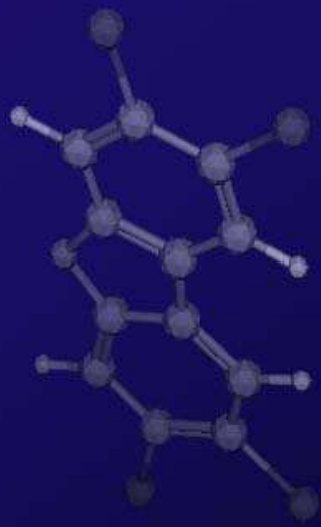
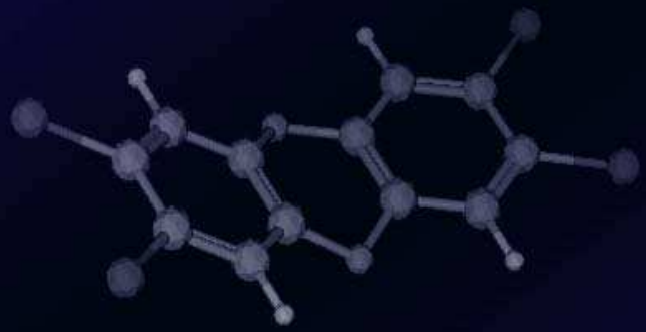
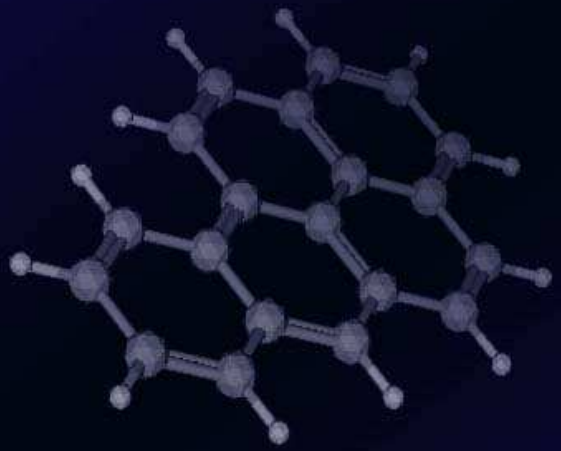
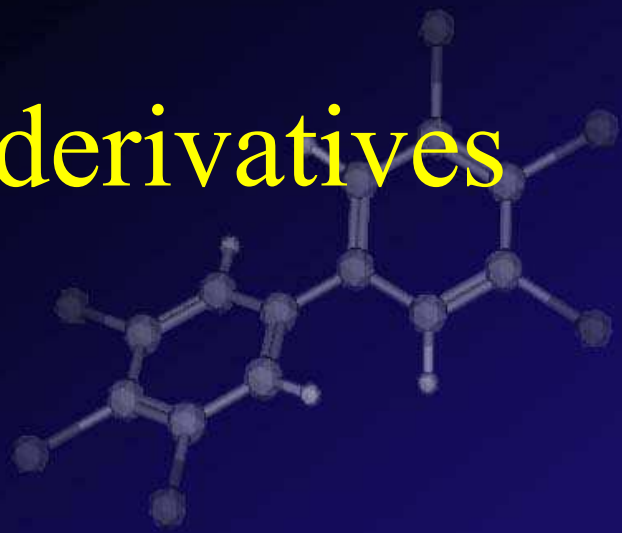
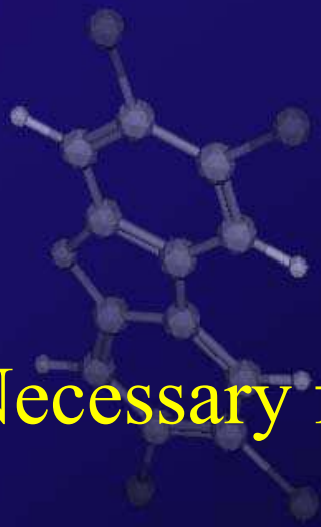



