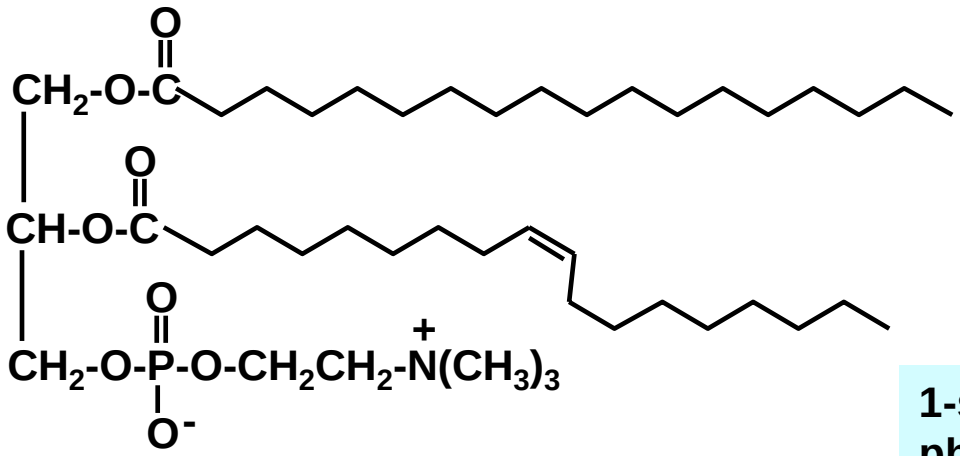
2. Phospholipids, triacylglycerols and complex Lipids

Membranes contain a variety of glycerophospholipids and sphingolipids



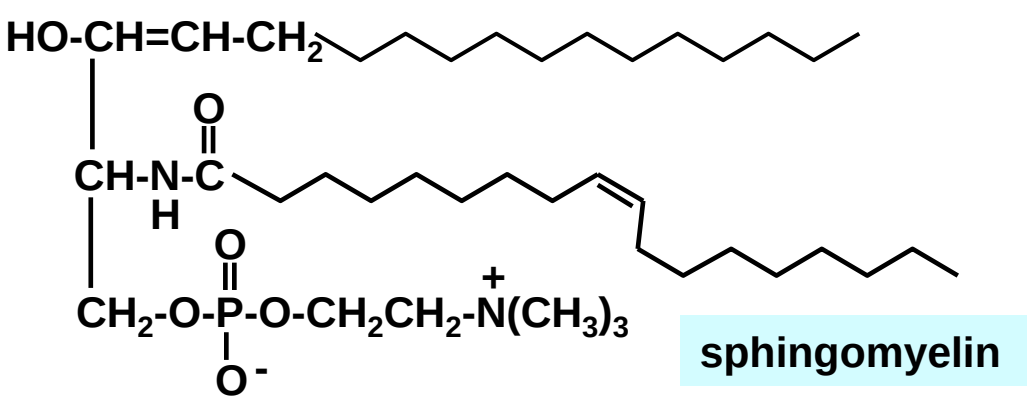
glycerol

phosphocholine

1-stearoyl-2-oleoyl-phosphatidylcholine

other common glycerophospholipids:

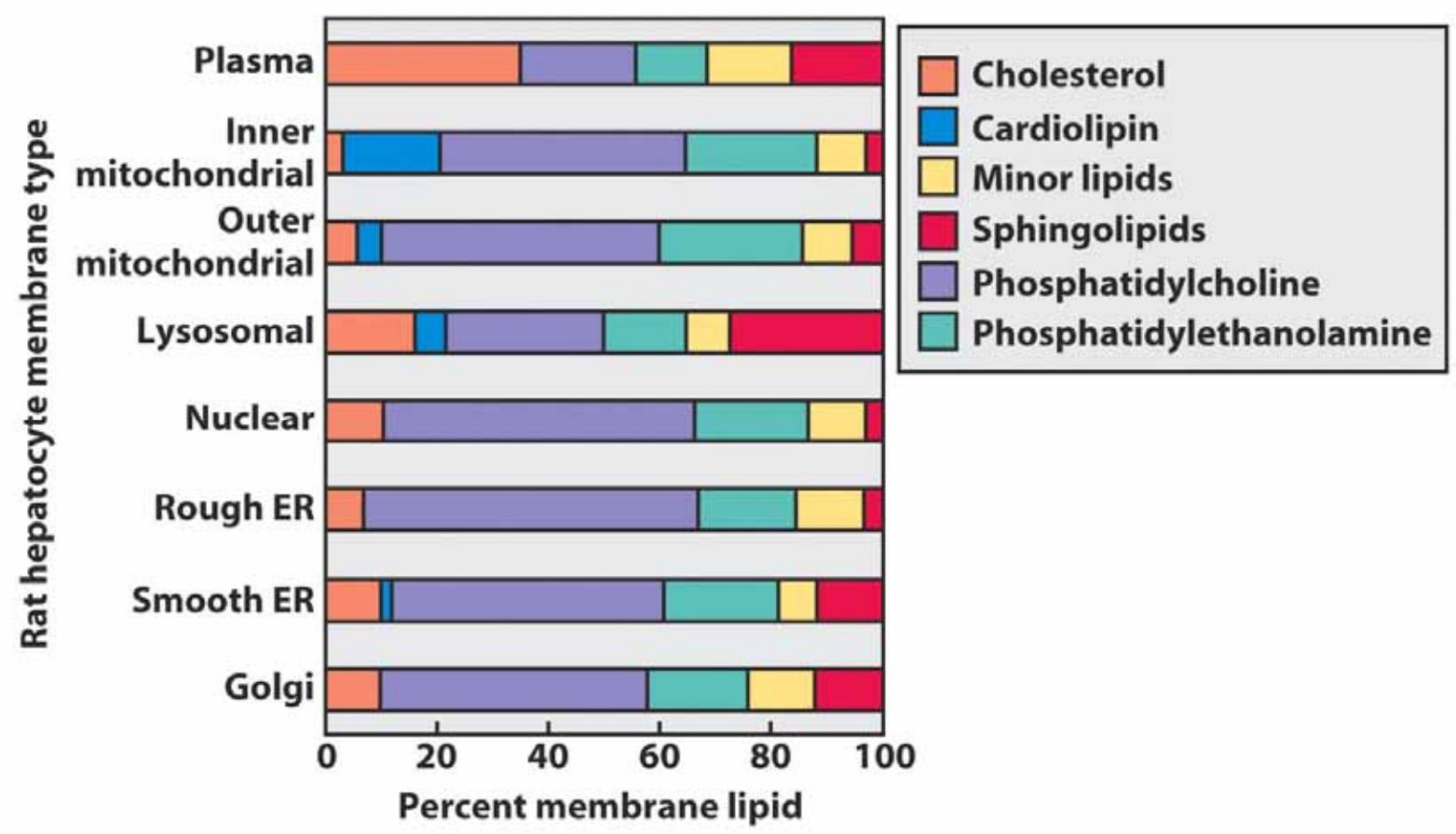
- phosphatidylethanolamine
- phosphatidylserine
- phosphatidylglycerol
- phosphatidylinositol



