



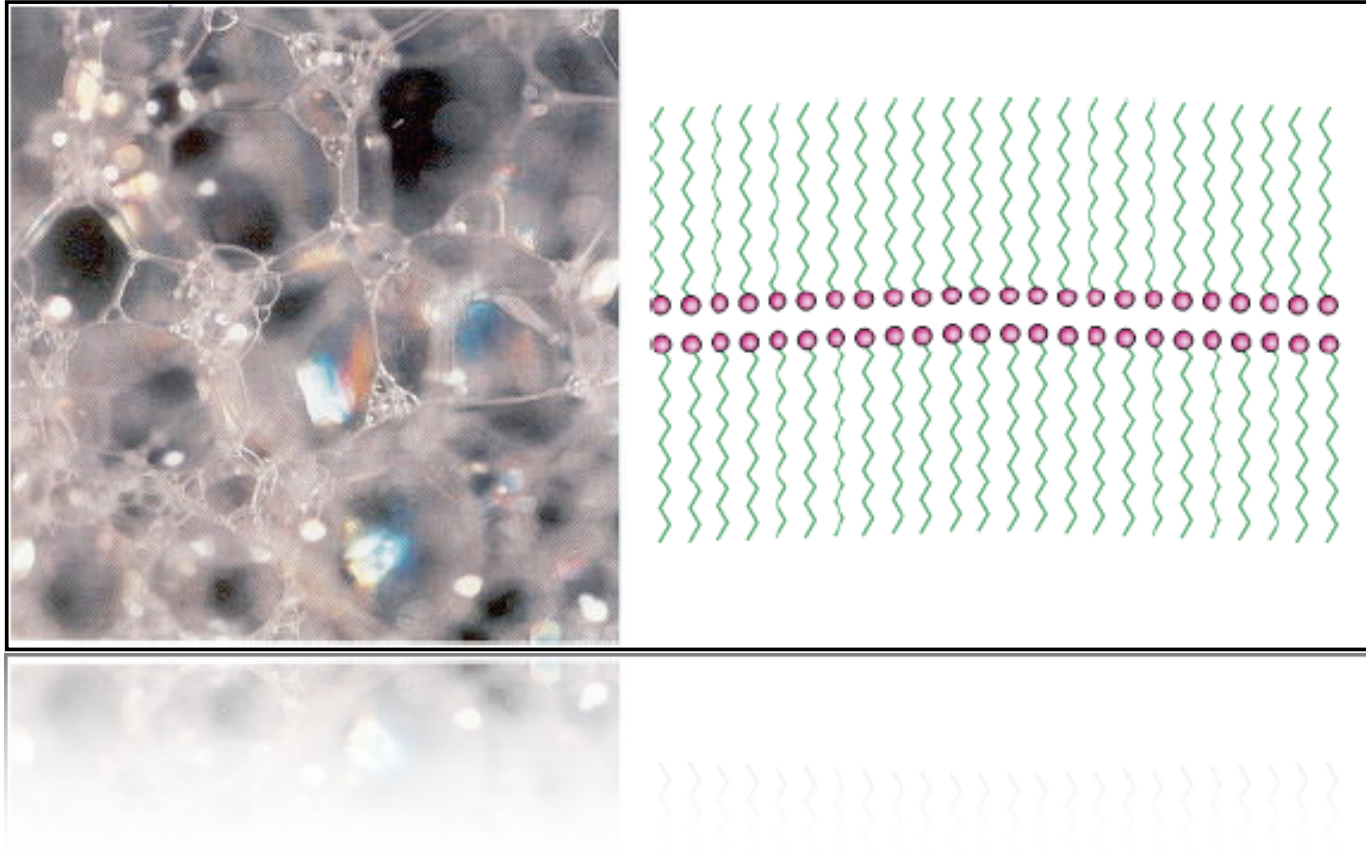
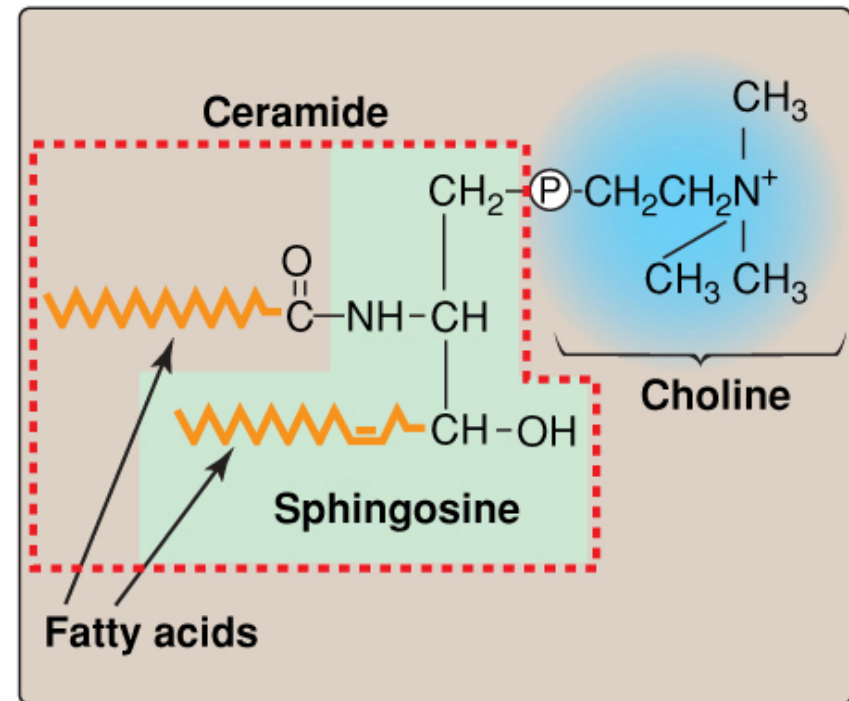
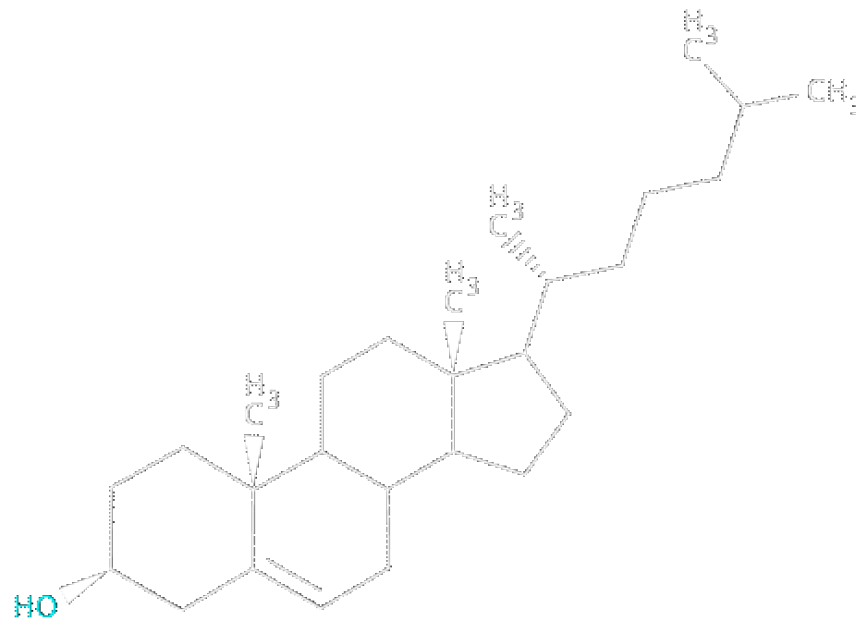
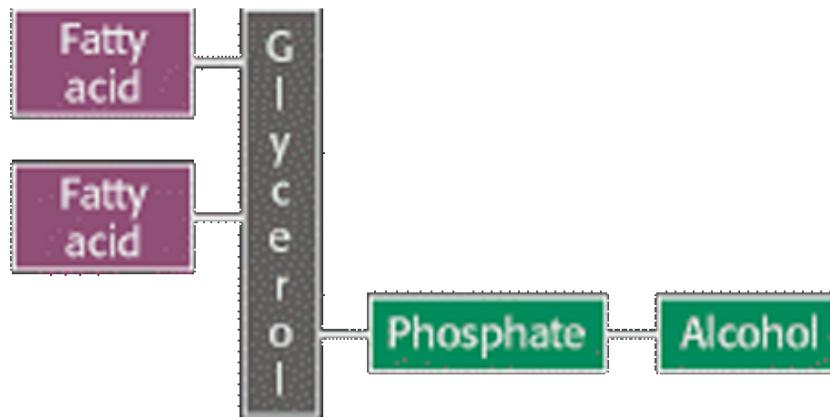
	<u>Approved Lists of Bacterial Names</u> Skerman, V.B.D.; McGowan, Vicki; Sneath, P.H.A., editors Washington (DC): <u>American Society for Microbiology</u> ; c1989
	<u>Basic Neurochemistry: Molecular, Cellular, and Medical Aspects</u> Siegel, George J.; Agranoff, Bernard W.; Albers, R. Wayne; Fisher, Stephen K.; Uhler, Michael D. Philadelphia: <u>Lippincott, Williams & Wilkins</u> ; c1999
	<u>Biochemistry</u> Berg, Jeremy M.; Tymoczko, John L.; and Stryer, Lubert. New York: <u>W. H. Freeman and Co.</u> ; c2002
	<u>Bioinformatics in Tropical Disease Research: A Practical and Case-Study Approach</u> Gruber, Arthur; Durham, Alan M.; Huynh, Chuong; del Portillo, Hernando A., editors Bethesda (MD) : <u>National Library of Medicine (US), NCBI</u> ; 2008
	<u>Blood Groups and Red Cell Antigens [Internet]</u> Dean, Laura Bethesda (MD): <u>National Library of Medicine (US), NCBI</u> ; 2005

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db=Books&itool=toolbar](http://www.ncbi.nlm.nih.gov/sites/entrez?db=Books&itool=toolbar)**



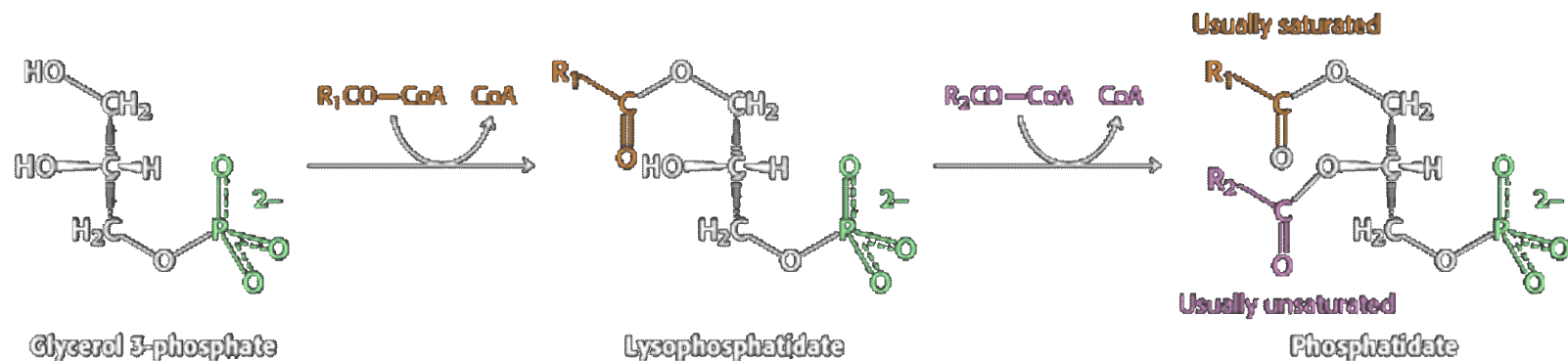
The surface of a soap bubble is a bilayer formed by detergent molecules



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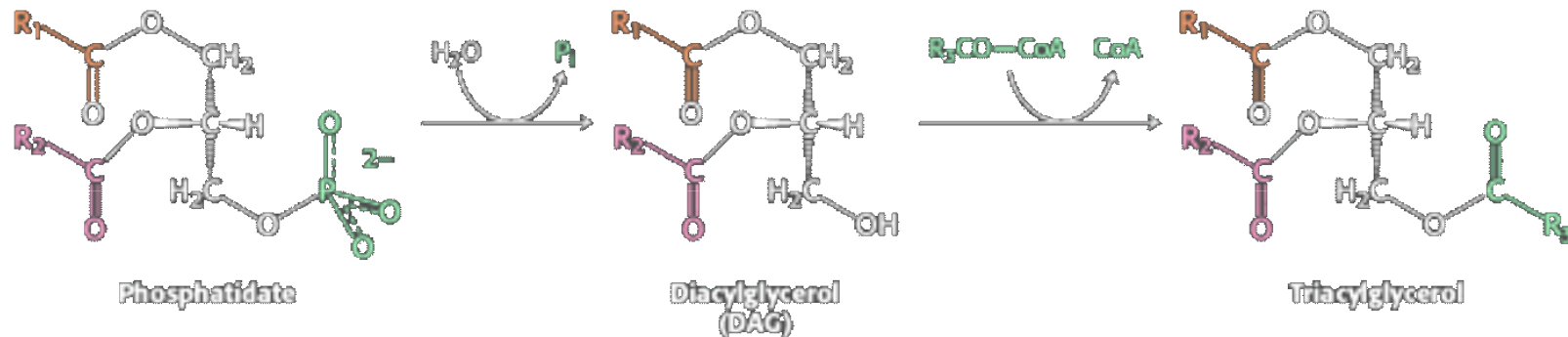
Chapter 17

