ALMA MATER STUDIORUM
UNIVERSITÀ DI BOLOGNA

Medicine and Surgery

A.Y. 2025/2026 - Programme Code: 6734

84284-Signaling pathways in health and disease I.C.

Module A – 84285 **Cell signaling** 4 CFU, 34 hrs – BIOS-07/A

+ asynchronous online activities (16 hrs)

Lecture A.03
Classification of hormones

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CHEMICAL SIGNALS

1- Type

- Neurotransmitters
- Hormones
- «Local hormones» (autacoids): cytokines
- Growth factors

2- Structure

- Amino acid derivatives
- Polypeptides
- Eicosanoids
- Steroids

HORMONES

Proteins and other small molecules produced at very low dosage by a gland tissue (*endocrine tissue*) and carried to target tissues through blood stream

(physiological concentration: 10^{-9}-10^{-15} M)

Hydrophilic hormones
(water-soluble)

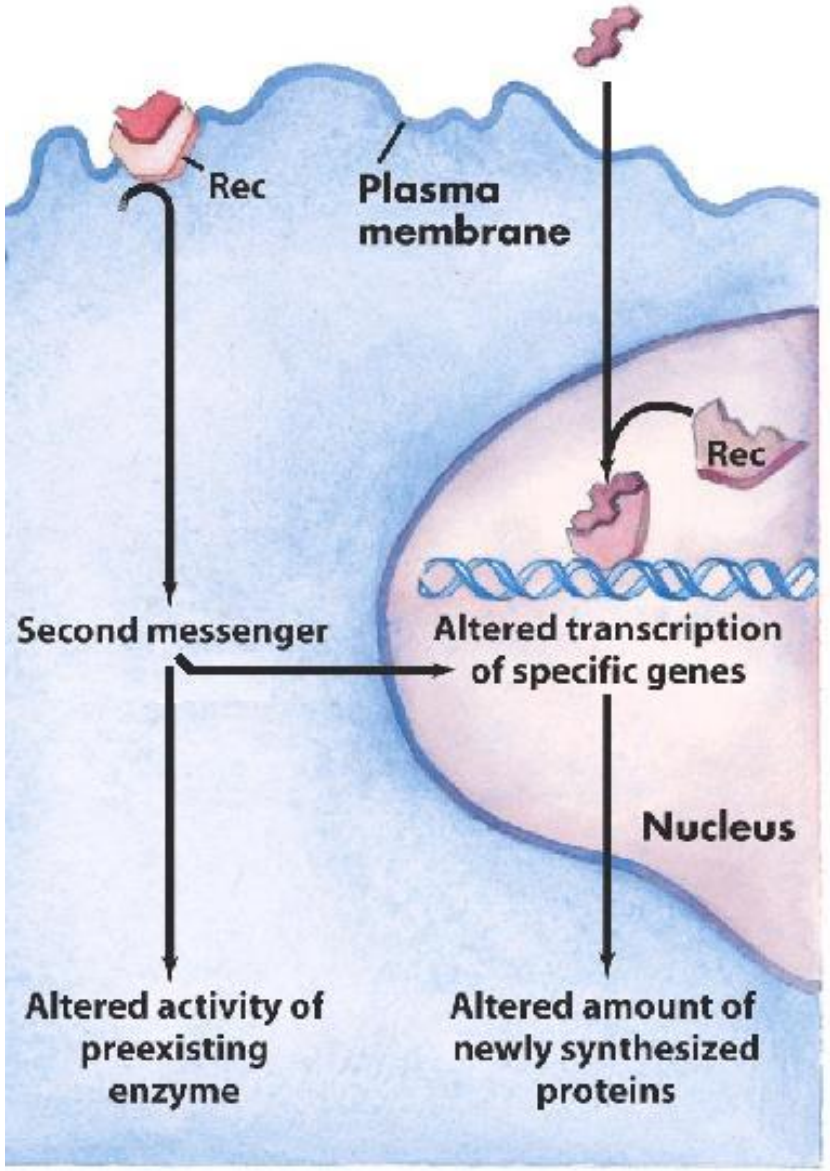
• bind to receptors on the outside of the cell

• trigger conformational modifications of plasma membrane receptors and cause a change in the intracellular concentration of low molecular weight metabolites acting as second messengers

• alter the activity of pre-existing enzymes

VERY RAPID METABOLIC RESPONSE

Amino acid derivatives
Peptides
(insulin, glucagon, epinèphrine)



Lipophilic hormones

• enter the cell
• reach receptor proteins in the cytoplasm/nucleus

• the RL complex itself carries the message and interacts with DNA to alter the expression of specific genes

• change the enzyme complement of the cell

METABOLIC RESPONSE AFTER HOURS/DAYS

Steroids
Retinoids
Thyroid hormones

HORMONES

- PEPTIDE
- CATECHOLAMINE
- EICOSANOID
- STEROID
- RETINOID
- THYROID
- NITRIC OXIDE

From 3 to more than 200 amino acid residues.

Precursor proteins (pro-hormones) packed into secretory vesicles and proteolytically cleaved to form the active peptides (carboxyl- and amino-terminal residues are modified to remove charges).

High density secretory granules → exocytosis

e.g. pancreatic hormones (insulin, glucagon, somatostatin); parathyroid hormone (calcitonin); hypothalamus and pituitary hormones.