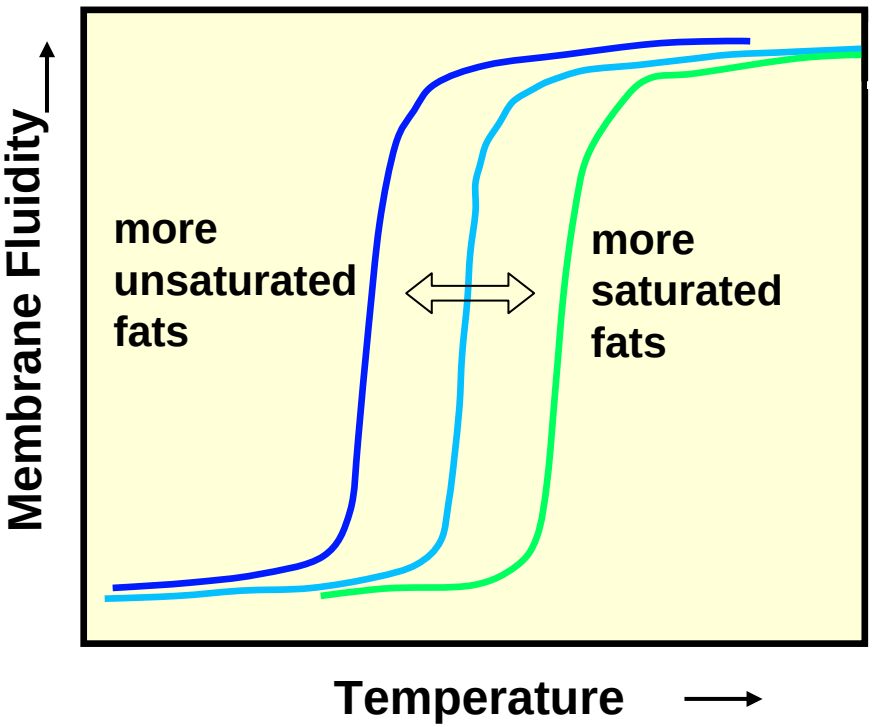
sphingomyelin

sphingolipids with carbohydrate groups serve as recognition factors on cell surfaces

Lipids in rat hepatocyte (liver cell) membranes

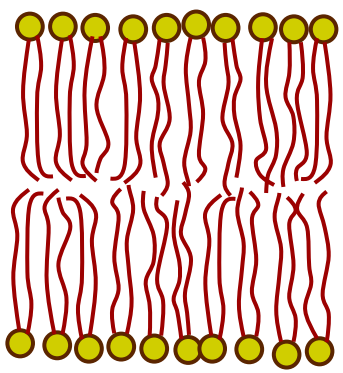


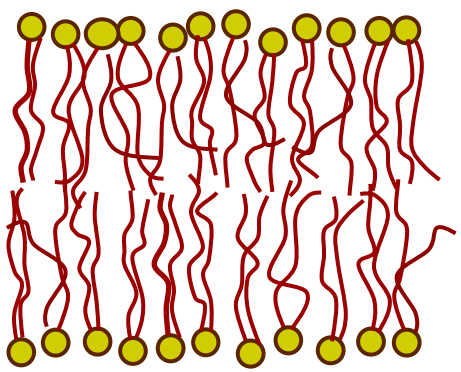
The fluidity of a phospholipid bilayer increases at a characteristic temperature (T_m), where the side chains become more disordered

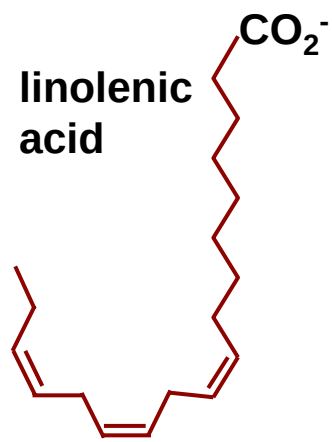


T_m depends on the composition of the phospholipids. Phospholipids with unsaturated side chains or short side chains melt at lower temperatures