Phospholipids are synthesized in the ER

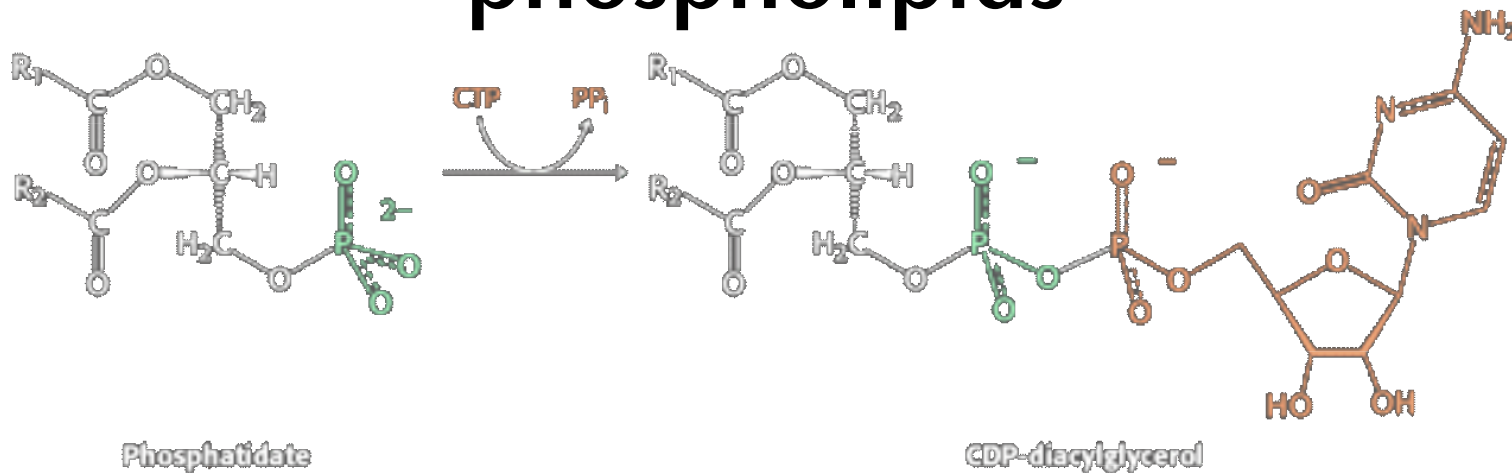


- The first step involves the synthesis of phosphatidate
- Glycerol 3-phosphate is acylated by acyl-CoA to form lysophosphatidate, and acylated again by acyl-CoA to form phosphatidate

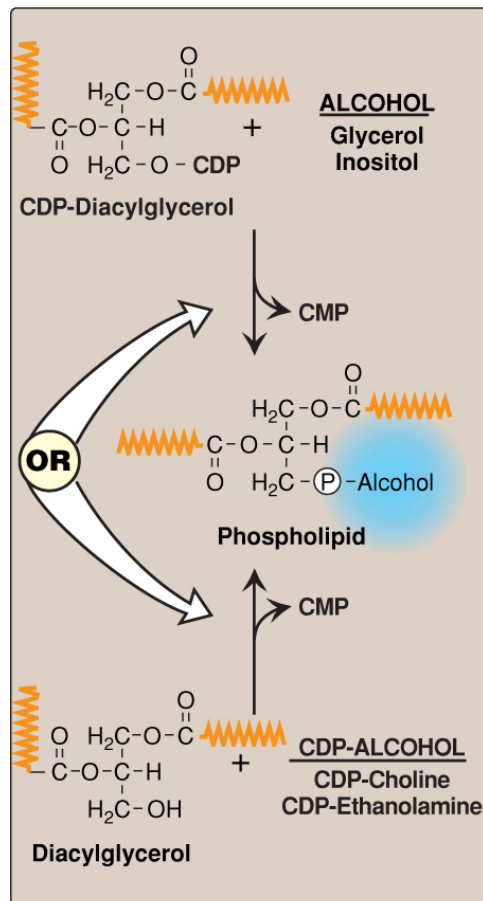
1) Phosphatidate can form triacylglycerol via *triacylglycerol synthetase* on the ER membrane



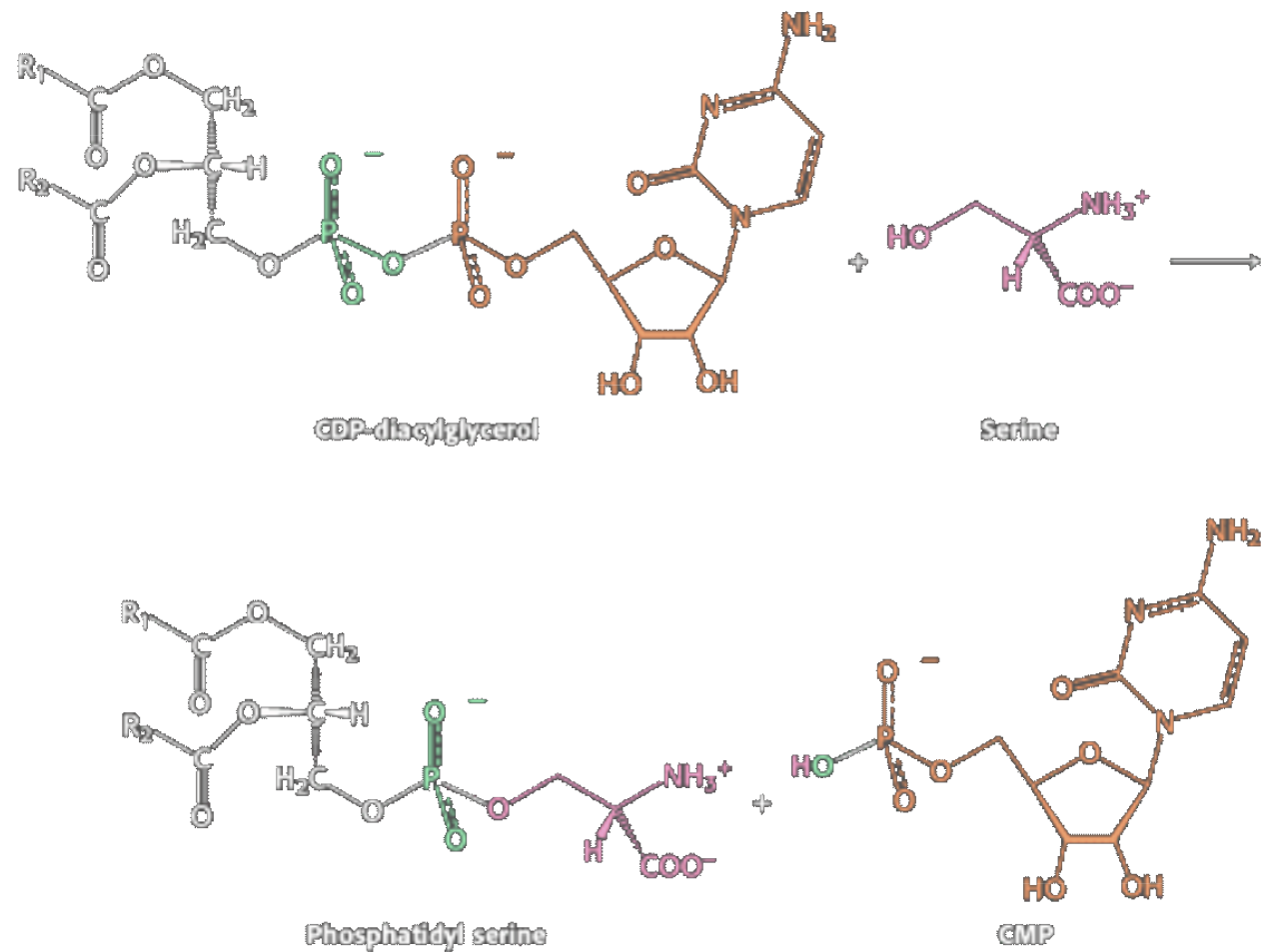
2) Phosphatidate can instead form phospholipids



- 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.

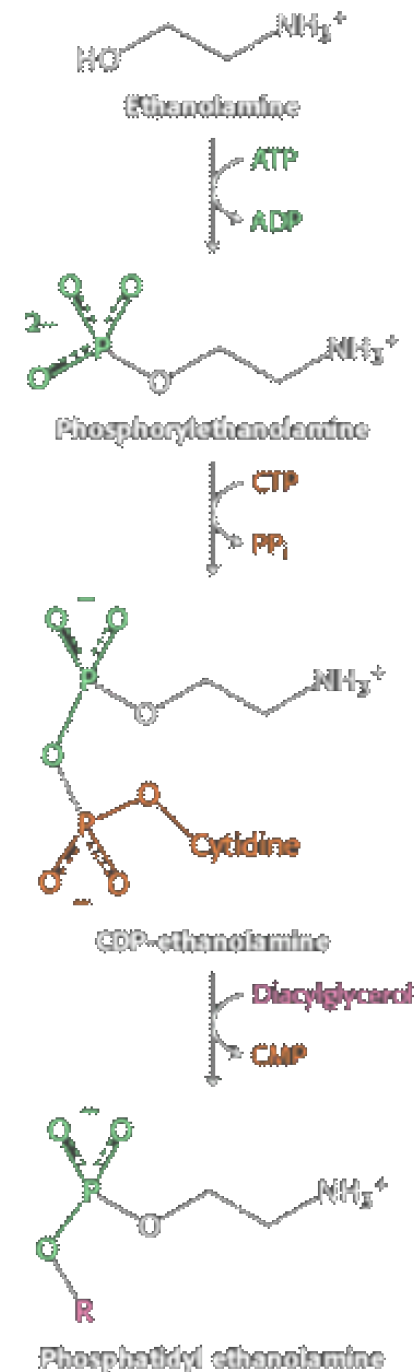


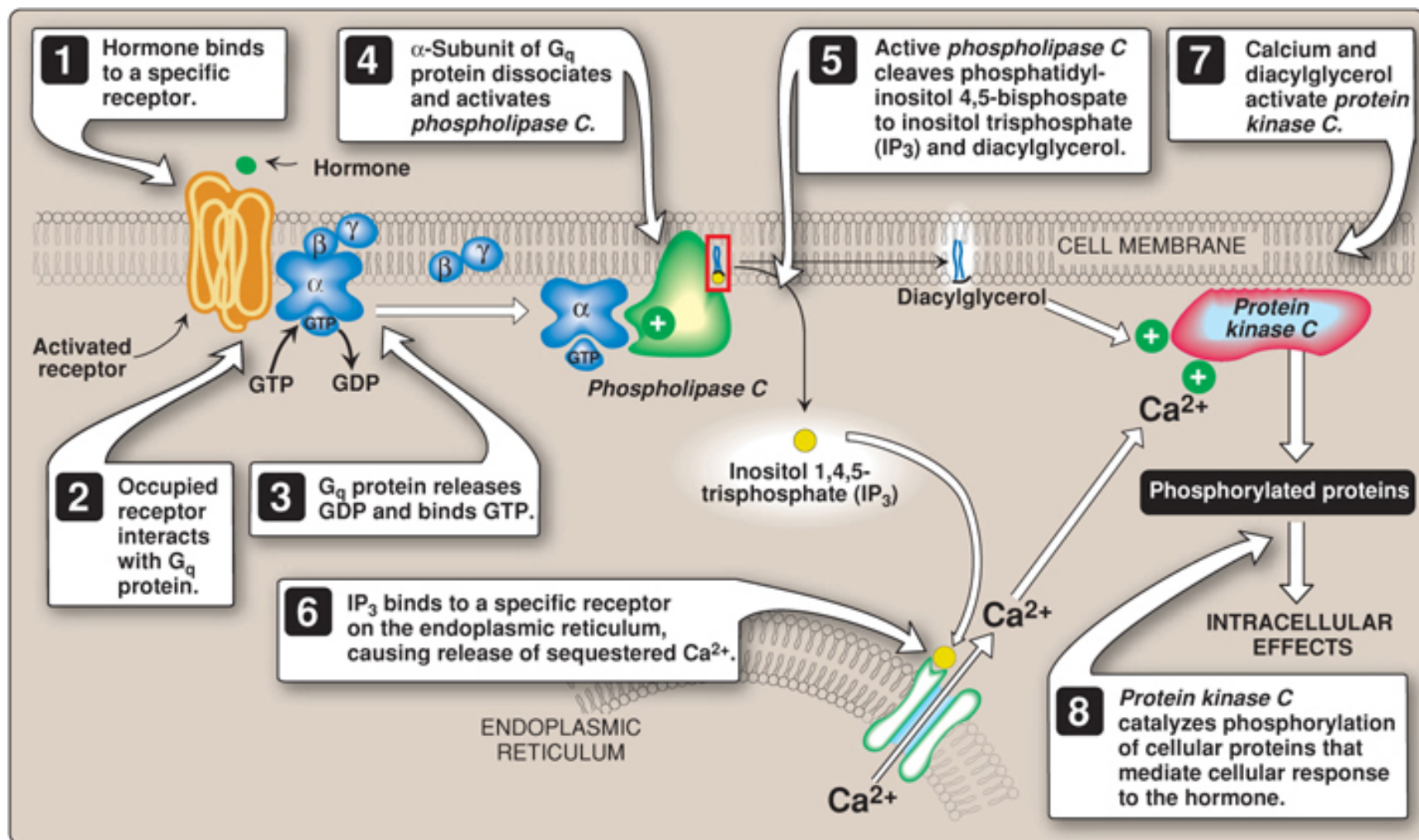
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Serine	+ PA →	phosphatidylserine
Ethanolamine	+ PA →	phosphatidylethanolamine (cephalin)
Choline	+ PA →	phosphatidylcholine (lecithin)
Inositol	+ PA →	phosphatidylinositol
Glycerol	+ PA →	phosphatidylglycerol

- 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 PP_i to inorganic phosphate makes the activation of these components irreversible.

