LIPIDS

oxylipins

Marek Vecka

OXYLIPINS

OXYLIPINS = oxygenated fatty acids biologically active as lipid mediators

eicosanoids

- products of transformation of FA with 20 C

  AA (20:4n-6), EPA (20:5n-3), DHGLA (20:3n-6)

docosanoids

- products of transformation of FA with 22 C

  DHA (22:6n-3)

octadecanoids

- products of transformation of FA with 18 C

  ALA (18:3n-3) *(important to plants)*

OXYLIPINS

OXYLIPINS = oxygenated fatty acids biologically active as lipid mediators

I. production by enzymes

- FA are transformed via several pathways:

Cyclic structures of oxylipins

1. cyclooxygenase pathway

Linear structures of oxylipins

2. lipoxygenase pathway

3. epoxygenase pathway

oxidative stress

II. nonenzymatic production

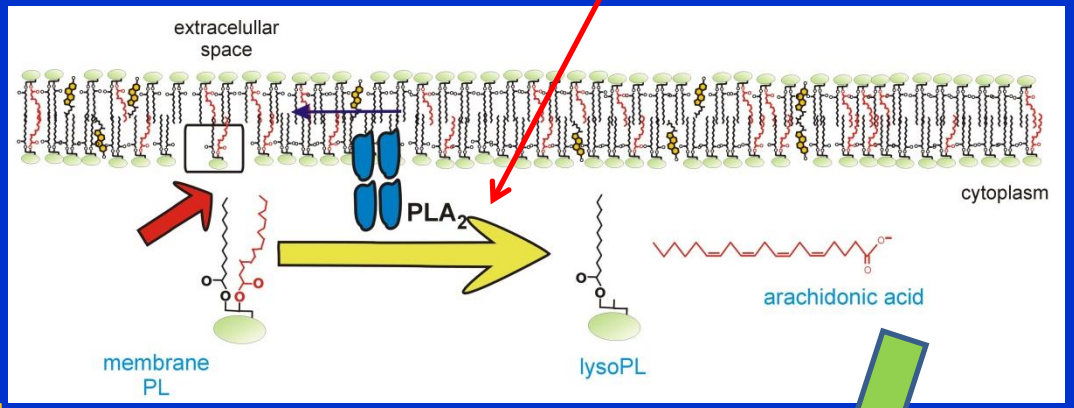
- the reactions are catalysed by free radicals *in vivo*
- reactions usually lack stereospecificity

EICOSANOIDS

Oxylipins derived from 20 C fatty acid precursor

Arachidonate pathway (cascade)

inhibited by glucocorticoids
↑lipocortins = inhibitors of PLA_2



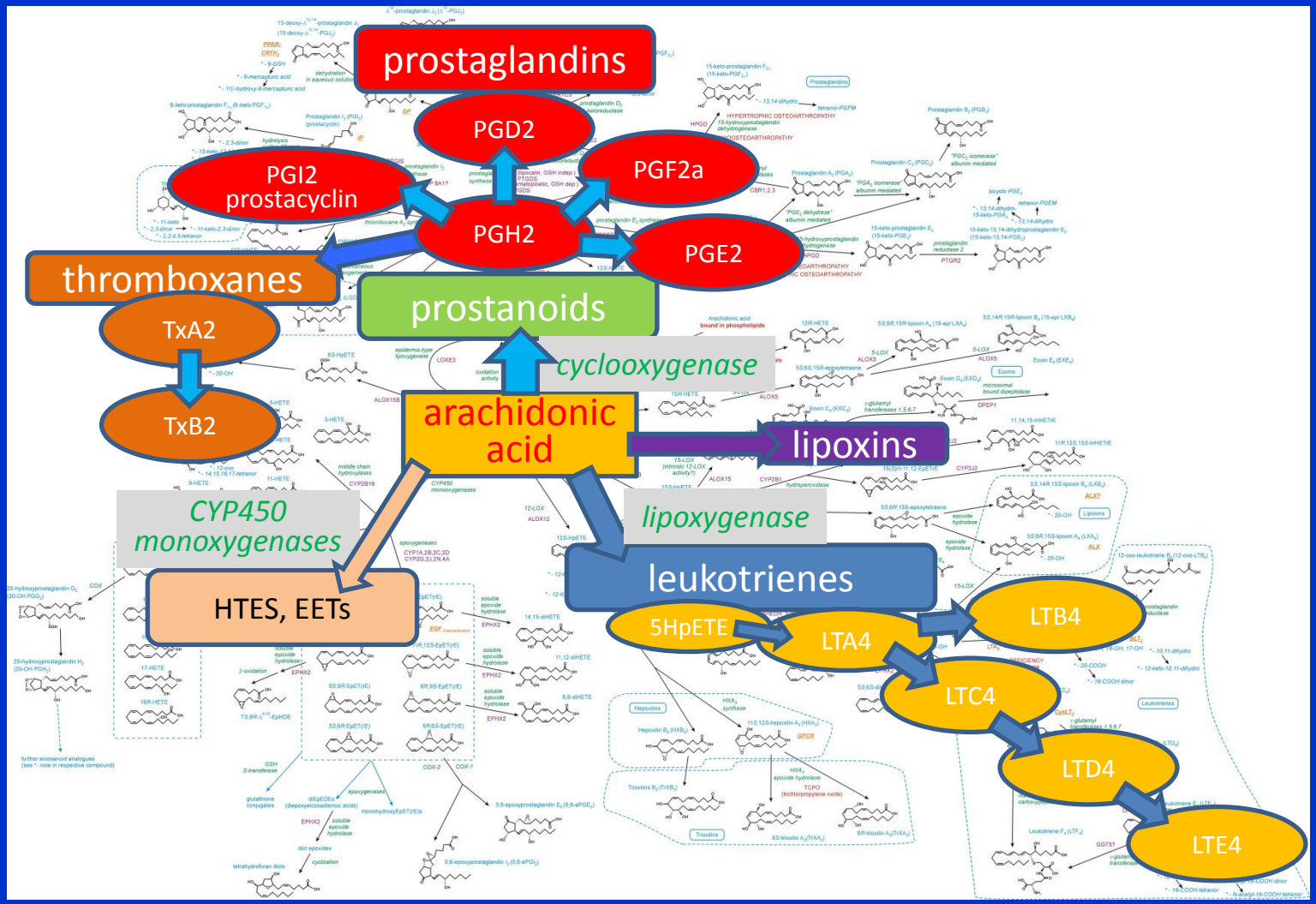
I. Initiation: AA release from PL by PLA_2

II. Further metabolization by enzymes

- prostanoids (prostaglandins (PG) + thromboxanes (Tx))
- Leukotrienes (LT)
- Lipoxins (Lx)
- HETEs, EETs