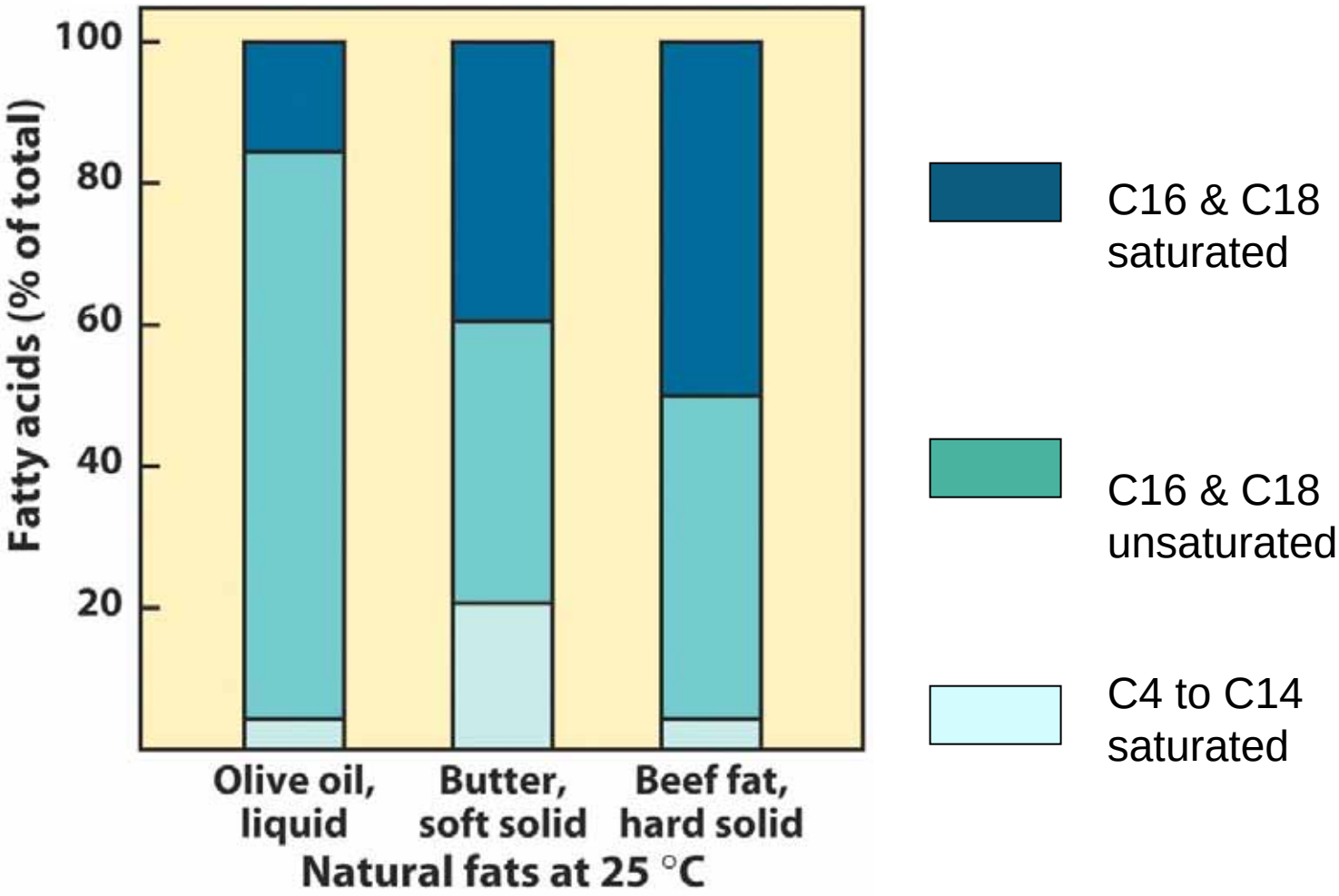
Most natural unsaturated fatty acids have *cis* double bonds. Phospholipids with unsaturated fatty acid side chains don't pack well with phospholipids that have saturated side chains.





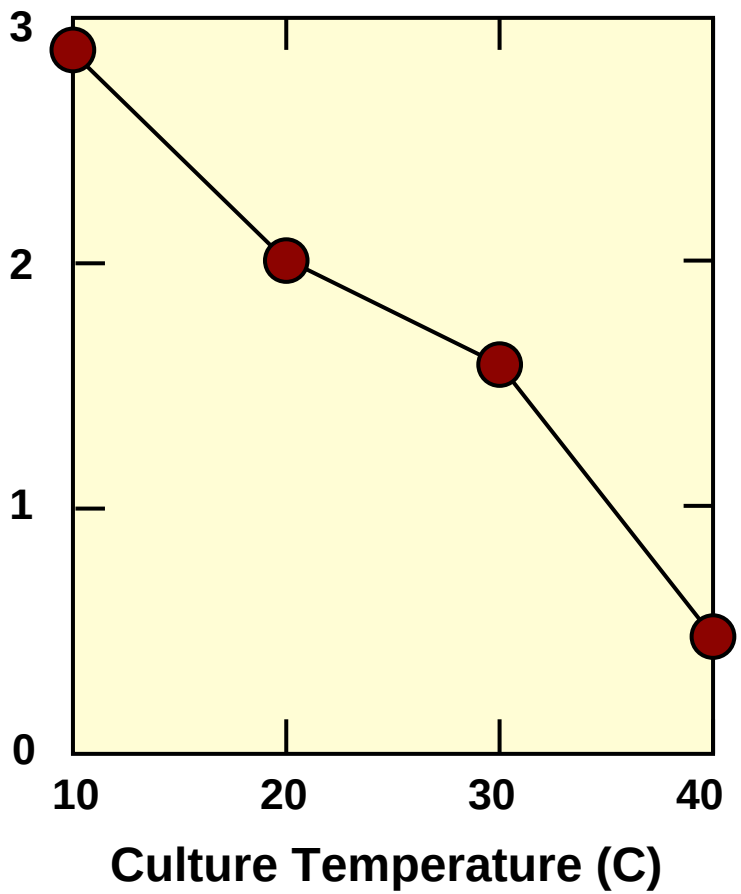


Unsaturated fatty acids and short-chain fatty acids also make natural fats more fluid



Cells adjust their phospholipid composition so that T_m typically is slightly below the growth temperature