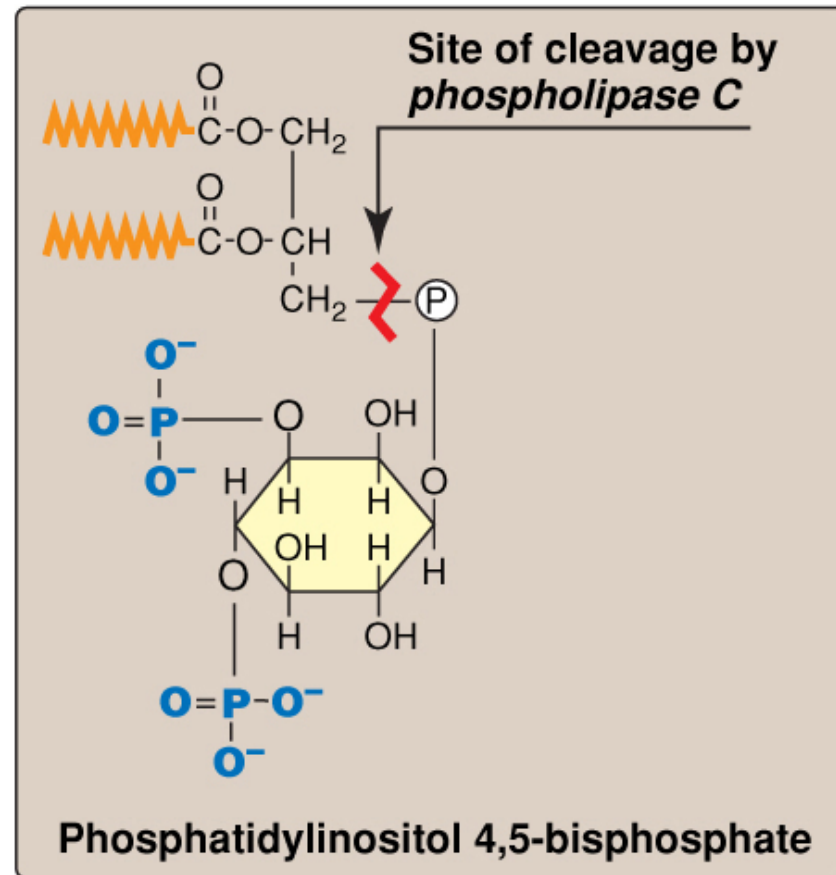
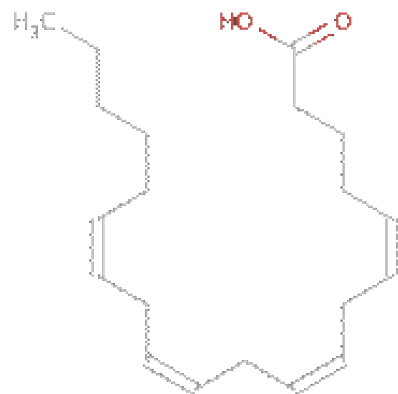


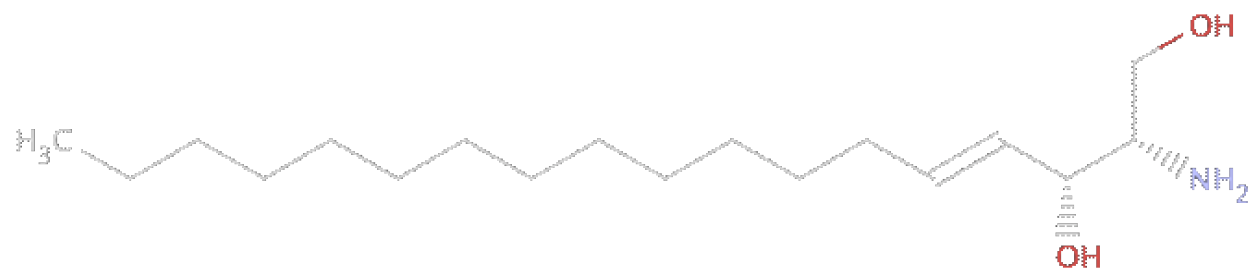
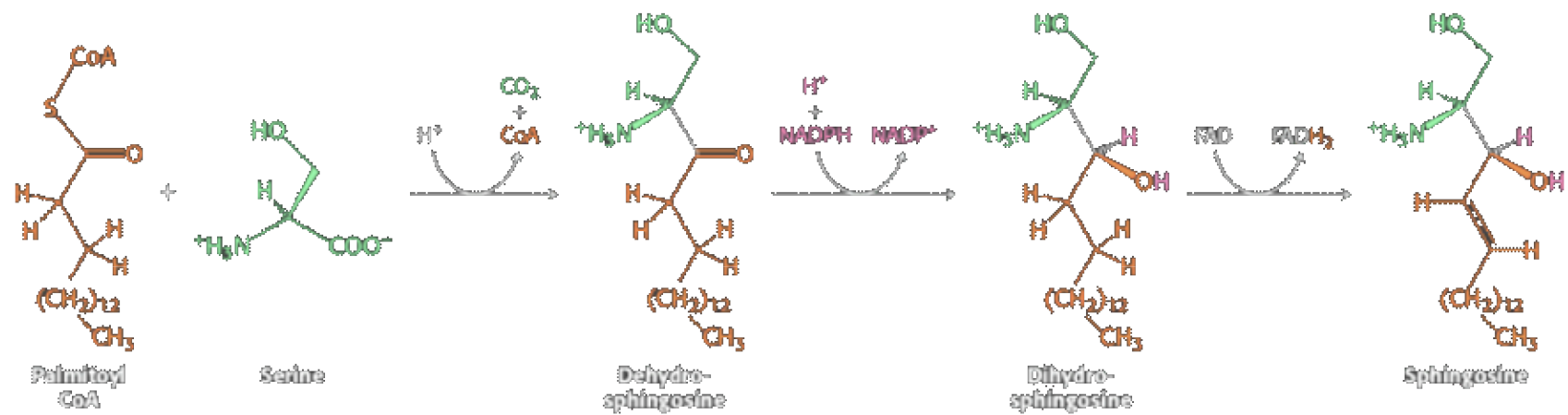


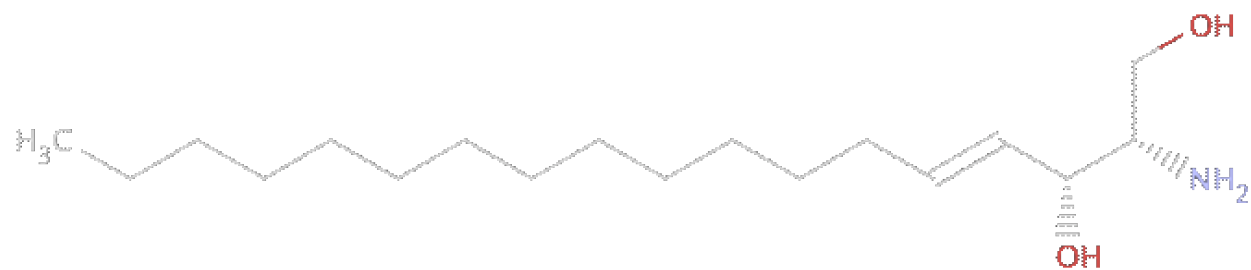
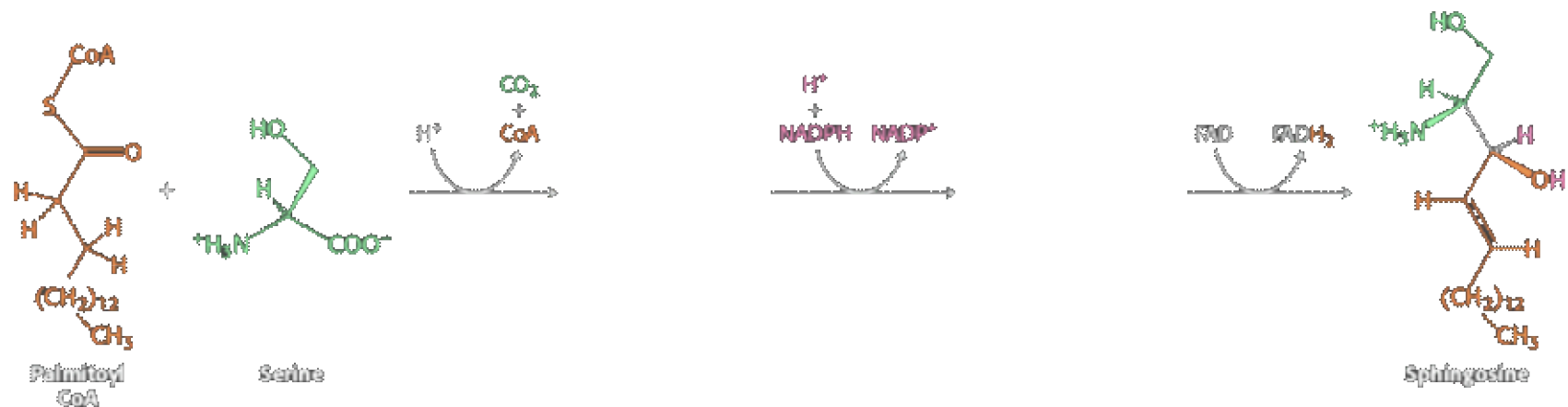