ANTI-DIURETIC HORMONE
Regulates water levels in the body; affects blood pressure and volume

CORTICOTROPIN-RELEASING HORMONE
Drives the body's response to physical and emotional stress; stimulates anxiety; suppresses appetite

GONADOTROPIN-RELEASING HORMONE
Stimulates release of hormones that act on testes and ovaries to initiate and maintain reproductive function; levels increase in puberty to trigger sexual maturation (puberty depends upon the appropriate timing and release of hormones)

GROWTH HORMONE-RELEASING HORMONE
Controls normal physical development in children, metabolism in adults; increased by sleep, stress, exercise, and low blood glucose

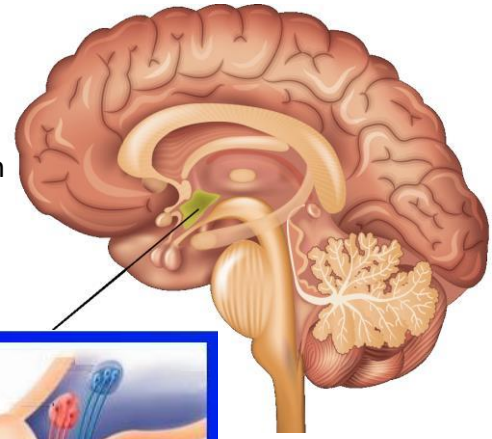
OXYTOCIN
Controls aspects of some human behavior (sexual arousal, recognition, trust, anxiety, and mother-infant bonding) and key aspects of reproductive system (childbirth and lactation in women, ejaculation and conversion of testosterone into dihydrotestosterone in men)

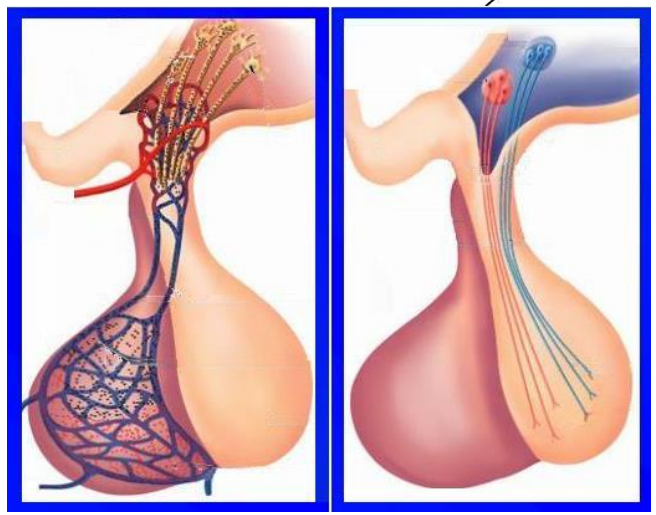
SOMATOSTATIN
In the central nervous system, works to inhibit other hormones, most notably growth and thyroid-stimulating hormones

THYROTROPIN-RELEASING HORMONE
Stimulates production of thyroid hormone, which plays important role in the body's metabolism, heart and digestive functions, muscle control, brain development, and preservation of bones

The hypothalamus is located on the undersurface of the brain.

It is attached by a stalk to the pituitary gland.





One set of nerve cells in the hypothalamus produces stimulating and inhibiting hormones that reach the anterior lobe (ADENOHYPOPHYSIS) of the pituitary gland via a network of blood vessels that run down through the pituitary stalk.
[HRHs that stimulate secretion of adenohypophyseal hormones]

The other set sends the hormones they produce down through the pituitary stalk to the posterior lobe (NEUROHYPOPHYSIS) of the pituitary gland where these hormones are stored/released as needed into the bloodstream.
[ADH; oxytocin]

HORMONES

- PEPTIDE
- CATECHOLAMINE
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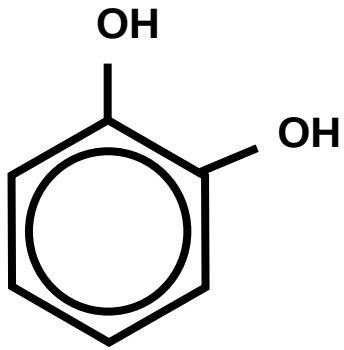
Aromatic amines named after catechol (1,2 dihydroxybenzene), a structurally related compound



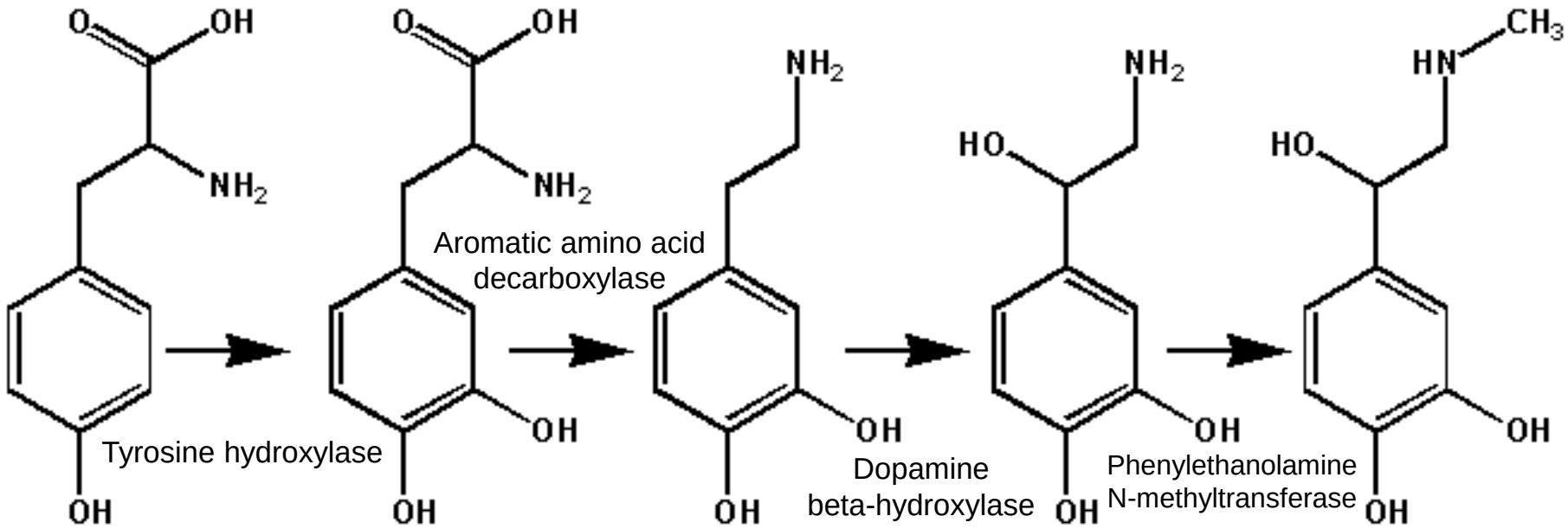
In the nervous system, they function as neurotransmitters