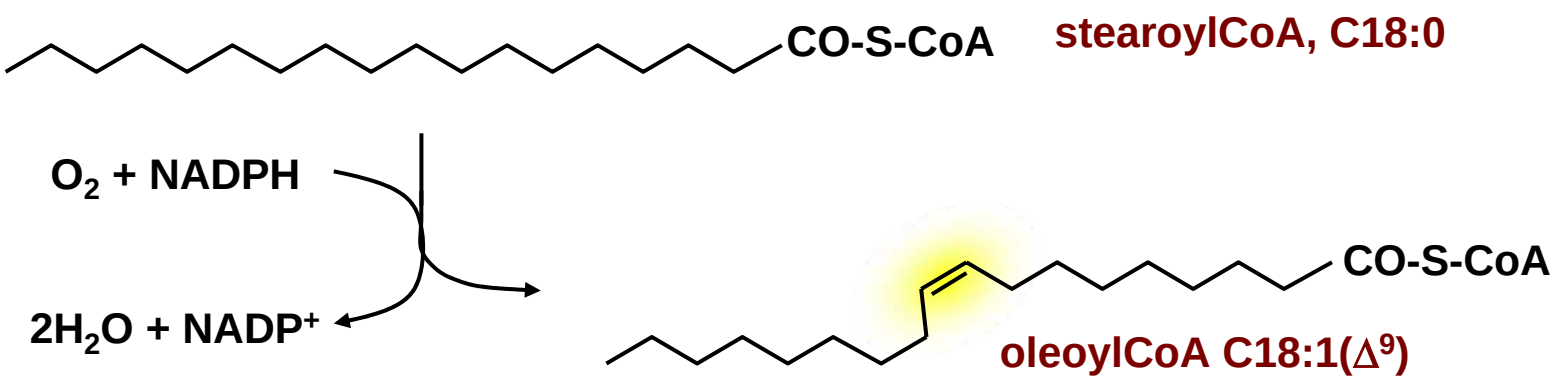
Ratio of unsaturated to saturated fatty acids in *E. coli* grown at different temperatures



cool → warm

Lehninger Table 11-2; A. G. Marr & J. L. Ingraham, *J. Bact.* 84: 1260 (1962)

Animals snthesize oleic acid (C18:1) from stearoylCoA by an enzyme system that uses molecular O_2 as an oxidant



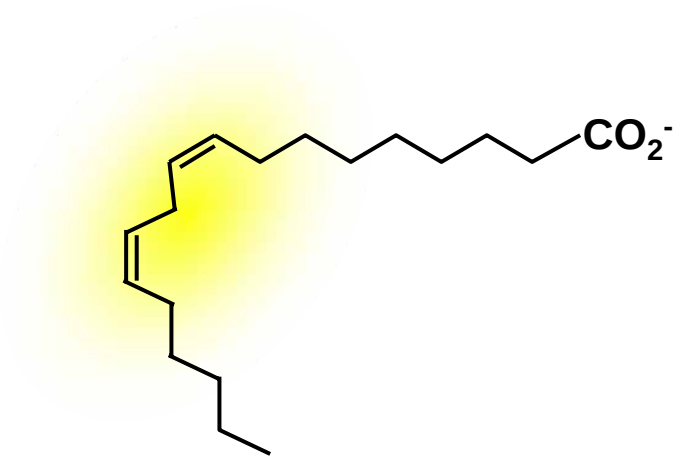
This process occurs in the ER. The fatty acid and NADPH each provides two electrons for the reduction of O_2 to water, which requires 4 electrons:

$$O_2 + 4\ e^- + 4\ H^+ \longrightarrow 2\ H_2O$$

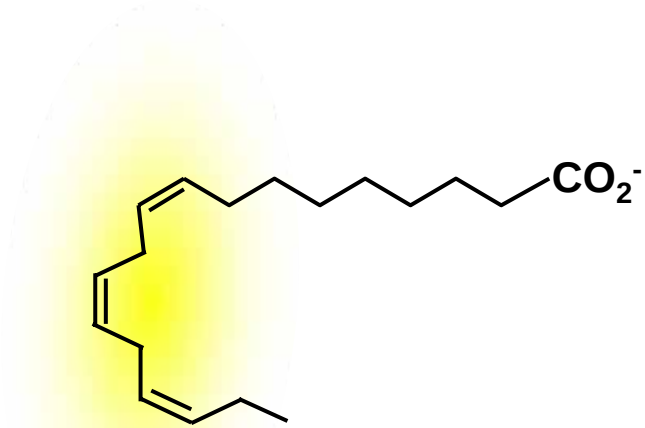
A cytochrome (cytochrome b_5) and a flavoprotein (cytochrome b_5 reductase) carry electrons from NADPH to the oxidase.