Stearic acid

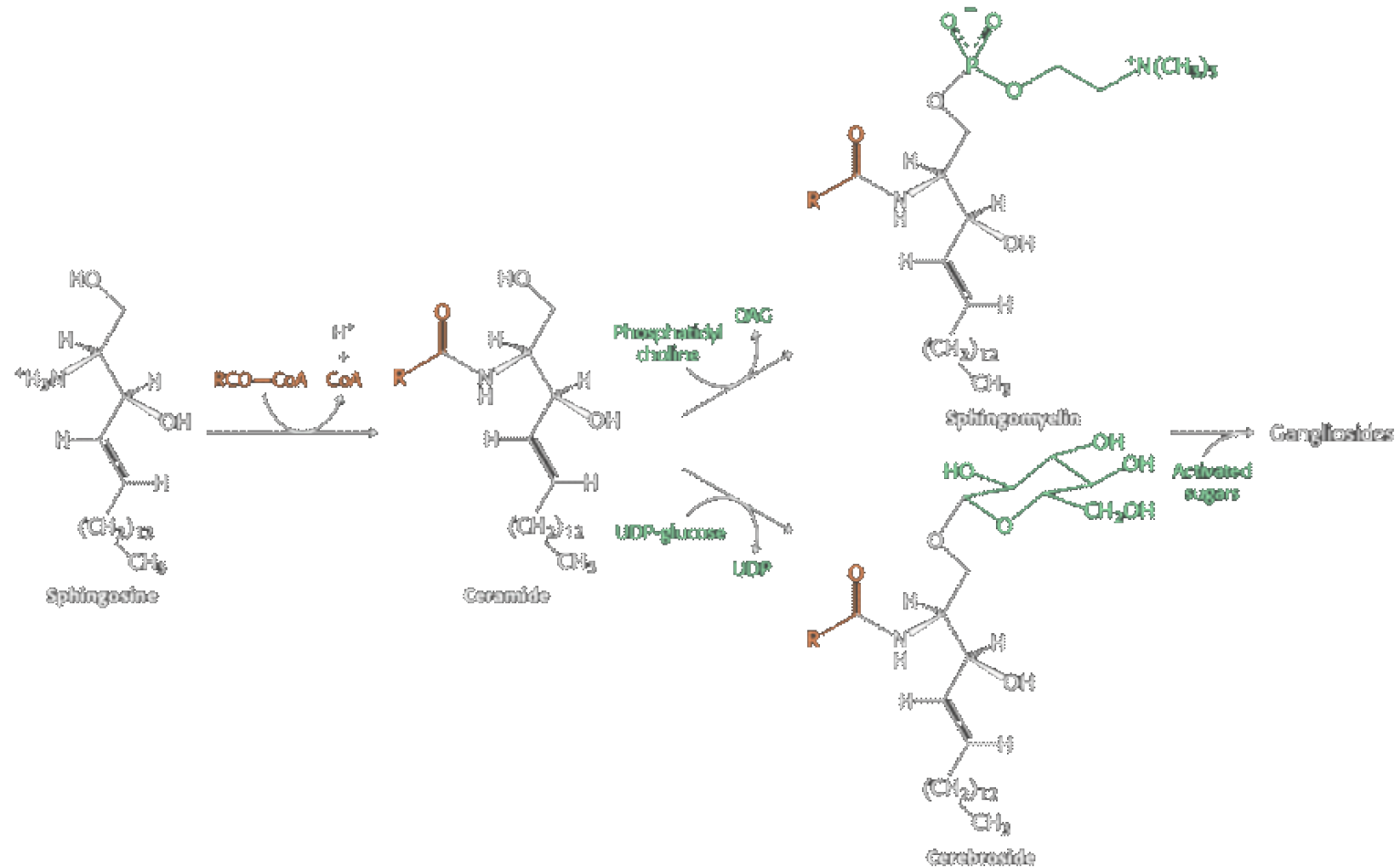
Arachadonic acid

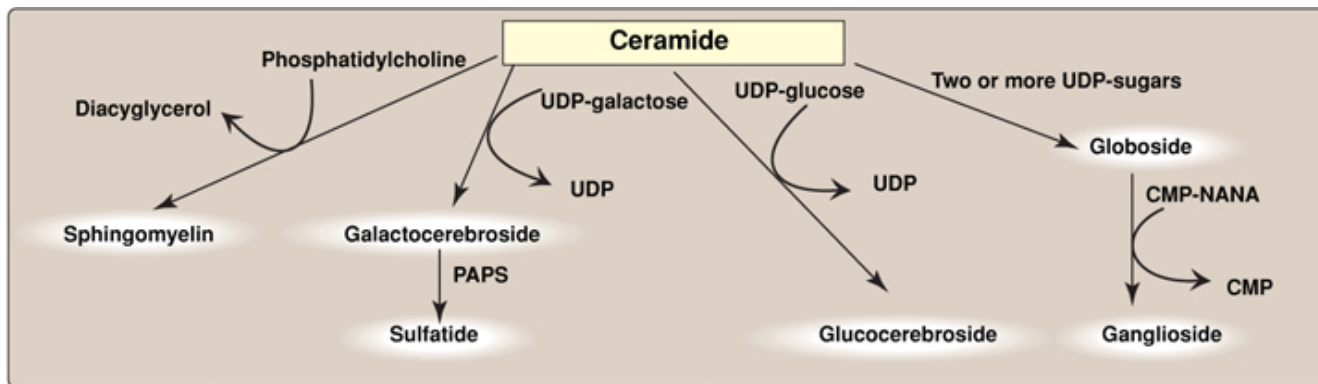




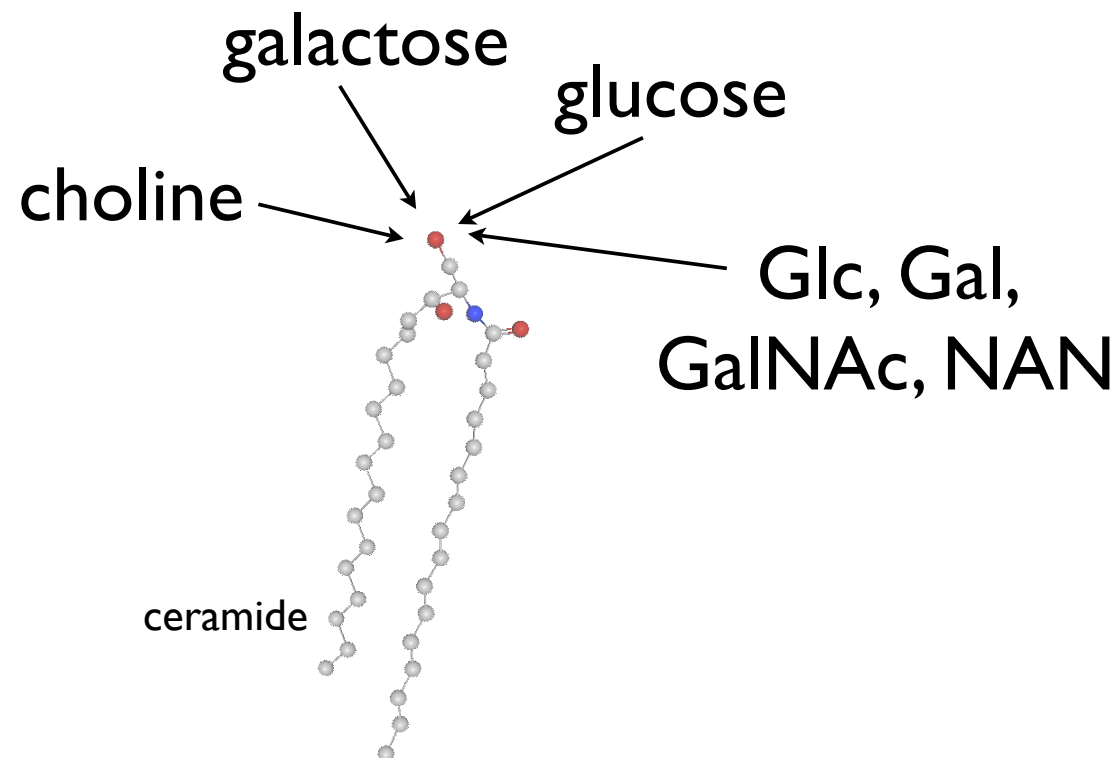


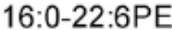
Ceramide is produced in the ER through acylation of sphingosine





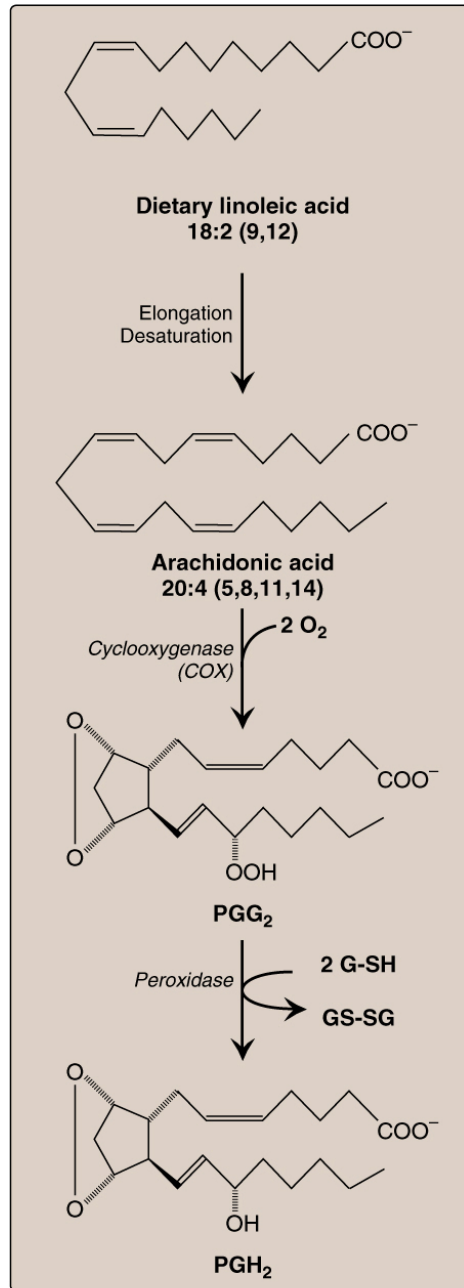
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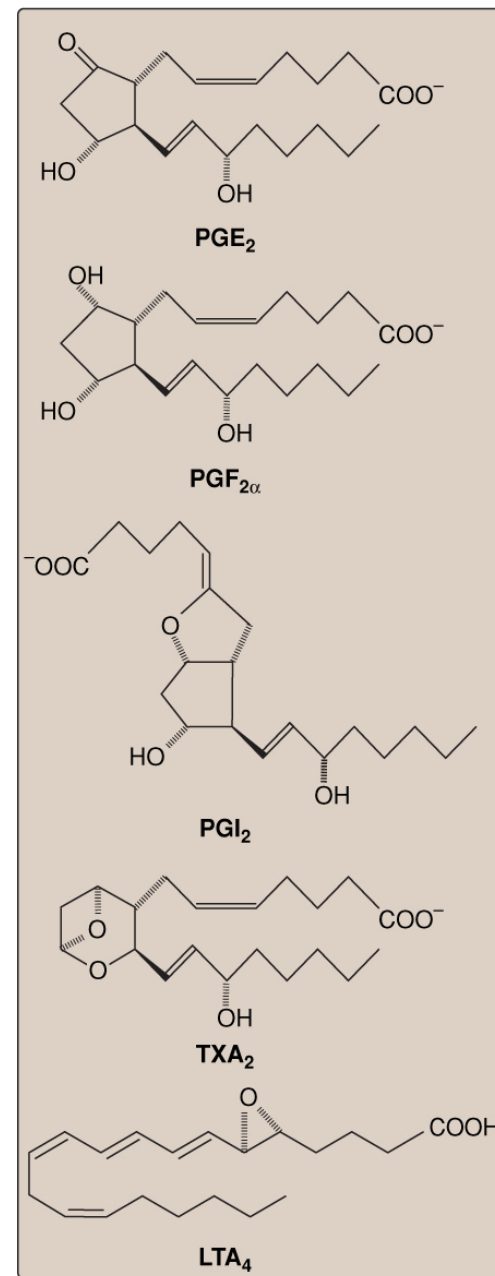


Eicosanoids are derived from long-chain fatty acids

- 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



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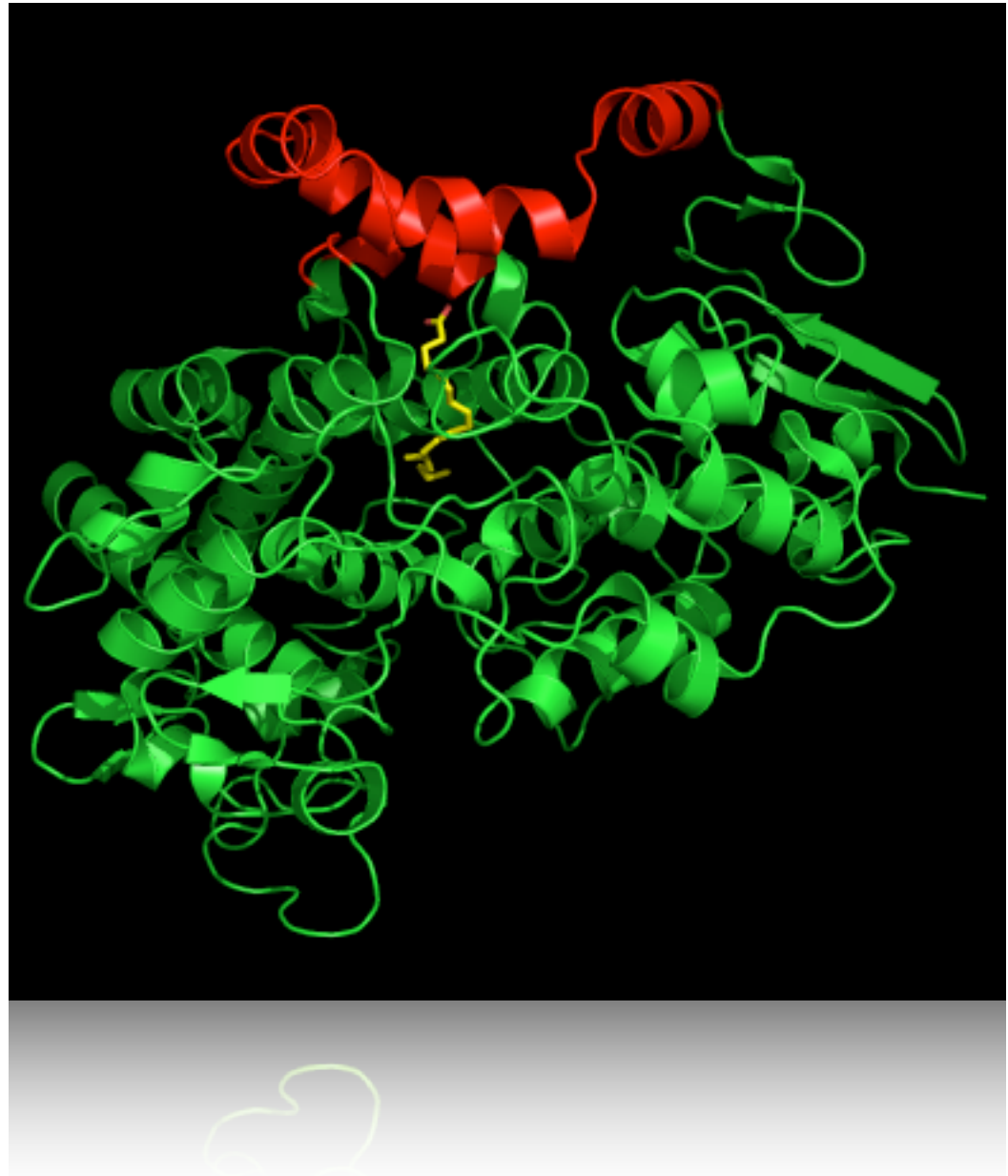
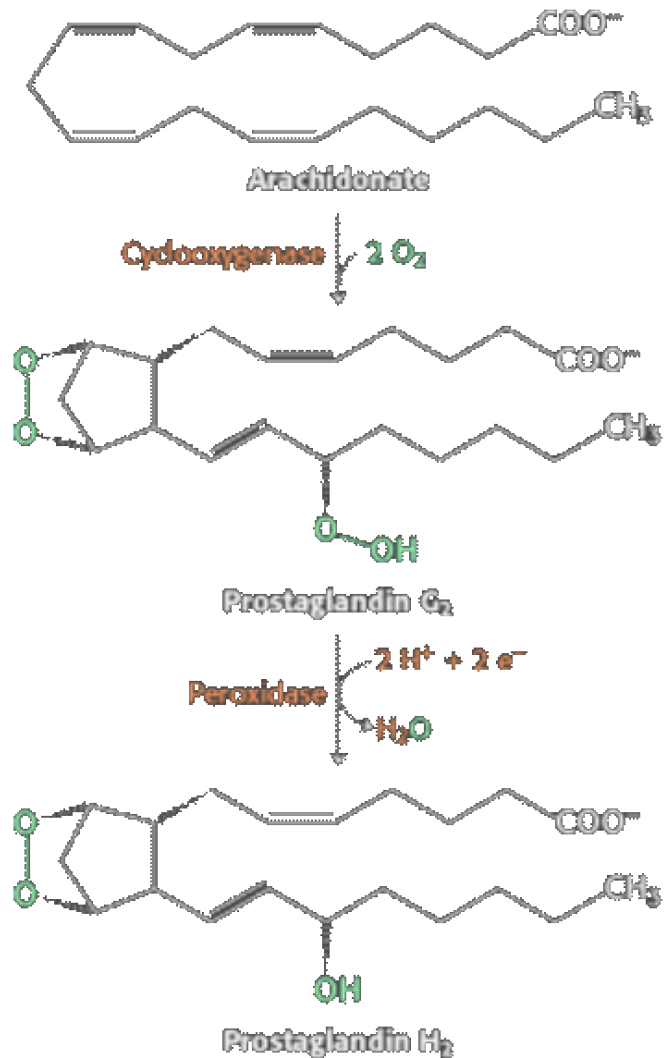