BUT ARE ALSO

secreted by the adrenal gland (exocytosis)

→ hormones – metabotropic receptors

e.g. epinèphrine (adrenaline), norepinèphrine (noradrenaline).



TYROSINE Dihydroxyphenylalanine DOPAMINE NOREPINEPHRINE EPINEPHRINE

DOPA

HORMONES

- PEPTIDE
- CATECHOLAMINE
- EICOSANOID
- STEROID
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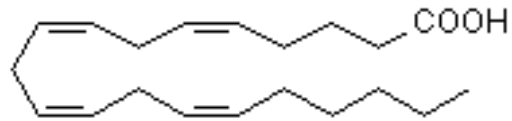
Derived from arachidonate (20:4).

Not stored.

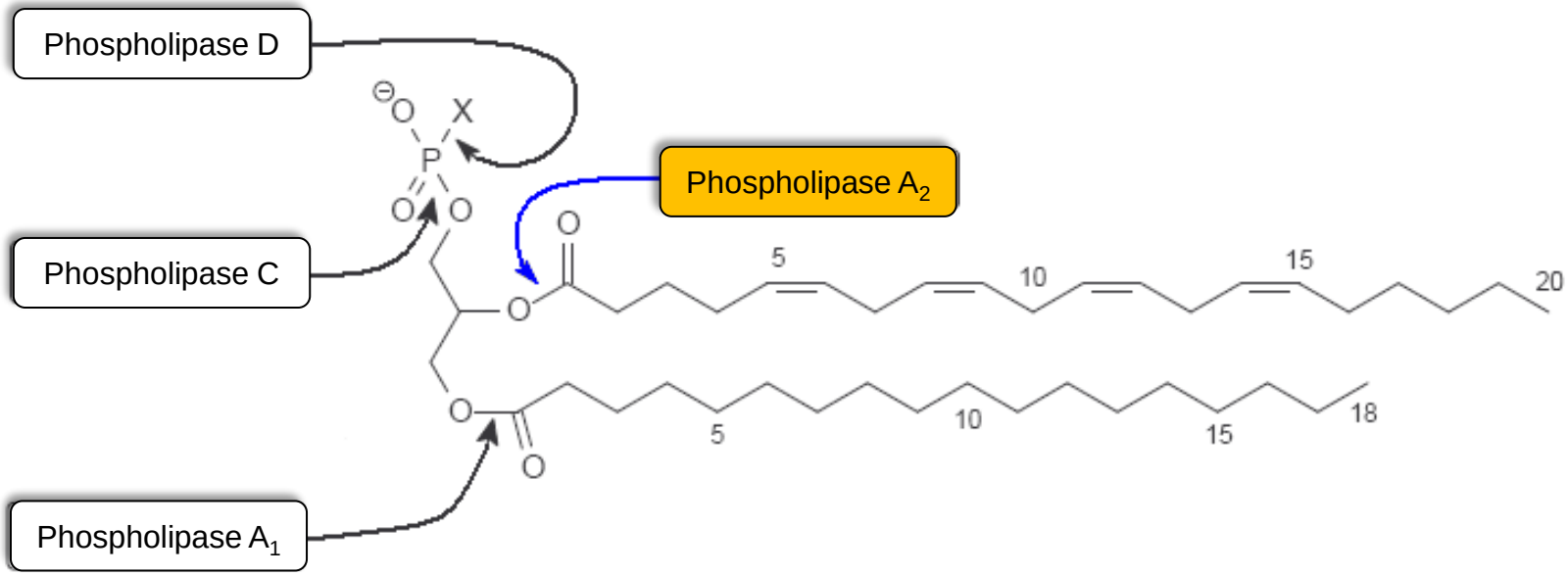


Paracrine hormones

(secreted into the interstitial fluid of cells and acting nearby) widely produced/distributed in mammalian tissues

