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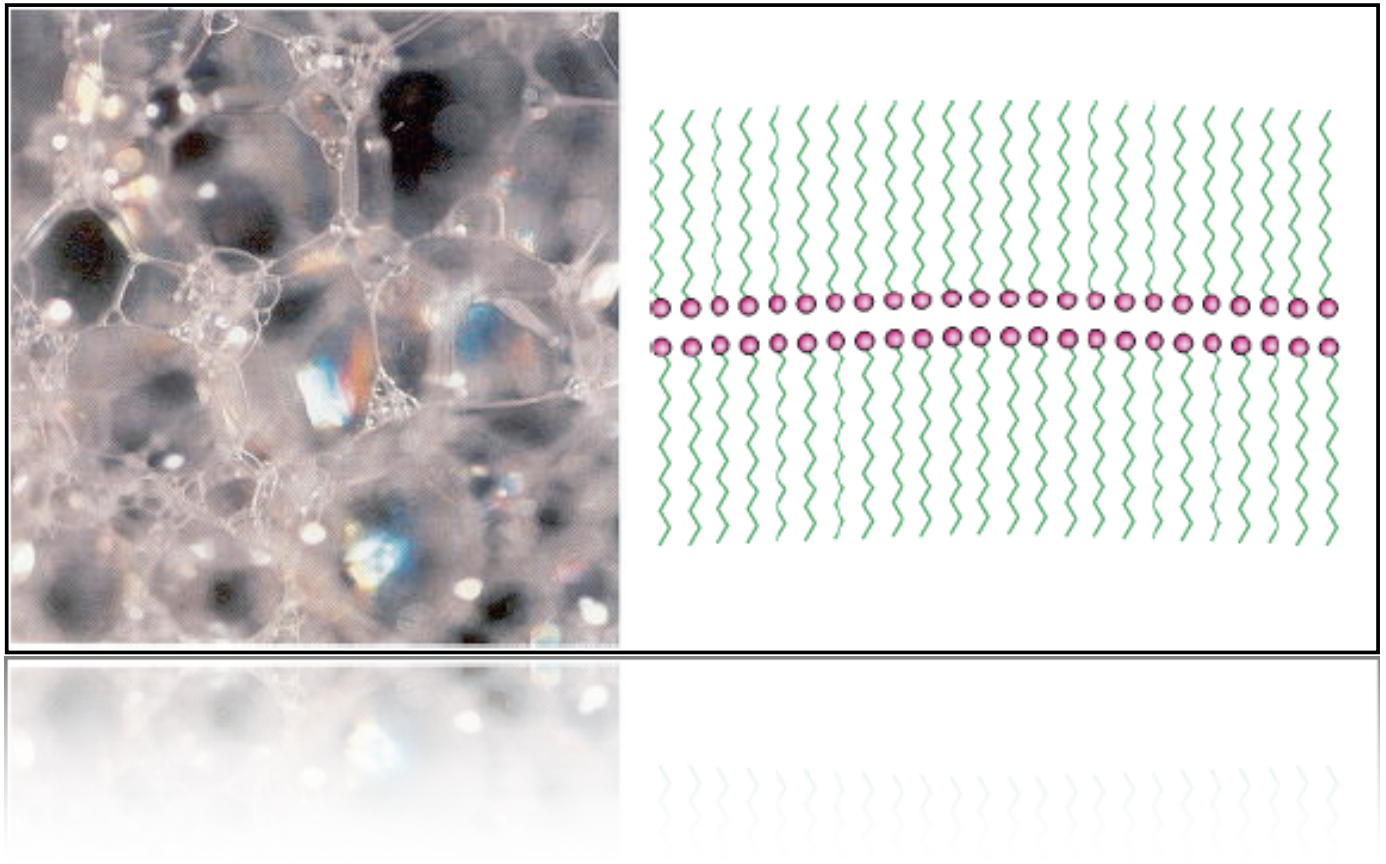
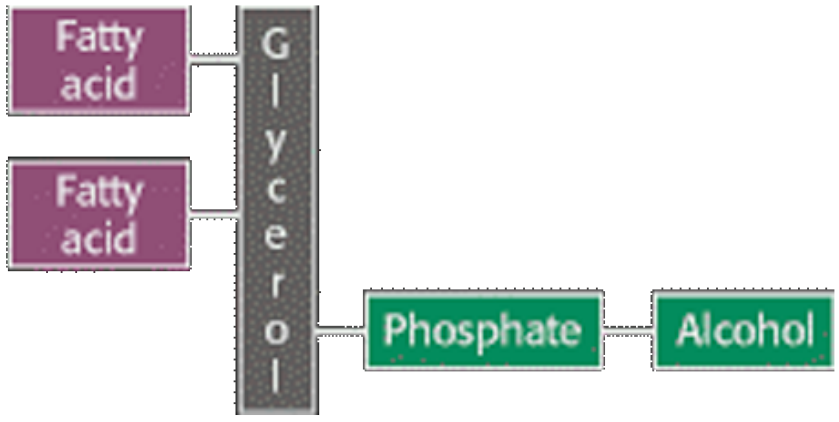
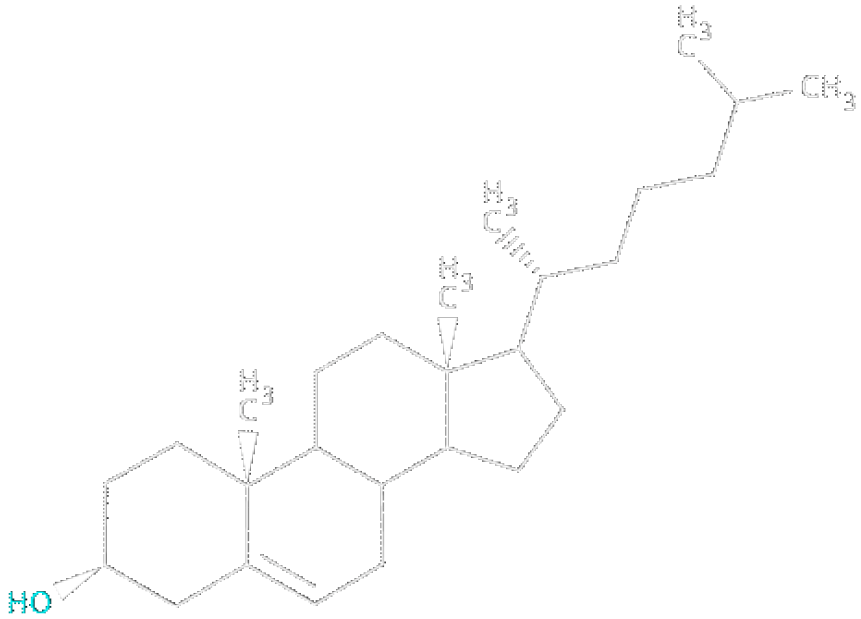
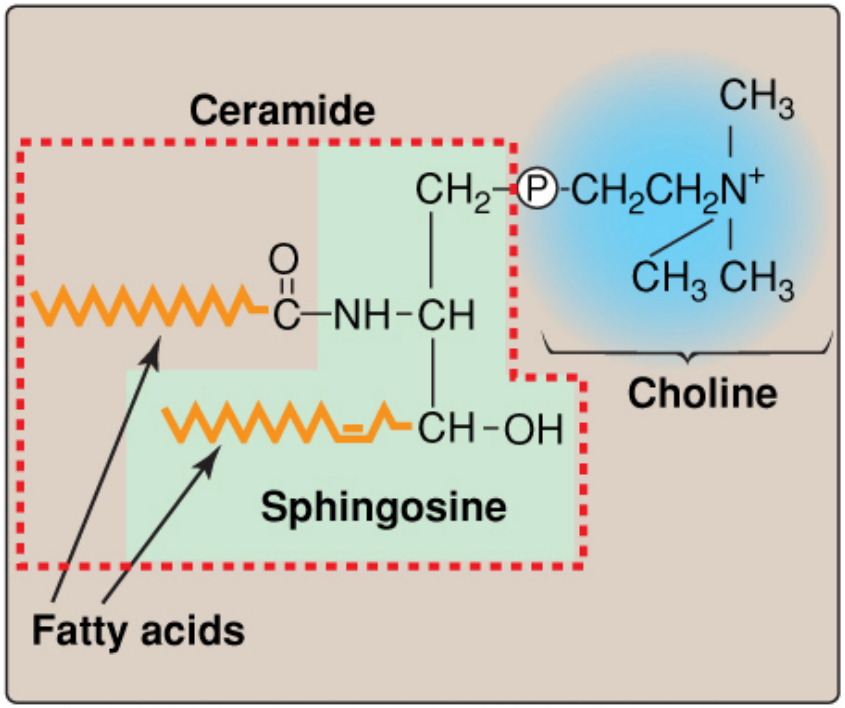