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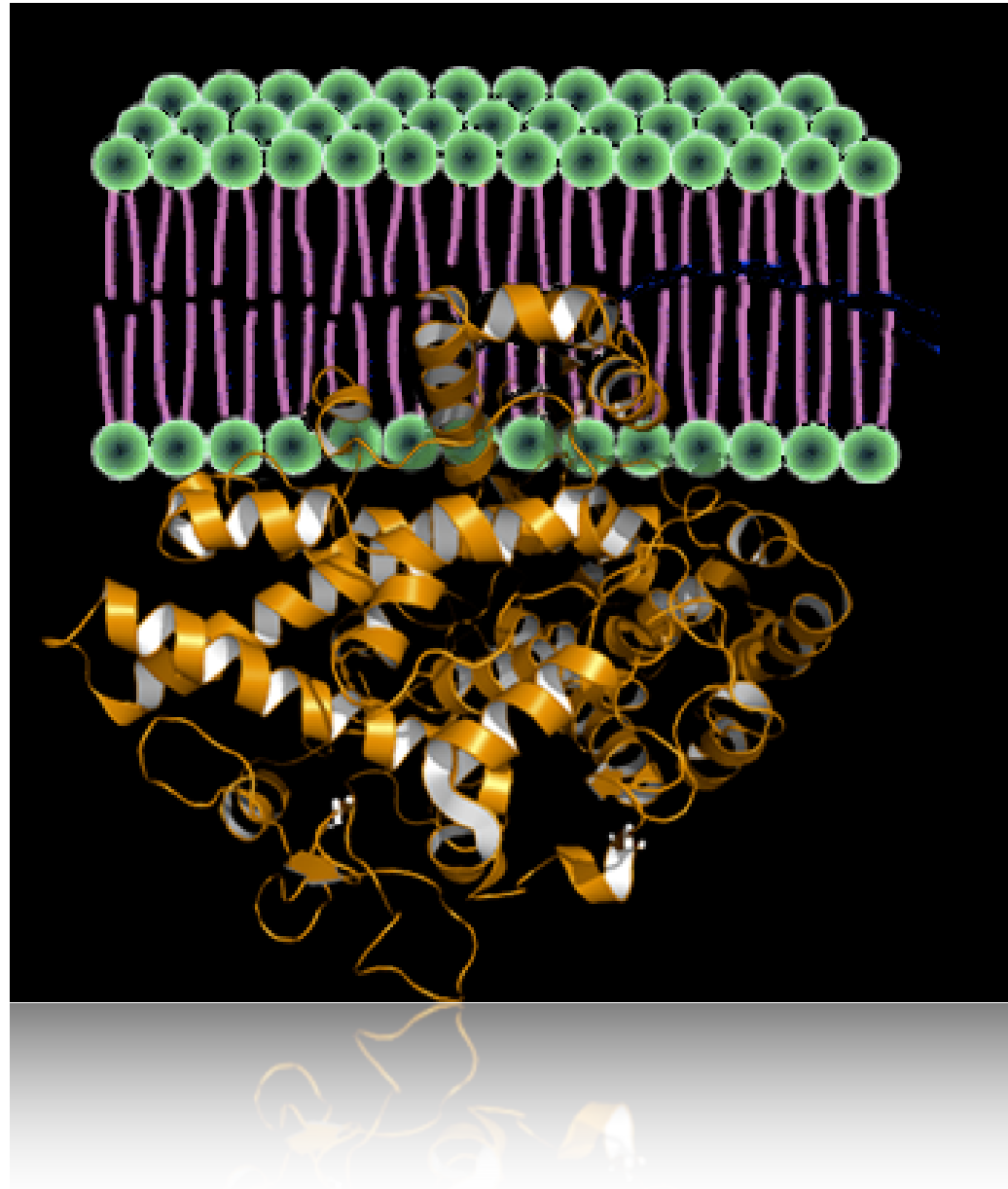
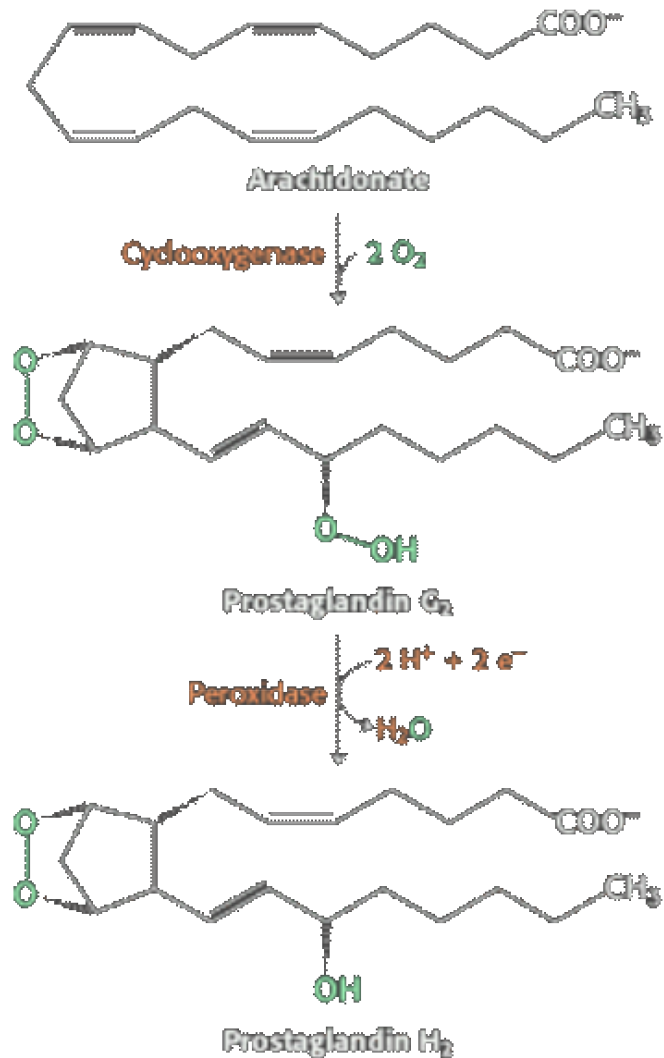
Prostaglandins

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

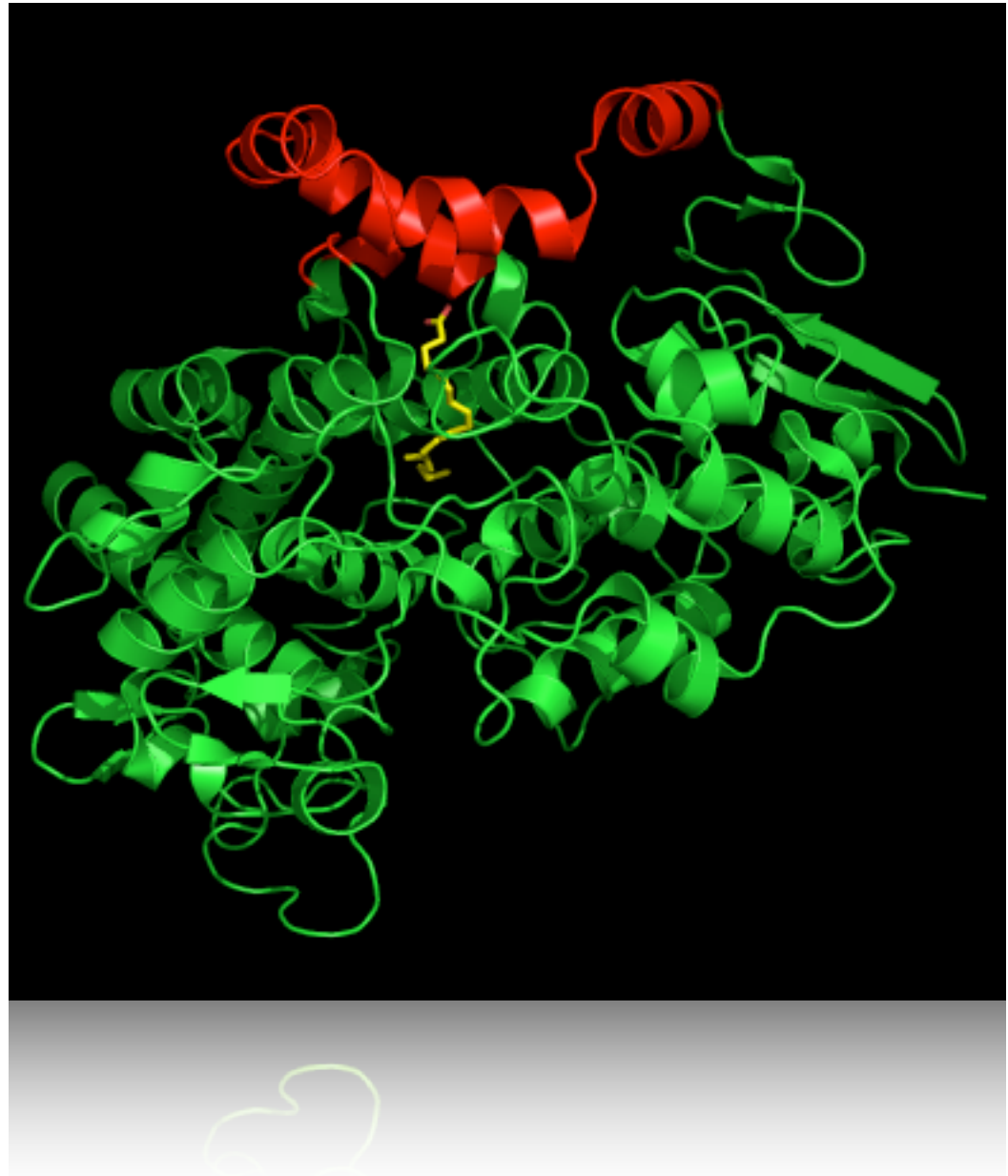
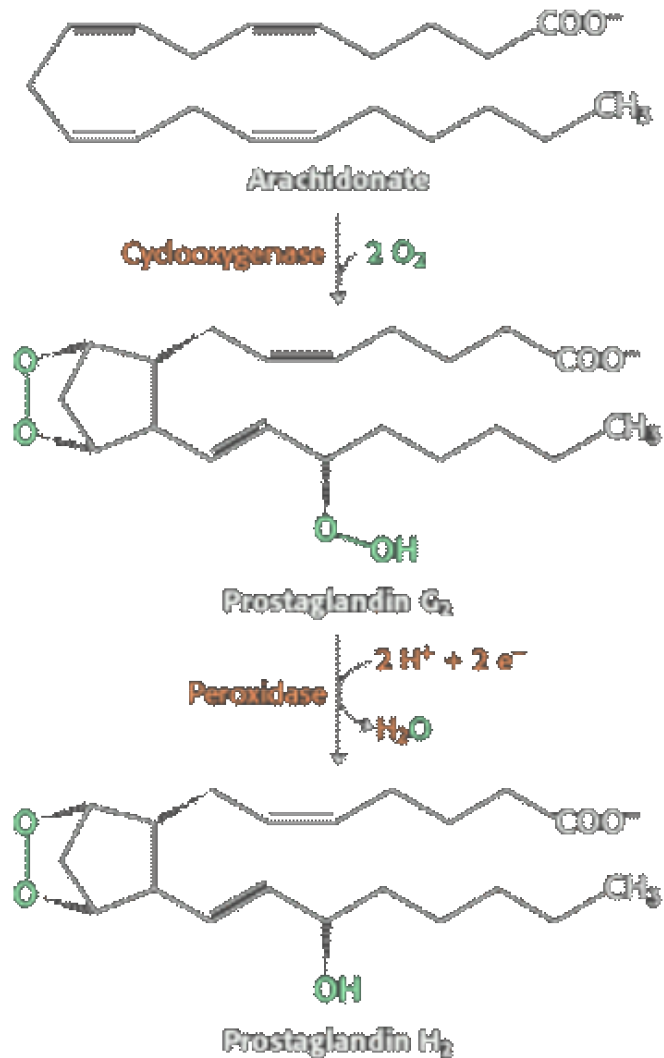
Prostaglandin H₂ synthase-1 (COX1)