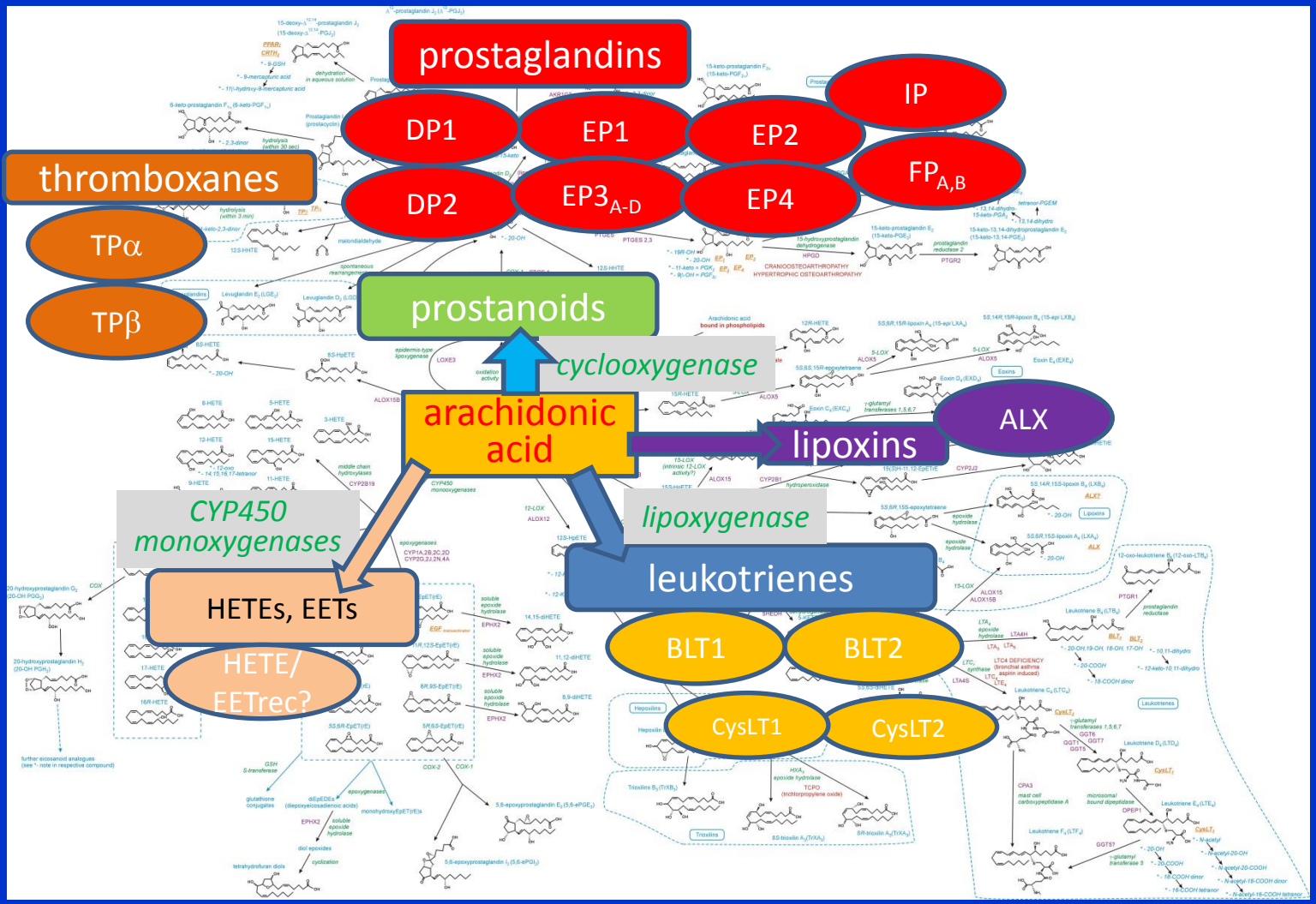
EICOSANOIDS

oxylipin pathways (cascades)



EICOSANOIDS

mode of action – ligands of receptors



EICOSANOIDS

Mode of action

1. **ligands of receptors**
   (G-protein coupled)
2. **interaction with nuclear receptors**

Short half lives (sec – 5 mins)

- **only autocrine/paracrine action**
- **produced in many cell types (x not in specialized glands)**
  - **PG (many cell types)**
  - **Tx (platelets/endothelium)**
  - **LT (immune system), Lx (immune system)**
- **wide variety of effects**

EICOSANOIDS

Nomenclature of prostanoids

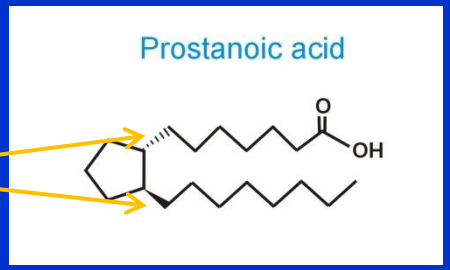
theoretically from prostanoic acid structure

20 C structure

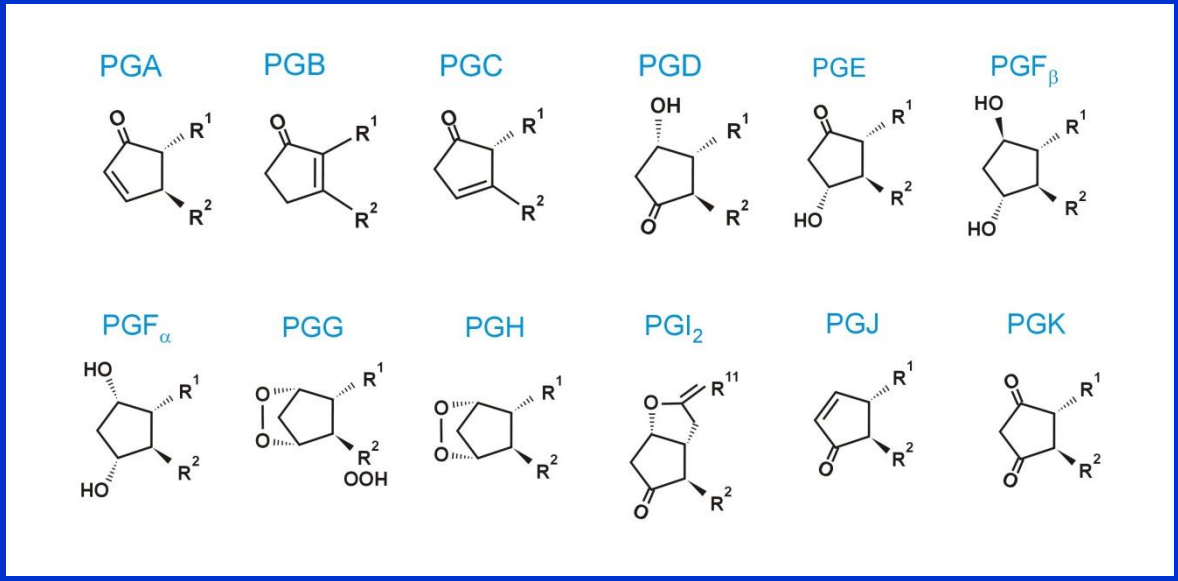
cyclopentane ring

substituents are added *trans-*

on adjacent carbons



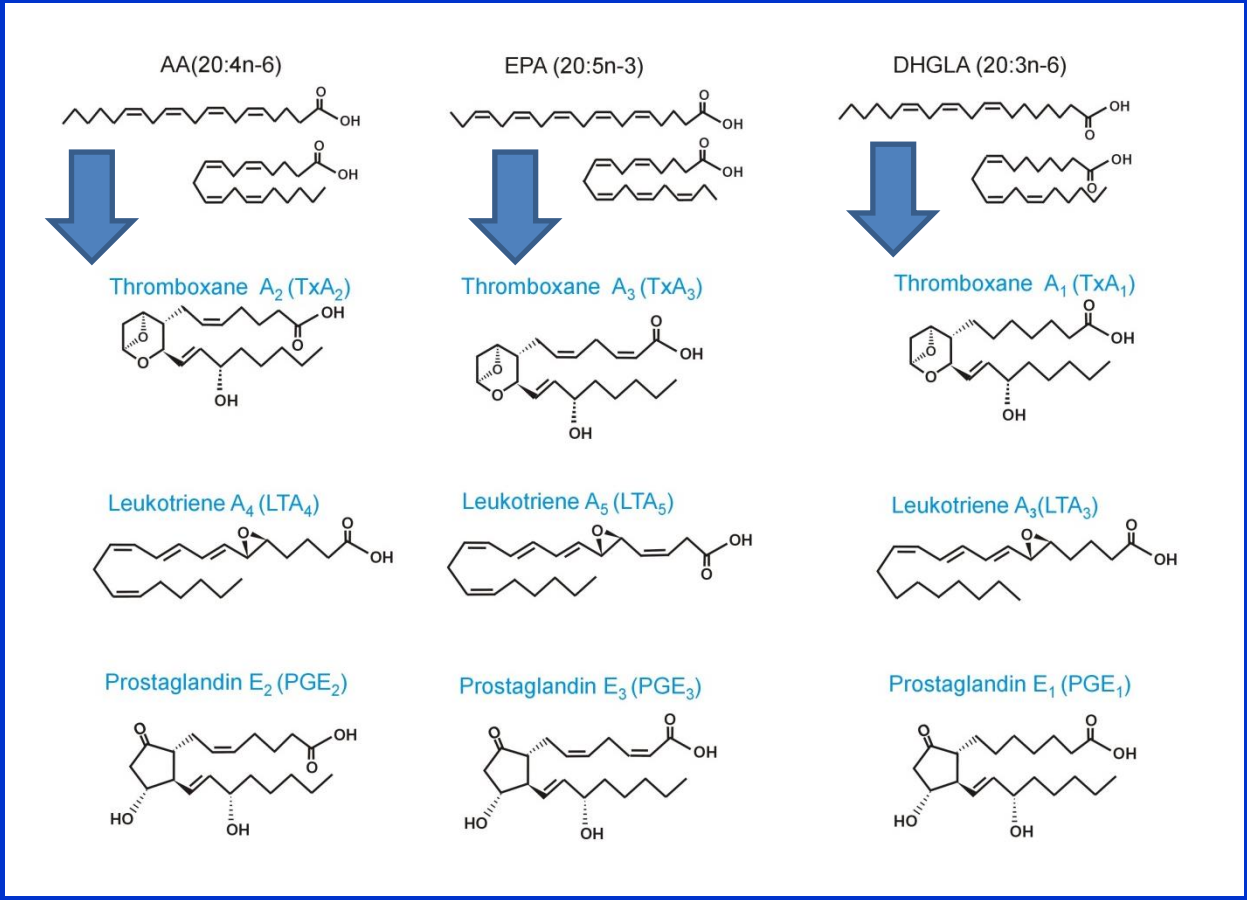
1. type of ring structure *(the third letter)*



