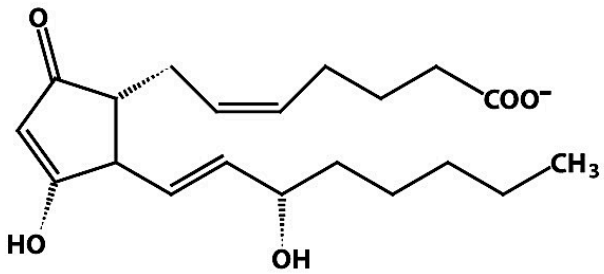
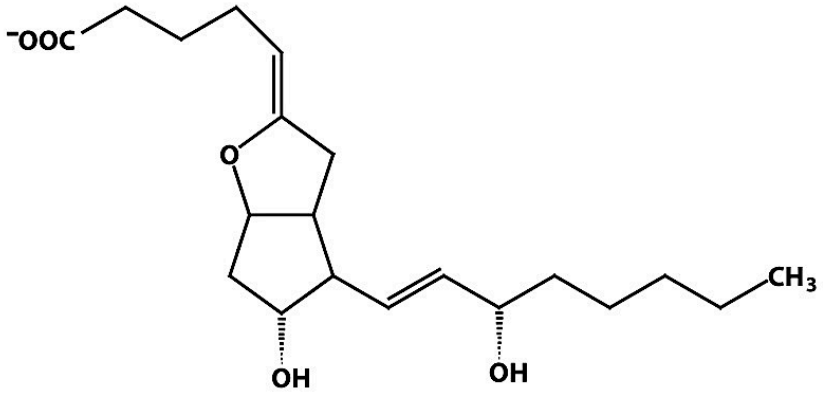
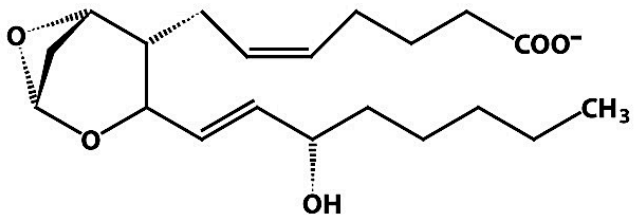
Eicosanoider



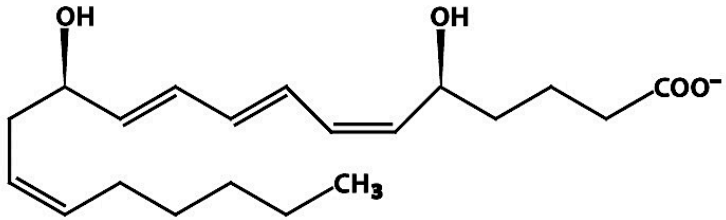
Prostaglandin E_2



Prostacyclin (PGI_2)



Thromboxane A_2 (TXA_2)



Leukotriene B_4

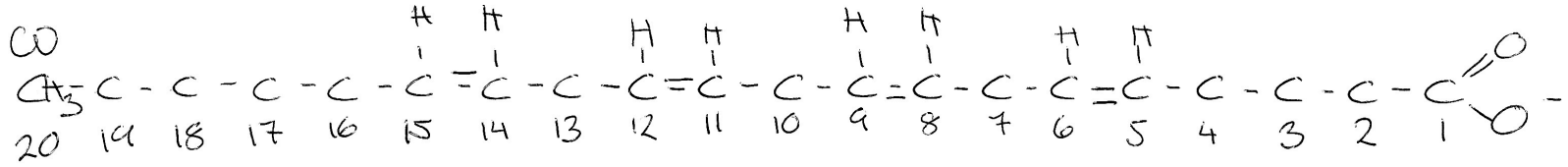
Table 1. Role of Prostaglandins in Tissue Functions