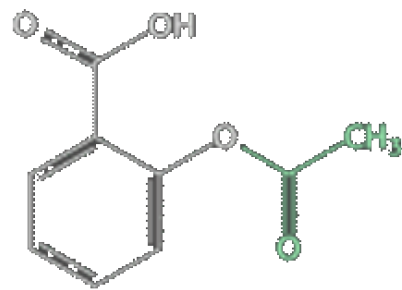
Prostaglandin H₂ synthase-1 (COX1)



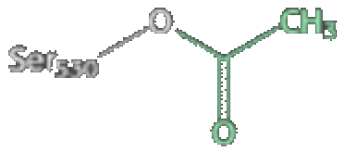
Prostaglandin H₂ synthase-1 (COX1)



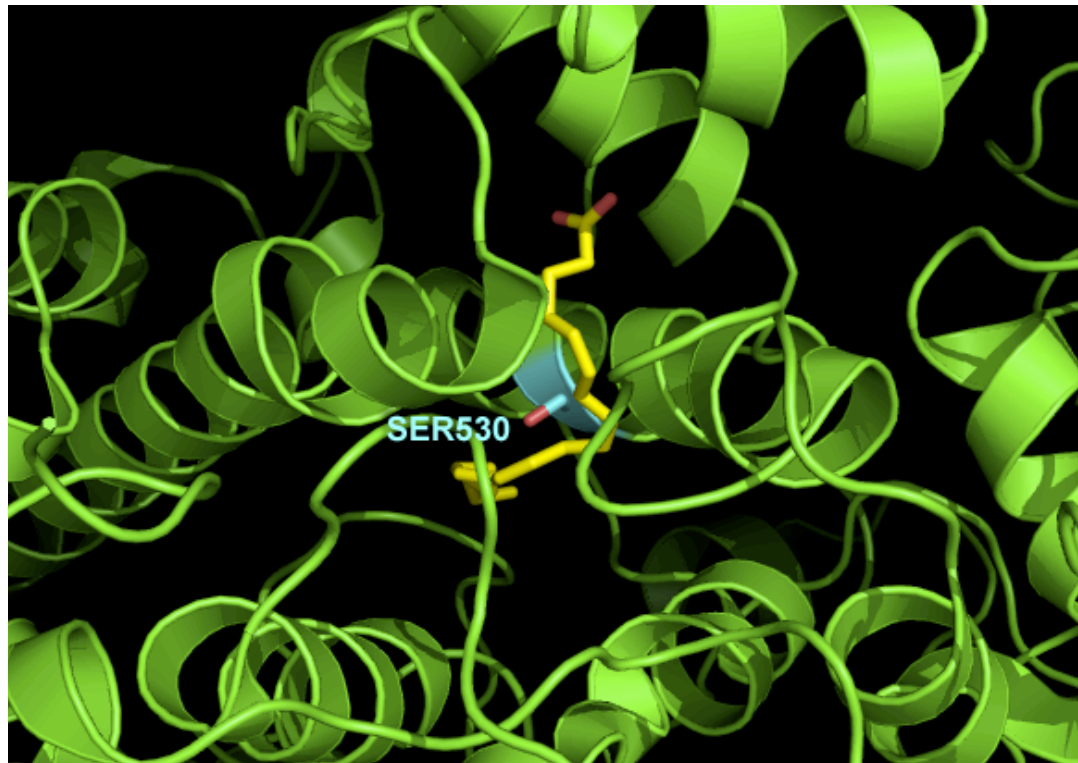
Aspirin's effects on prostaglandin H₂ synthase-1 (COX-1)



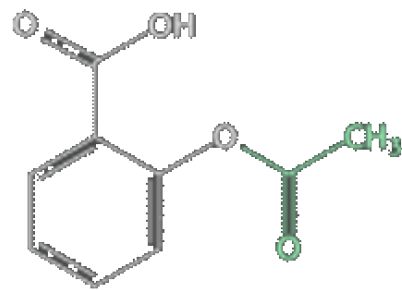
Aspirin
(Acetylsalicylic acid)



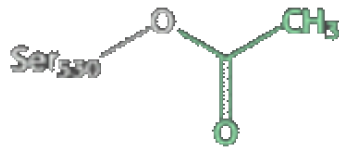
COX-1 Ser530 Arachidonate 3-AcetylOxy-Ser530



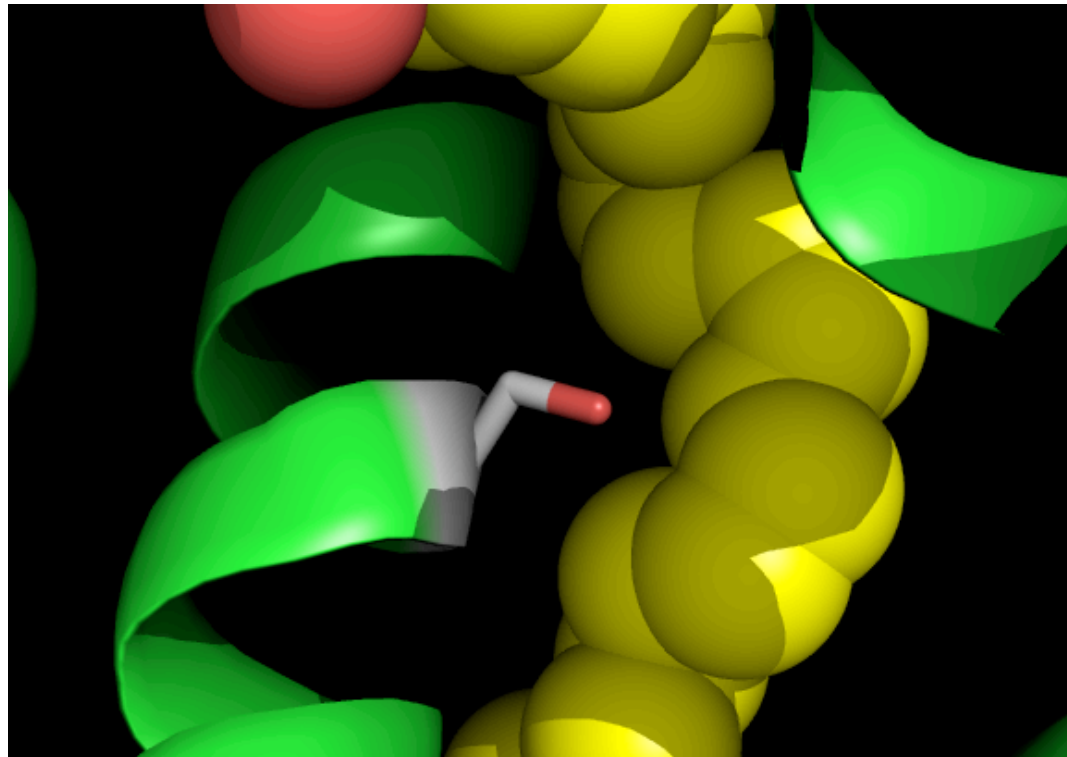
Aspirin's effects on prostaglandin H₂ synthase-1 (COX-1)



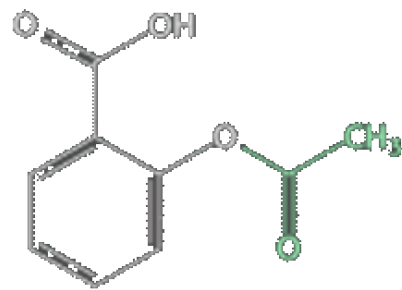
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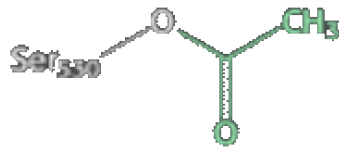
COX-1 Ser530 Arachidonate 3-AcetylOxy-Ser530