e.g. prostaglandins, thromboxanes, leukotrienes

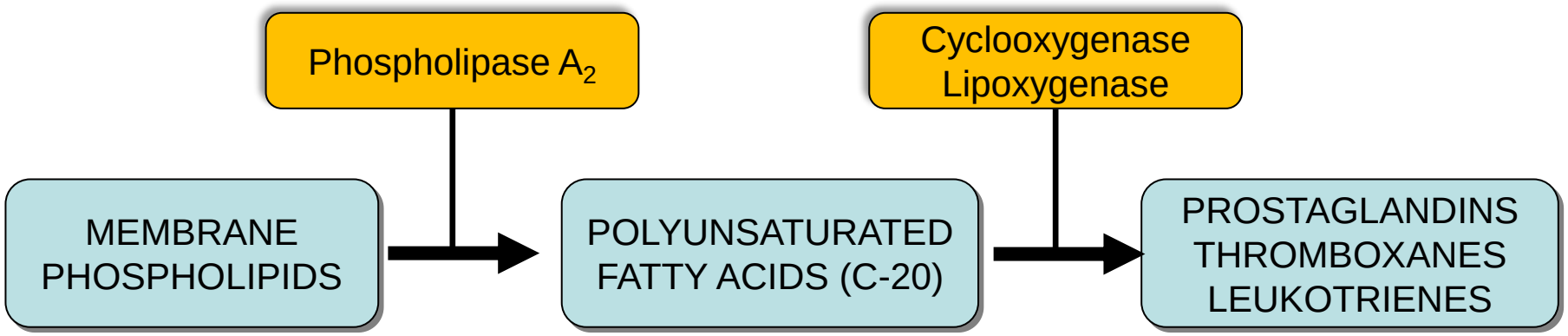
Since the concentration of free arachidonic acid in the cells is very low, the biosynthesis of the eicosanoids depends mainly on the availability of phospholipase A_2 (hydrolases) capable of releasing arachidonate from the middle carbon of glycerol of the phospholipids

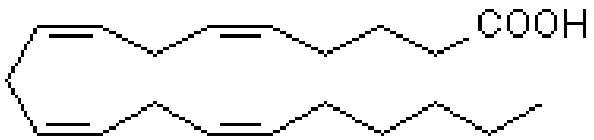


Arachidonic acid esterified in membrane phospholipids

Since the concentration of free arachidonic acid in the cells is very low, the biosynthesis of the eicosanoids depends mainly on the availability of phospholipase A_2 (hydrolases) capable of releasing arachidonate from the middle carbon of glycerol of the phospholipids

BIOGENESIS OF EICOSANOIDS





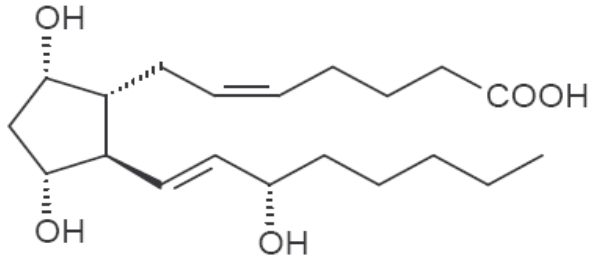
arachidonic acid
(omega-6 fatty acid)

Nomenclature and abbreviations

- PROSTAGLANDINS PG
- THROMBOXANES TX
- LEUKOTRIENES LT

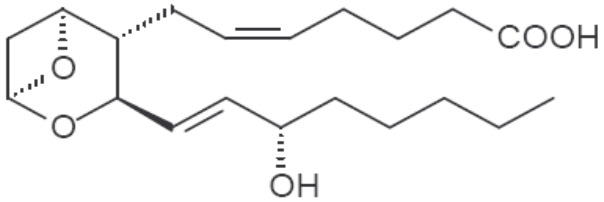
Numbering and meaning of the other descriptive symbols
e.g. $PGF_2\alpha$

- PG = prostaglandin
- F = type of ring substitution in C9 and C11 (e.g. –OH; =O)
- 2 = degree of unsaturation (double bonds)
- α = *cis* isomerism of substituents in C9 and C11 (β = *trans*)



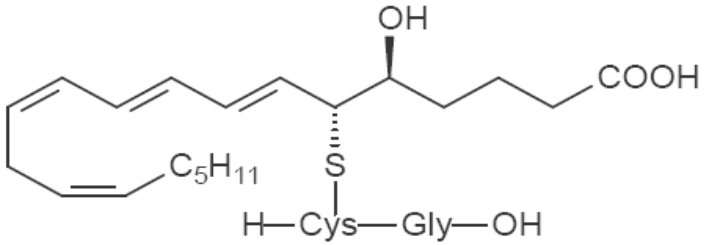
PROSTAGLANDINS
(Prostaglandin $F_2\alpha$)

PGF2alpha is a potent vasoconstrictor produced by the uterus when stimulated by oxytocin; stimulates the contraction of uterine and bronchial smooth muscle.
It is used in medicine to induce labour and to terminate pregnancy, including missed or partial abortion.
(pharmaceutically termed Dinoprost)



THROMBOXANES
(Thromboxane A_2)

TXA2 is a potent vasoconstrictor produced by endothelial cells, macrophages and platelets upon platelet activation.
Its main role is in amplification of platelet activation and recruitment of additional platelets to the site of injury.



LEUKOTRIENES
(Leukotriene D_4)

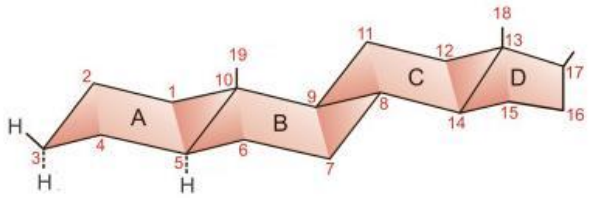
LTs are important inflammatory lipid mediators derived from arachidonic acid following its oxidation by 5-lipoxygenase (5-LO) on the nuclear envelope.
Important role in airway inflammation:

- mucus hypersecretion,
- increased vascular permeability
- mucosal edema,

→ potent bronchoconstriction.
(so named due to their source from leukocytes and the presence of three conjugated double bonds in their structure)