palmitoleate (C16:1(Δ^9)) is synthesized in the same way from palmitate

Animals can't synthesize unsaturated fatty acids with two or three double bonds



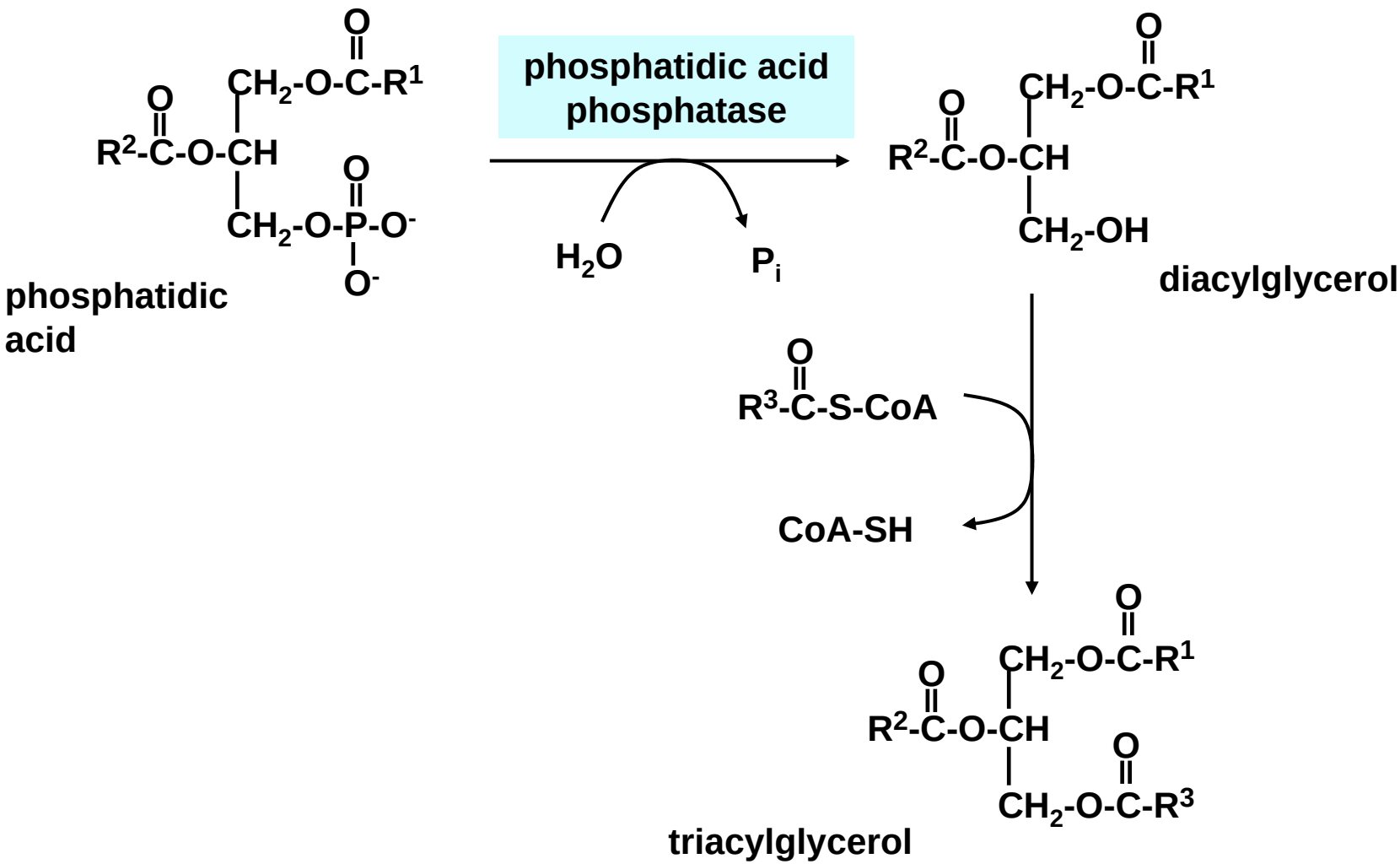
linoleate, 18:2($\Delta^{9,12}$)



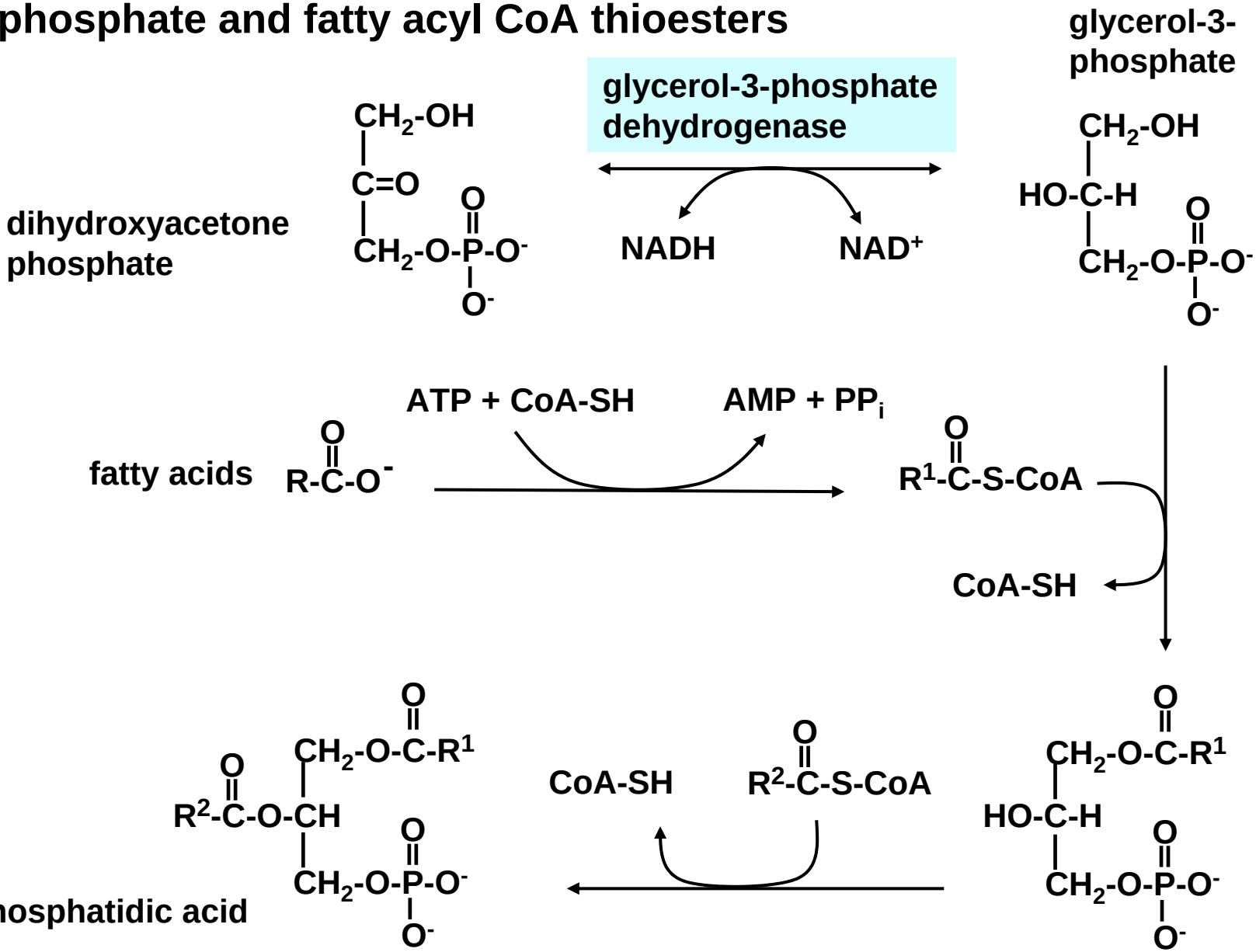
linolenate, 18:3($\Delta^{9,12,15}$)