The surface of a soap bubble is a bilayer formed by detergent molecules

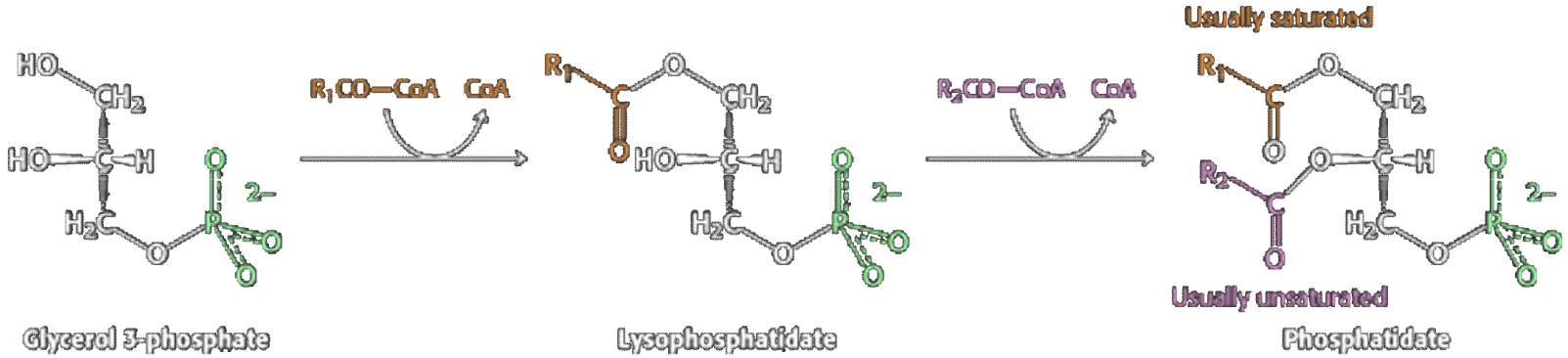






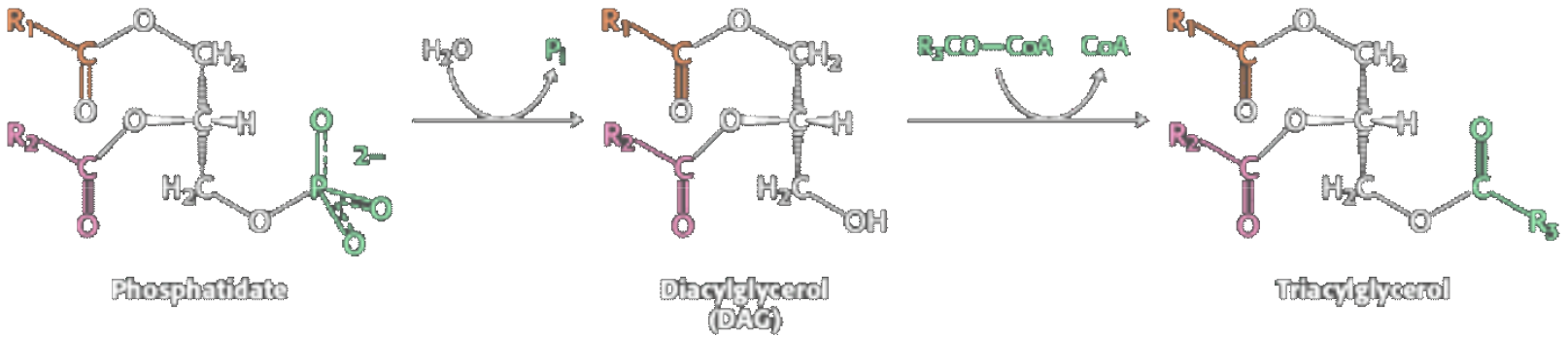
Chapter 17

Phospholipids are synthesized in the ER

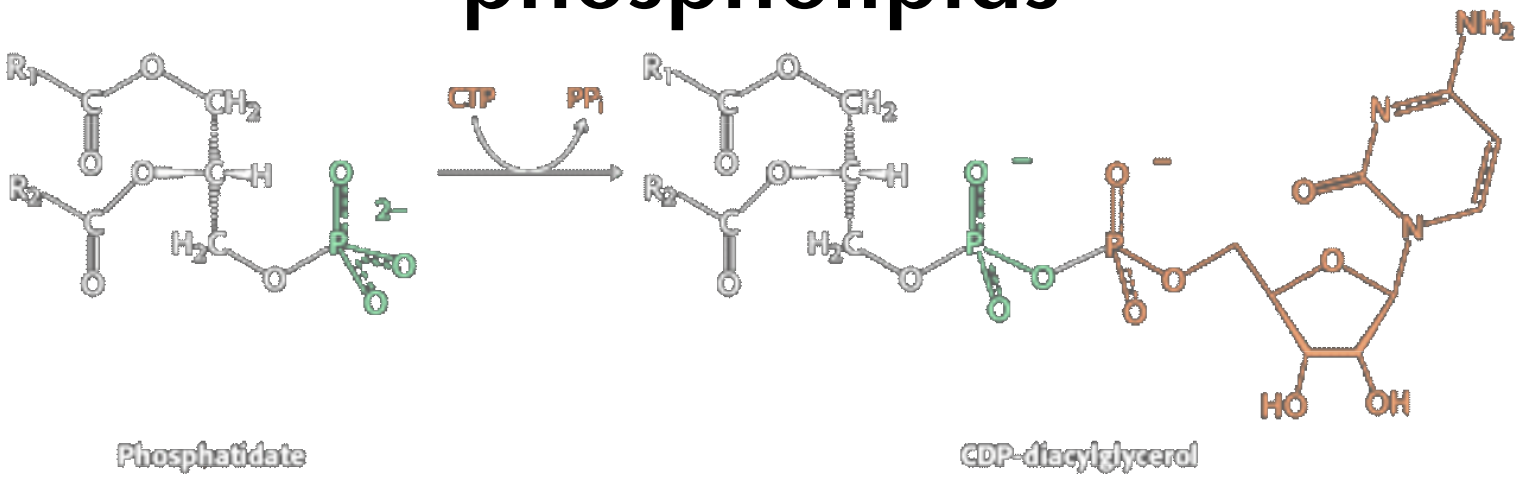


- The first step involves the synthesis of phosphatidate
- Glycerol 3-phosphate is acylated by acyl-CoA to form lysophophatidate, and acylated again by acyl-CoA to form phasphatidate

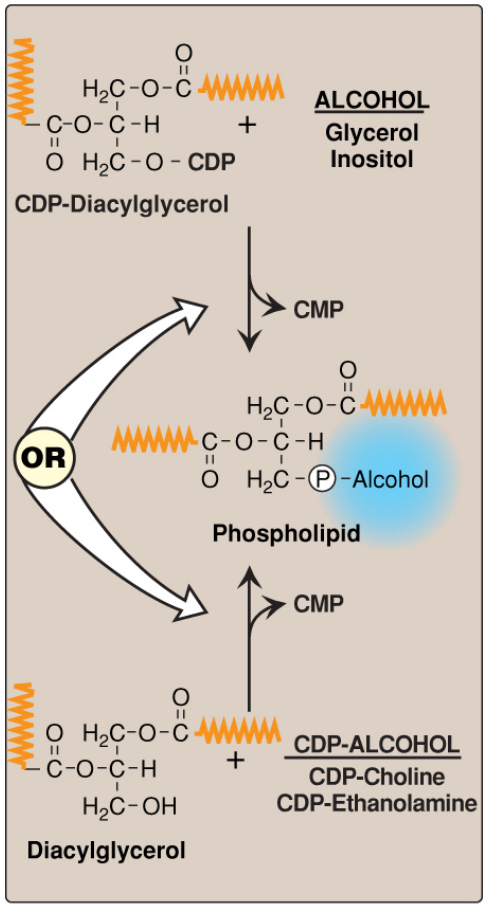
1) Phosphatidate can form triacylglycerol via *triacylglycerol synthetase* on the ER membrane

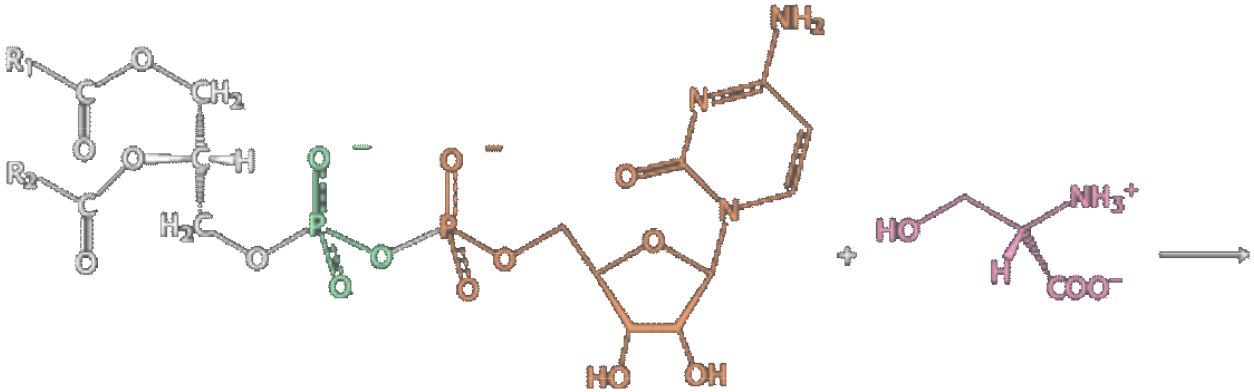


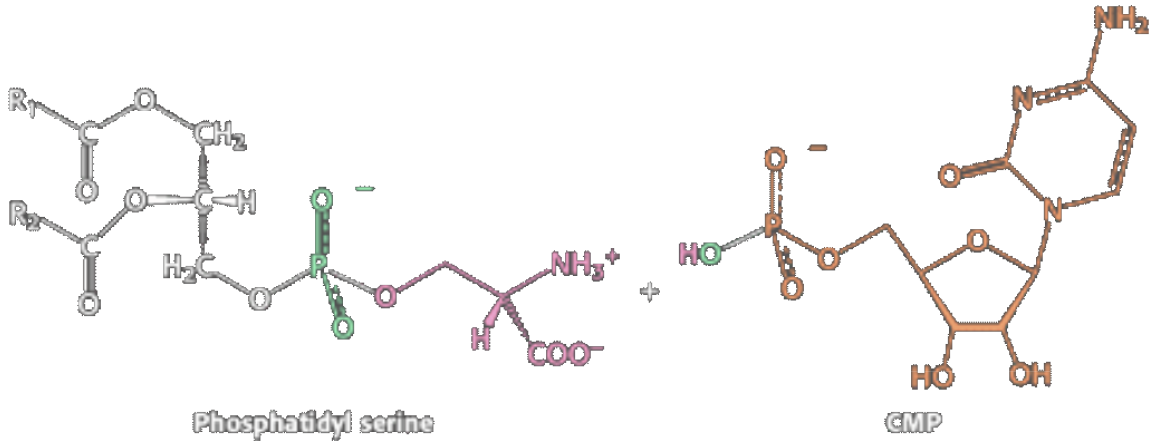
2) Phosphatidate can instead form phospholipids



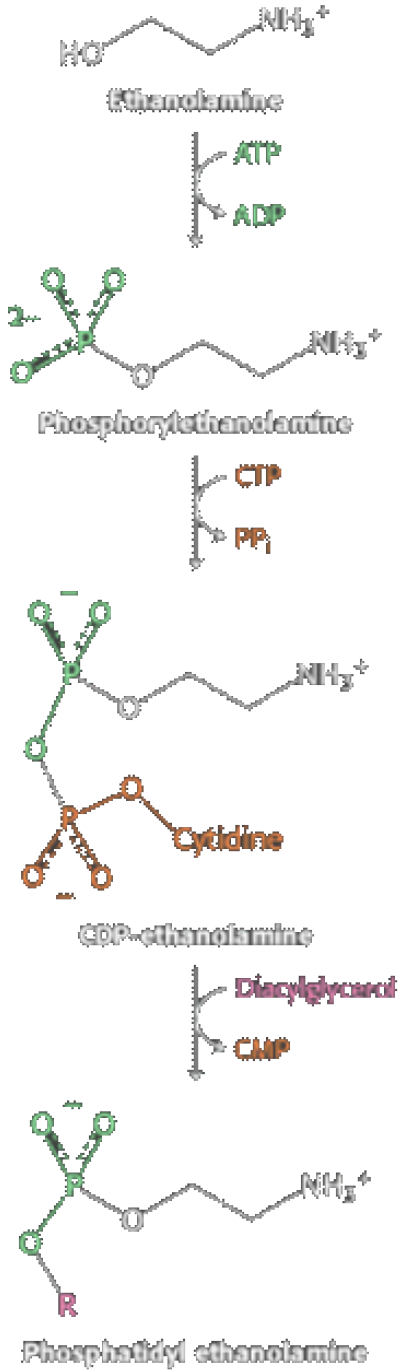
- The synthesis of phospholipids requires an activated intermediate (in this case, CTP is key).
- Many different alcohol-bearing compounds can react with CDP-diacylglycerol to form different types of phospholipids.





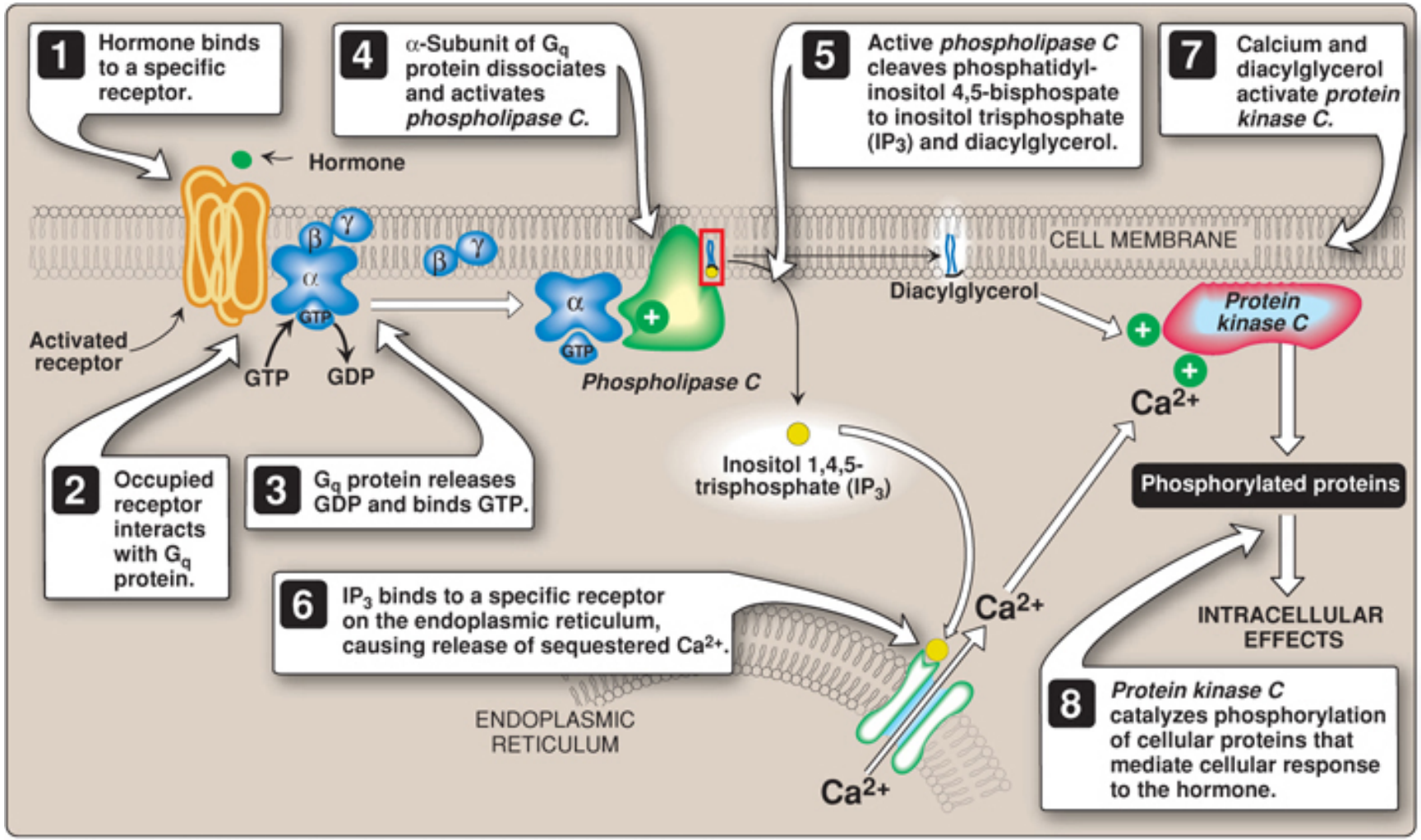


Serine	+ PA →	phosphatidylserine
Ethanolamine	+ PA →	phosphatidylethanolamine (cephalin)
Choline	+ PA →	phosphatidylcholine (lecithin)
Inositol	+ PA →	phosphatidylinositol
Glycerol	+ PA →	phosphatidylglycerol