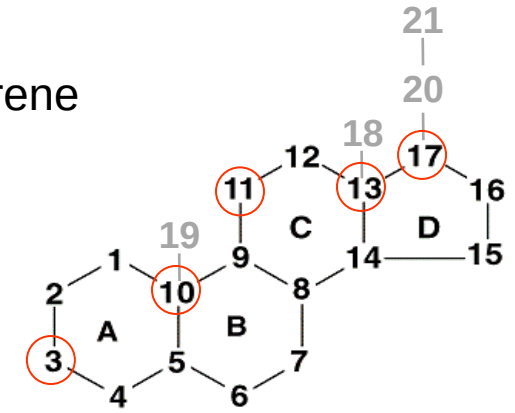
HORMONES

- PEPTIDE
- CATECHOLAMINE
- EICOSANOID
- STEROID
- RETINOID
- THYROID
- NITRIC OXIDE

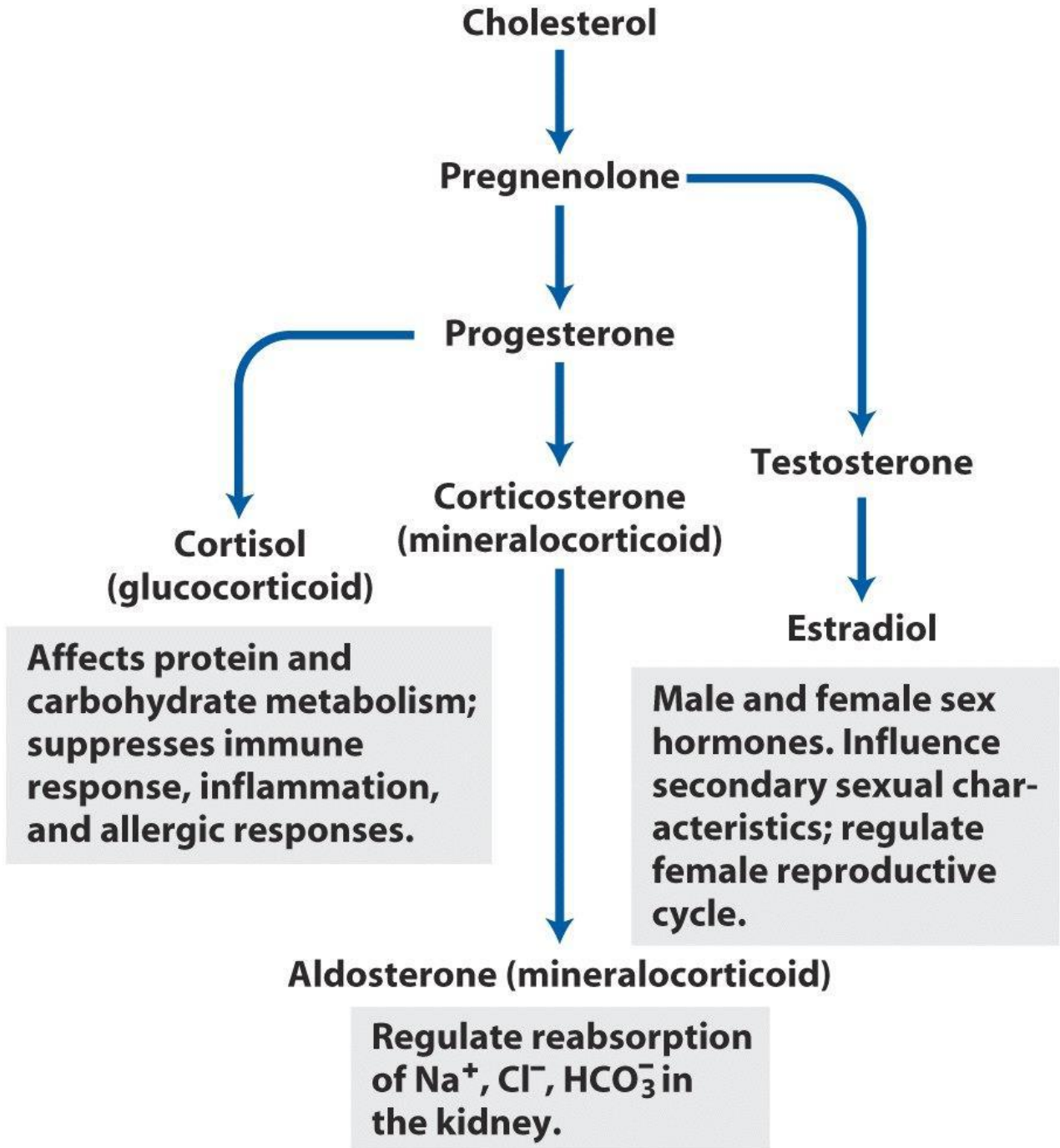


Spatial conformation - Hexagonal cycles adopt the chair configuration.

Structures derived from cyclopentanoperhydrophenanthrene
- Steranes -
(4 rings. C-17+).
Not storable.



Since liposoluble, they require protein carriers in order to circulate in the plasma: albumin (low affinity), α-globulin. [protection against inactivating metabolism while travelling to the target organ]


Cholesterol
Pregnenolone
Progesterone
Testosterone
Corticosterone (mineralocorticoid)
Cortisol (glucocorticoid)
Estradiol
Affects protein and carbohydrate metabolism; suppresses immune response, inflammation, and allergic responses.
Male and female sex hormones. Influence secondary sexual characteristics; regulate female reproductive cycle.
Aldosterone (mineralocorticoid)
Regulate reabsorption of Na^+, Cl^-, HCO_3^- in the kidney.

