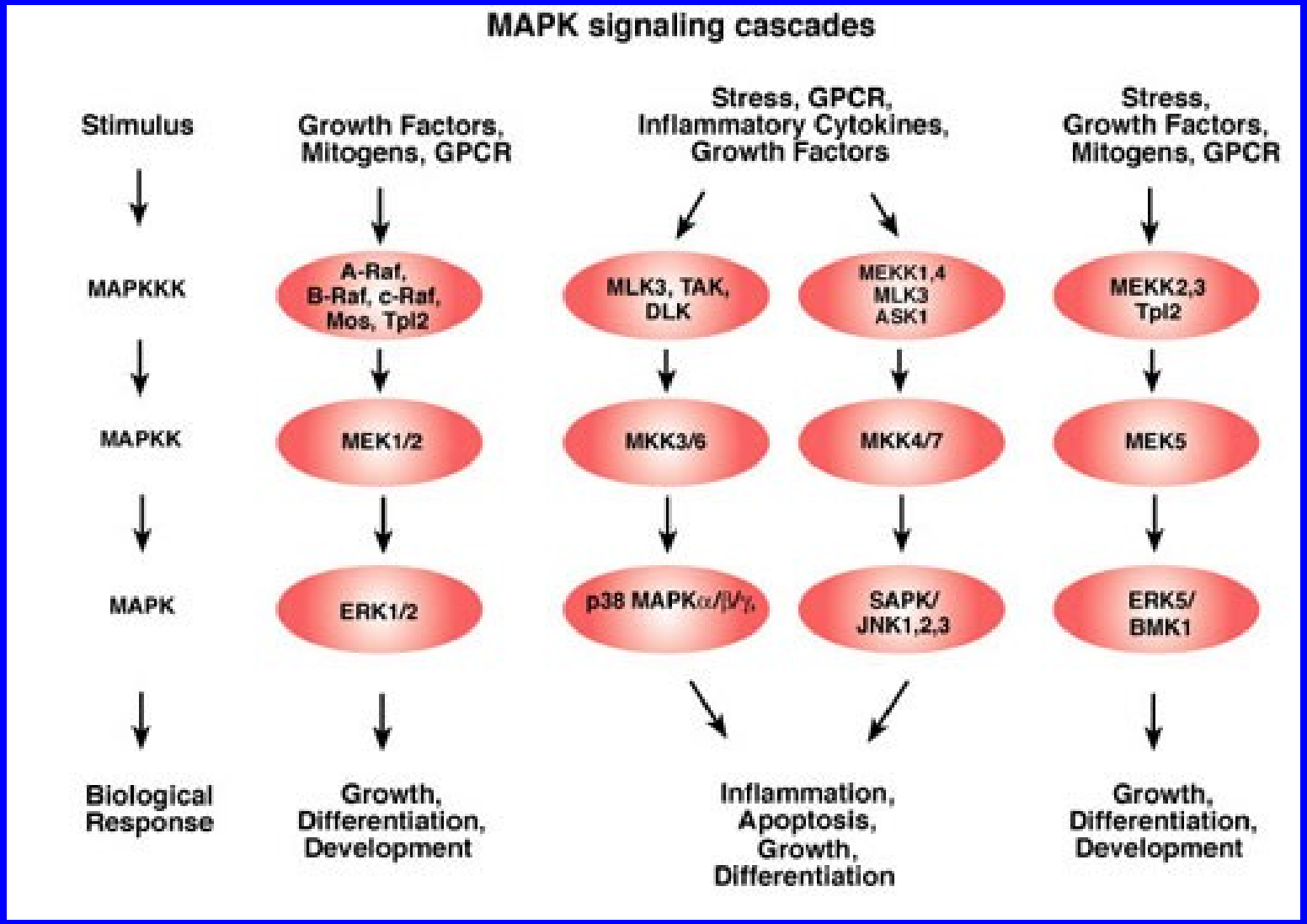
1: Membrane receptors (PKs)