EICOSANOIDS

Nomenclature of prostanoids

2. number of double bonds present *(the number)*



LEUKOTRIENES

Oxylipins derived from 20 C fatty acid precursor

leukos → white blood cells
dendritic cells

biosynthetic pathway

1. lipoxygenase (5-LOX)
in nuclear membrane

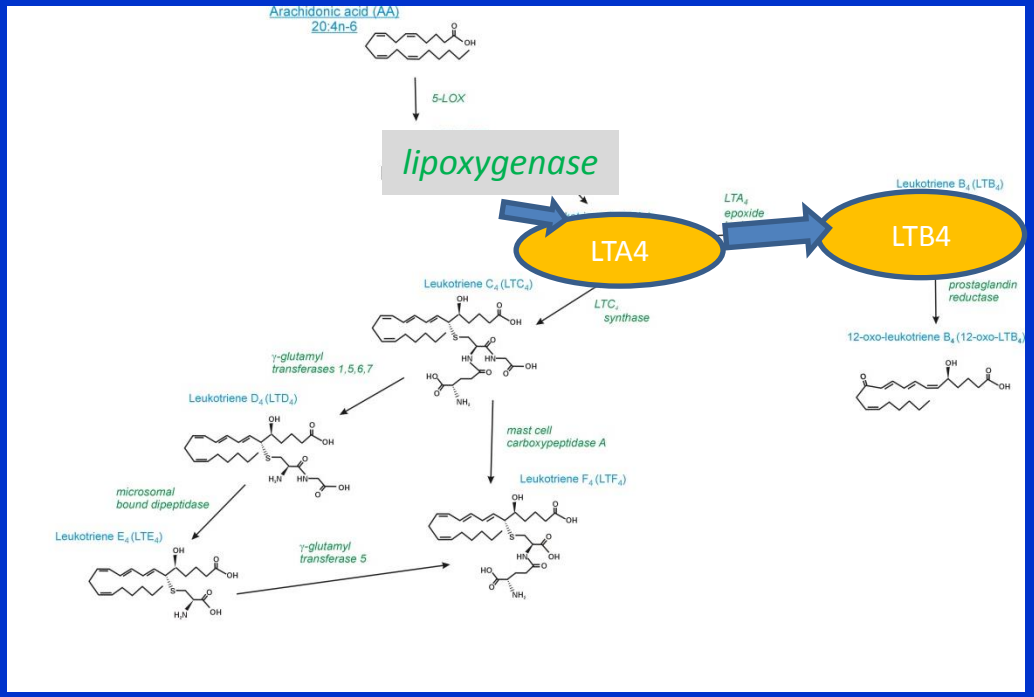
LTA4

branching point

a)*LTA4 hydrogenase*

LTB4

- **in leukocytes, promotes inflammation**
  enhances extravasation, chemoattractant (mechanism)



LEUKOTRIENES

Oxylipins derived from 20 C fatty acid precursor

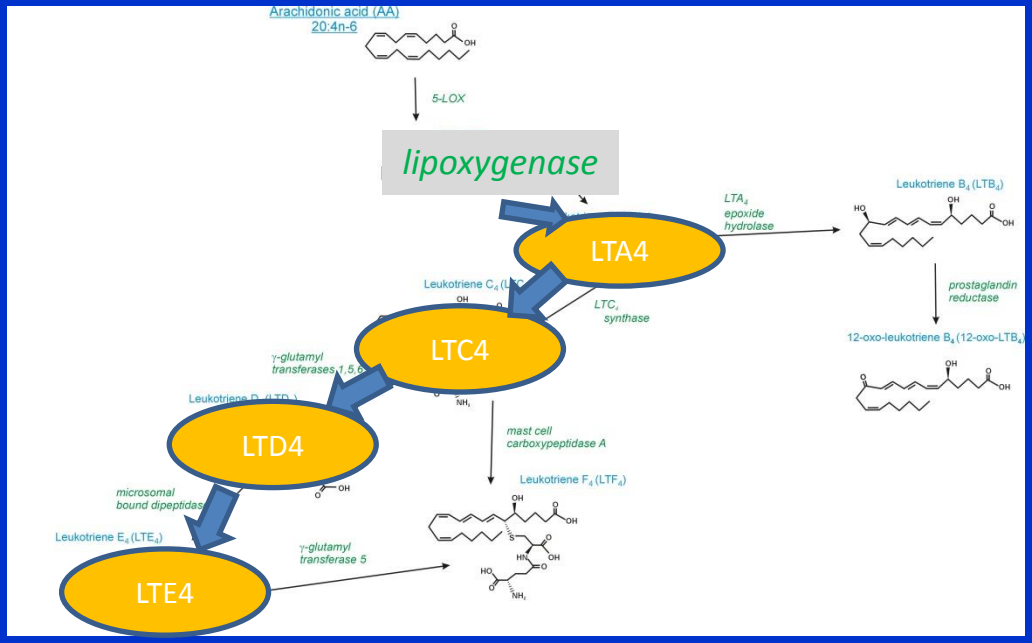
LTA4

branching point

b)*LTC4 synthase*

LTC4, LTD4, LTE4

= peptide leukotrienes (glutathione residue)



promote inflammation

enhance bronchoconstriction (asthma!)

smooth muscle constriction, vasoconstriction

(LTs 100 x more potent than histamine (hist acts in early stage), late response)

mediate allergic reaction: *Slow Reacting Substance of Anaphylaxis (SRS-A)*

mediate later response to an allergen

LEUKOTRIENES

Oxylipins derived from 20 C fatty acid precursor

Pharmacology note

LT rec antagonists (cysLT1 rec)

- LT induce bronchospasms → asthma treatment

generic names -lucasts

montelukast, zafirlukast, pranlukast

PROSTANOIDS

Oxylipins derived from 20 C fatty acid precursor

Prosta-→ ***prostate (1st isolation of PG from seminal fluid)***

biosynthetic pathway

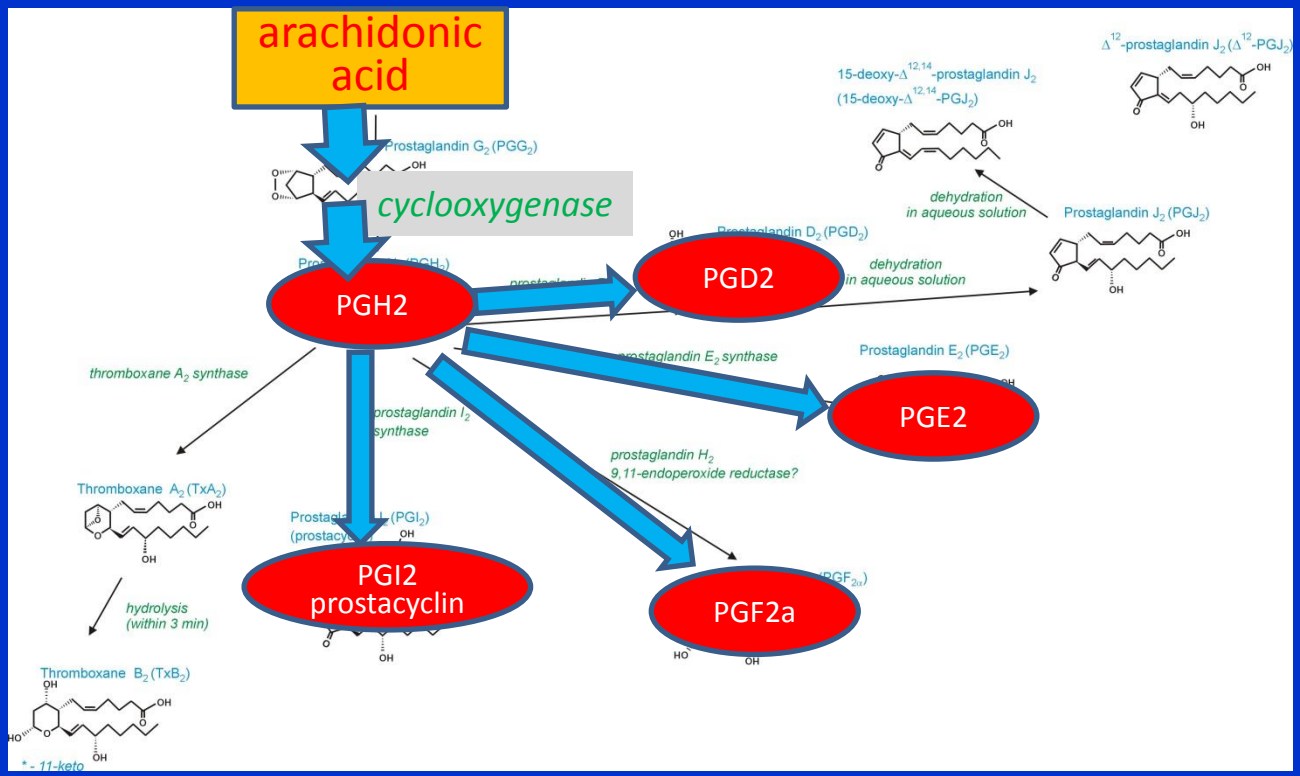
1. cyclooxygenases (COX-1, COX-2)