HORMONES

- PEPTIDE
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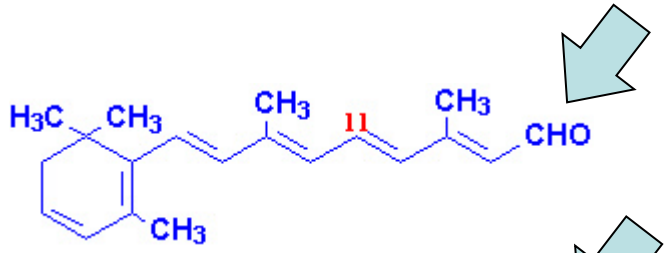
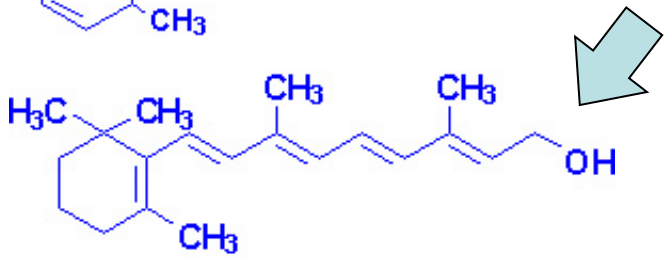
Structure derived from Vitamin A.
Many tissues convert retinol into retinoic acid.
Nuclear receptors.

Intestine:
• ingested **β-carotene** is **cleaved by** β-carotene dioxygenase to yield retinal (all *trans*)
• **retinal** is reduced to retinol by retinaldehyde reductase, an NADPH requiring enzyme
• r**etinol** (Vitamin A alcohol) is esterified to palmitic acid and delivered to the blood via chylomicrons



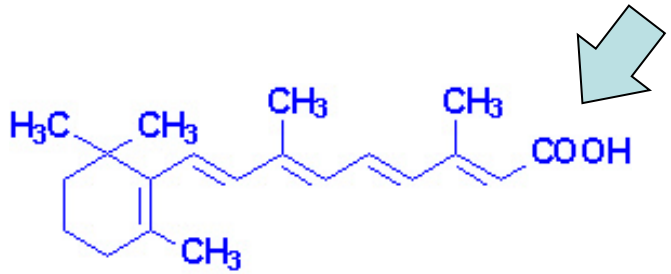
- Liver:

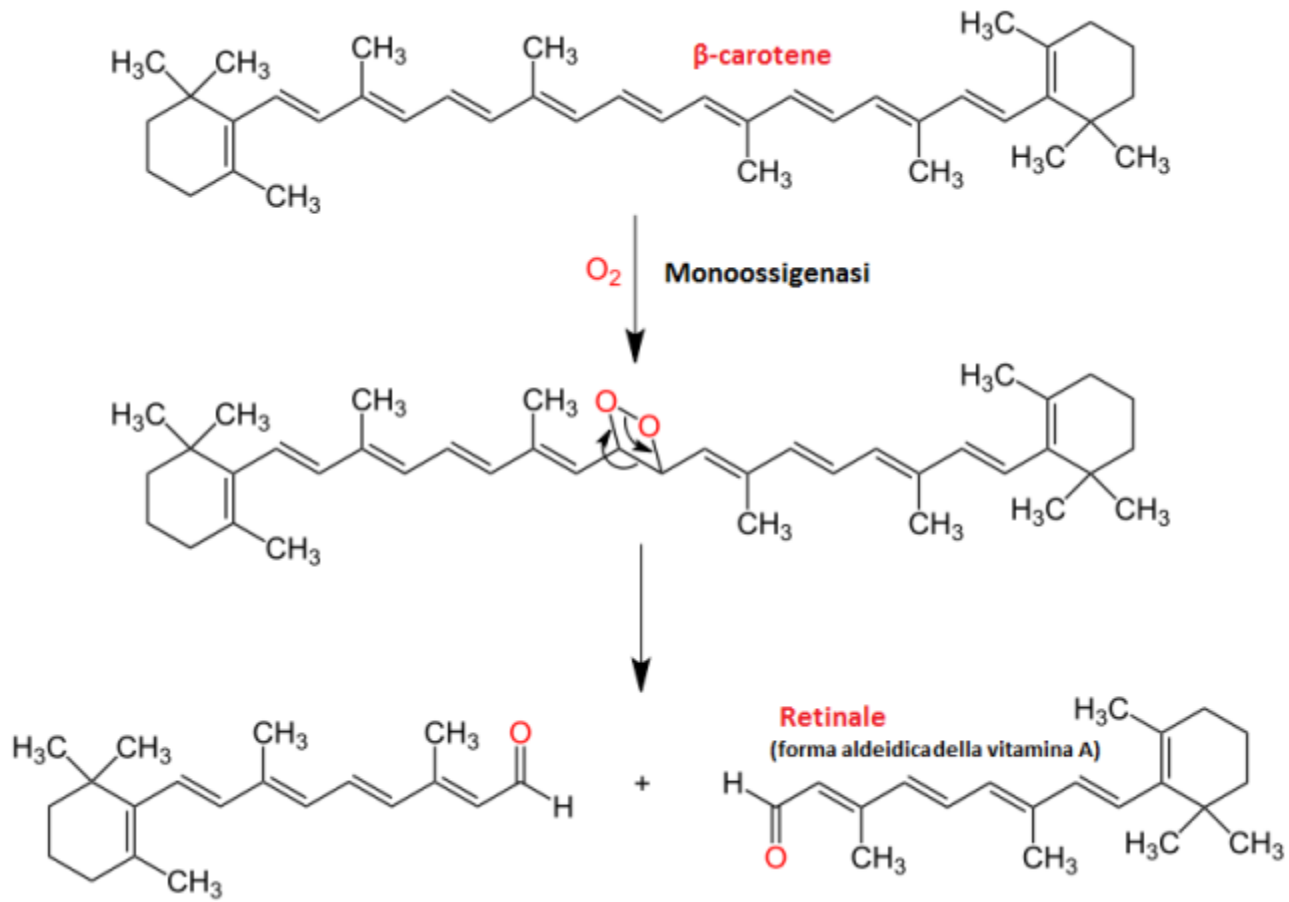
• the uptake of chylomicron remnants results in delivery of retinol to this organ for storage as a lipid ester (also in adipose tissue)
• transport of retinol from the liver occurs by binding of hydrolyzed retinol to aporetinol binding protein (RBP). The retinol-RBP complex is then transported to the cell surface within the Golgi and secreted.
Plasma transport of retinoic acid is accomplished by binding to albumin.