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

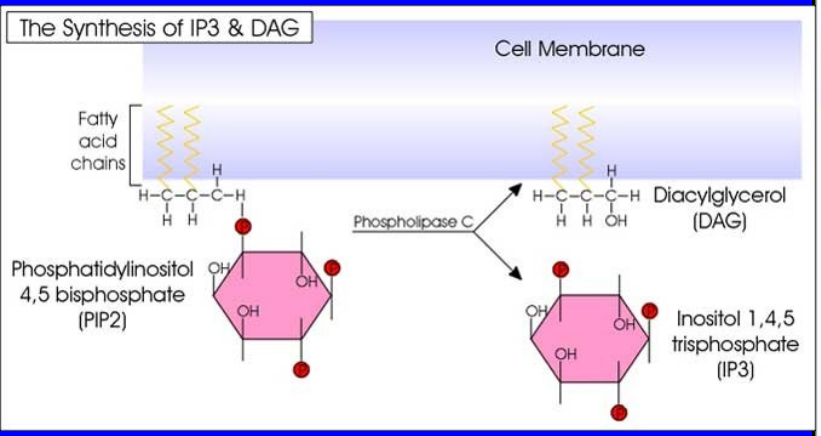


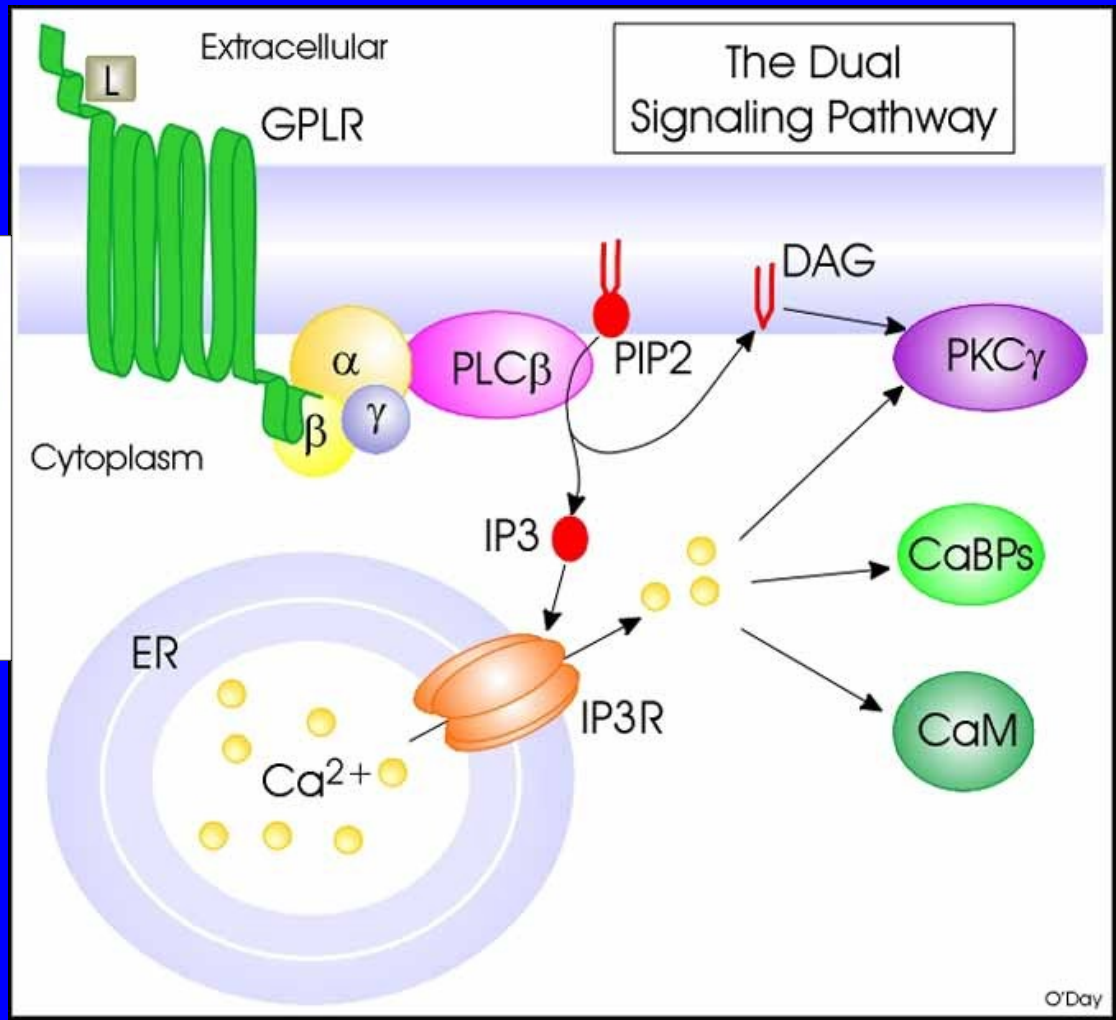

Ion Channels
[Ca++]
RTKs
Integrins
RTKs
PLCγ
SOS
Ras
SOS
GRB2
Pax
Tal
CAS
FAK
Fyn
Rap1
C3G
CRK
PI3K
Rac
EPAC
[cAMP]
Src
PYK2
[Ca++]
PAK
PKA
PKC
KSR
c-Raf
14-3-3
B-Raf
14-3-3
SOS
PD98059
U0126
Ion channels,
Receptors