PGH2

branching point precursor for

prostaglandins

thromboxanes



PROSTANOIDS

Oxylipins derived from 20 C fatty acid precursor

Cyclooxygenases (*prostaglandin endoperoxide H synthases*)

enzymes catalyzing transformation of AA → PGG2 → PGH2

located in ER/nuclear envelope

COX-1

constitutive

in many tissues

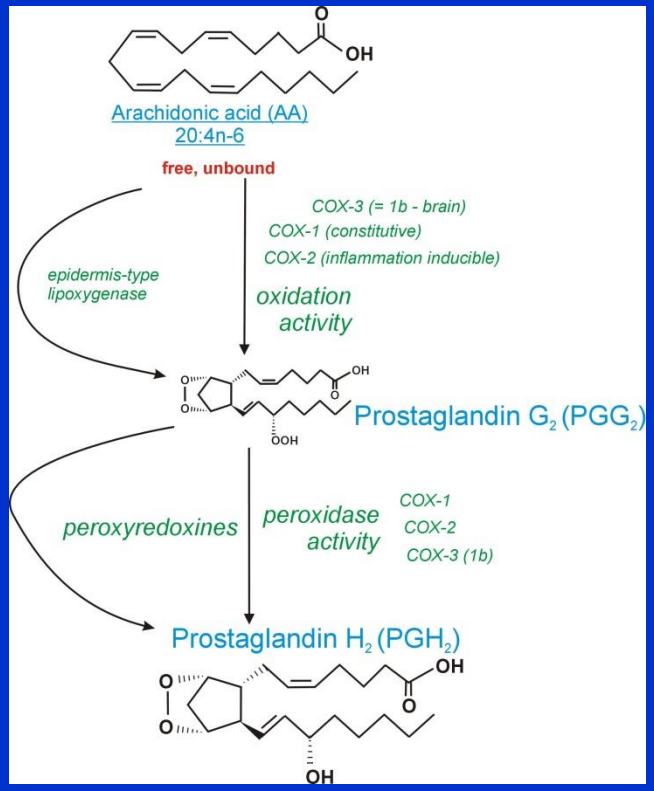
COX-2

inducible (constitutive in kidney/brain)

induced by NFkB (proinflamm. transcr fact**)**

lower substrate specificity than COX-1

(+DHGLA, EPA, 2-AG, anandamide…)



PROSTANOIDS

Oxylipins derived from 20 C fatty acid precursor

Prostaglandin effects

1. Essential homeostatic functions

GIT

- cytoprotection of gastric mucosa (PGs)

increase mucus, water, and electrolyte secretion in the stomach (and the intestine)

- decrease in transit time

PGE2 and PGF2a: increase the rate of longitudinal contraction

renal physiology

PGE2: maintaining vascular tone, blood flow, and salt and water excretion (Na^+ reabsorption)

PGI2 (PGE2?): increases K^+ secretion

PGI2: vasodilator → renal blood flow↑

PROSTANOIDS

Oxylipins derived from 20 C fatty acid precursor

Prostaglandin effects

1. Essential homeostatic functions

smooth muscles

- vascular

PGE2, PGI2: vasodilatation (↑blood flow → can prolong oedema)

- bronchial

PGFs: bronchial contraction

PGEs: bronchial relaxation

blood physiology

PGE2: erythropoiesis induction (↑ renal EPO release)

PGI2, PGE2: inhibition of platelet aggregation

PGI2, PGD2: inhibition of histamine release

PROSTANOIDS

Oxylipins derived from 20 C fatty acid precursor

Prostaglandin effects

1. Essential homeostatic functions

brain/peripheral neuronal tissue

- body temperature

PGD2: ↓body temperature during sleep (sleep induction)

PGE2: ↑body temperature as an inflammatory response

thermal centre in brain (anterior hypothalamus)

- pain

dorsal root ganglion neurons expressing IP receptor (PGI2)

PGD2, PGE2: inflammatory pain (*sensitizing pain receptors*)

PROSTANOIDS

Oxylipins derived from 20 C fatty acid precursor

Prostaglandin effects

2. Special circumstances

Birth induction, gestation

PGE2, PGF2a: uterine smooth muscle contraction (pregnancy)

x nonpregnant: PGE2 contraction, PGF2a relaxation of uterus

Maintain patent DA (ductus arteriosus)

DA : contains muscle sensitive to

oxygen tension (low O2)

vasoactive substances (PGE2 vasodilat.)

(neonatal cardiac surgery)

PROSTANOIDS

Oxylipins derived from 20 C fatty acid precursor

Prostaglandin effects

2. Special circumstances

Inflammation

PGE2: pro-inflammatory (fever induction, pain enhanc.)

anti-inflammatory [inhibits LO-5(LT) and lymphoc. proliferation]

PGI2: mediator of pain and oedema

PGD2: in mast cells

PROSTANOIDS

Treatment by prostanoids - special cases

Raynauld´s disease

overreaction of limbs to cold/stress → cold fingers/toes in pain

PGEs as vasodilators

Glaucoma (open-angle)

clogged eye's drainage canals → ↑internal eye pressure →

damage to the optic nerve

PGEs, PGFs: ↑ outflow of aqueous humor

(cave: change in iris color, ↑growth of eyelashes)

Peptic ulcers

high doses NSAID → acidic + ↓ protection of GIT → ulcers

PGE1: restoration of PG protective effects

Erectile dysfunction

damaged function of corpora cavernosa

PGE1: vasodilator → ↑ blood flow

PROSTANOIDS

Oxylipins derived from 20 C fatty acid precursor

Thromboxanes

thrombus → platelets (clotting)