Retinoids

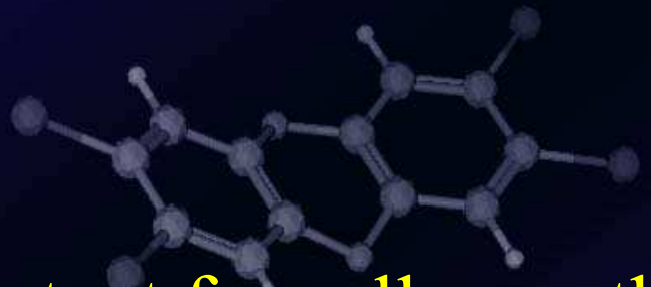
Vitamin A and its derivatives

Retinoids



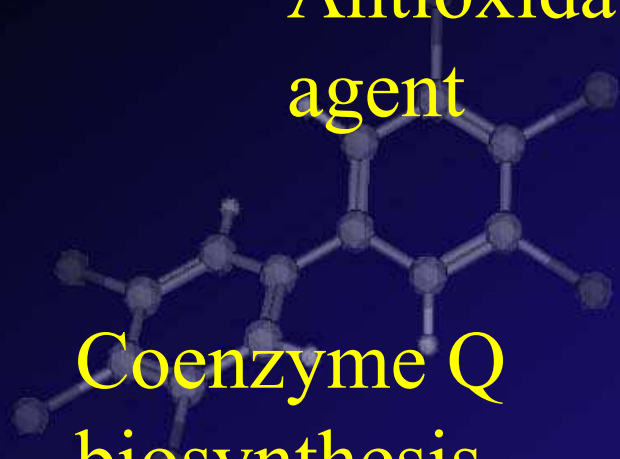
Necessary for vision



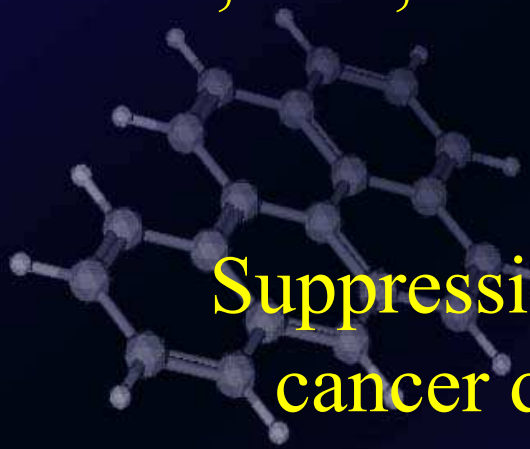
Important for cell growth, apoptosis and differenciation

Development of embryonic, epithelial cells (gastrointestinal tract, skin, bones)