MEK1/2
PP1/
PP2A
MP1
PLA2
Translation
control
MNK1/2
ERK1/2
ERK1/2
Cytoskeletal
Proteins
MAPKAPK2
p90RSK
MKP-3
ERK1/2
ERK1/2
MKP-1/2
MAPKAPK2
MSK1/2
p90RSK
Nucleus
SRF
Histone
H3
CREB
SRF
c-Fos
PPARγ
ER
Ets
Elk-1
Stat1/3
c-Myc/
N-Myc
TRANSCRIPTION

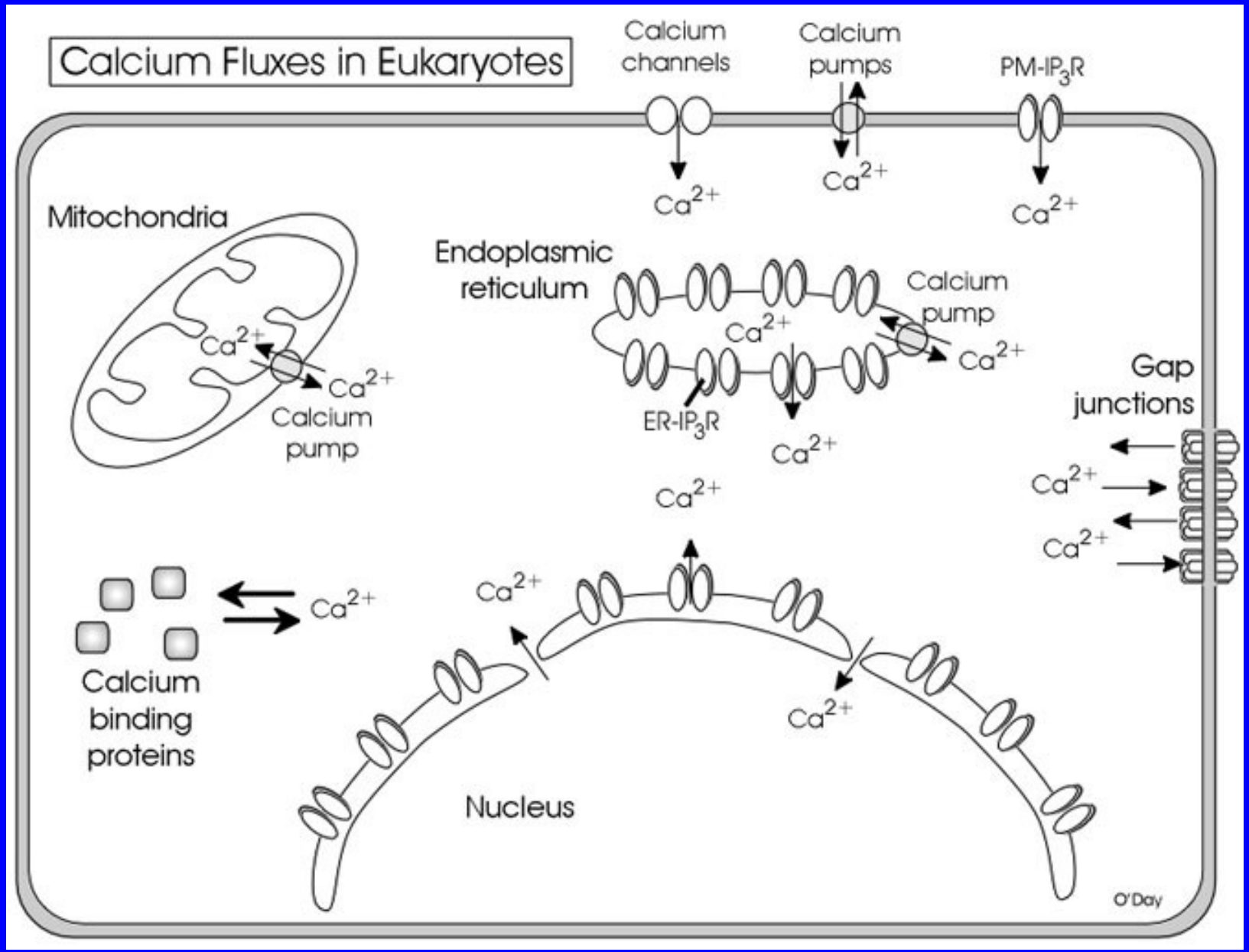
(!!!) Mitogen Activated Protein Kinases (MAPK) – dependent effects