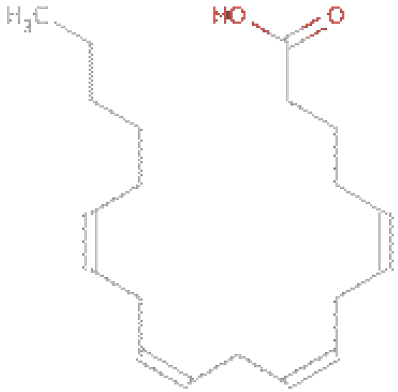
- The activation of either the phosphatidate or the alcohol partner by CTP represents the committed /rate-limiting step in phospholipid synthesis

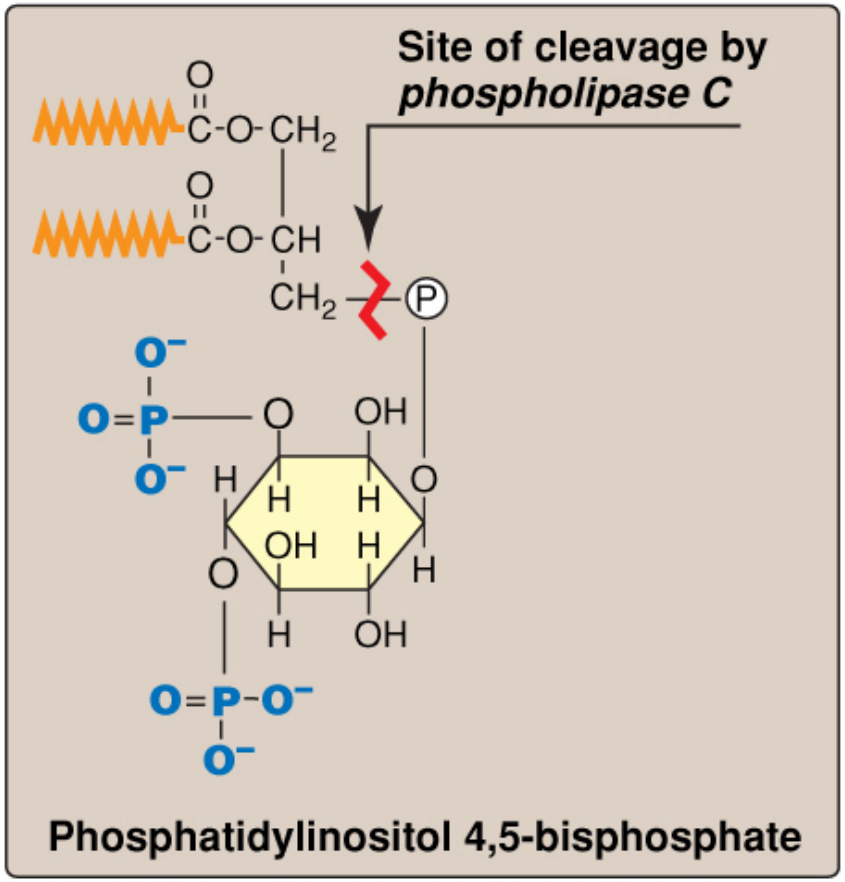
- Once again, the hydrolysis of PPi to inorganic phosphate makes the activation of these components irreversible.