biosynthetic pathway

1. TX synthase

in ER

TxA2

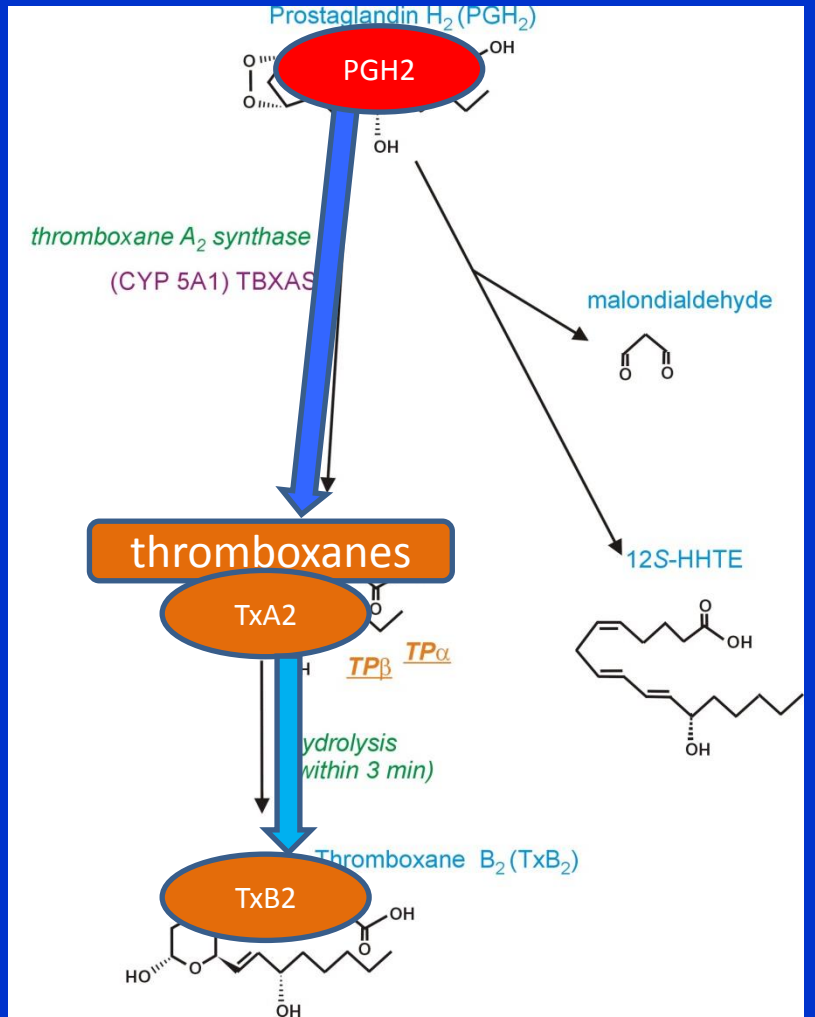
induction of vasoconstriction

platelet aggregation

spontaneously **(~30s)**

TxB2

inactive



LIPOXINS

Lipoxygenases products of arachidonic acid II

Lipoxins

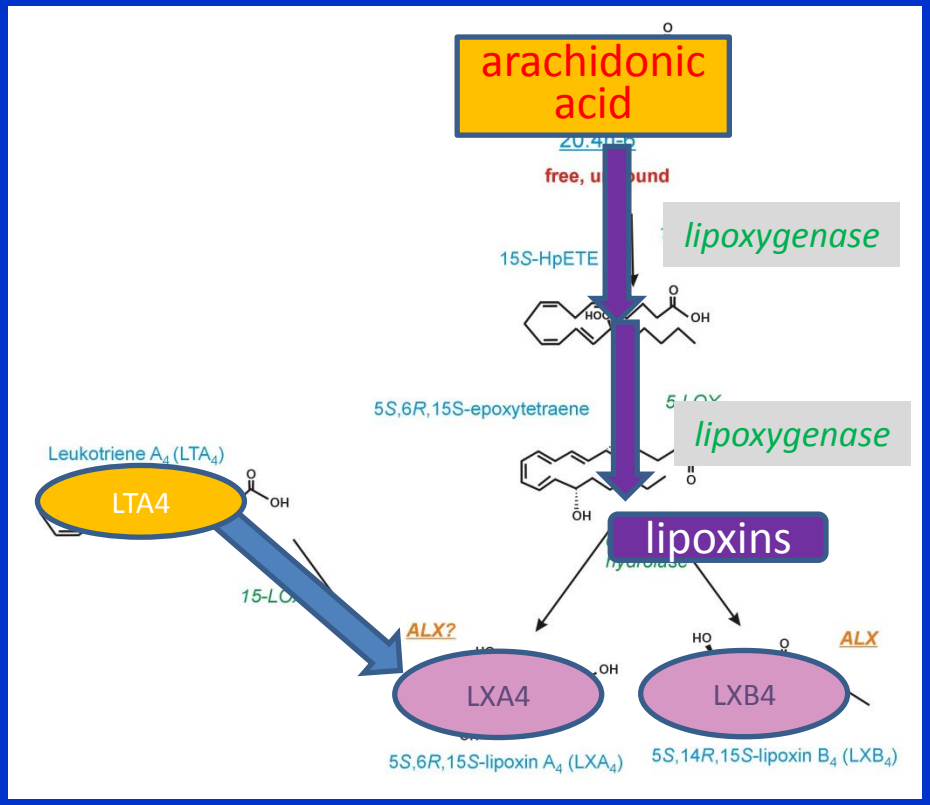
Inflammation

Resolution of inflammation

PMN infiltration↓
antiangiogenic effects
chemoattraction of monocytes
→wound healing

I. airways (monocytes/epithelium)
II. platelets (need LTA4)

III. aspirin → forming epi-LXs



EPOXYEICOSATRIENOIC AND HYDROXYEICOSATETRAENOIC ACIDS

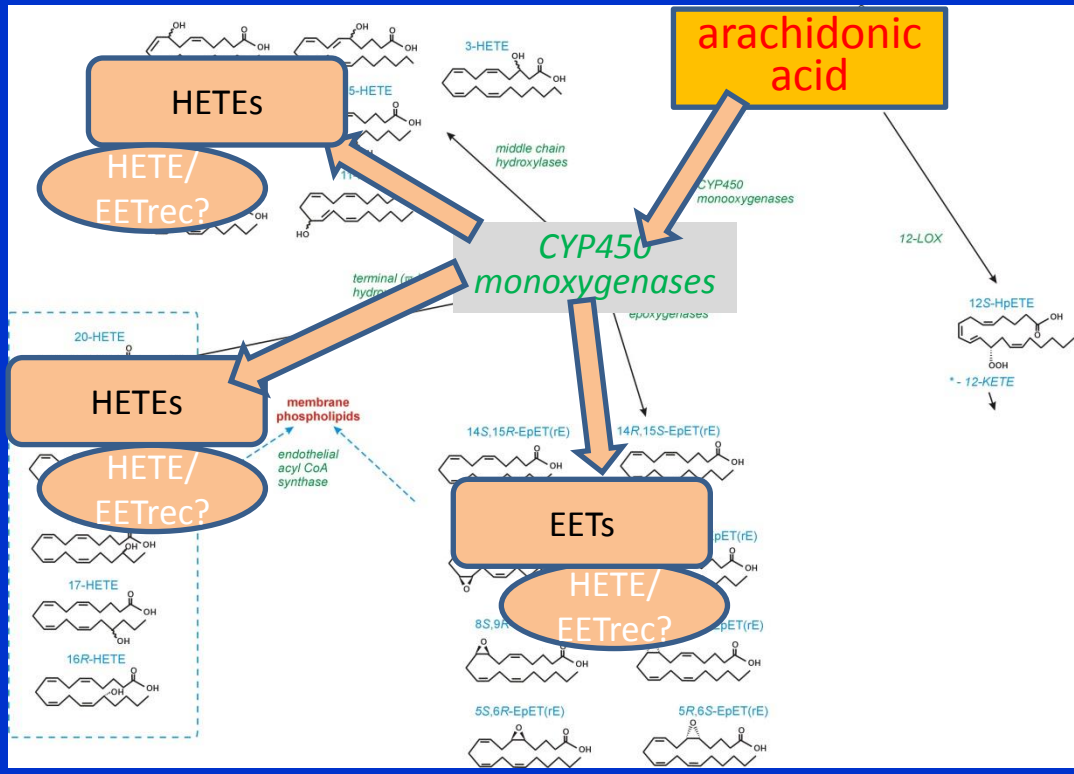
CYP450 monooxygenases products from arachidonic acid

AA is transformed via monooxygenases

ion transport regulation
vascular tone?
renal/lung function

hypertension?

cancer progression?



NSAIDS

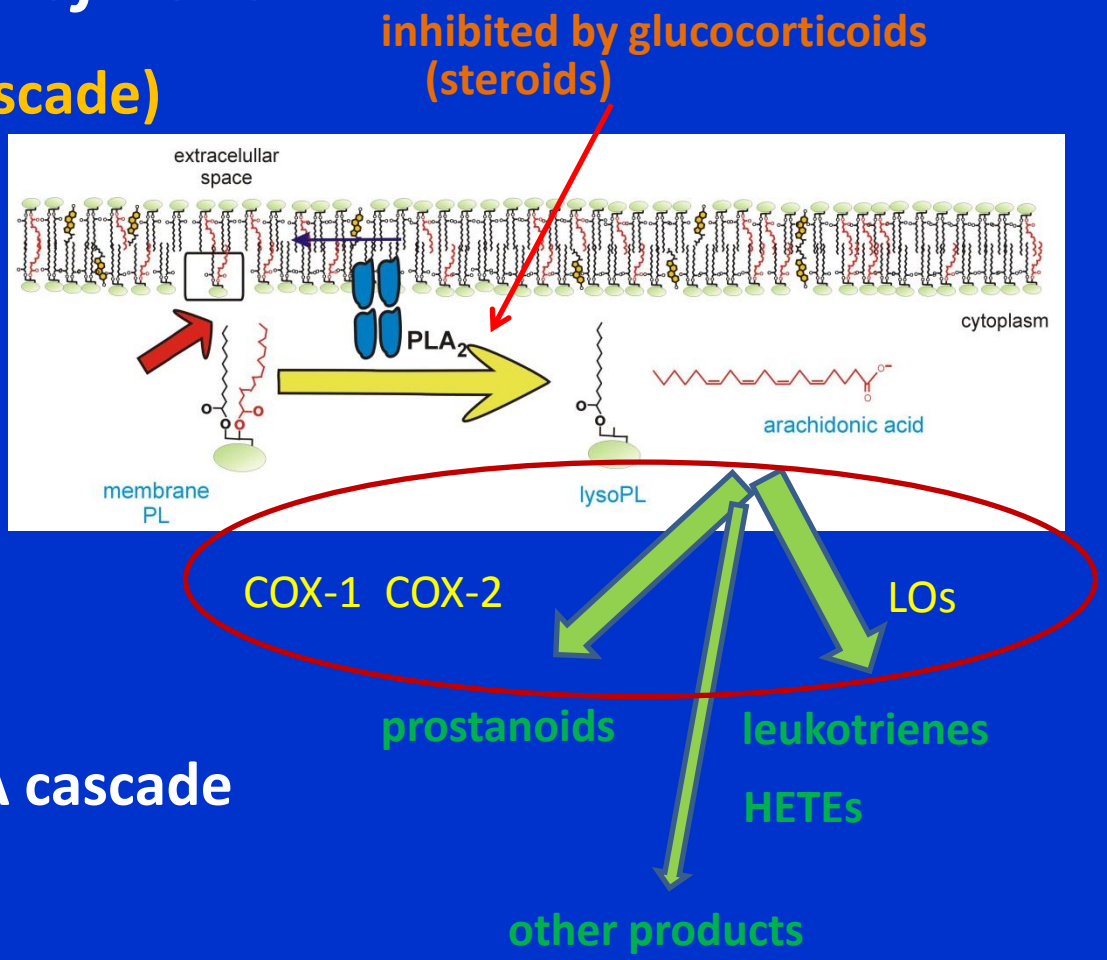
Non-steroidal inhibition of COXs

Arachidonate pathway (cascade)

AA must be released from PL by PLA_2

free AA is metabolized

NSAIDs:
act on distal part of the AA cascade



NSAIDS

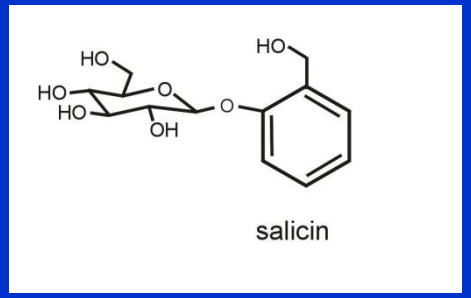
Non-steroidal inhibition of COXs

types of NSAID

1. Irreversible inhibitors

aspirin: acetylation of COXs serine530 (1971 Vane et al.)