- Extrahepatic tissues:

• retinol is bound to cellular retinol binding protein (CRBP)
• retinol is converted to all-trans-**retinoic acid**
• following binding, the receptor-vitamin complex interacts with specific sequences in several genes involved in growth and differentiation and affects expression of these genes.
In this capacity retinol and retinoic acid are considered hormones.




β-carotene
O_2
Monoossigenasi
Retinale
(forma aldeidica della vitamina A)

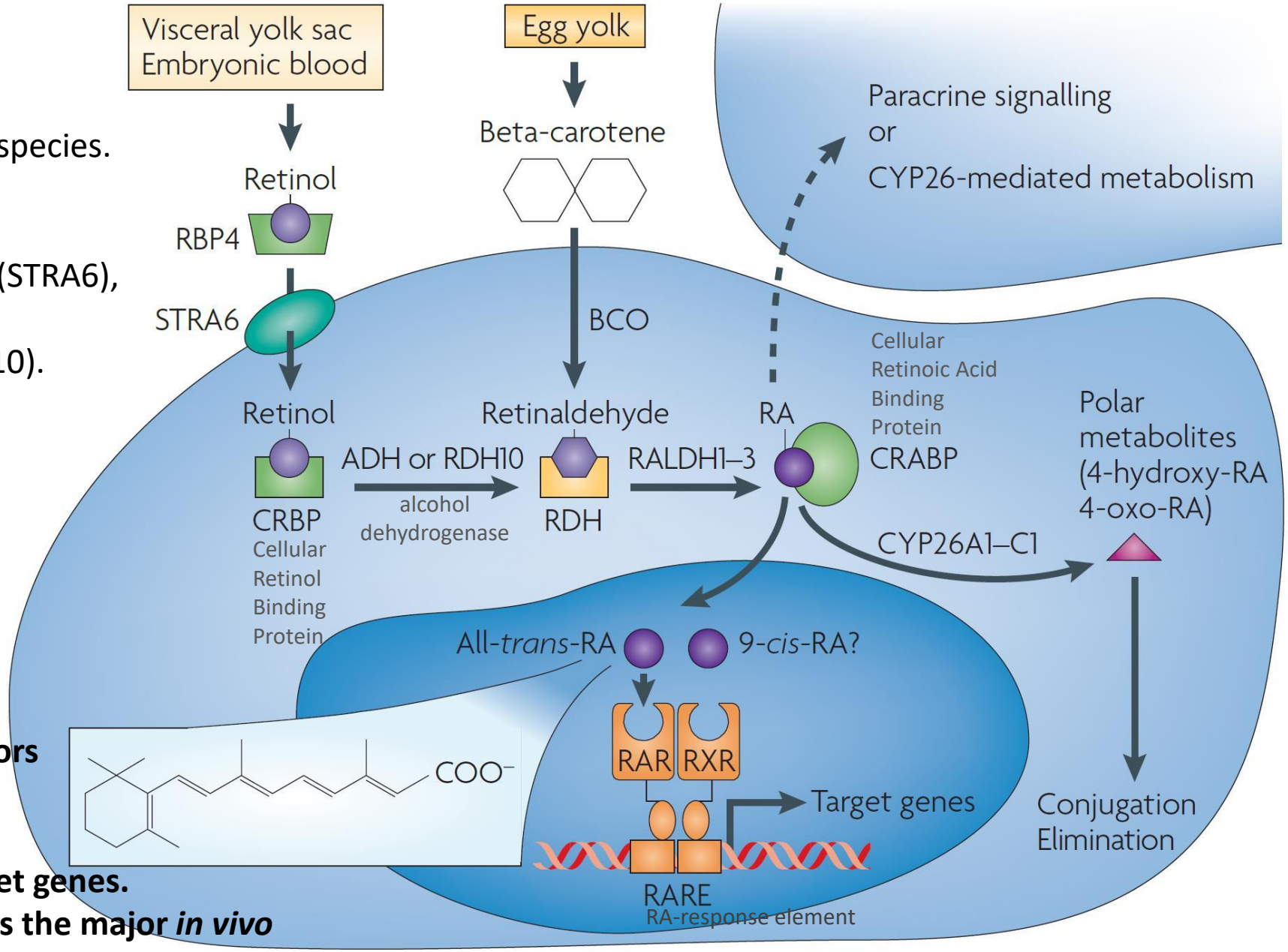
https://doi.org/10.1038/nrg2340

Regulation of retinoid signalling in embryonic cells.