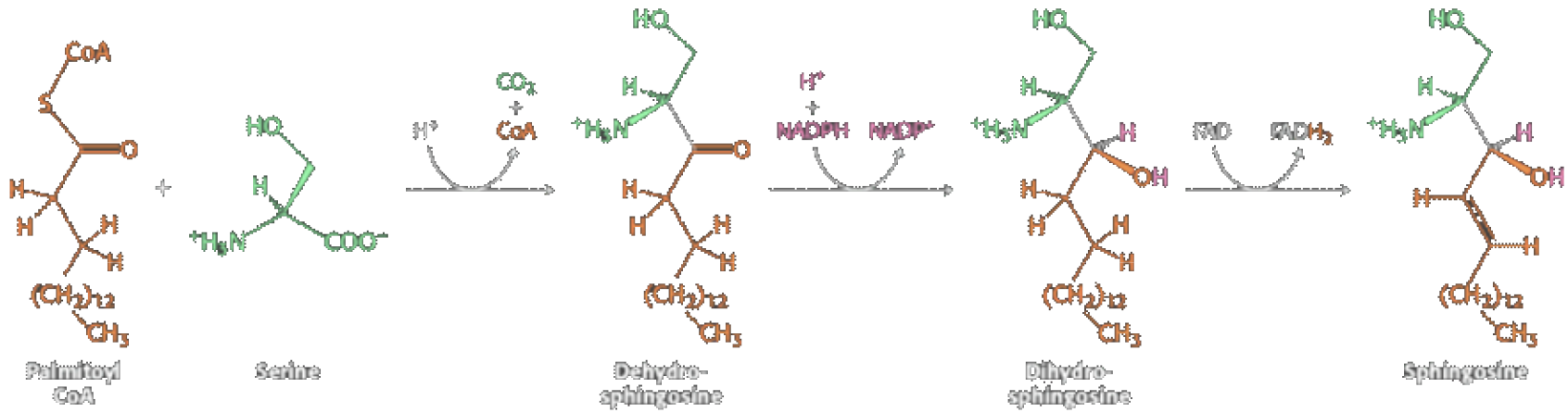


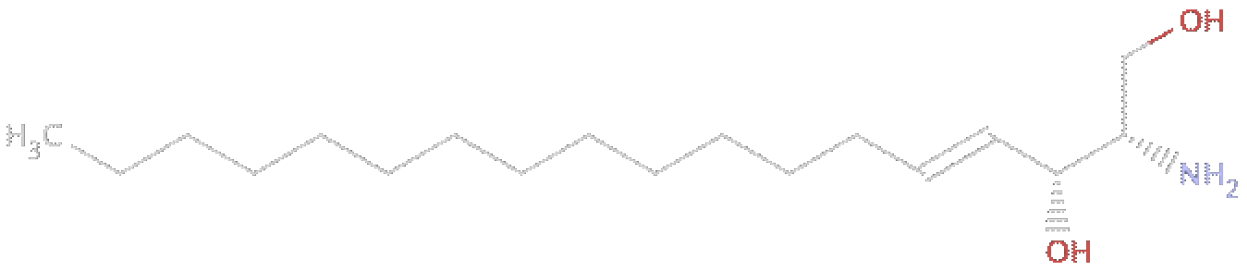
Stearic acid

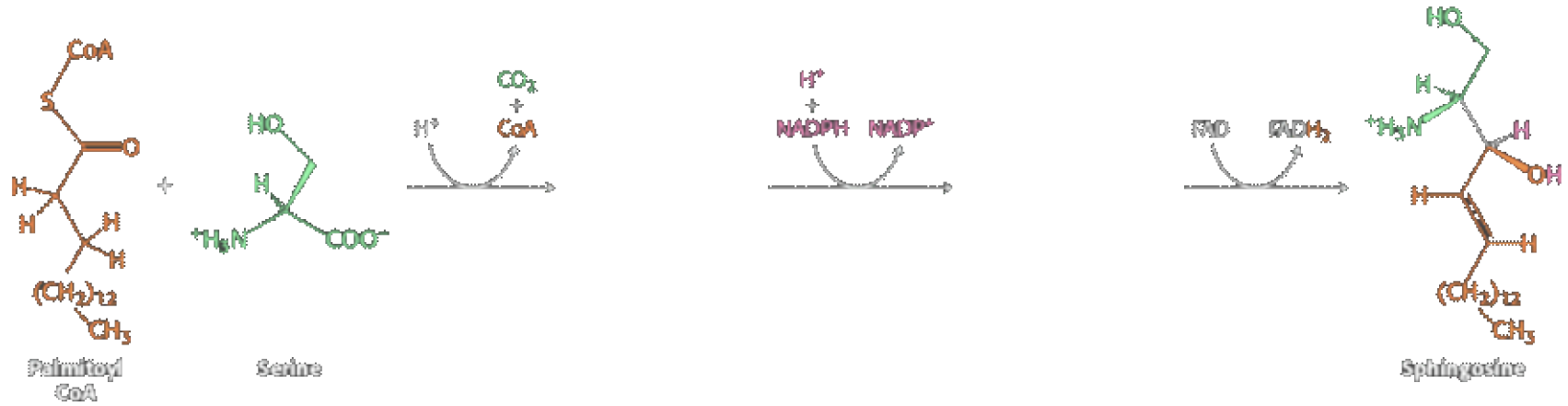
Arachadonic acid

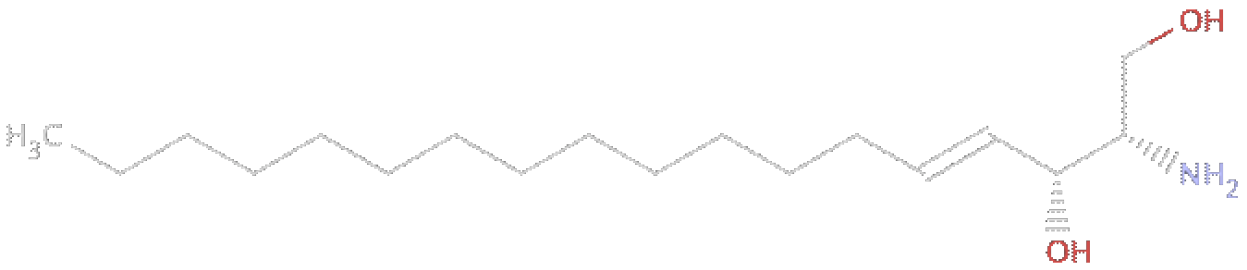




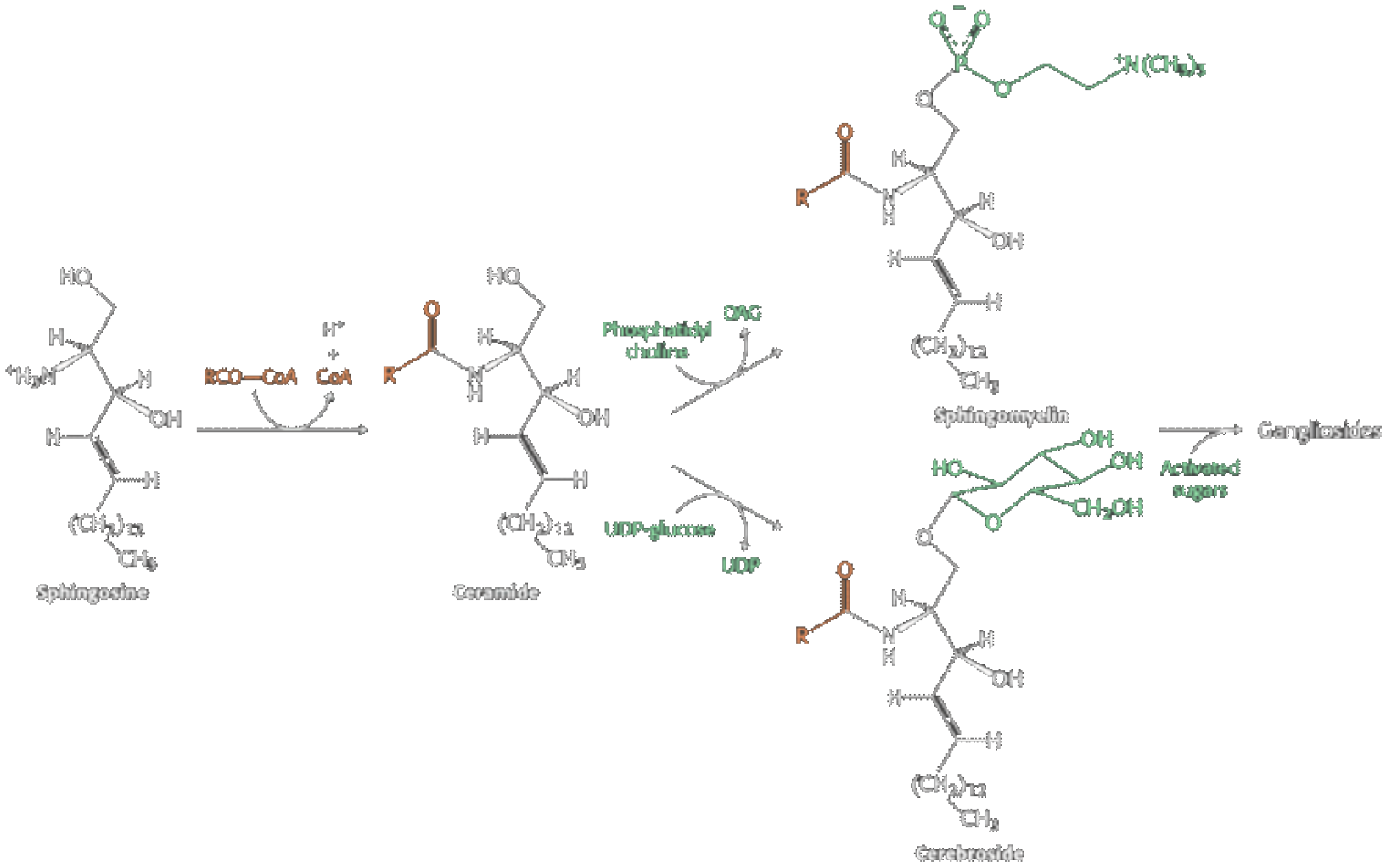

CoA
S
O
HO
H
^+H_3N
COO^-
CO_2
+
H+
CoA
NADPH
NADP+
FAD
$FADH_2$
OH
$(CH_2)_{12}$
CH_3
Palmitoyl CoA
Serine
Dehydro-sphingosine
Dihydro-sphingosine
Sphingosine

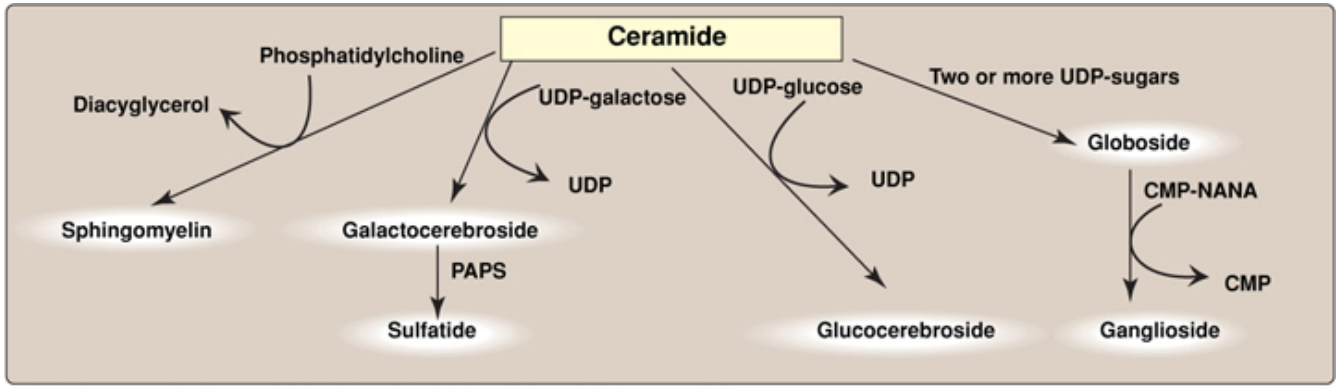

OH
H_3C
NH_2
OH

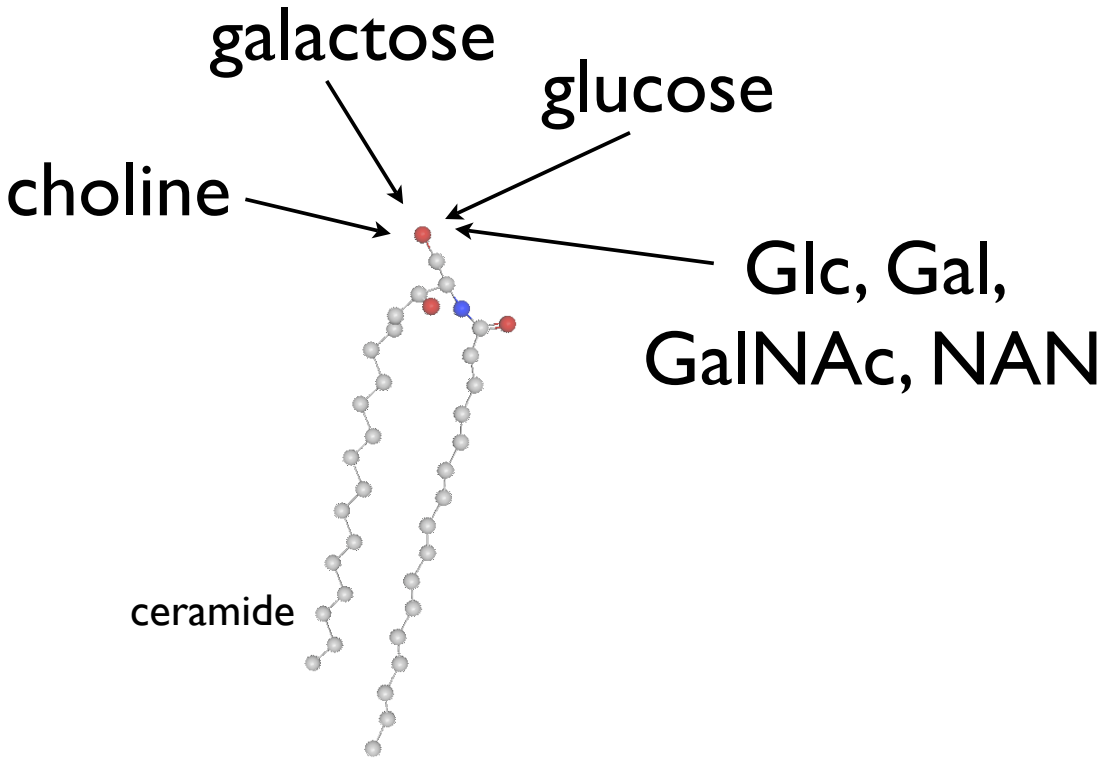

CoA
S
O
H
H
H
H
(CH2)12
CH3
Palmitoyl CoA
+
HO
H
+H3N
COO−
Serine
CO2
+
CoA
H+
H+
+
NADPH
NADP+
FAD
FADH2
HO
H
+H3N
H
OH
H
H
(CH2)12
CH3
Sphingosine

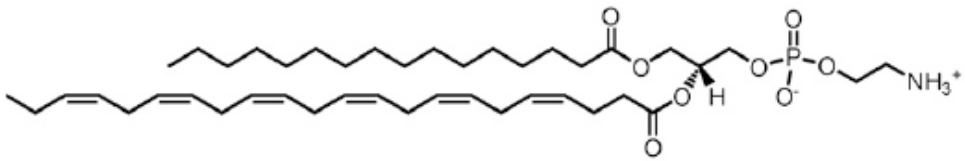

OH
H3C
NH2
OH

Ceramide is produced in the ER through acylation of sphingosine









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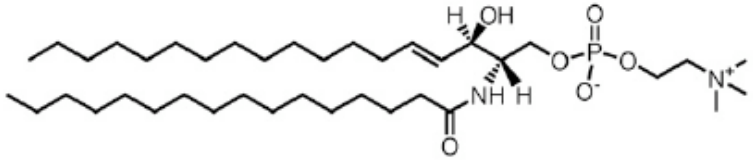
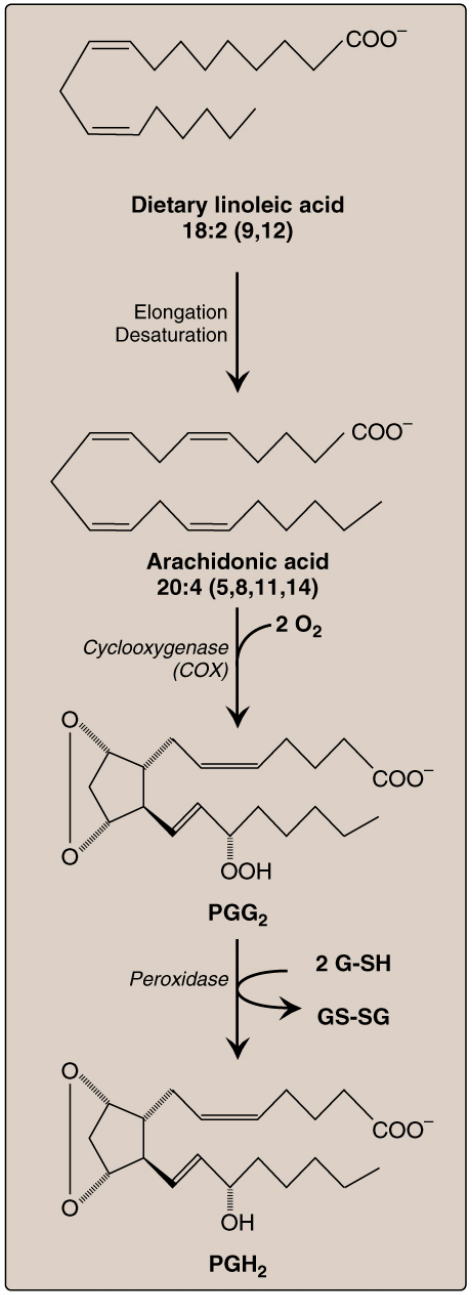
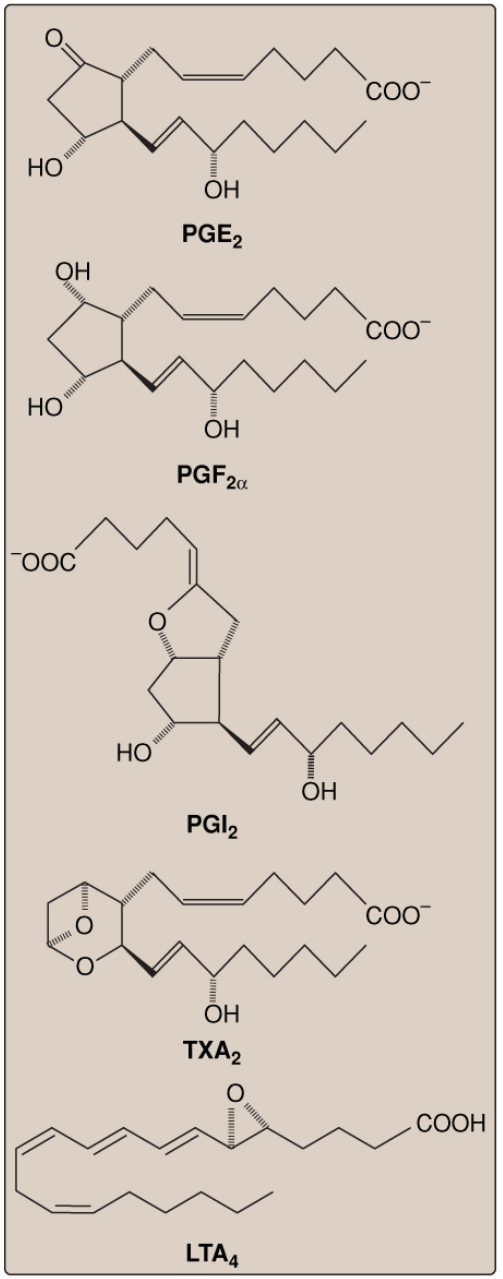


16:0SM

Eicosanoids are derived from long-chain fatty acids

- Eicosanoids are specialized signaling molecules derived from polyunsaturated fatty acids with twenty carbons: e.g. arachidonate (from linoleate)
- They are not secreted by a gland and do not circulate. Rather, they act locally at or near their site of synthesis.
  - Prostaglandins
  - Thromboxanes
  - Leukotrienes