Stomach
Mucous secretion
Bicarbonate secretion
Phospholipid layer
Mucosal circulation
Mucosal re-epithelialization
Leukocyte margination
Hemostasis
Platelet aggregation
Vessel wall adhesion
Kidney
Modulate renin production
Modulate renal blood flow
Vasodilation (PGE_2, PGI_2)
Vasoconstriction (Thromboxane A_2)
Affect sodium and water resorption in the medulla
Reproduction
Contribute to ovulatory cycle
Role in pregnancy
Inflammation
Vasodilation
Vascular permeability
Sensitizes nerve receptors to other inflammatory mediators
Fever

Adapted with permission from *Inflamm Res.*[9]

ESSENTIELLA FETTSYROR = Fettsyror med dubbelbindning bortom kolatom nr 9

Exempel: Linolenic acid 18:3 $c\Delta^{9,12,15}$



20:4 cis $\Delta^{5,8,11,14}$

ARACHIDONSYRA

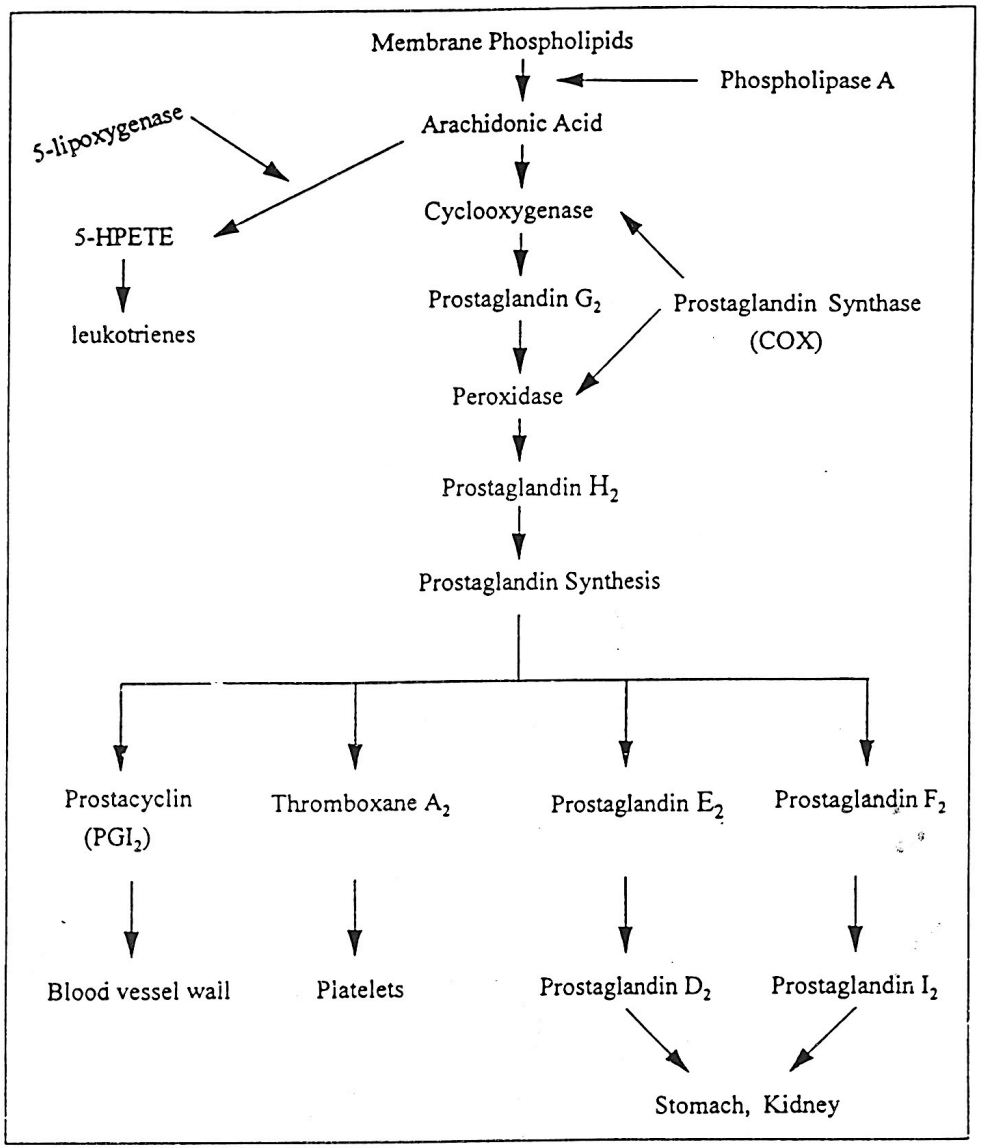
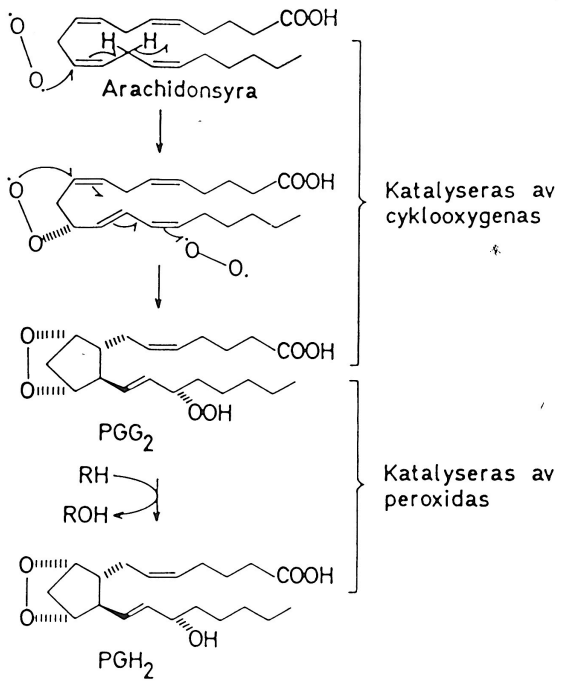