Retinoid sources comprise circulating maternal retinol in placental species and carotenoid stores in the yolk of oviparous species. Retinol is taken up by embryonic retinol binding protein 4 (RBP4), transferred intracellularly by the receptor (STRA6), and transformed into retinaldehyde, mainly by retinol dehydrogenase 10 (RDH10).

Cleavage of beta-carotene by beta-carotene oxygenase (BCO) enzyme(s) directly generates retinaldehyde.

Retinaldehyde dehydrogenases (RALDH1 to RALDH3) then generate retinoic acid (RA), which acts within the nucleus as a ligand for nuclear receptors [i.e. heterodimers of RA receptors (RARs) and retinoid X receptors (RXRs)] to regulate transcriptional activity of target genes. All-*trans*-RA (formula depicted in figure) is the major *in vivo* RAR ligand.



HORMONES

- PEPTIDE
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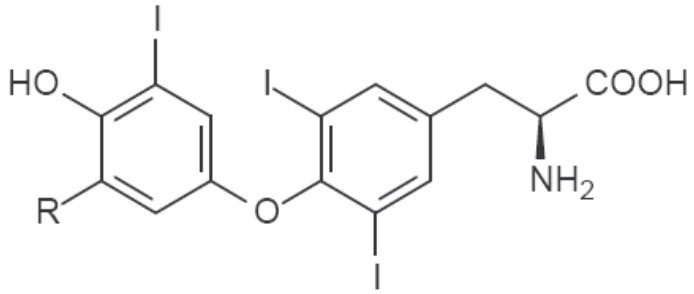
Nuclear receptors.

Thyroglobulin, a protein precursor with numerous enzymatically condensated residues of iodinated-Tyr, accumulates in thyroid follicles (colloid).

Release of both thyroid hormones as a result of proteolytic processes (stimulated by TSH).



3,5,3'-Triiodotironina (T_3) **R = H**

Tiroxina (T_4) **R = I**

HORMONES

- PEPTIDE
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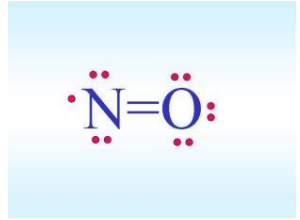
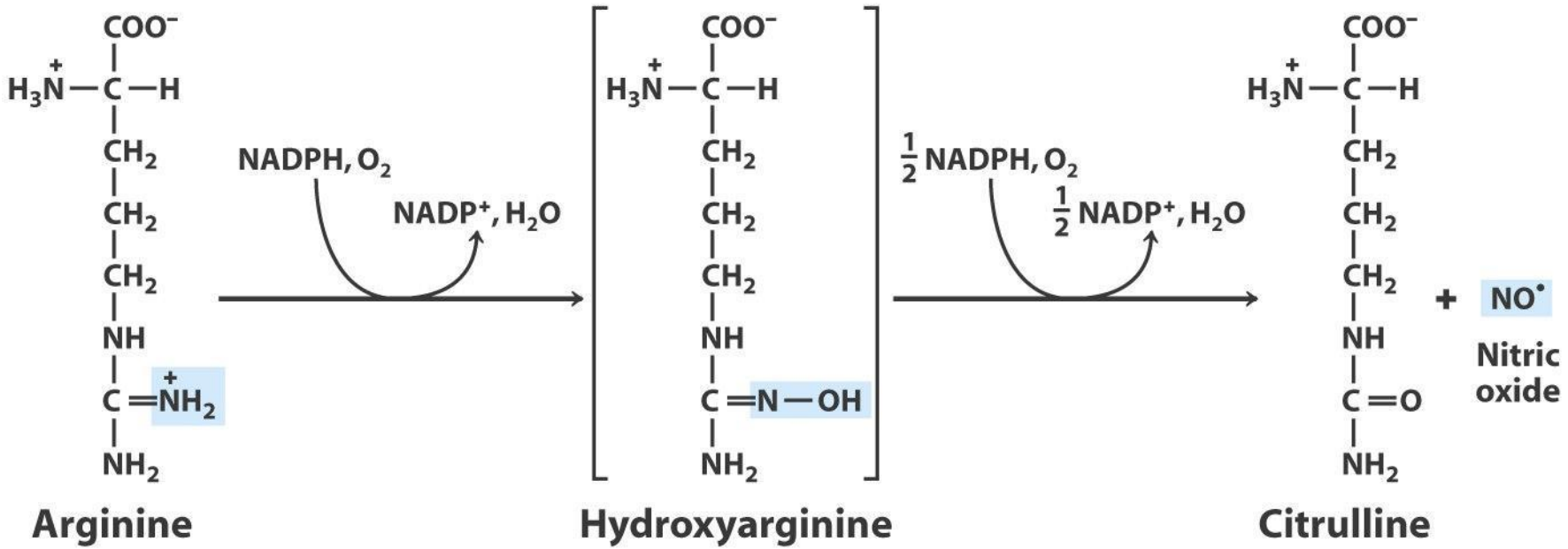
Free radical (gas, poor stability).
Acts near its synthesis/release site.
Freely diffusible through membranes.
'endothelium-derived relaxing factor', EDRF



Nitric oxide synthase, NOS
(related to cytochrome P450 reductase)



3 different genes encoding NO synthases:

nNOS (or NOS-1): found in neurons (hence the "n").
iNOS (or NOS-2): found in macrophages. (the "i" stands for "inducible". Whereas the levels of nNOS and eNOS are relatively steady, expression of iNOS genes awaits an appropriate stimulus (e.g., ingestion of a parasite).
eNOS (or NOS-3): found in the endothelial (hence the "e") cells that line the lumen of blood vessels.