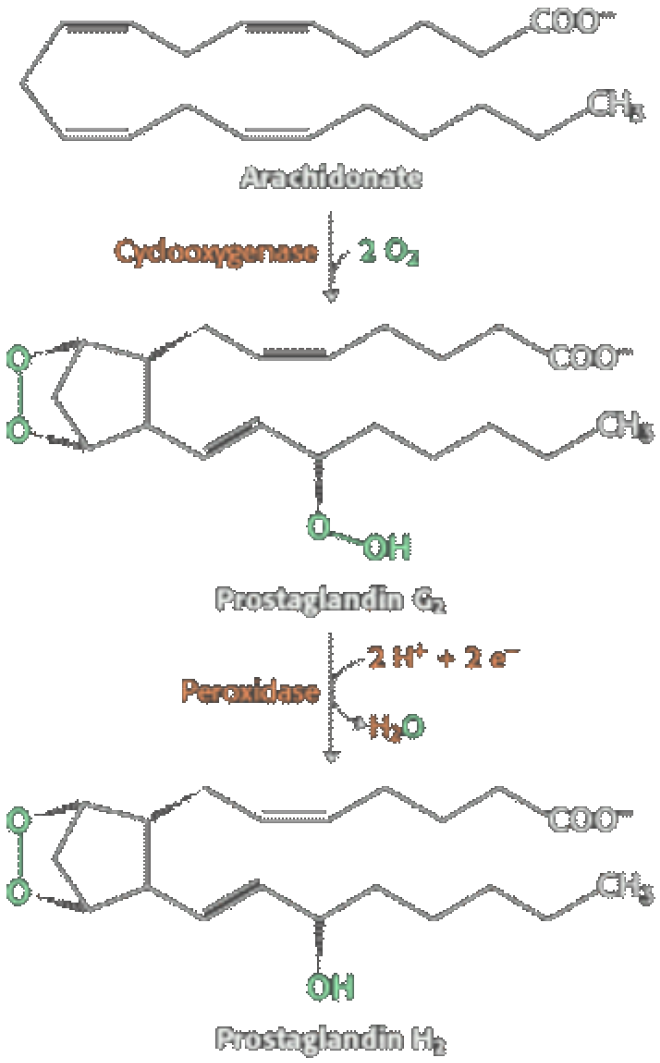




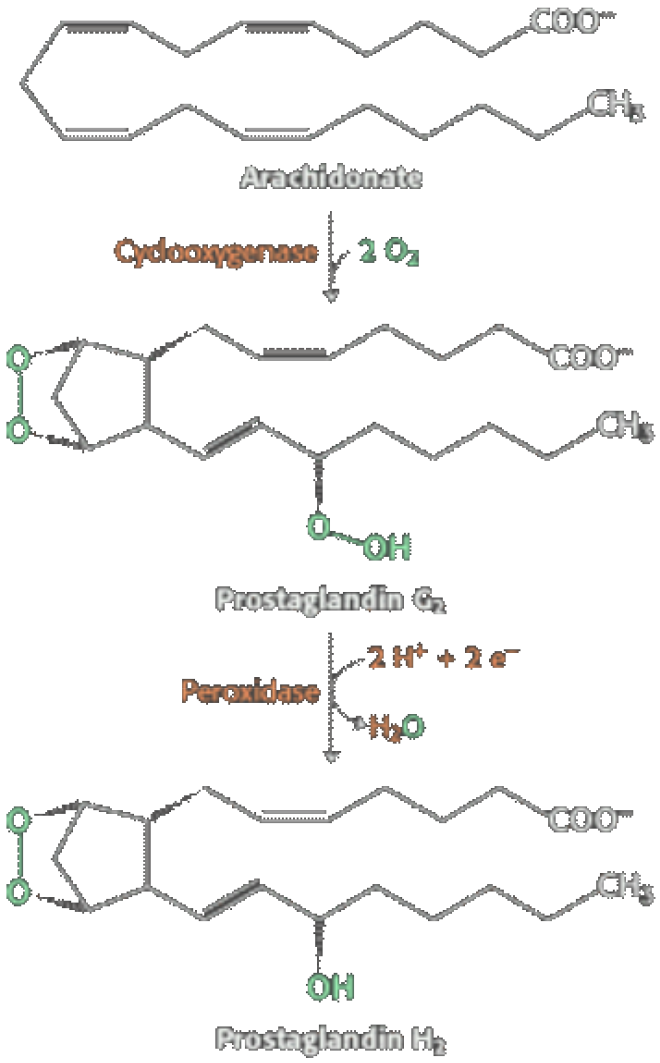
Prostaglandins

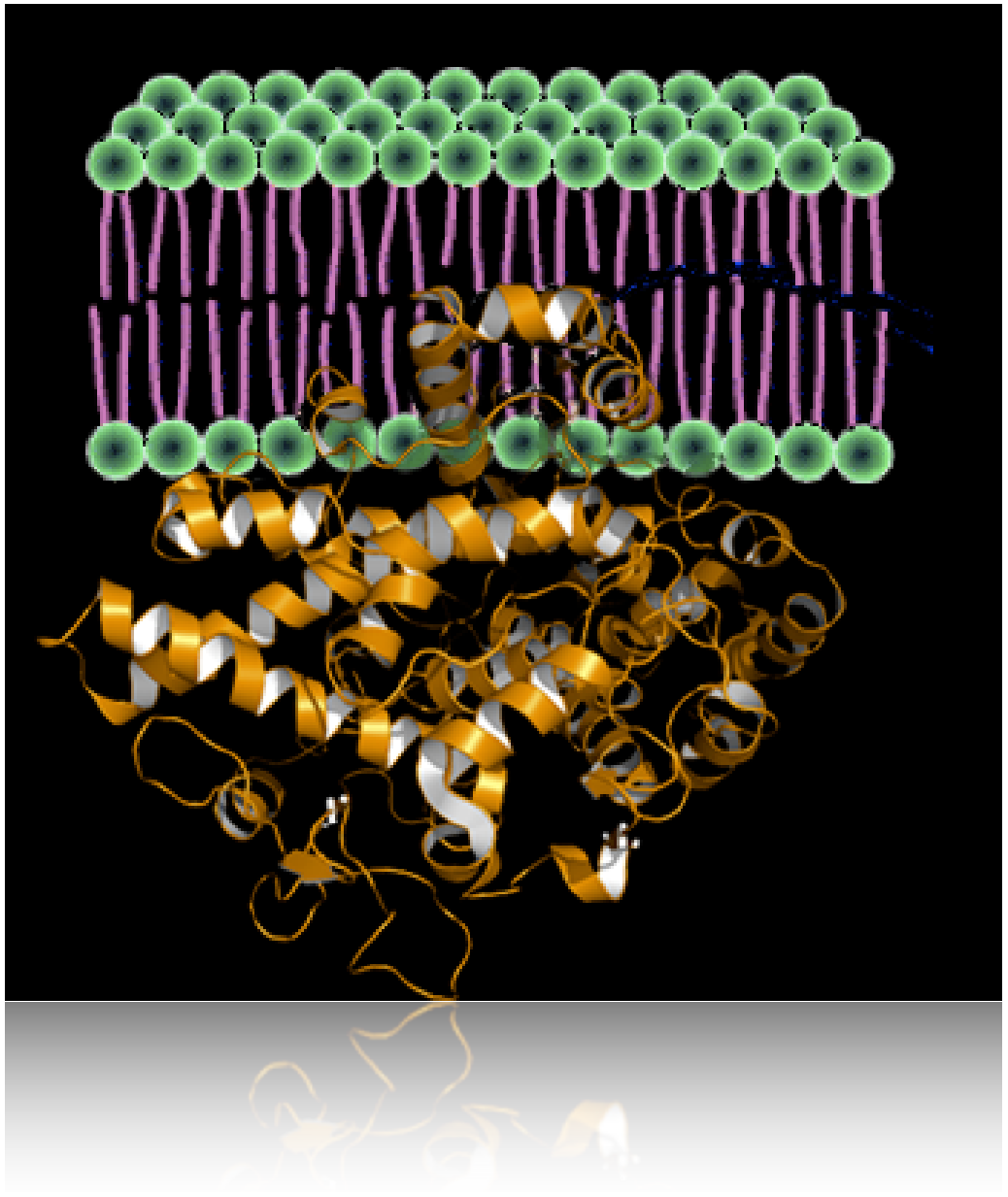
- Generated by COX1 (constitutive) and mediates gastric function, renal homeostasis, and platelet aggregation
- COX2 (inducible) mediates pain, swelling, inflamation and fever.
- Aspirin is an irreversible inhibitor of both COX1 and COX2, while celecoxib (Celebrex or Vioxx) only inhibits COX2.

Prostaglandin H_2 synthase-1 (COX1)

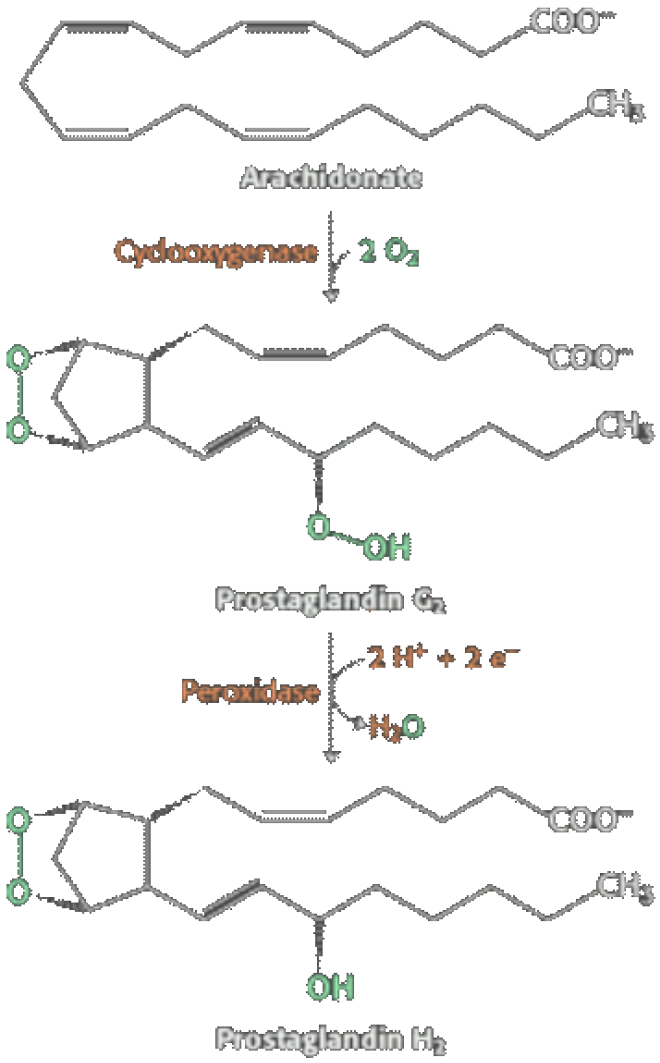


Prostaglandin H_2 synthase-1 (COX1)

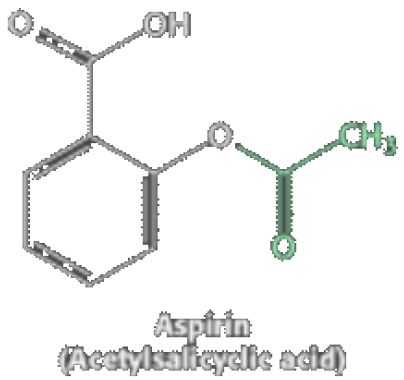




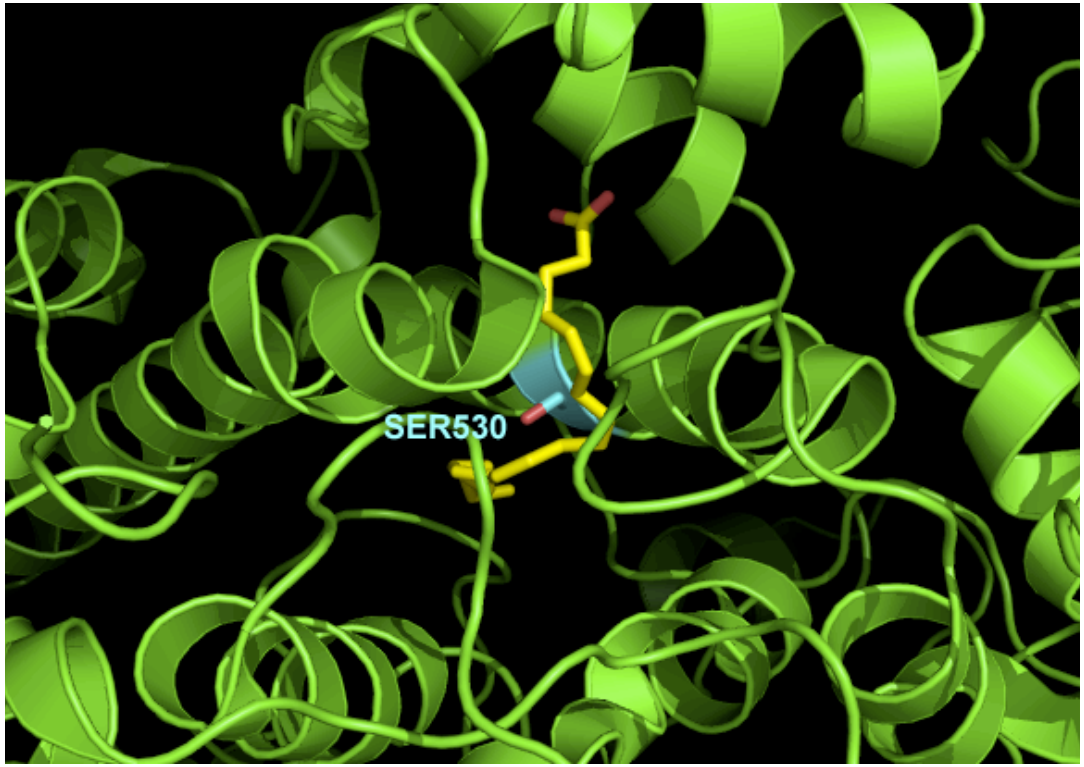
Prostaglandin H_2 synthase-1 (COX1)