Antioxidative agent



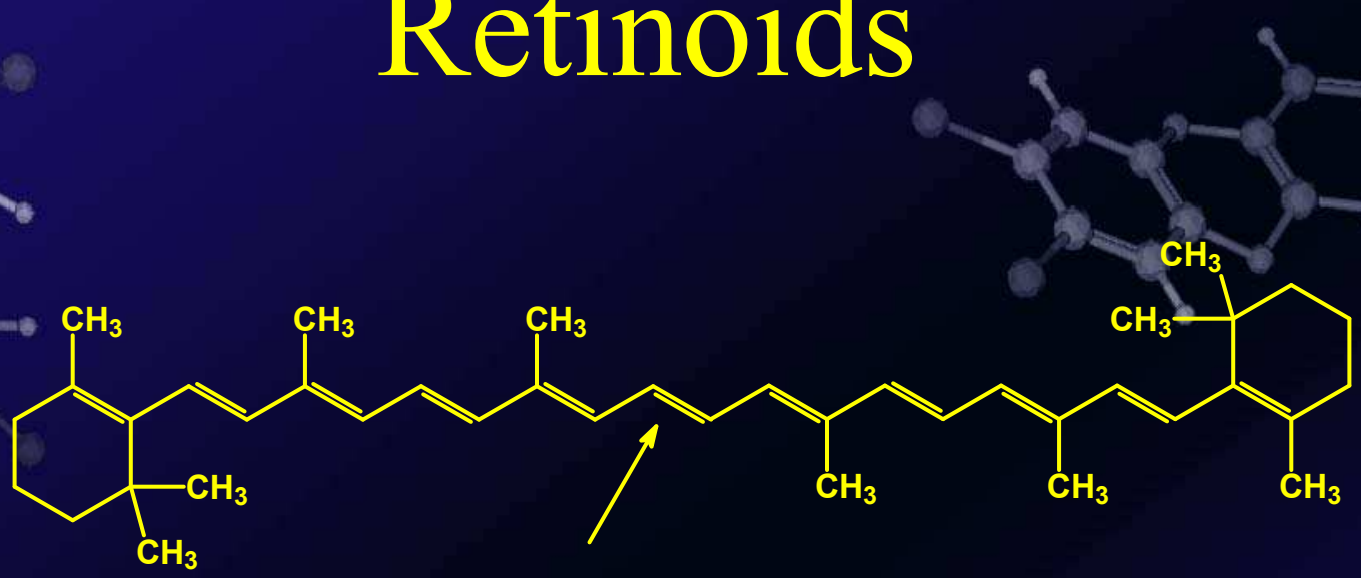
Coenzyme Q biosynthesis



Suppressive effects in cancer development

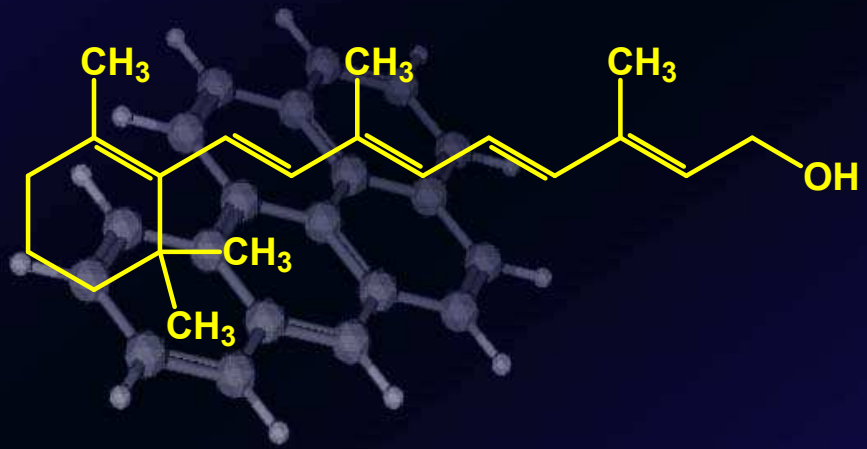
Retinoids

β-karoten

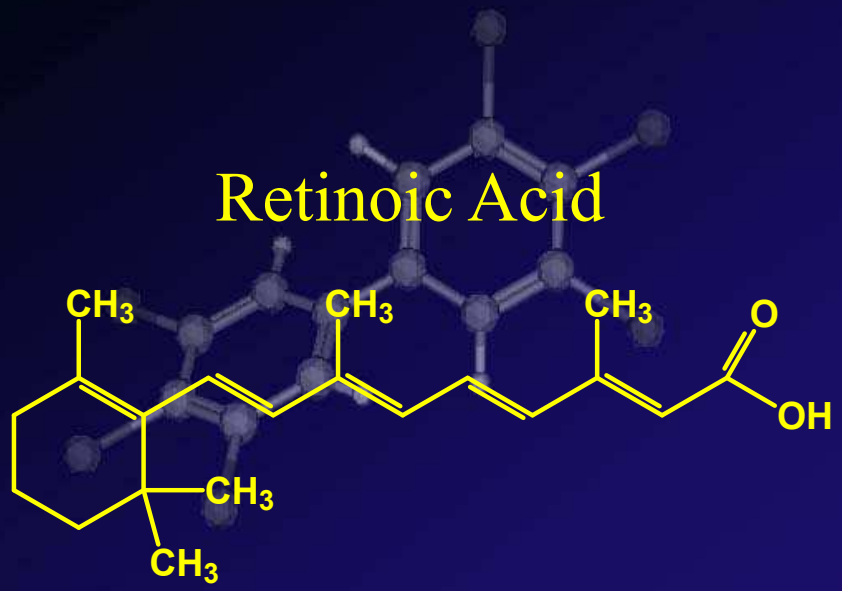


Bond cleavage

Retinol (vitamin A)