Linoleate and linolenate are required in the diet. They're "essential" fatty acids. But once ingested, they can be converted into other polyunsaturated fatty acids including arachidonate (20:4($\Delta^{5,8,11,14}$)).

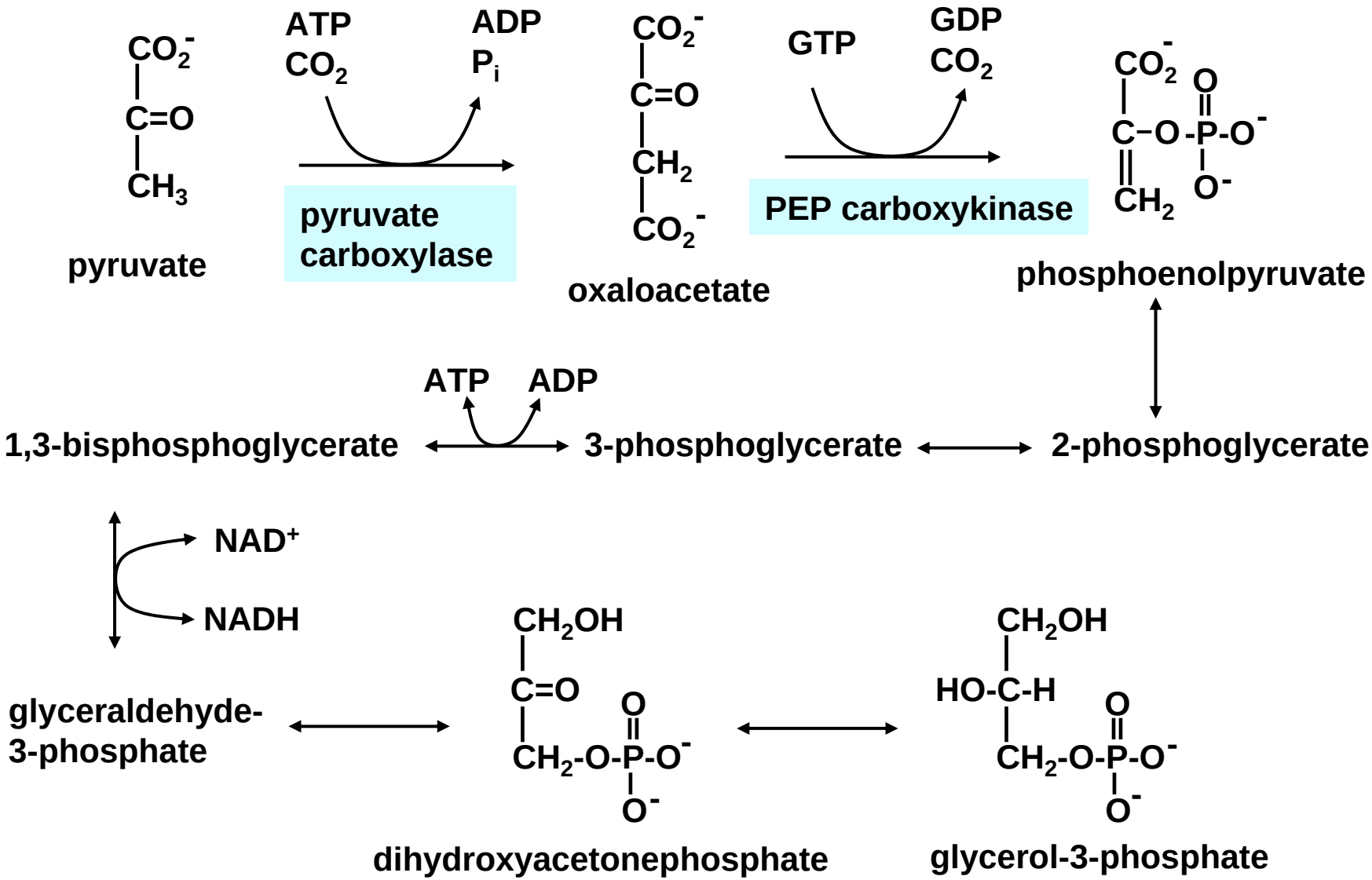
Triacylglycerols & diacylglyerols are formed from phosphatidic acids