Aspirin's effects on prostaglandin H_2 synthase-1 (COX-1)



COX-1 Ser530 Arachidonate 3-AcetylOxy-Ser530



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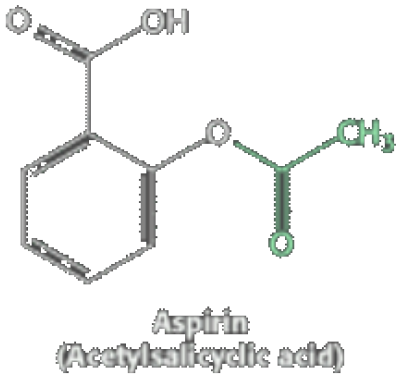
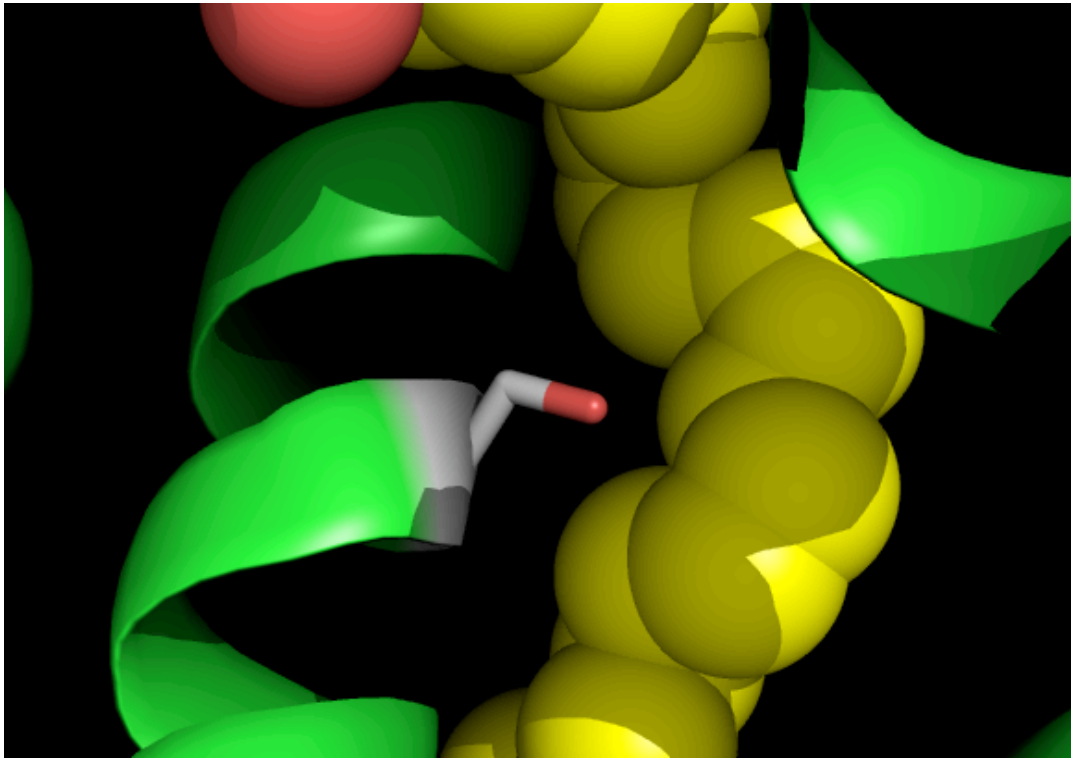


COX-1 Ser530 Arachidonate 3-AcetylOxy-Ser530



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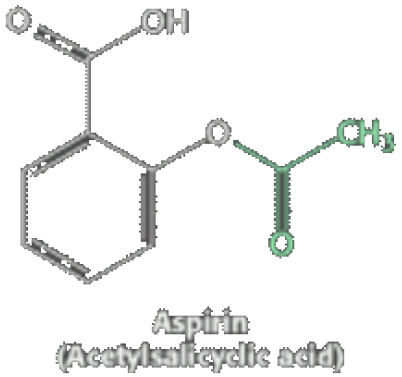

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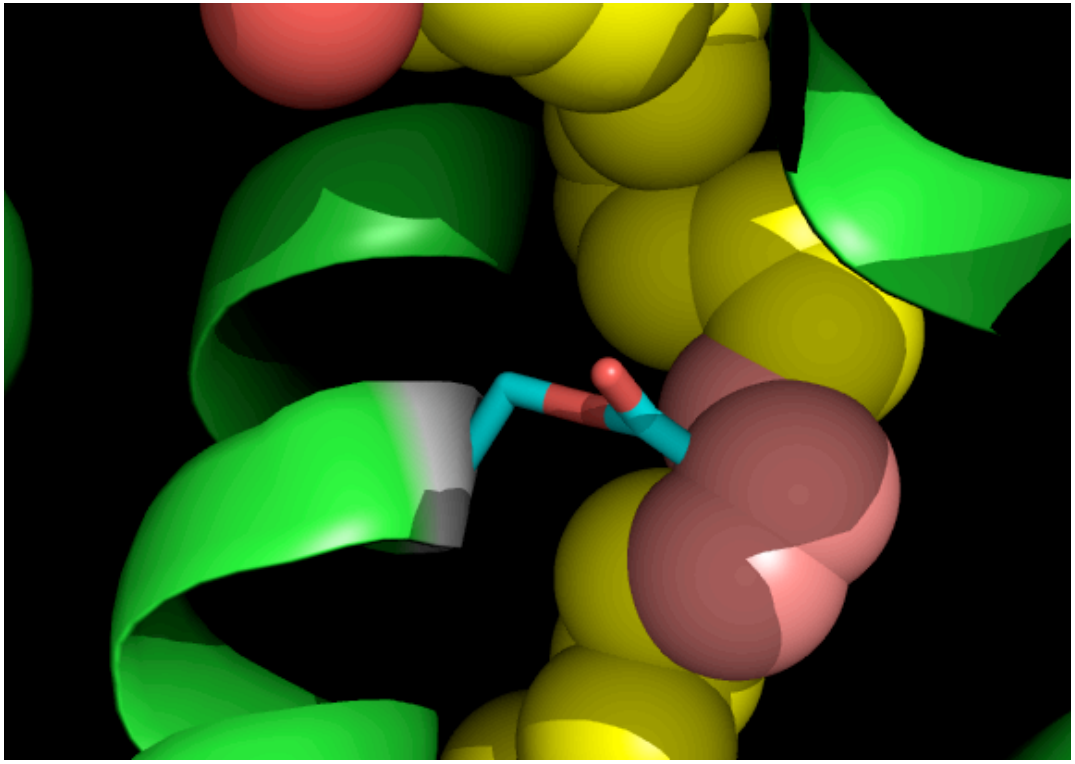

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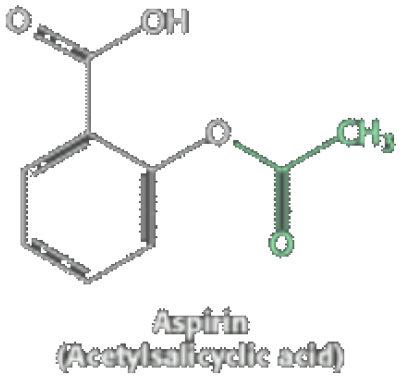

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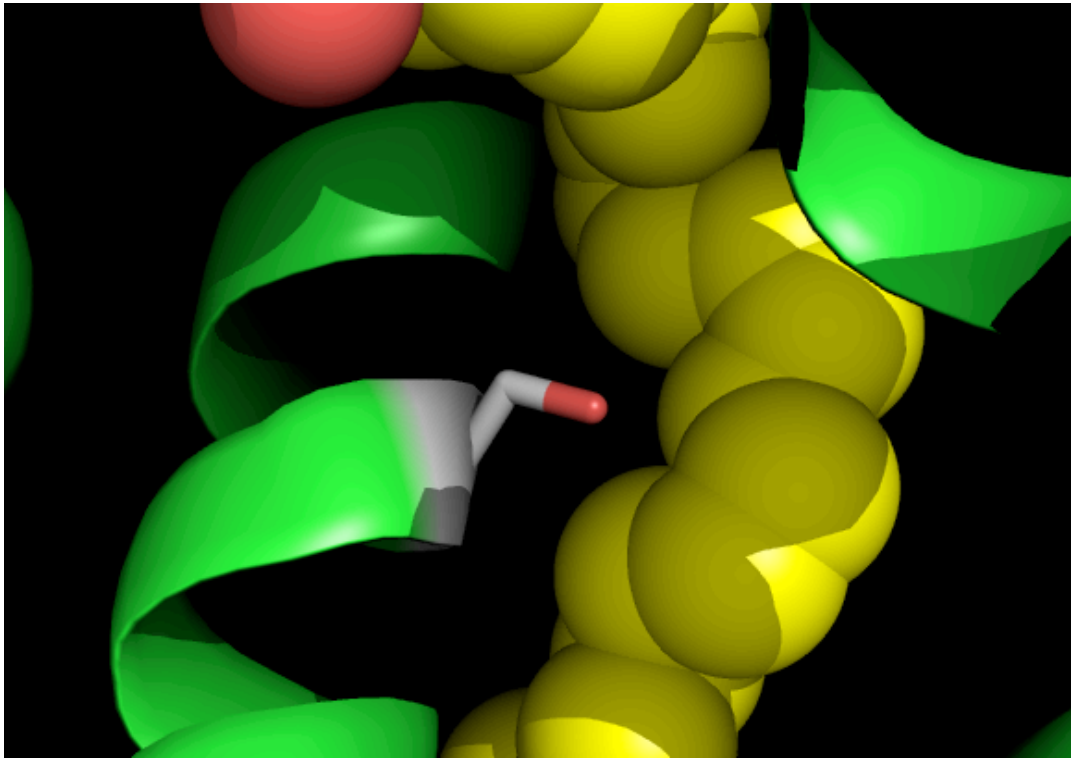