Figure 1. Prostaglandin production from arachidonate using cyclo-oxygenase (prostaglandin H synthase) enzymes.



PGH SYNTAS = bifunktionellt enzym med 2 katalytiska site

1. Cyklooxygenas = COX
2. Peroxidas

<u>COX</u>

1. Väteeliminering vid kolatom 13 samt introduktion av molekylärt syre vid kolatom 11
2. Bildning av endoperoxidbrygga mellan kolatom 9 och 11
3. Bildning av en bindning mellan kolatom 8 och 12 vilket leder till en cyklopentanring
4. Bildning av en hydroperoxidgrupp genom introduktion av ytterligare en syremolekyl vid kolatom 15

$\Rightarrow \Rightarrow \Rightarrow$ bildning av den instabila produkten PGG_2

<u>Peroxidas</u>:

1. Reduktion av hydroperoxidgruppen vid kolatom 15 $\Rightarrow \Rightarrow \Rightarrow$ PGH_2

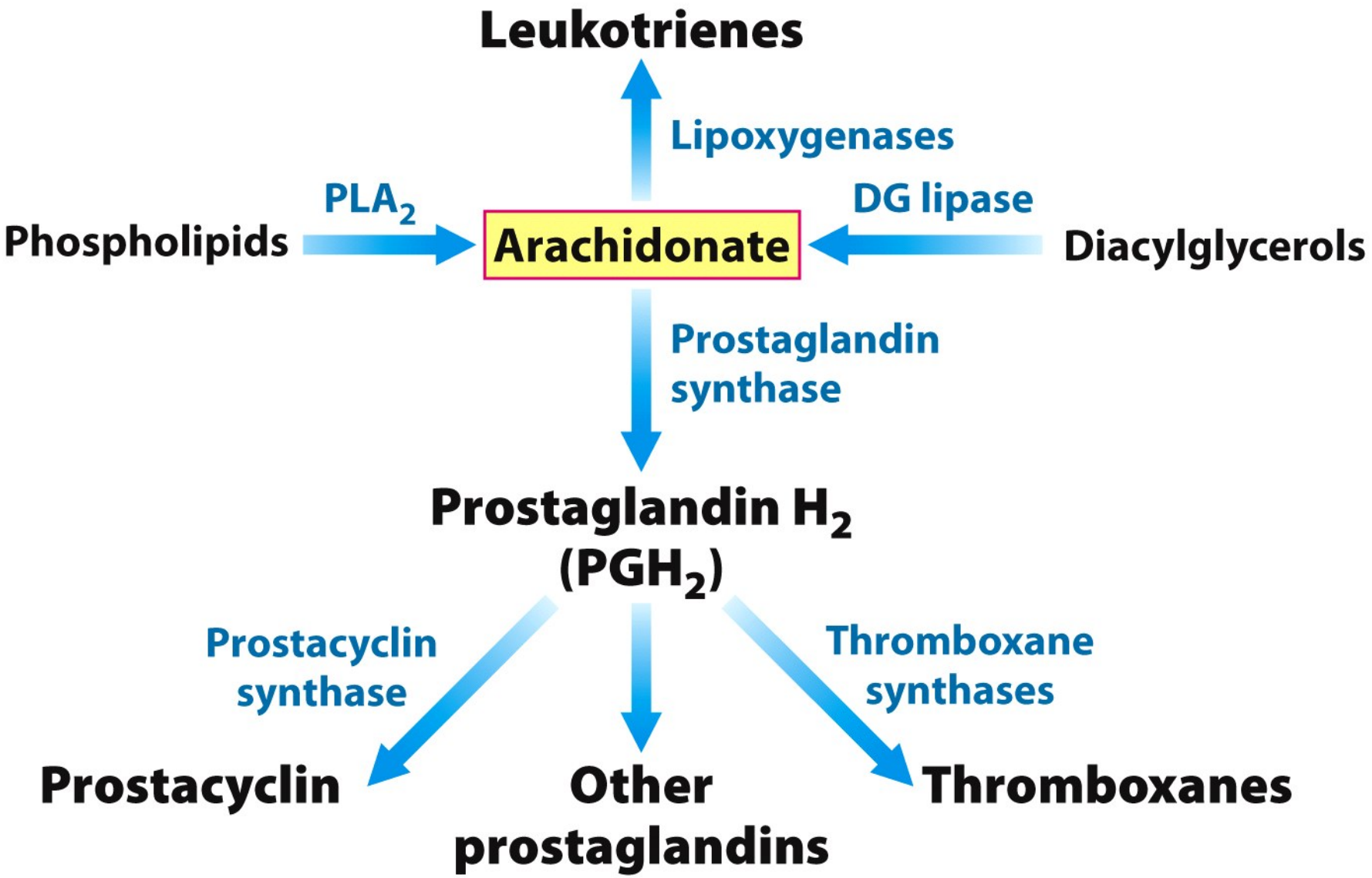