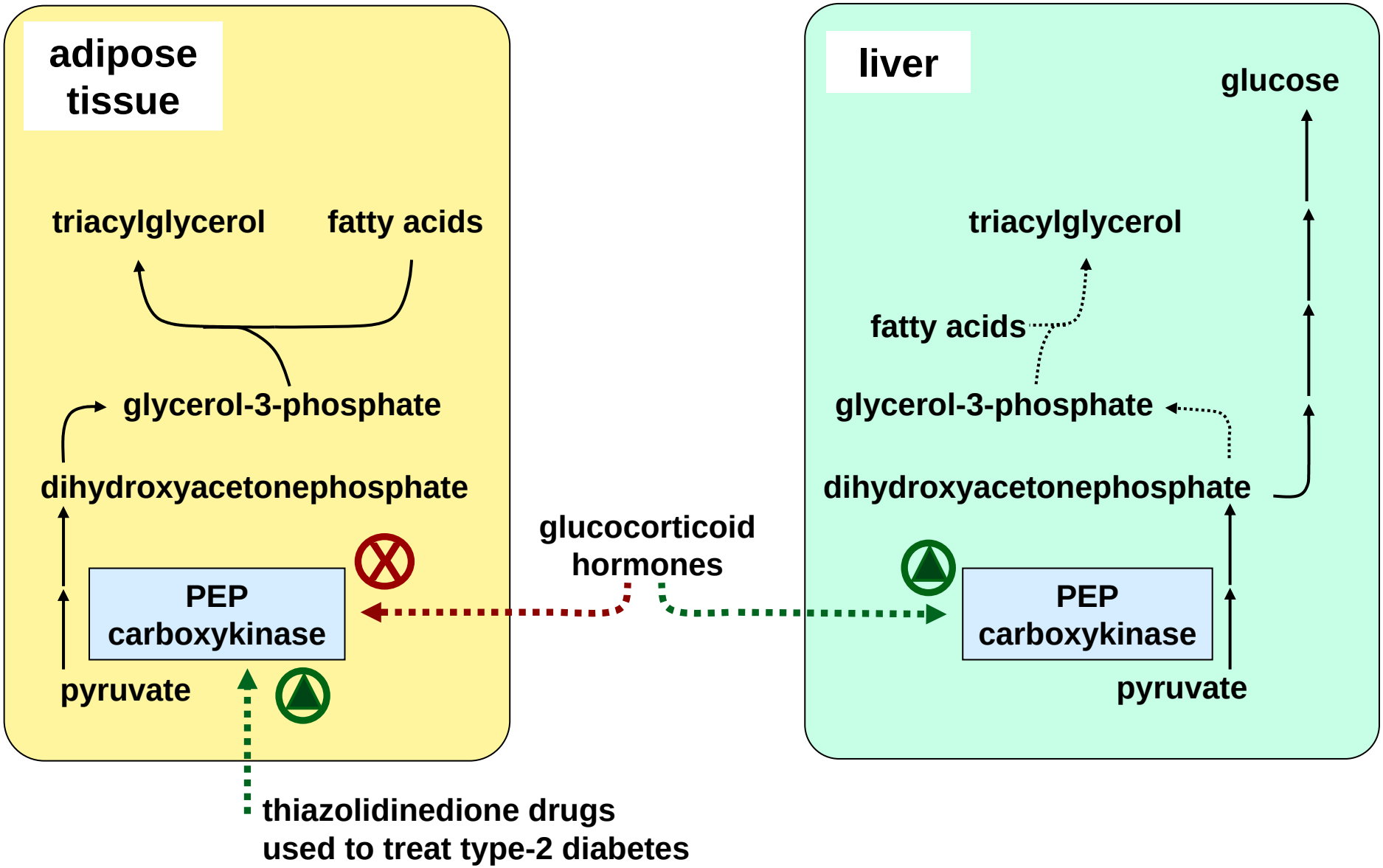
Phosphatidic acids can be synthesized from glycerol-3-phosphate and fatty acyl CoA thioesters



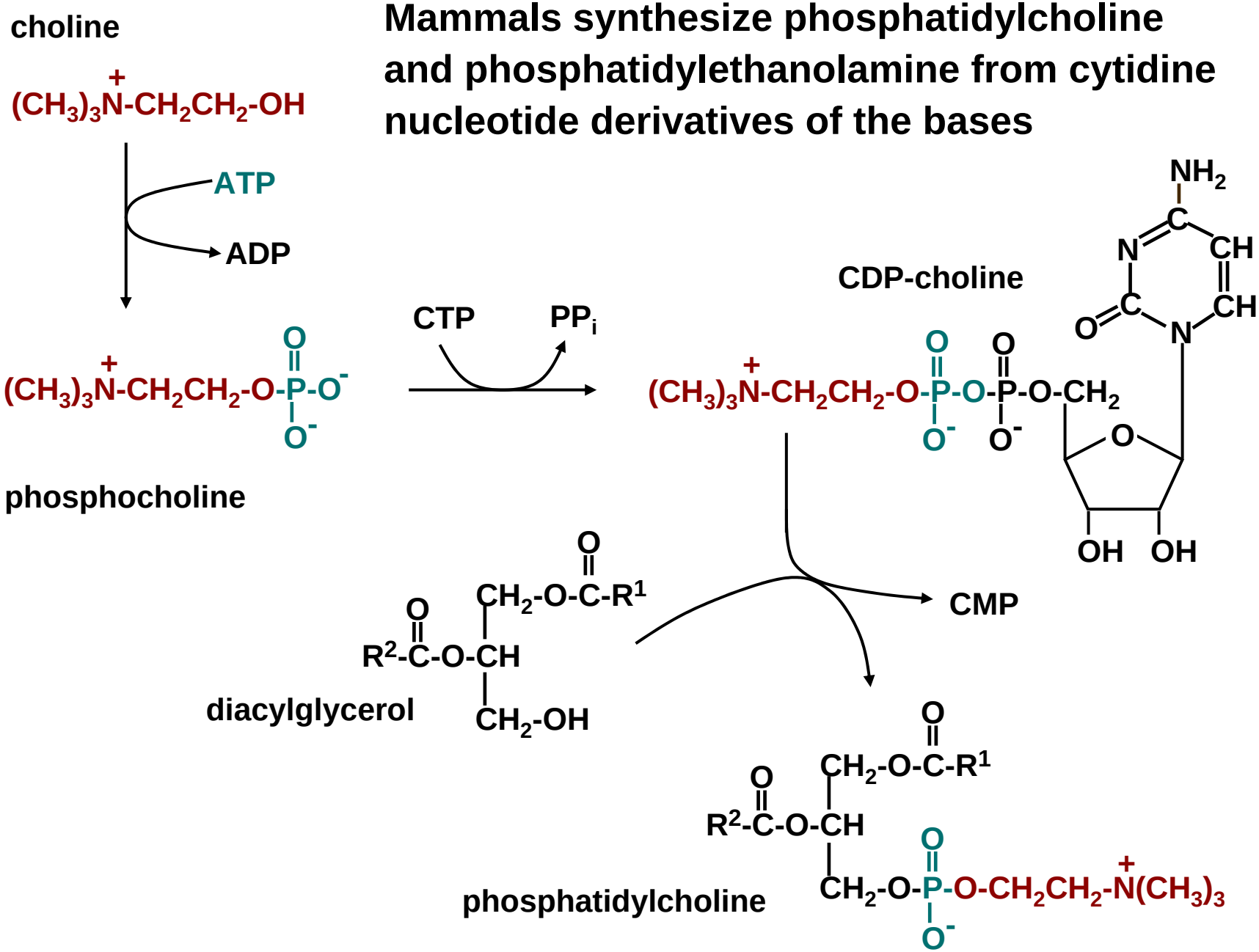
Adipose tissue can generate glycerol-3-phosphate from glucose or by glyceroneogenesis