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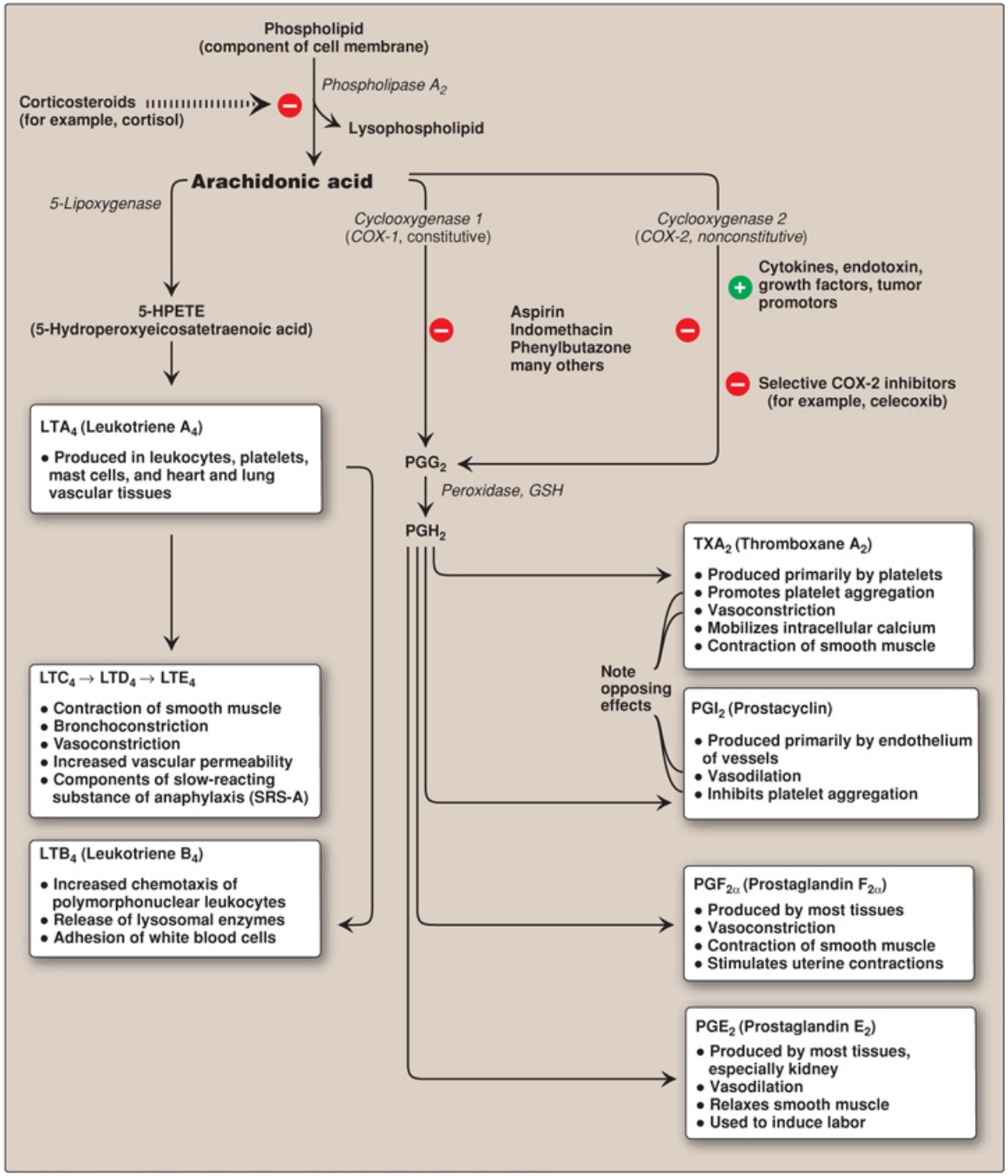
The Lancet 2007; **370**:2138-2151

DOI:10.1016/S0140-6736(07)61909-6

Review

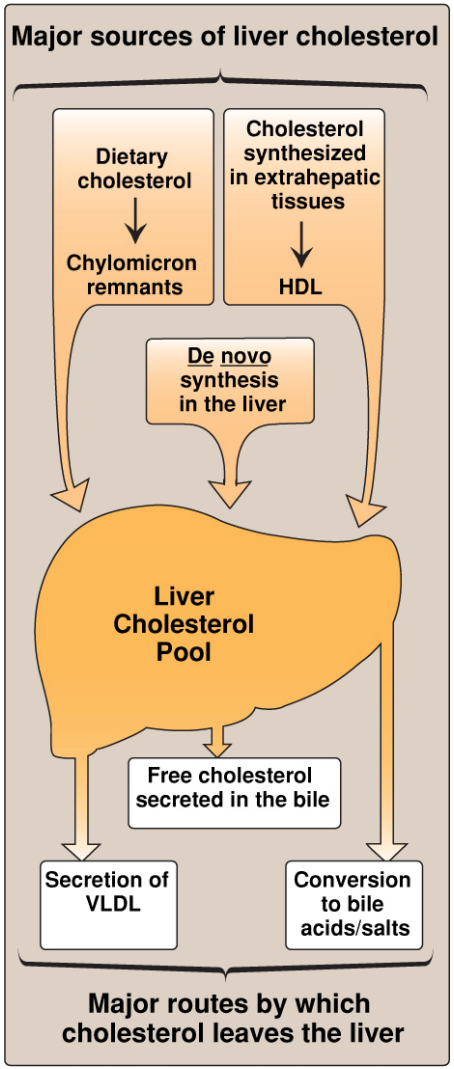
Are COX-2 inhibitors preferable to non-selective non-steroidal anti-inflammatory drugs in patients with risk of cardiovascular events taking low-dose aspirin?

Prof Vibeke Strand MD



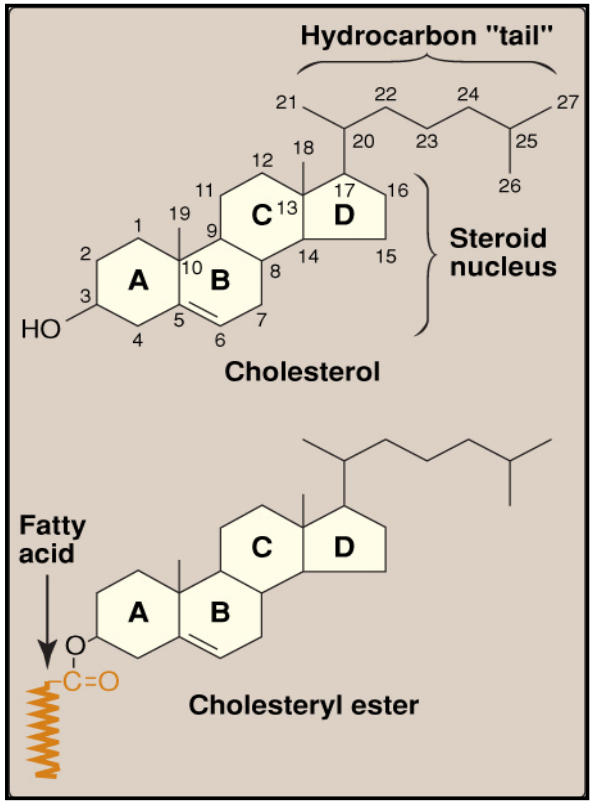
Cholesterol (chapter 18)

- Cholesterol is synthesized by all tissues in humans, although liver, intestine, adrenal cortex, and reproductive tissues make the most.
- All the carbon atoms in cholesterol come from acetate, with reducing equivalents from NADPH.
- Energy for synthesis comes from hydrolysis of thioester bonds of acetyl CoA and terminal phosphate bond of ATP.
- Synthesis occurs in the cytoplasm, with some enzymes found in the membrane of the ER.

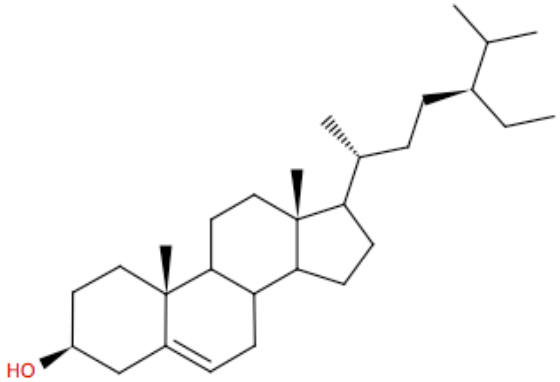


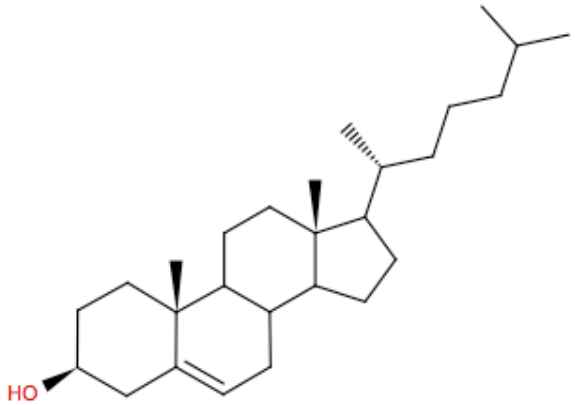
cholesterol structure

- most plasma cholesterol is in the esterified form (not found in cells or membranes)
- cholesterol functions in all membranes (drives formation of lipid microdomains)
- cholesterol is the precursor for steroid hormones
- note 4 fused rings, single dbl bond, single hydroxyl, acyl chain at C17



plant sterol margarines (Benecol, sitosterol) lower LDL cholesterol by inhibiting intestinal absorption of cholesterol





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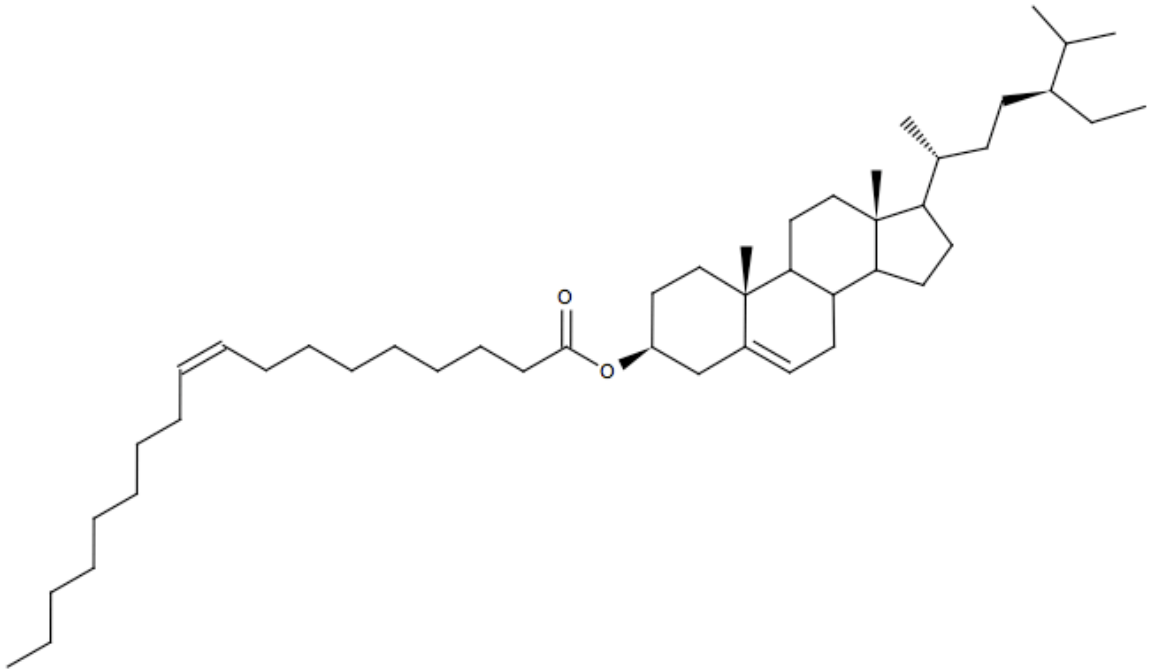
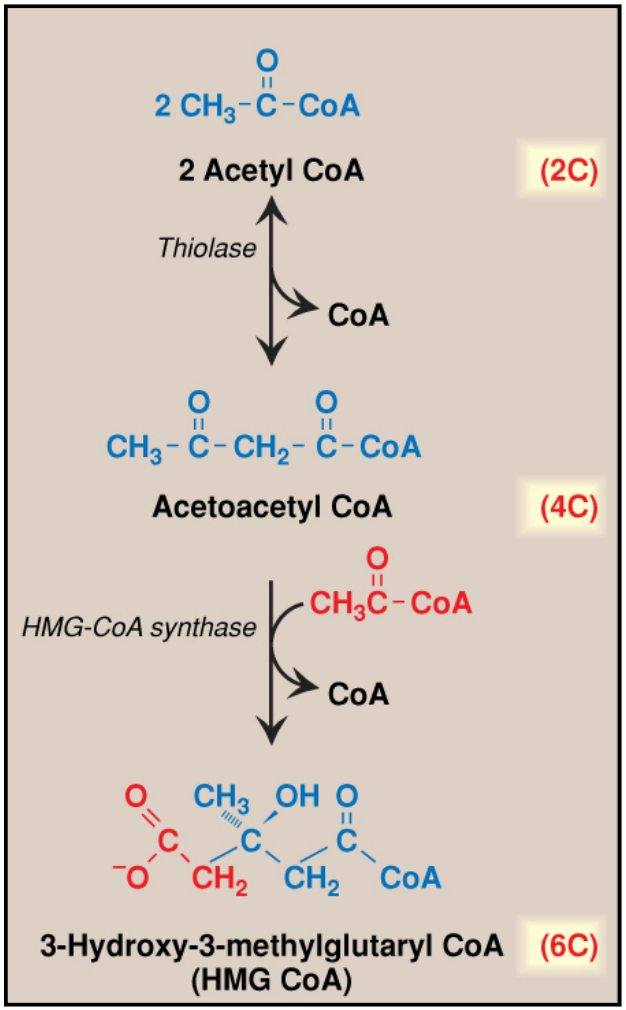