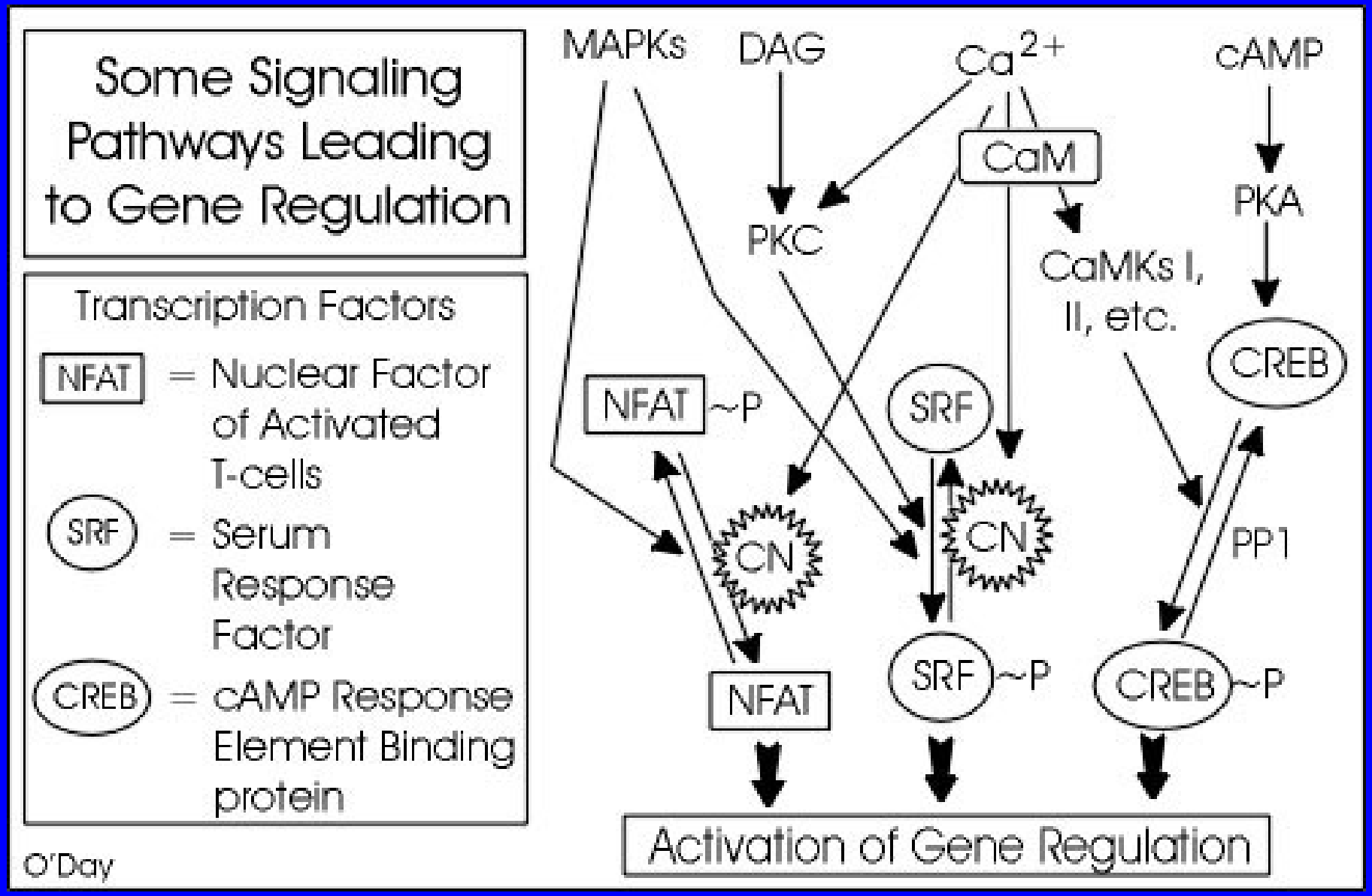
2: Membrane receptors
-> Phospholipase C:
PIPs -> DAG -> PKC / arachidonic acid
+ IP3 -> Ca^{2+}