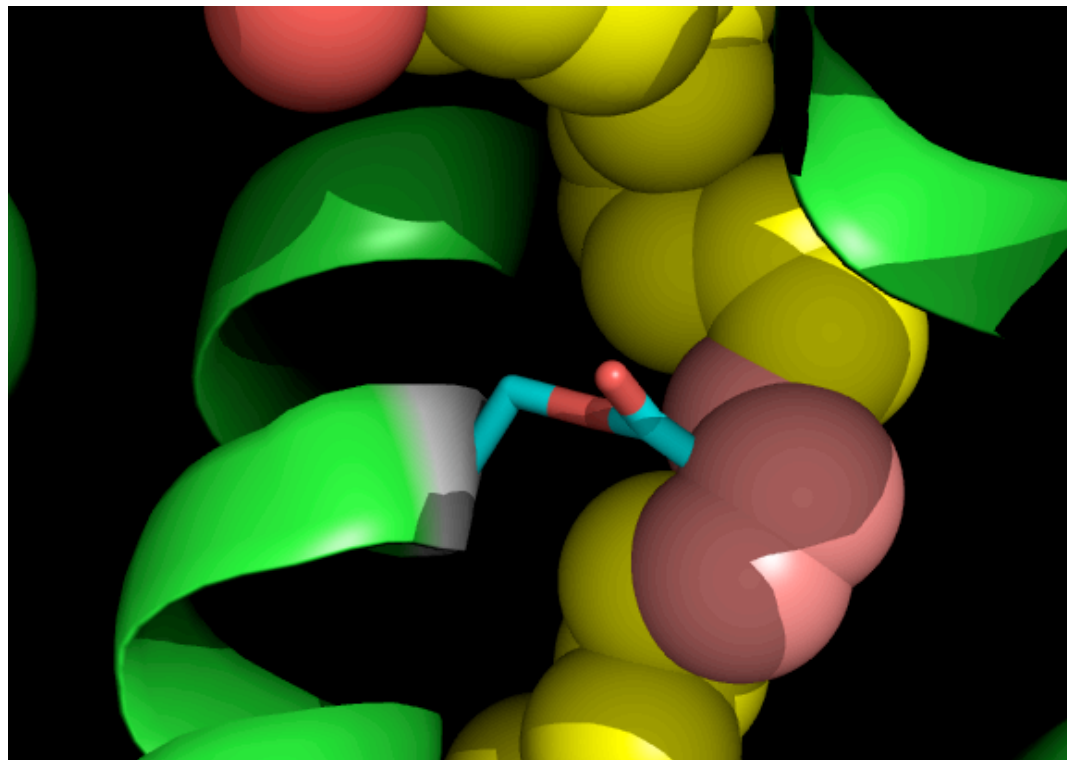
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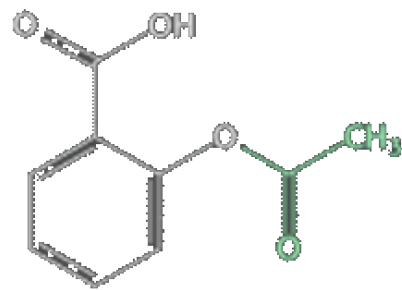
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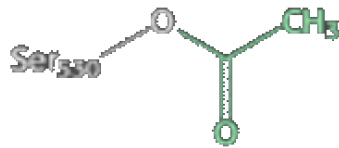
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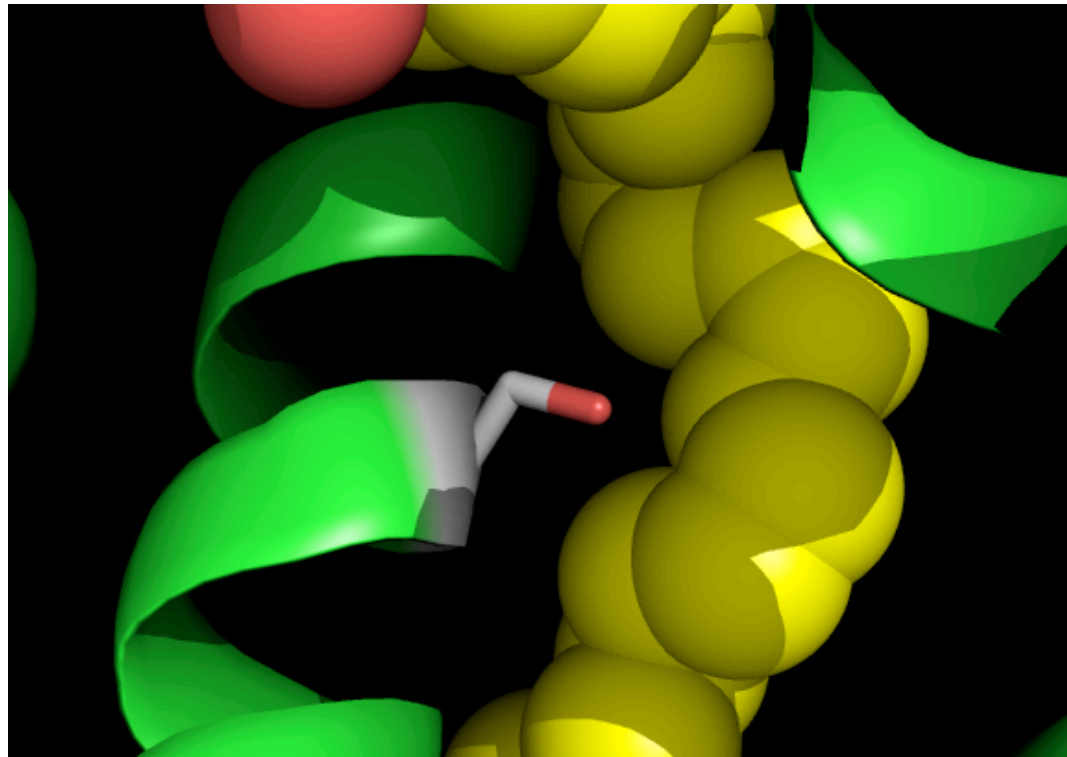
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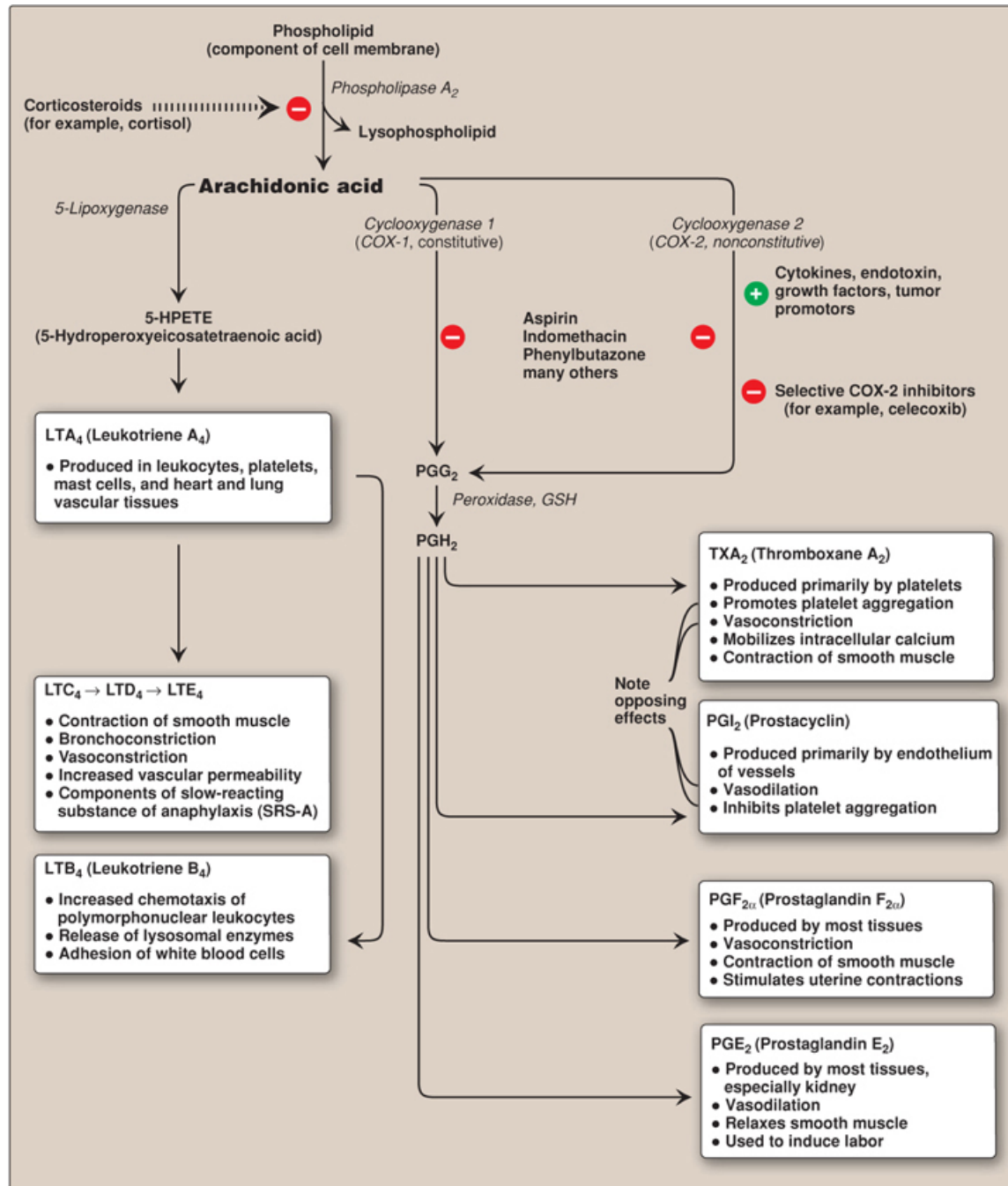
Aspirin
(Acetylsalicylic acid)



COX-1 Ser530 Arachidonate 3-AcetylOxy-Ser530

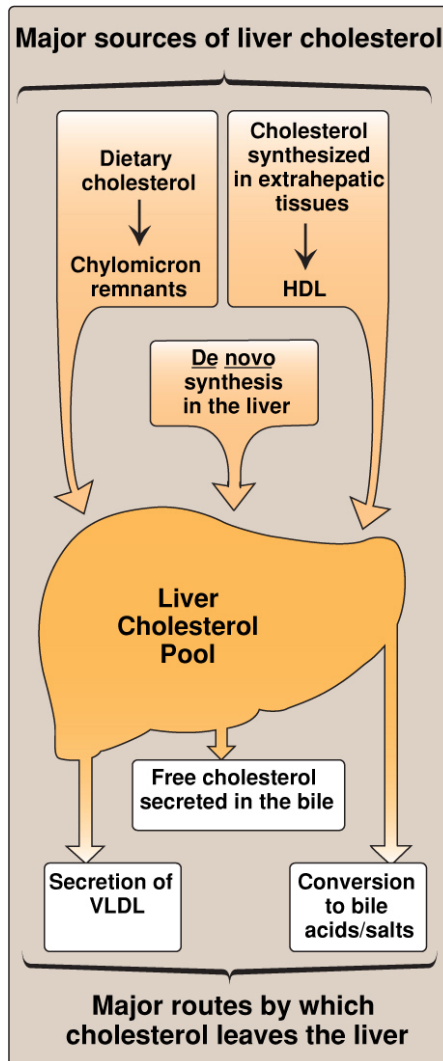


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<ul style="list-style-type: none"> Log In Free Registration Premium Content Subscriptions Email Alerts Audio RSS 	<p><i>The Lancet</i> 2007; 370:2138-2151 DOI:10.1016/S0140-6736(07)61909-6</p> <p>Review</p> <p>Are COX-2 inhibitors preferable to non-selective non-steroidal anti-inflammatory drugs in patients with risk of cardiovascular events taking low-dose aspirin?</p> <p>Prof Vibeke Strand MD </p>					
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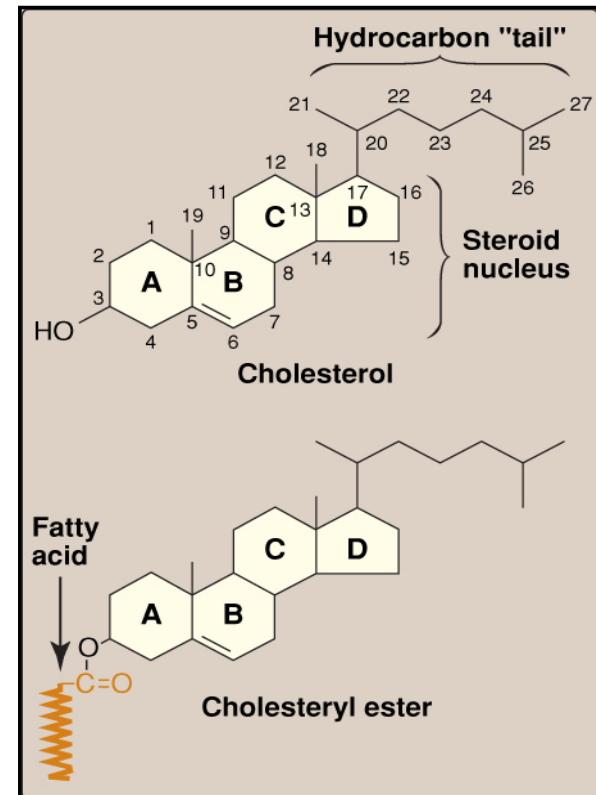
Cholesterol (chapter 18)

- 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.

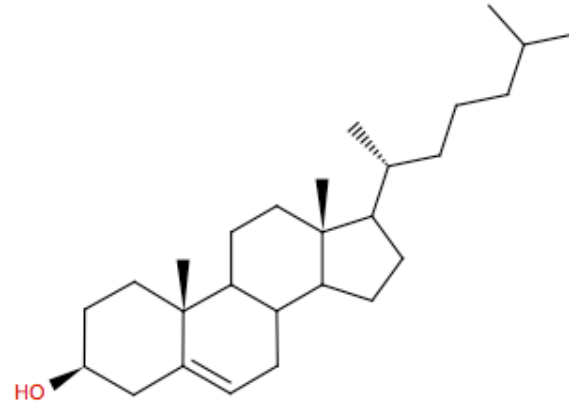
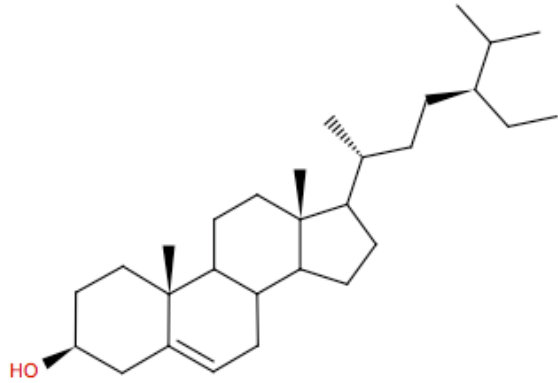


cholesterol structure

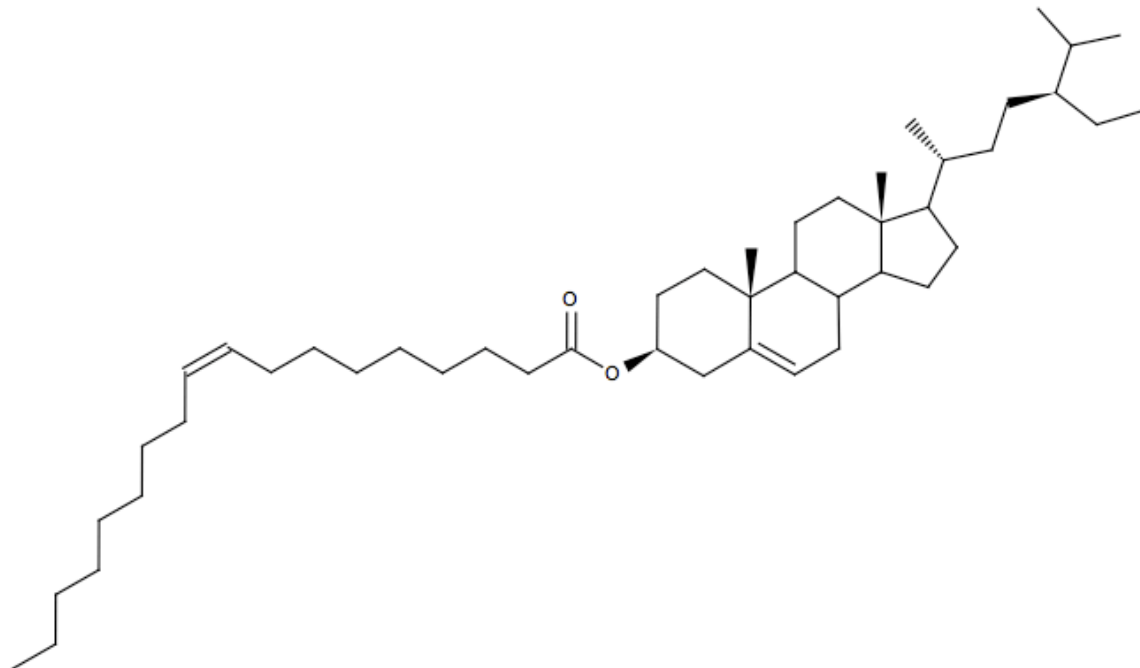
- most plasma cholesterol is in the esterified form (not found in cells or membranes)
- cholesterol functions in all membranes (drives formation of lipid microdomains)
- cholesterol is the precursor for steroid hormones
- note 4 fused rings, single dbl bond, single hydroxyl, acyl chain at C17