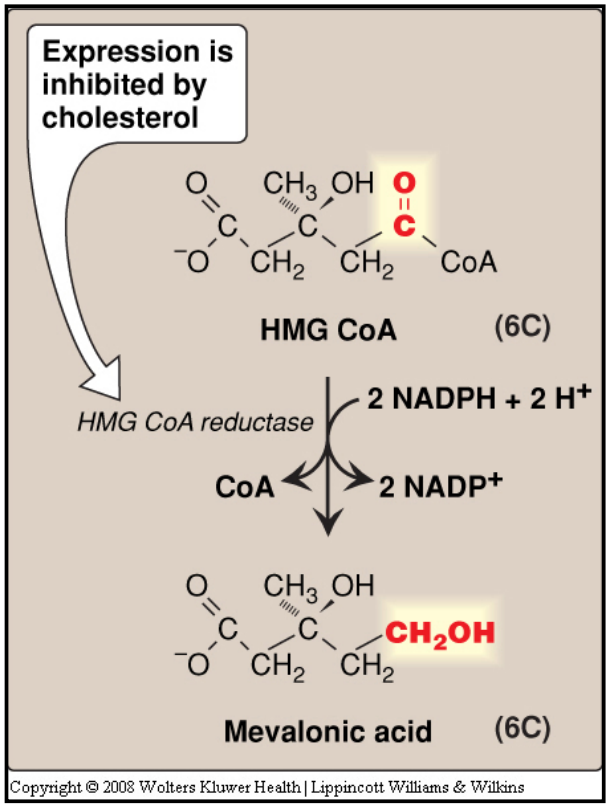
Cholesterol synthesis initially follows that of ketone bodies

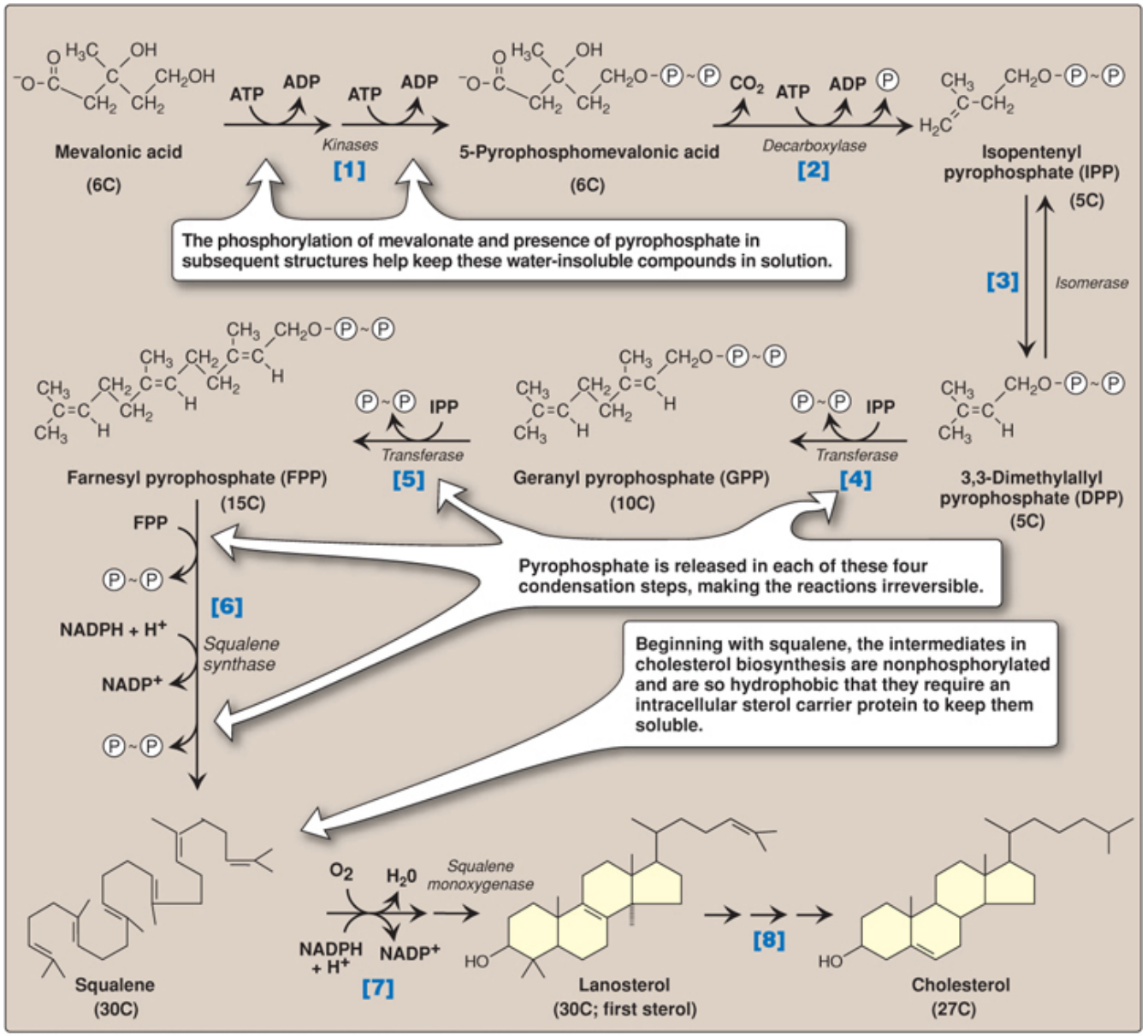
3 cytoplasmic acetyl CoA molecules are sequentially condensed to form HMG CoA (6 carbons)

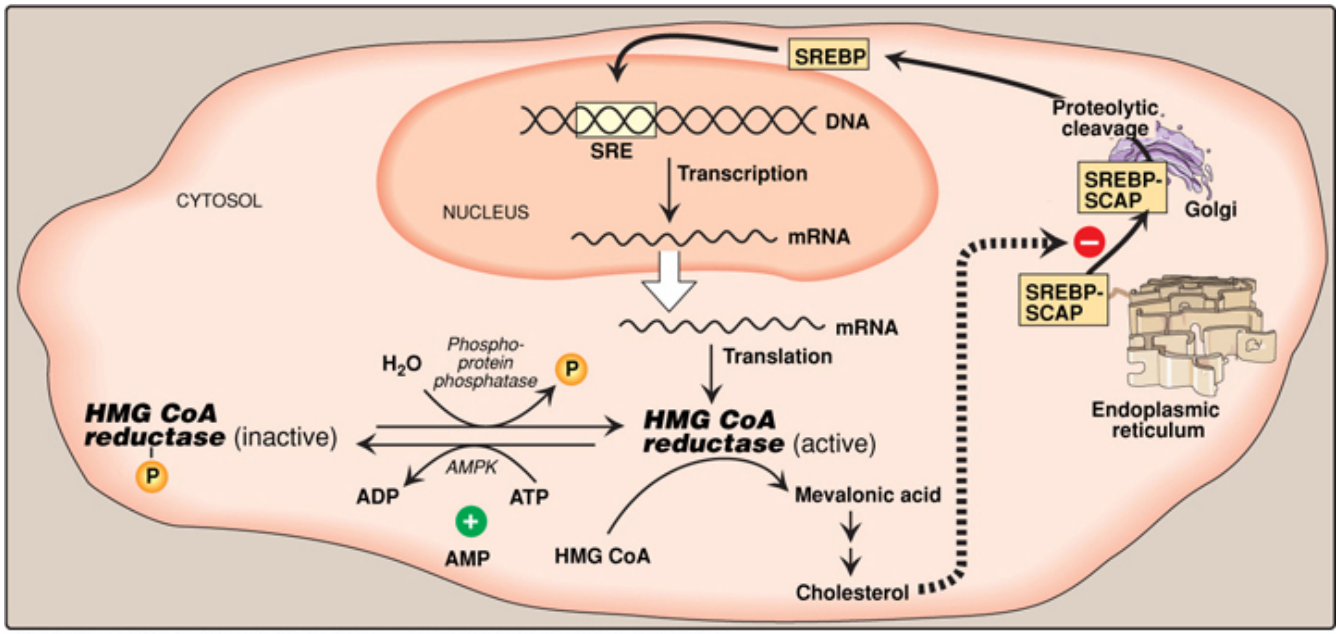


The rate-limiting step of de novo cholesterol biosynthesis is catalyzed by HMG CoA reductase

- The reduction of HMG CoA by HMG CoA reductase results in the oxidation of two NADPH and results in mevalonate.
- HMG CoA reductase is a membrane protein of the ER: catalytic domain projects into the cytoplasm.
- Target of statin drugs

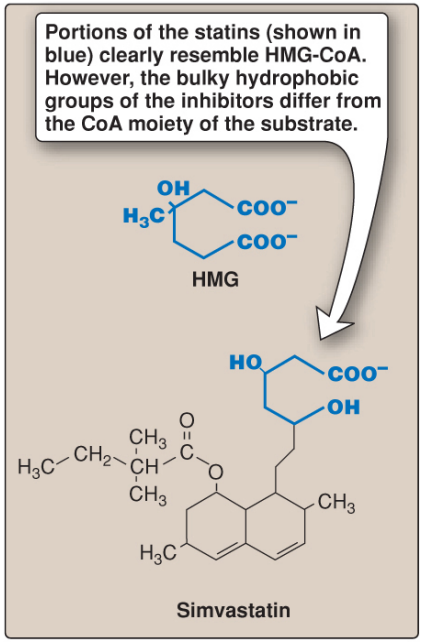






Regulation of HMG CoA reductase

1. regulation of gene expression by SREBP
2. phosphorylation state
3. regulation by hormones (insulin, glucagon)
4. inhibition by statin drugs



Regulation of HMG CoA reductase

1. regulation of gene expression by SREBP
2. phosphorylation state
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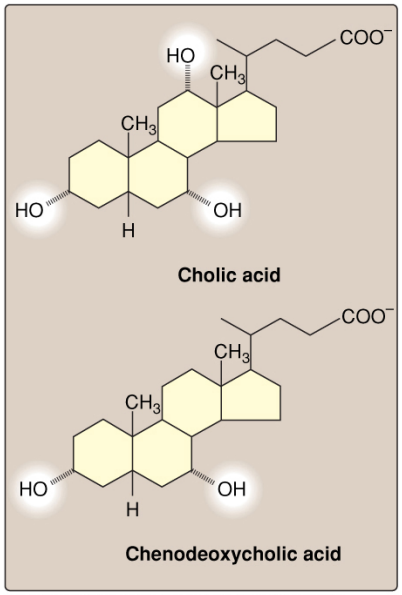
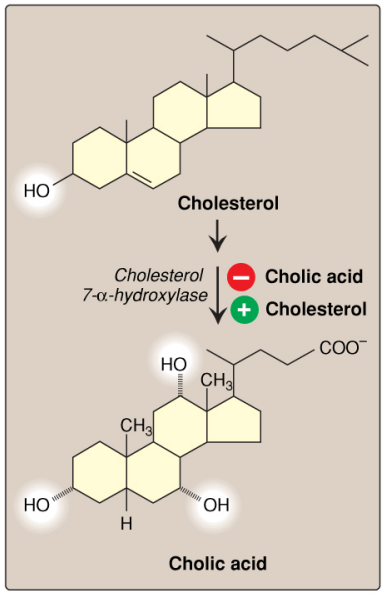
4. inhibition by statin drugs

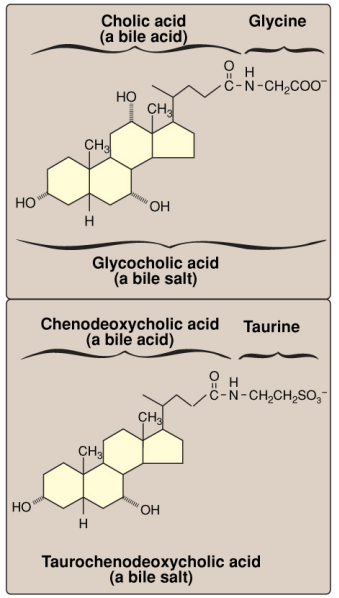
Degradation of Cholesterol

- The ring structure of cholesterol cannot be metabolized to CO_2 and H_2O in humans.
- The sterol ring nucleus is eliminated from the body by conversion to bile acids and bile salts.

Degradation of Cholesterol







- The theme is for cholesterol to be converted to a relatively soluble amphipathic molecule.
- As a bonus, these molecules are used as emulsifying agents during digestion.