→ AA cannot reach the active site of COXs



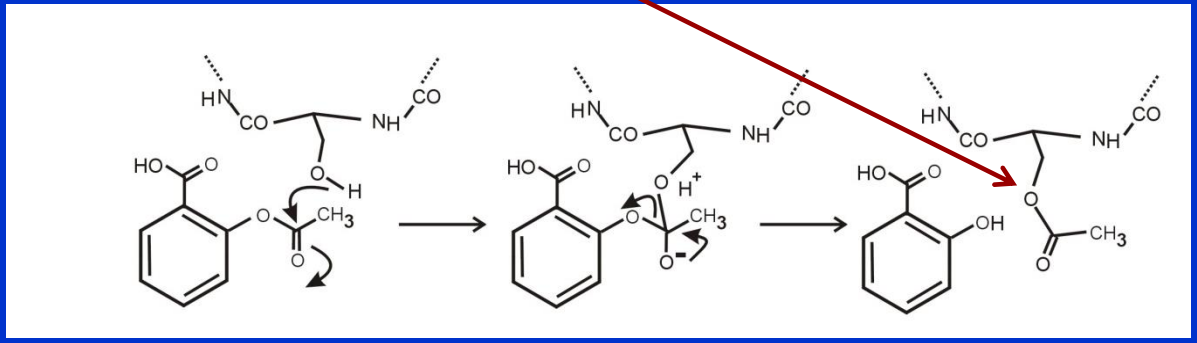
ancient Egypt: treating fever with bark of willow

1826-8 isolation of salicin

(bark of willow/poplar trees)

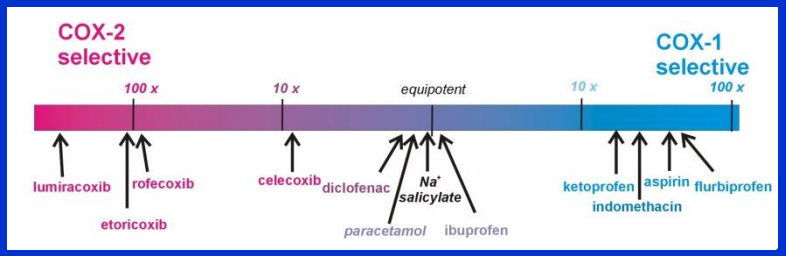
Aspirin:

better tolerated



NSAIDS

Non-steroidal inhibition of COXs



types of NSAID

2. reversible inhibitors of COX-1 and COX-2

competing with AA on the active site of enzymes

→ inhibition of all PG production

via COX-1 (→unwanted side effects):

including protective effect on GIT mucosa → ulcers (20% long-term)

(some are prodrugs not active in stomach → ulcers ↓)

via COX-2 (→beneficial effects):

inflammatory/fever/pain responses

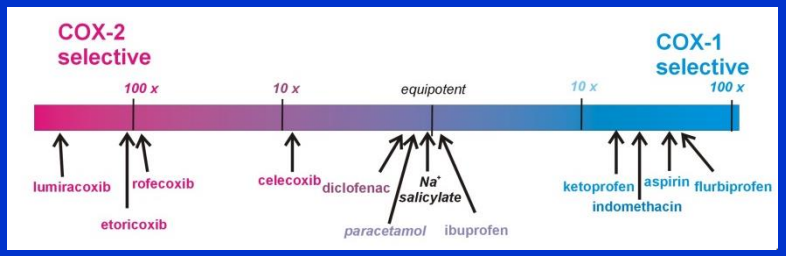
indomethacin, acetaminophen (not for inflammation)

some NSAIDs can also lower LO → LT↓

(some NSAIDs and antiinflammatory effects ↑ diclofenac)

NSAIDS

Non-steroidal inhibition of COXs



types of NSAID

3. reversible inhibitors of COX-2 (coxibs)

COX-1 isoenzyme is affected only marginally

rofecoxib, celecoxib

→ only inducible effects of COX products are inhibited

by inflammation… (not brain/kidney)

- platelets (COX-1) ↛ TxA2 production ↑ (some coxibs and MI ↑)

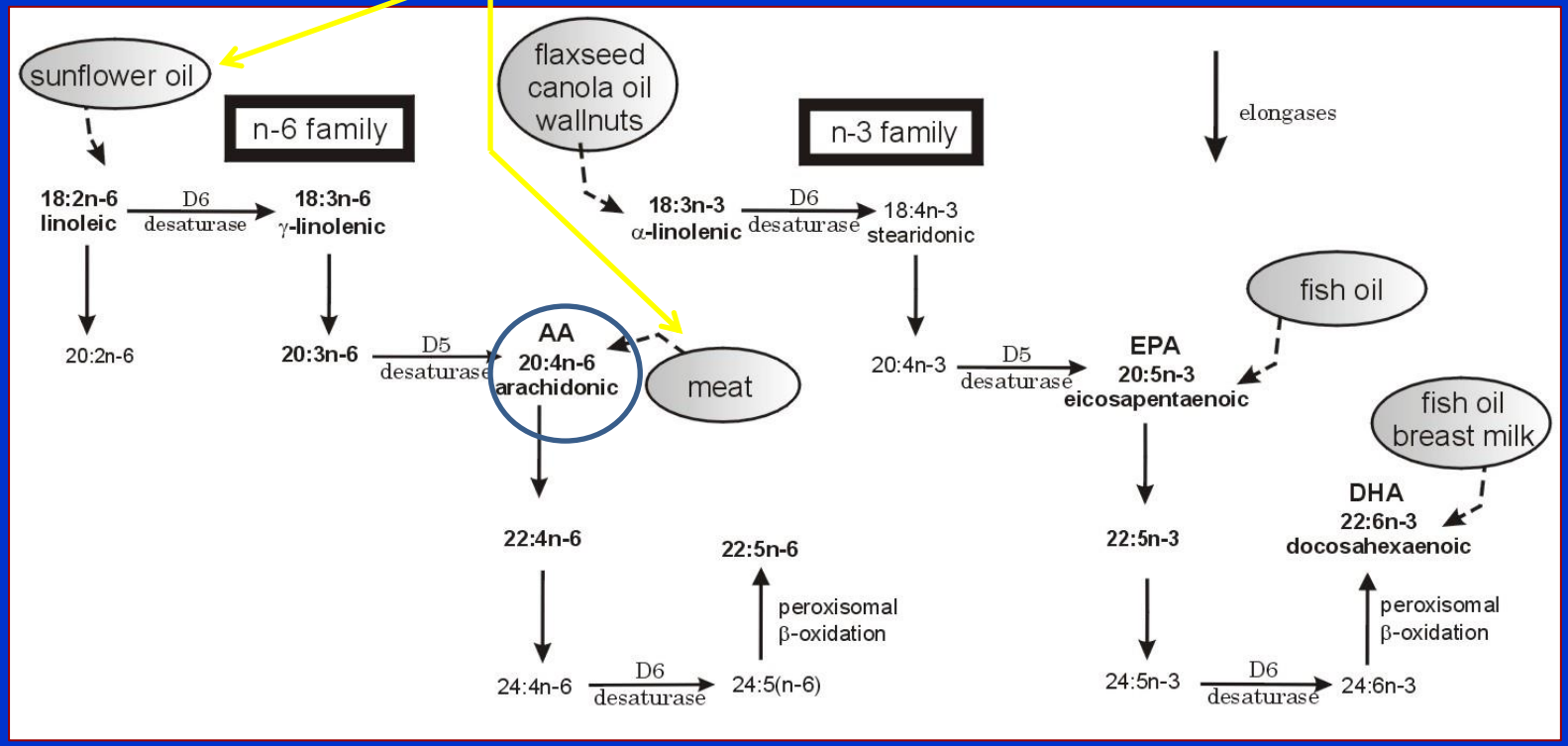
- effects on brain? (for those crossing BBB)