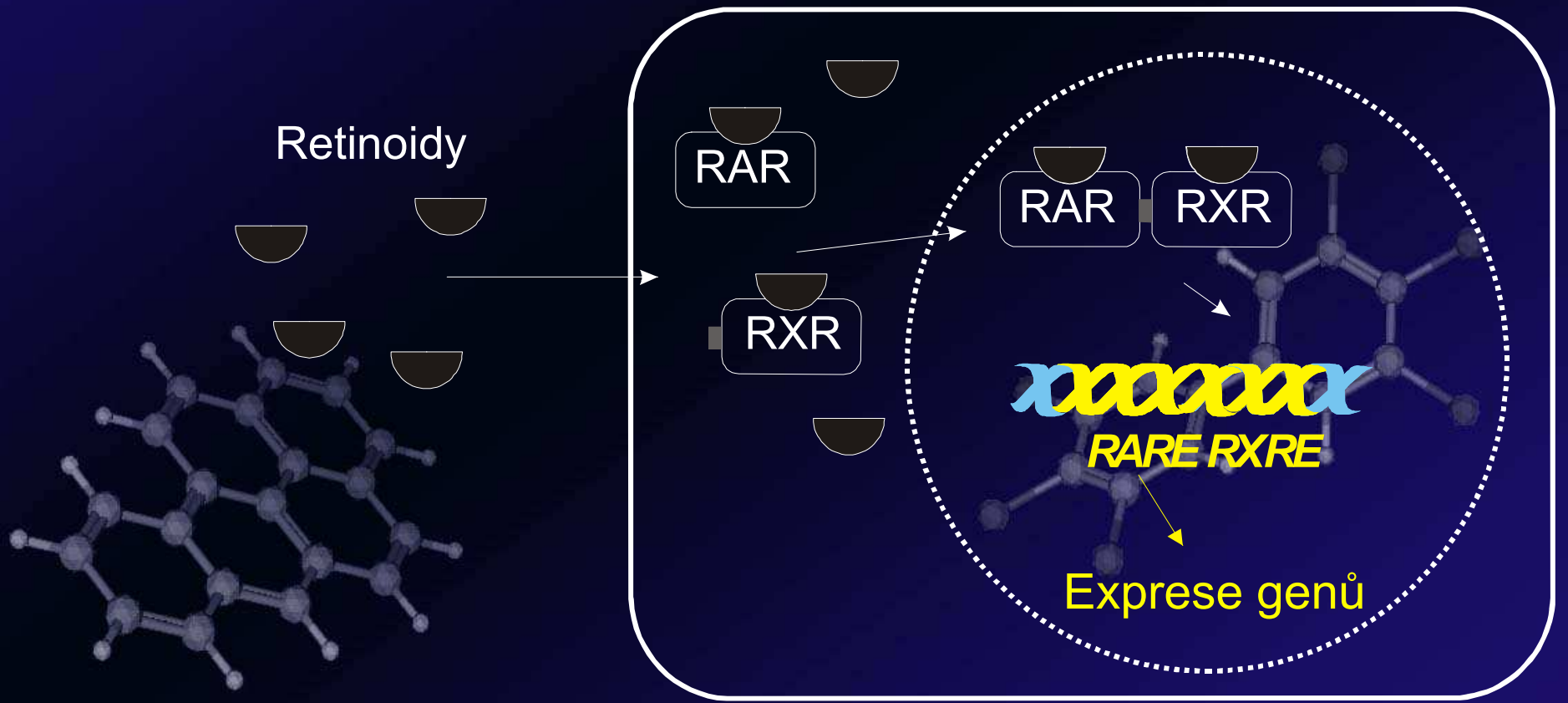


Retinoic Acid



Mode of action

- Nuclear receptors RAR a RXR

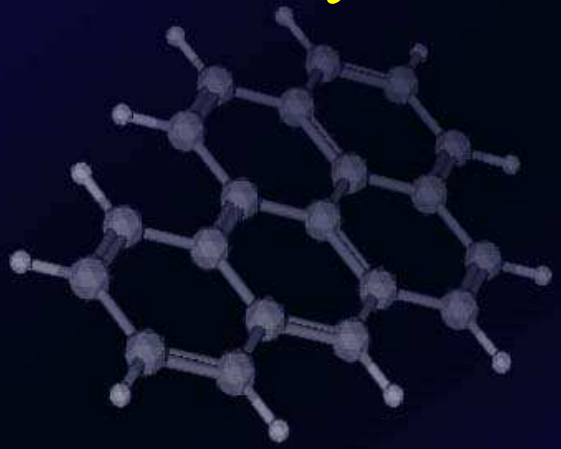


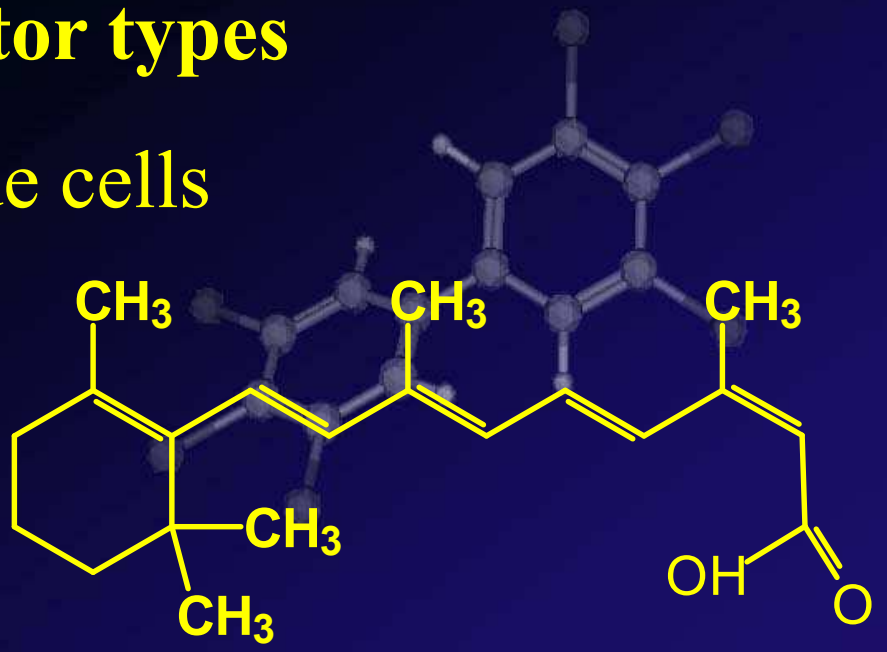
Mode of action

- Isoforms of RAR a RXR
- Both have isoforms α, β and γ, each of them several subtypes
- Formation of homo- and heterodimers
- 48 possible RAR-RXR heterodimers =>sensitive regulation of gene expression
- RXR – heterodimers even with other receptors like VDR, TR, PPAR

Retinoic acid

- 3 basic subtypes