Calcium Fluxes in Eukaryotes
Calcium channels
Calcium pumps
PM-IP3R
Ca2+
Ca2+
Ca2+
Mitochondria
Ca2+
Ca2+
Calcium pump
Endoplasmic reticulum
Calcium pump
Ca2+
Ca2+
ER-IP3R
Ca2+
Gap junctions
Ca2+
Ca2+
Ca2+
Ca2+
Calcium binding proteins
Ca2+
Ca2+
Ca2+
Nucleus
O'Day

Signalling crosstalk

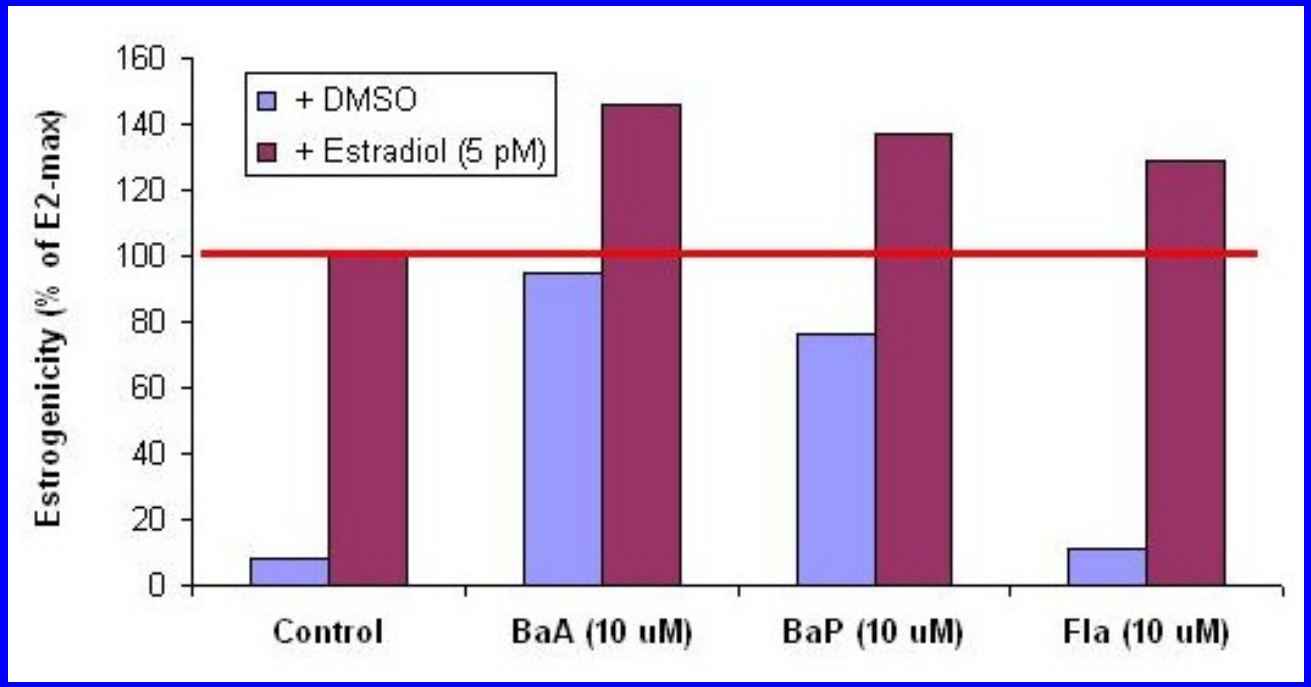


Examples

ER-independent estrogenicity (PAHs)