ESSENTIALITY OF FA

AA vs ALA/EPA/DHA

arachidonic acid (AA) is main precursor for eicosanoids in human

comes from dietary sources



EICOSANOIDS

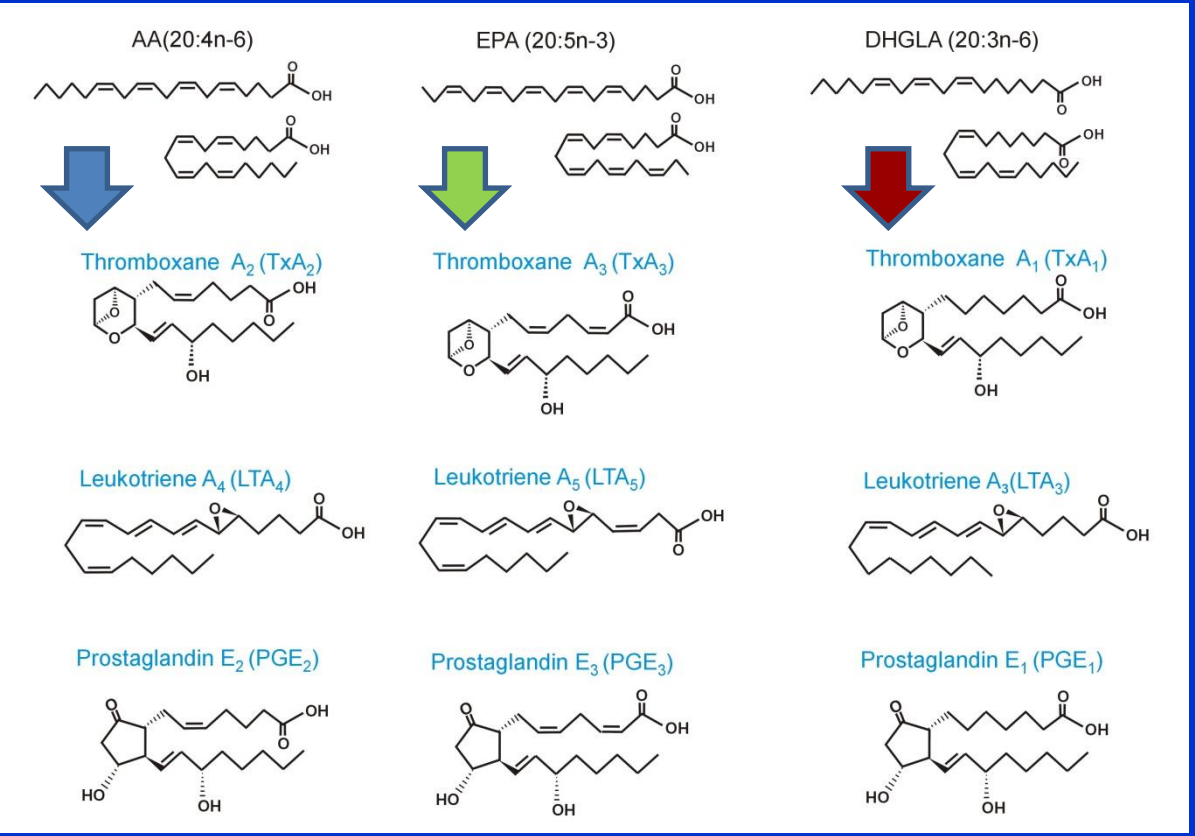
Oxylipins derived from 20 C fatty acid precursor

arachidonic acid (AA) is not sole substrate for the enzymes

other eicosanoids from

eicosapentaenoic acid EPA, (20:5n-3)

dihomo-γ-linolenic acid DHGLA, (20:3n-6)

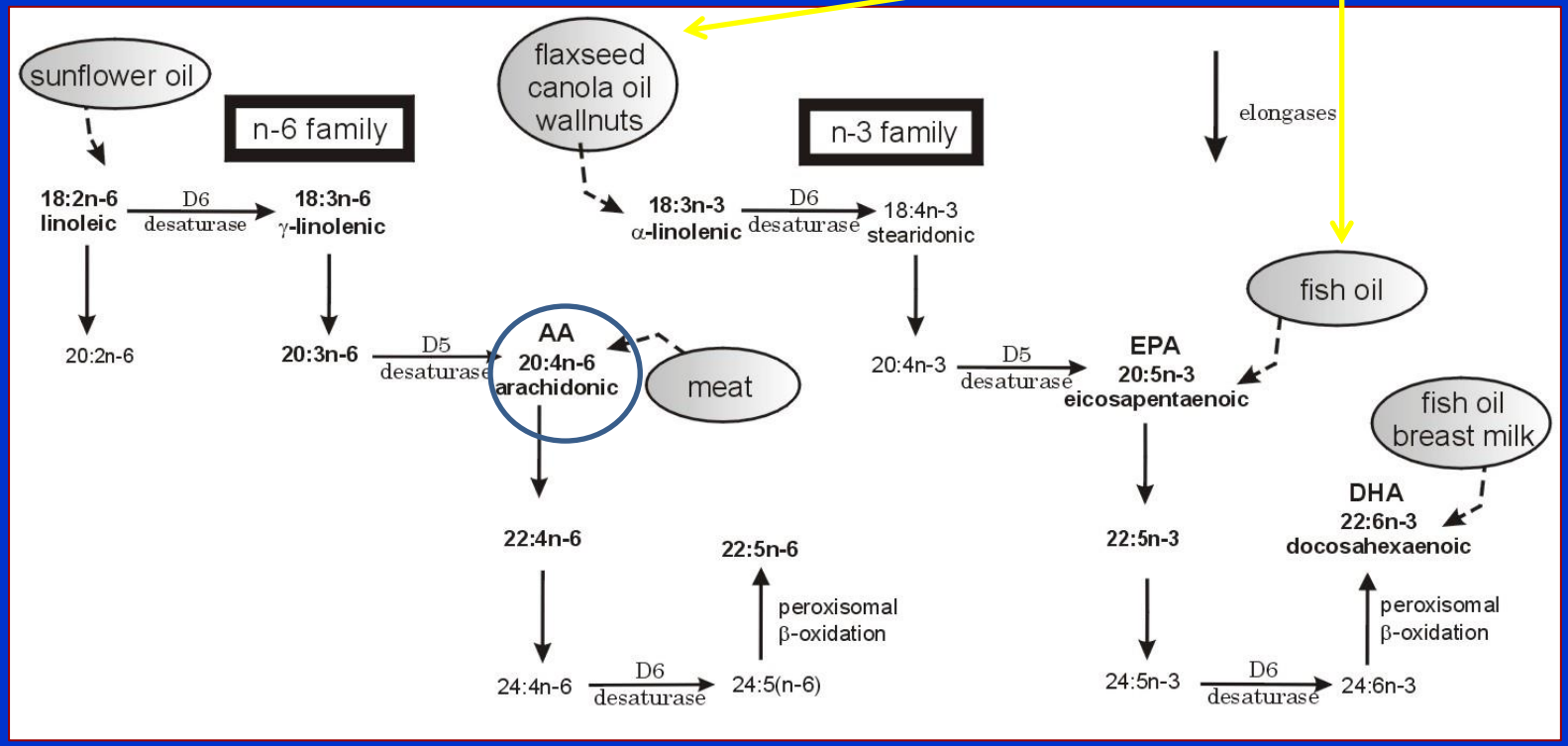


EICOSANOIDS II

Eicosanoids formed from other FA than AA

eicosapentaenoic acid (EPA) can be also precursor for eicosanoids in human

also comes from dietary sources

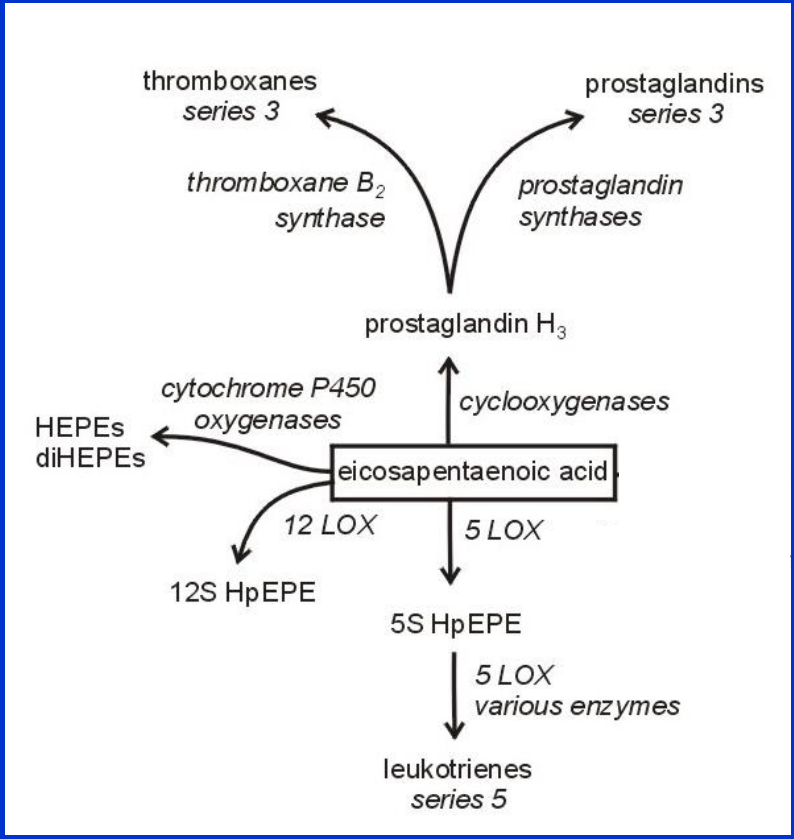


EPA EICOSANOIDS

EPA analogues of AA metabolites

Thromboxanes series 3
vasodilatating
Prostaglandins series 3
antiarrhytmic
antiinflammatory
Leukotrienes series 5
antiinflammatory