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

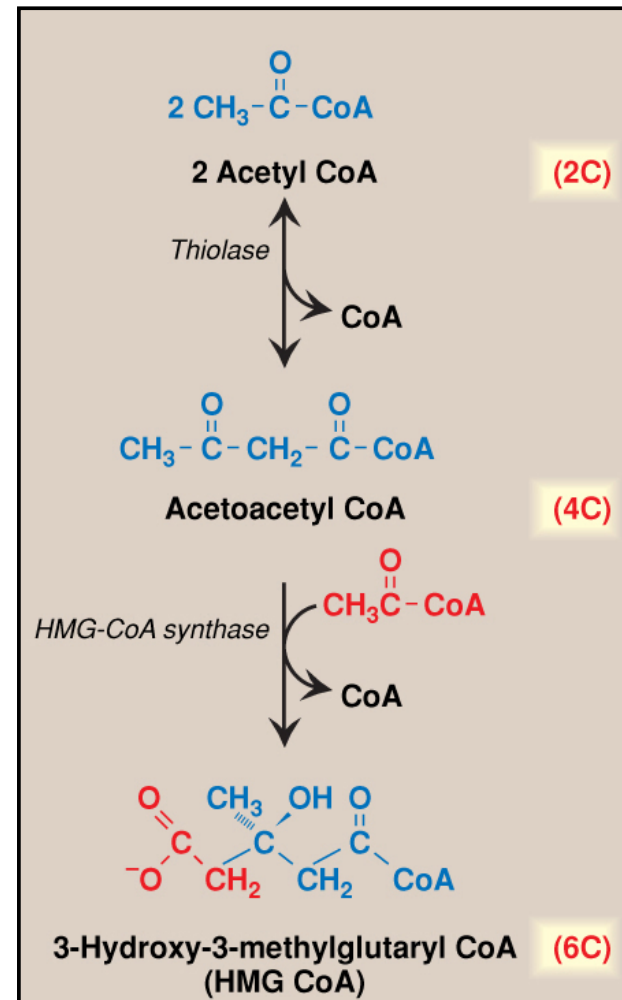


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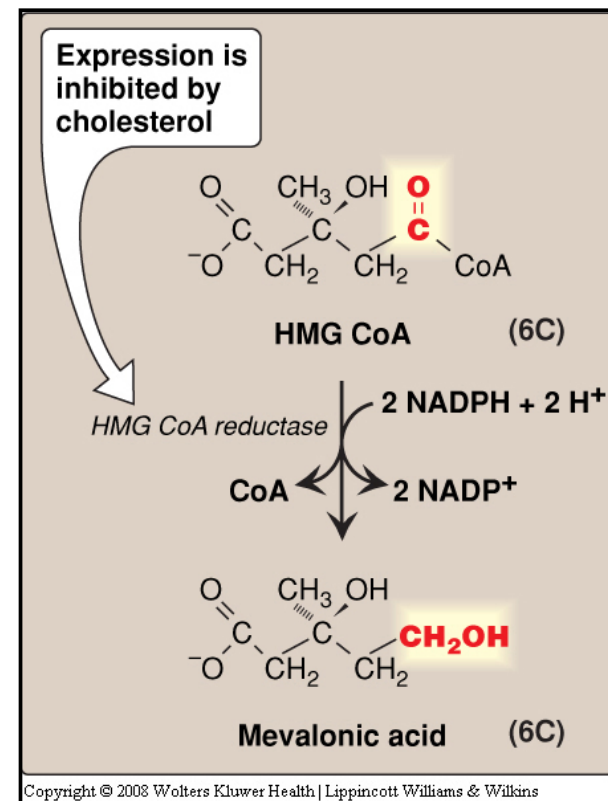
Cholesterol synthesis initially follows that of ketone bodies

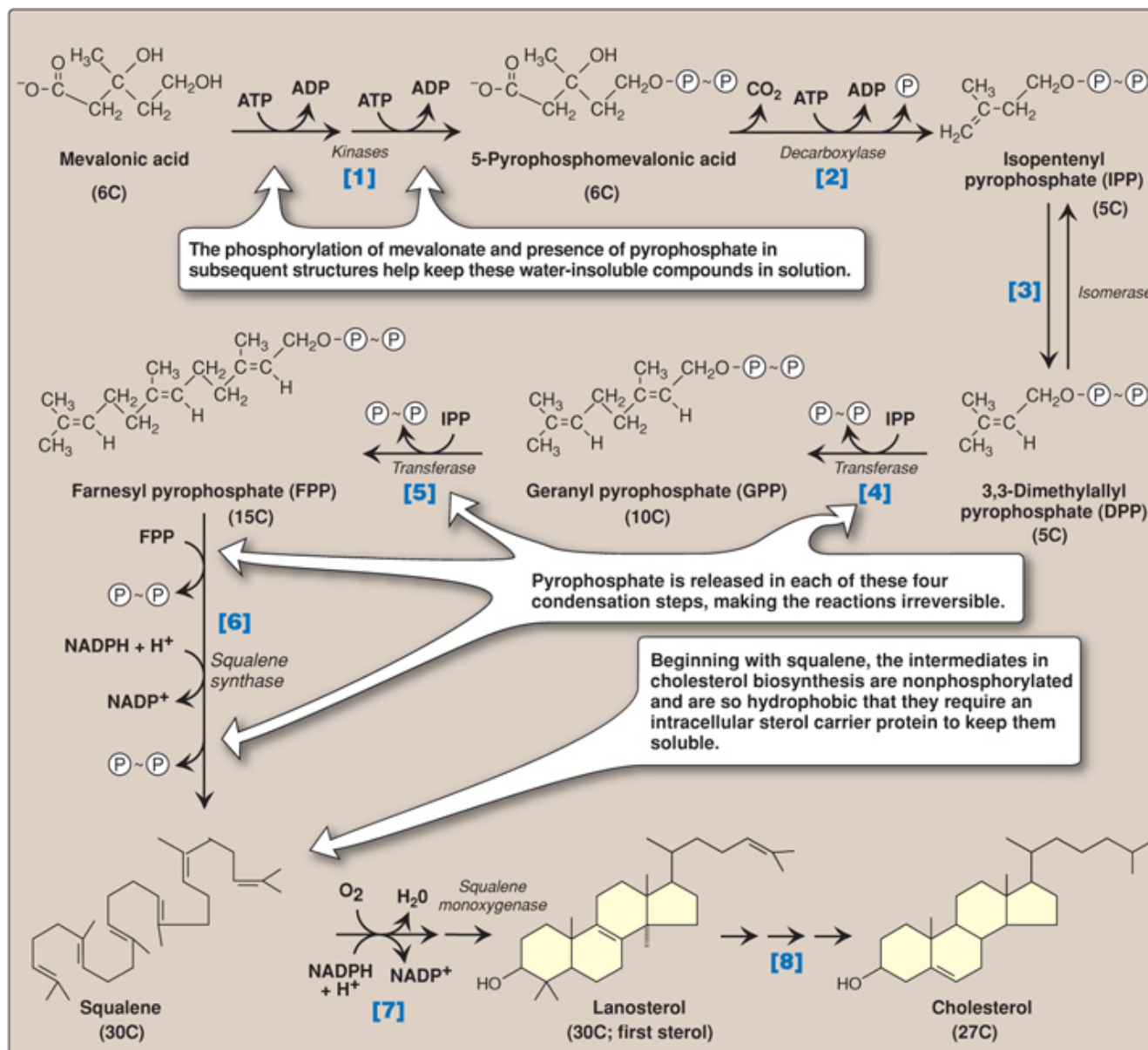
3 cytoplasmic acetyl CoA molecules are sequentially condensed to form HMG CoA (6 carbons)

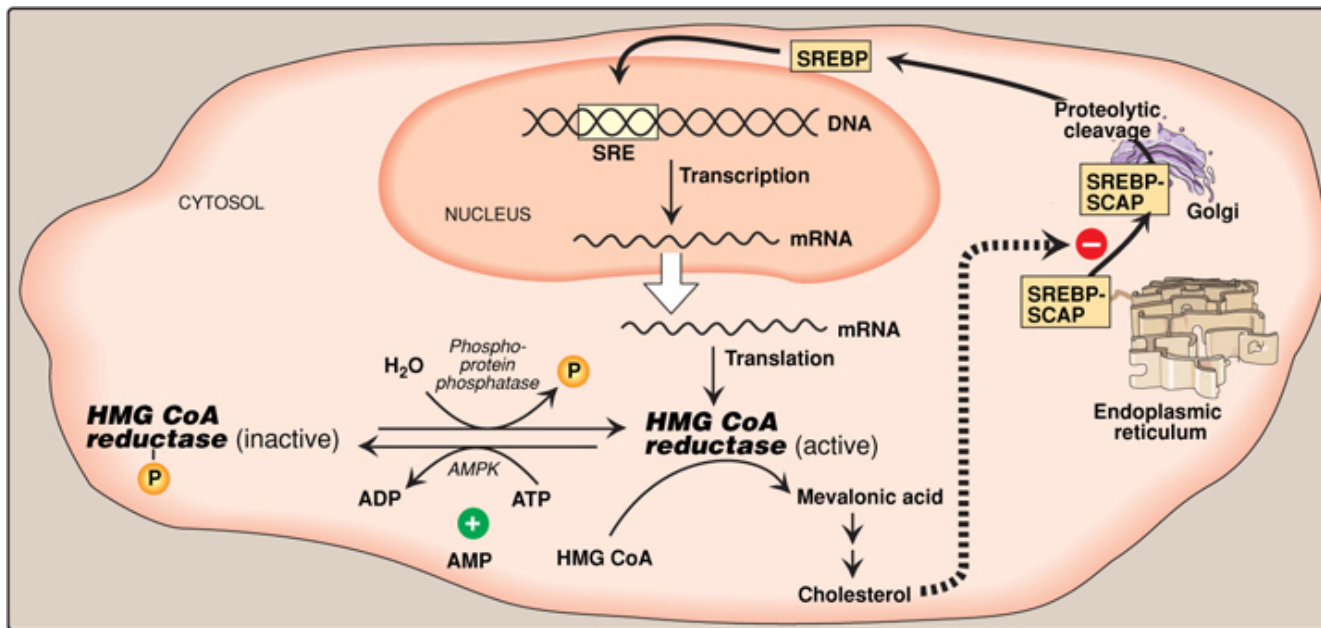


The rate-limiting step of de novo cholesterol biosynthesis is catalyzed by HMG CoA reductase

- 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



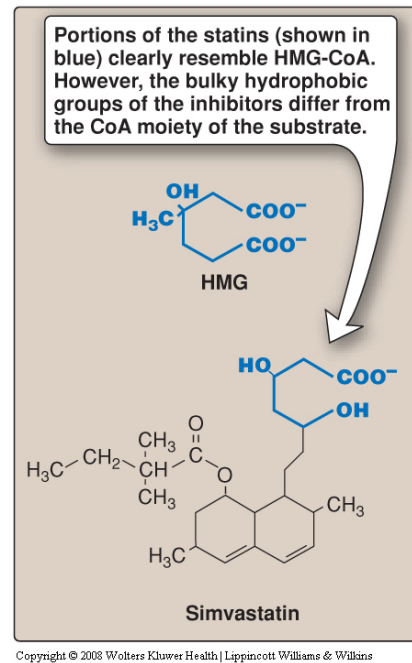




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Regulation of HMG CoA reductase

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



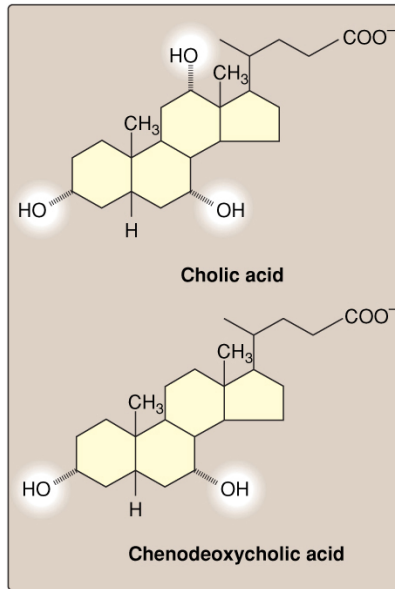
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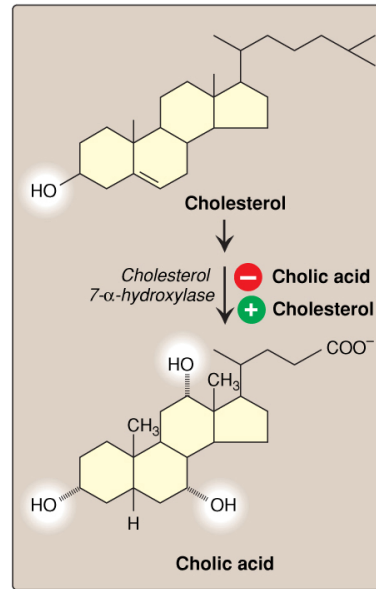
Degradation of Cholesterol

- 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.

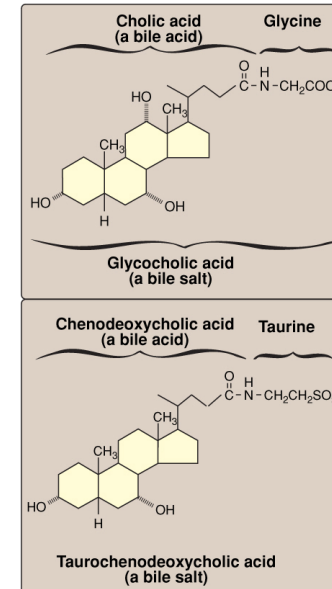
Degradation of Cholesterol



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- 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.