Figure 22.32
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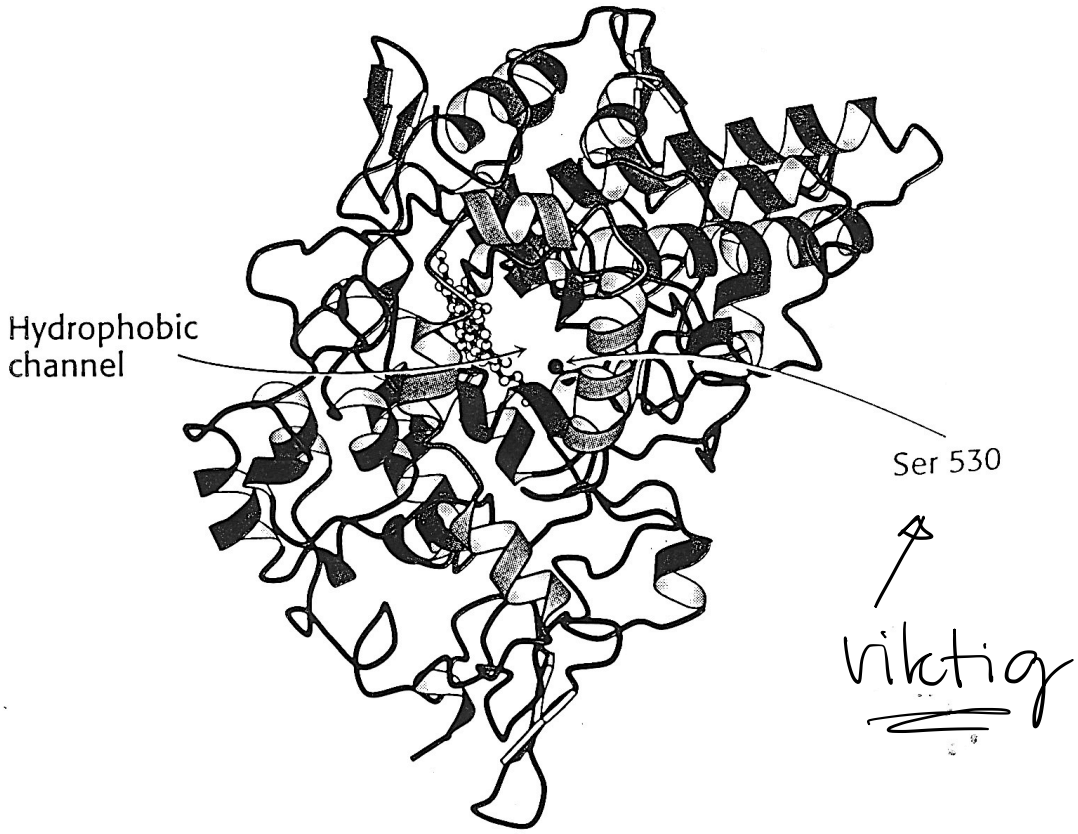
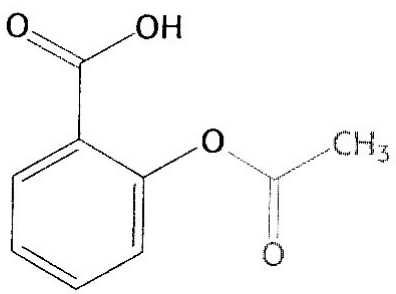

Hydrophobic
channel
Ser 530
viktig

hindrar bildandet av prostaglandiner etc.

kan förklara nästan alla anti-inflammatoriska preparats verkan.



Aspirin
(Acetylsalicyclic acid)

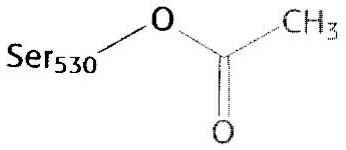


Figure 12.25 Aspirin's effects on prostaglandin H_2 synthase-1. Aspirin acts by transferring an acetyl group to a serine residue in prostaglandin H_2 synthase-1.

Table 2. Prostaglandin Endoperoxide H Synthase (COX) Isoforms: Differences

Feature	COX-1	COX-2
Gene	22 kb, chromosome 9 mRNA 2.8 kb	8 kb, chromosome 1 mRNA 4.3 kb (unstable)
Enzyme	70 KD membrane protein	70 KD membrane protein Unique 18 aa C-terminus
Location	Endoplasmic reticulum	Endoplasmic reticulum and nuclear envelope
Substrates	Arachidonate	Arachidonate and some similar fatty acids
Inhibition	Activity completely blocked	Produces 15-HETE

Table 3. Cyclo-oxygenase Isoenzymes

	Type 1	Type 2
Expression	Constitutive	Constitutively expressed only in brain
	Found in all tissues	Rapidly induced (1–3 h) in inflammatory tissue
		Induced by cytokines, growth factors (IL-2, TNF-α)
		Inhibited by anti-inflammatory cytokines (IL-10)
Functions	Housekeeping functions	Inflammatory process
	Platelet	Macrophages
	Stomach	Leukocytes
	Kidney	Fibroblasts
	Endothelium	Endothelium
		Apoptosis in tumor cells
Inhibition	Aspirin, NSAIDs	Aspirin, NSAIDs, glucocorticoids

NSAIDs = nonsteroidal anti-inflammatory drugs.