beneficial effects of EPA

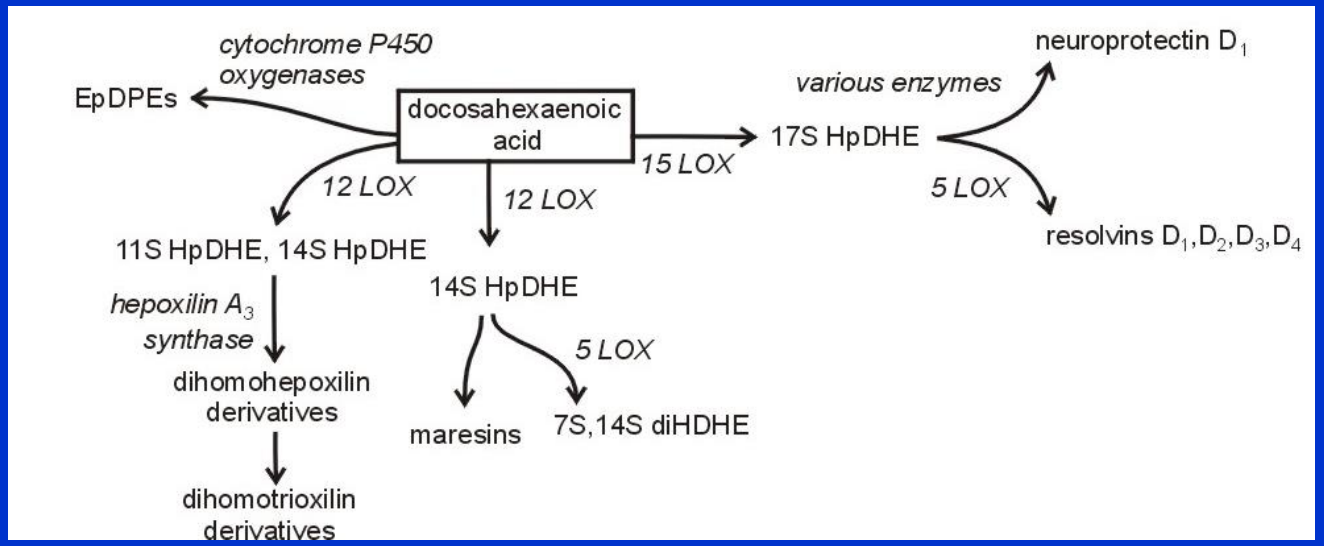


DOCOSANOIDS

Oxylipins derived from DHA

DHA is not a substrate for COX (unless aspirin acetylated)

Neuroprotectins (neuroprotective effects)
antiinflammatory mode of action
→ resolution of inflammation (**resolvins**)



EFFECTS OF PUFAn-3

Oxylipins derived from DHA, EPA are beneficial

DHA, EPA are essential FA

I. dietary sources

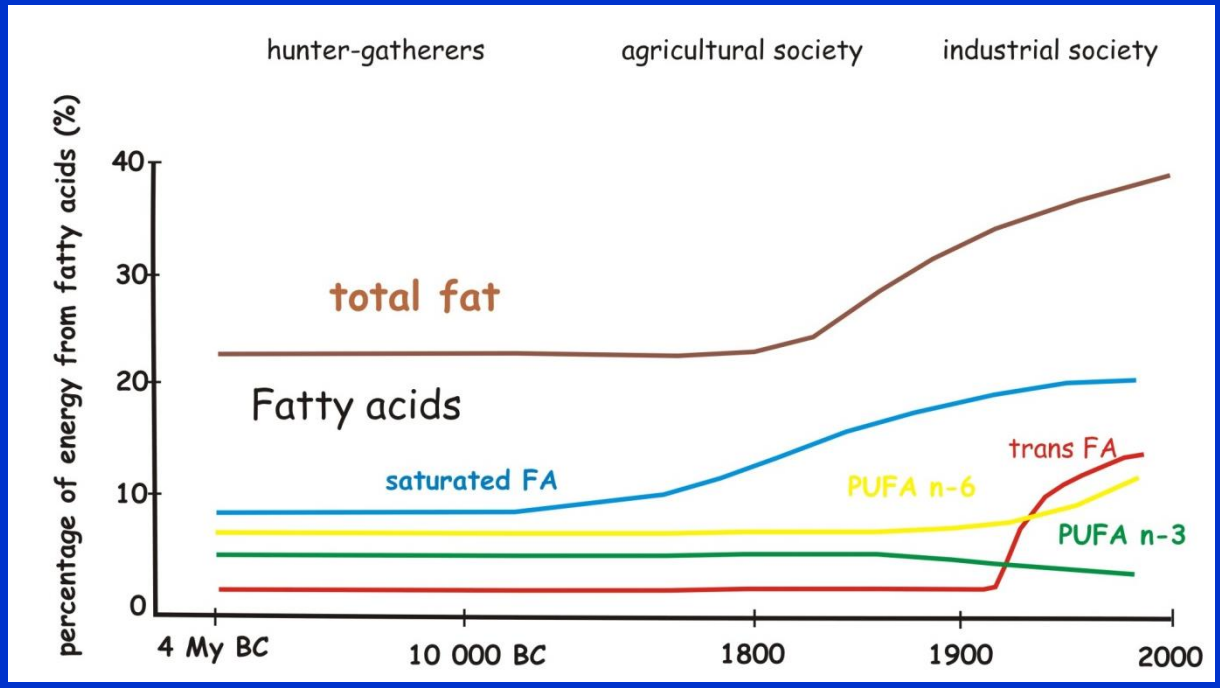
recommended ratio (PUFAn-6/PUFAn-3)

1-4/1

typical western diet:

14-25: 1

II. supplementation



NONENZYMATIC PRODUCTION OF OXYLIPINS

***FA bound in PL* are oxidized nonenzymatically**

Relatively high ROS (oxidative stress)

→ attack of C=C in PUFA-PL (-OOH, =O, -OH)

→ cyclizations, fragmentations

(some further reaction can be enzymatic)

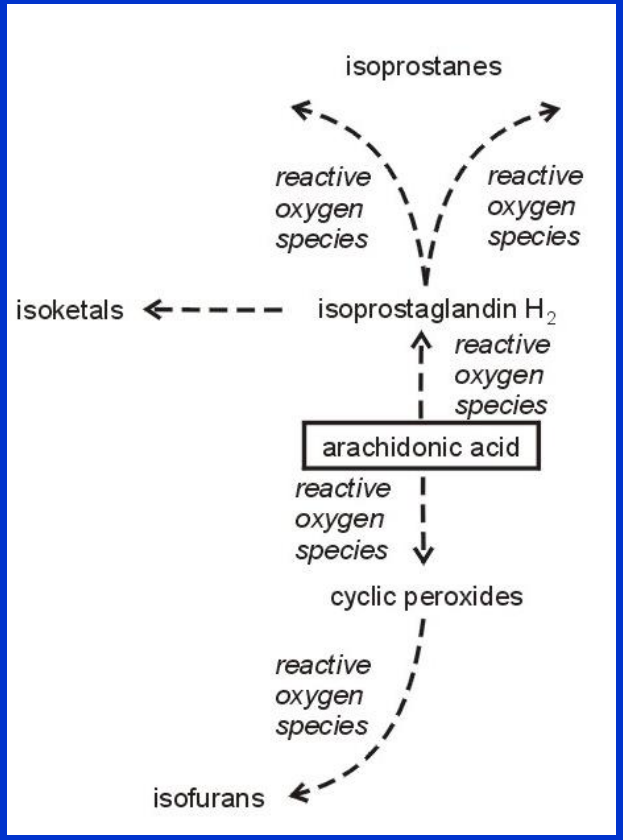
arachidonic acid → isoprostanes series 2

eicosapentaenoic acid → isoprostanes series 3

linoleic acid → HODEs

docosahexaenoic acid → neuroprostanes

indicators of oxidative stress



Further reading

Textbooks, monographs

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