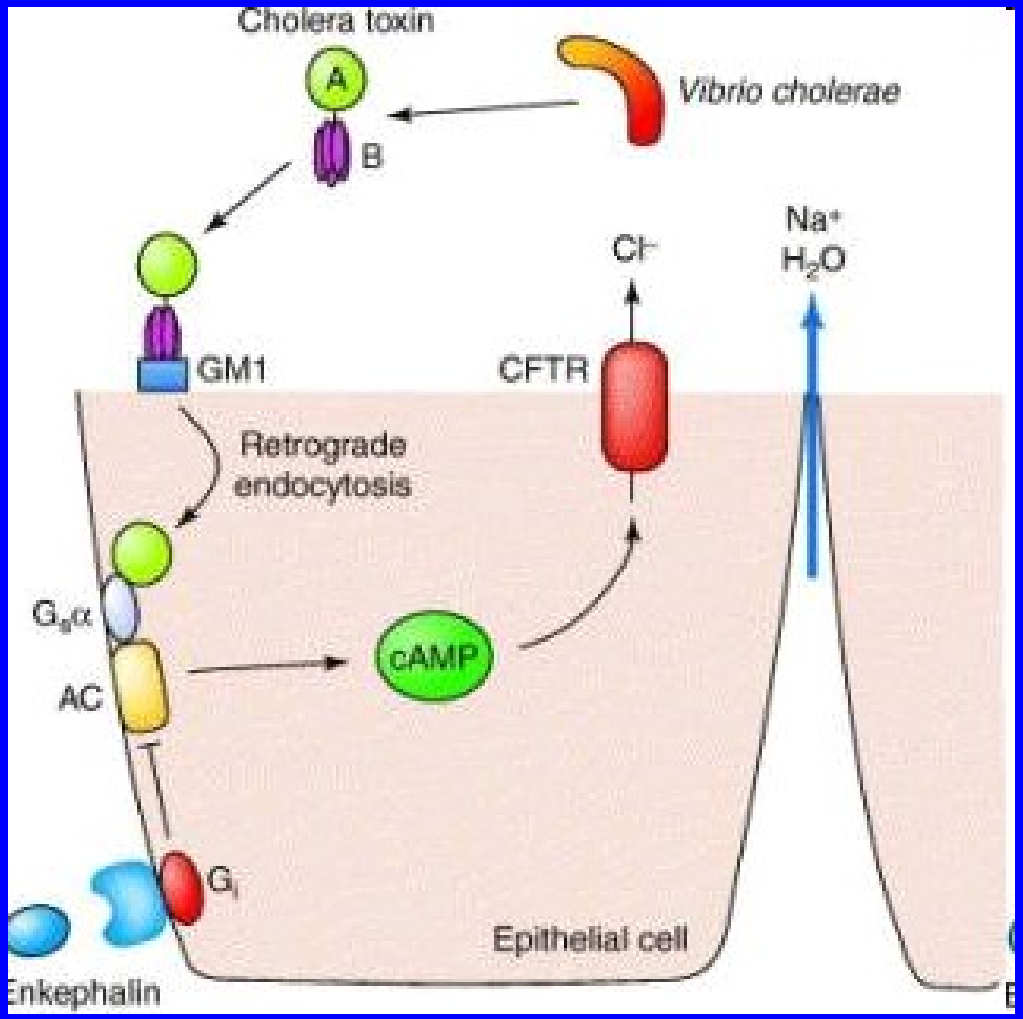
modulation of PKs/PPases: phosphorylation
-> activation of ER-dependent genes

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



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

Cholera toxin - activation of adenylate cyclase



Lipopolysaccharide (bacteria) - immunotoxicity