- all-trans-, 9-cis- and 13-cis-retinoic acid
- **All-trans RA binds selectively to RAR**
- **Cis RA bind to both receptor types**
- RA may be isomerized inside cells





13-cis-retinoic acid

Retinoid-binding proteins

- CRBP – cellular retinol binding protein

  - binding of retinol, immediate decrease of retinol concentration

- CRBAP – cellular retinoic acid binding protein

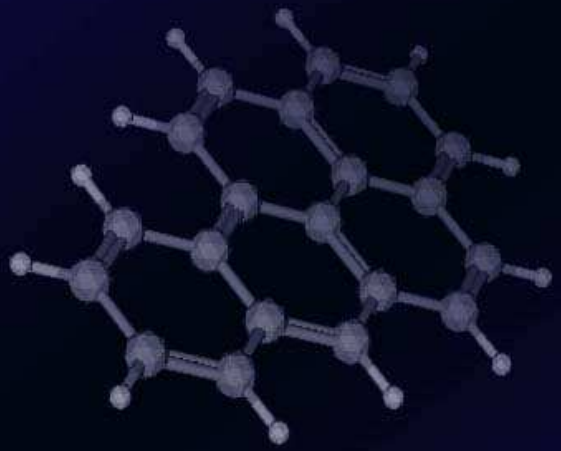
  -Controlling ratio free retinol/free retinoic acid and so retinoid signalling

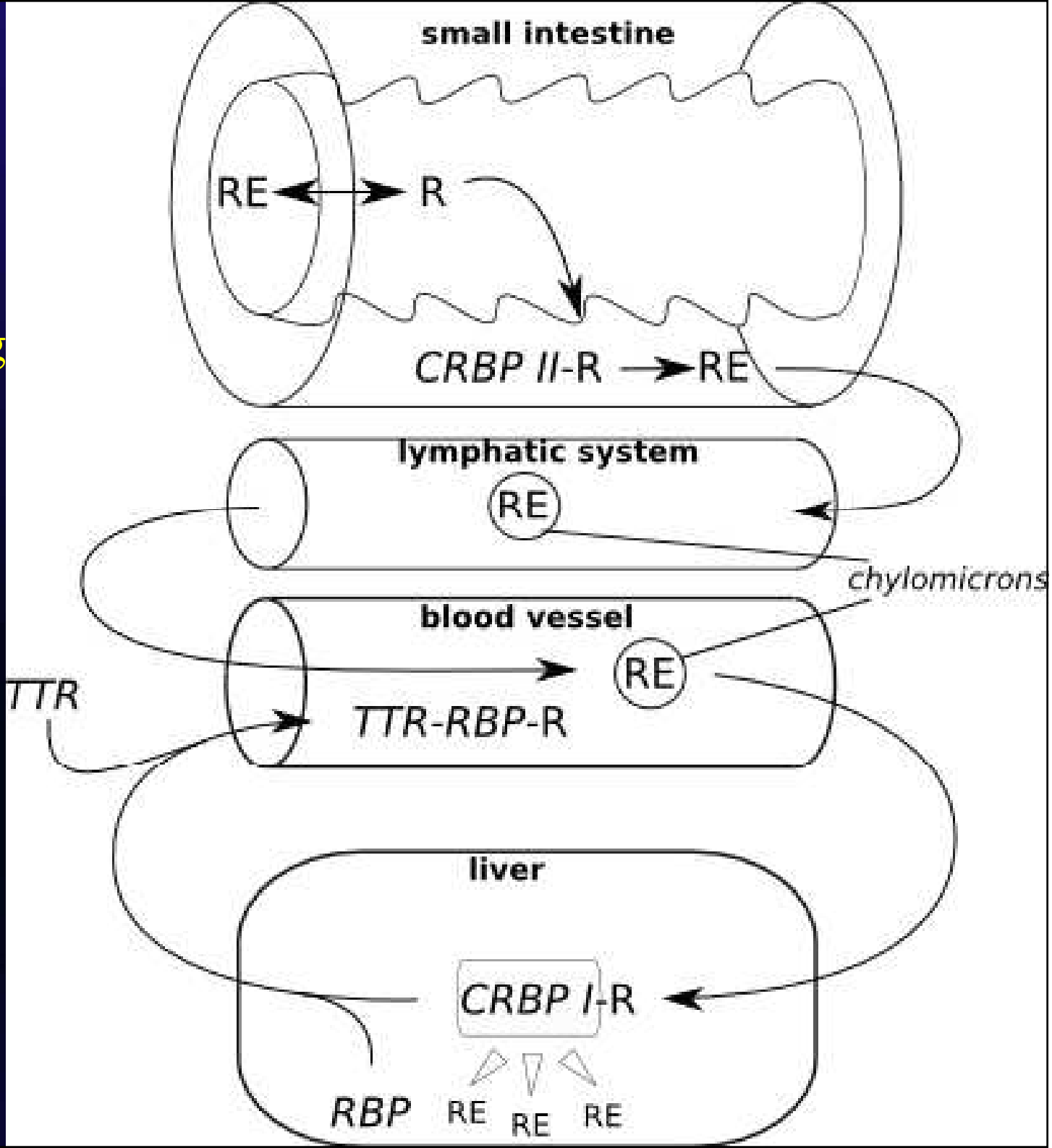
RE: Retinol-Ester

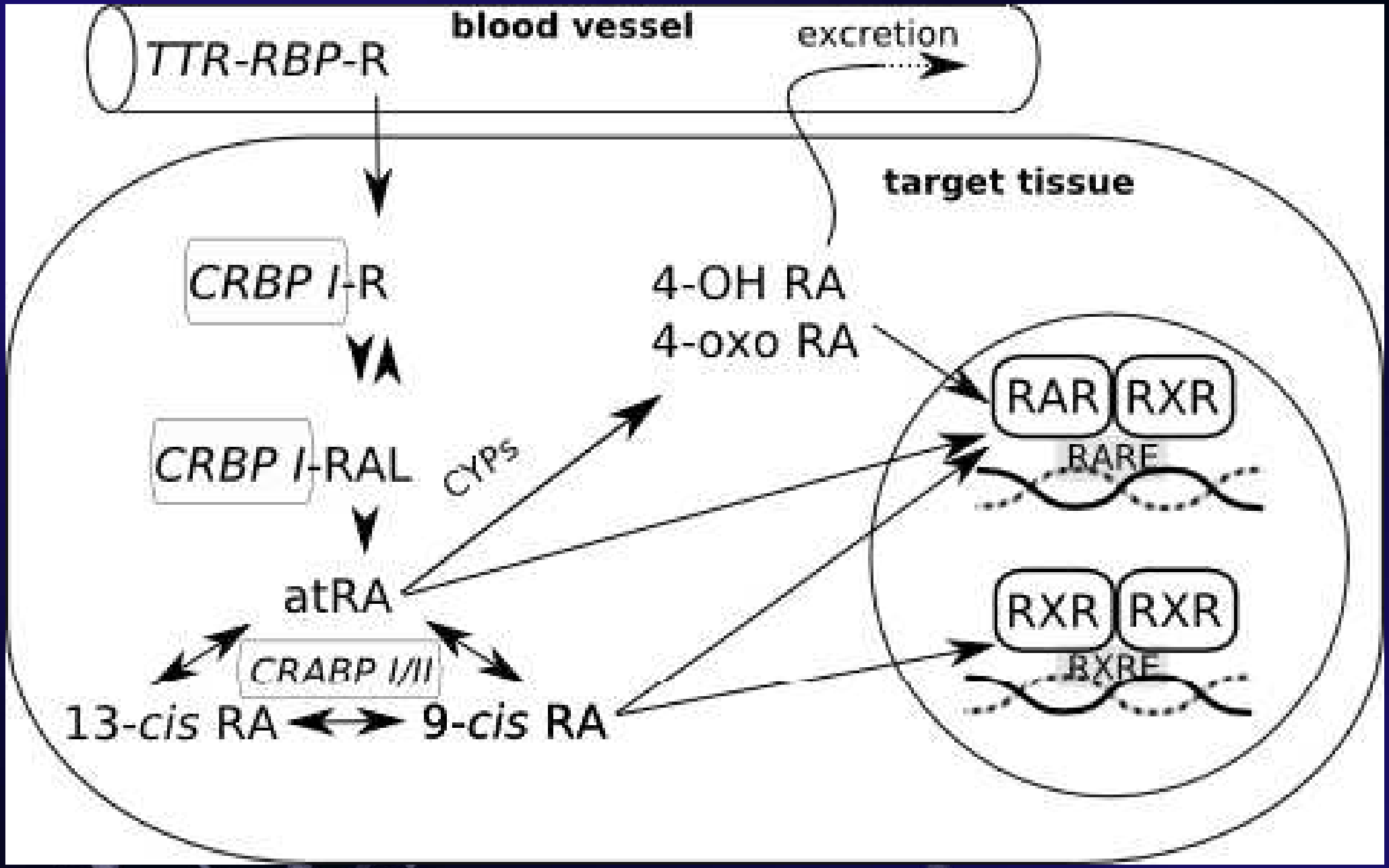
R: Retinol

RBP: Retinol Binding Protien (*LMW*)

TTR: Transthyrethin (*HMW*)






blood vessel
excretion
TTR-RBP-R
target tissue
CRBP I-R
4-OH RA
4-oxo RA
RAR
RXR
RARE
CRBP I-RAL
CYP's
atRA
RXR
RXR
RXRE
CRABP I/II
13-cis RA
9-cis RA

RAL - Retinal

Disruption of retinoid signalling by xenobiotics

- Relatively little is known
- Possible modes of action:
  - Metabolization of retinoids by detoxication enzymes
  - Disruption of binding retinoids to retinoid binding proteins
  - Retinoids as antioxidants may be consumed cause of oxidative stress caused by xenobiotics
  - Interference of chemicals (binding to RAR/RXR)

Consequences of retinoid signalling disruption

- Decreased retinoid levels in organisms
  - Downregulation of growth factors
  - Xerophtalmia, night blindness
  - Embryotoxicity, developmental abnormalities

X

- Increased ATRA concentration – teratogenic effect

⇓

Change may cause severe developmental anomalies

Disruption of retinoid signalling by xenobiotics

- Most studies focused on effects of PCBs, PCDDFs

- Exposure to these chemicals leads to:
  - Increased serum concentrations of retinol and RA
  - Mobilization of hepatic storage forms
  - In kidney, concentration of all forms elevated

In vivo tests to assess retinoid signalling disruption

- Mostly derived from classical toxicity tests, particularly of developmental toxicity
- Direct measurements of various retinoid forms in living organisms (laboratory and wildlife)

In vitro tests

- Mostly epithelial cell lines (keratinocytes)
- **Mouse embryonic cell lines P19**
  - pluripotent cells
  - differentiation dependent on circumstances
  - dif. triggered by ATRA
- Other cell lines – rainbow trout gonads, human salivary gland, breast or prostatic carcinomas etc.