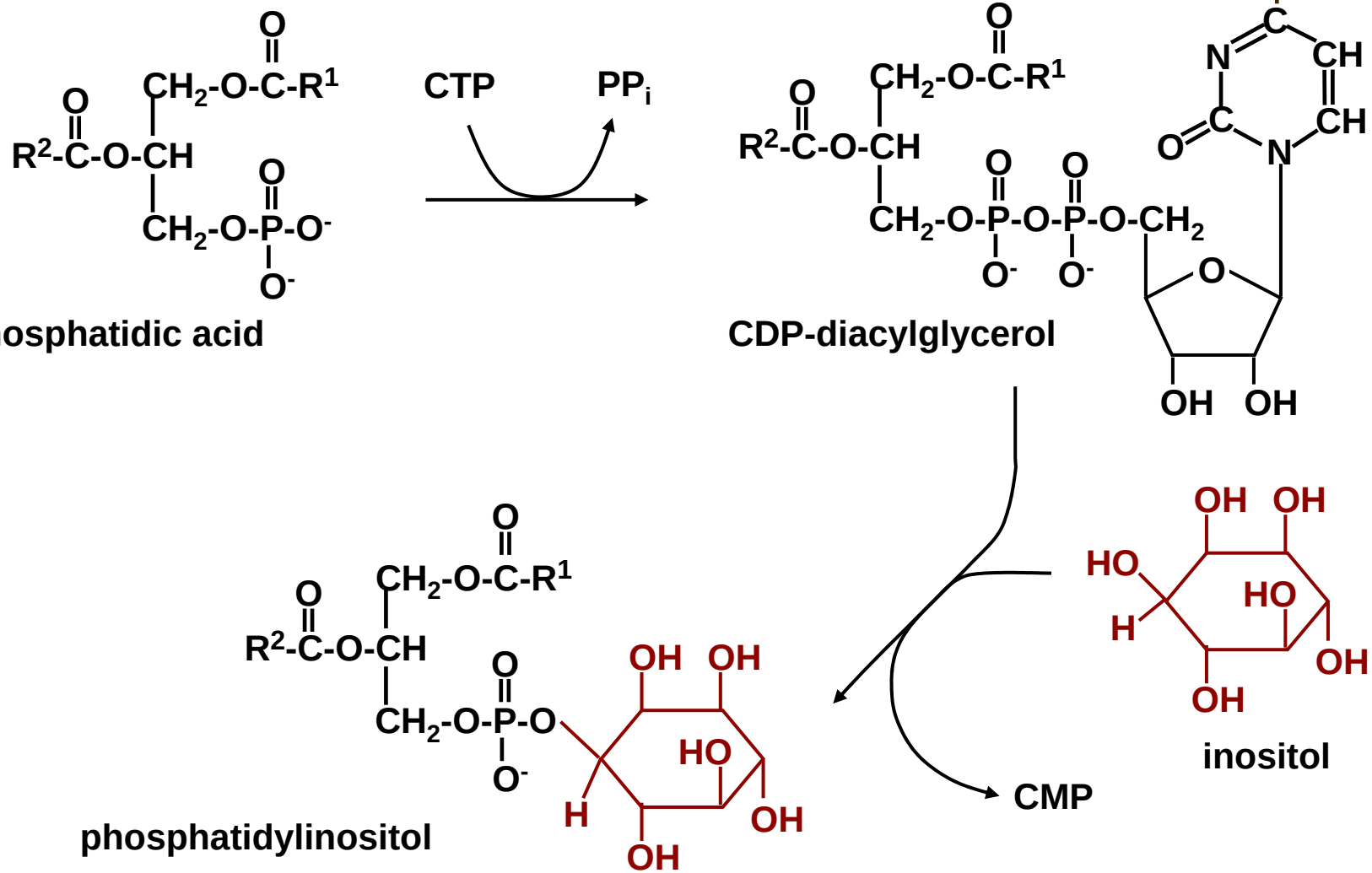
Glyceroneogenesis and gluconeogenesis are regulated reciprocally by changes in the amount of PEPcarboxykinase



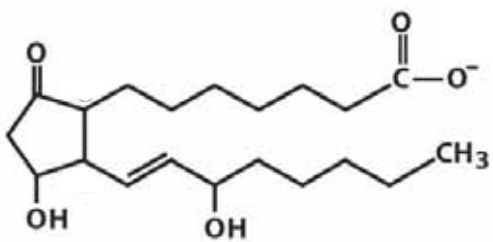
Mammals synthesize phosphatidylcholine and phosphatidylethanolamine from cytidine nucleotide derivatives of the bases



Phosphatidylinositol and some other glycerophospholipids are formed from CDP-diacylglycerol



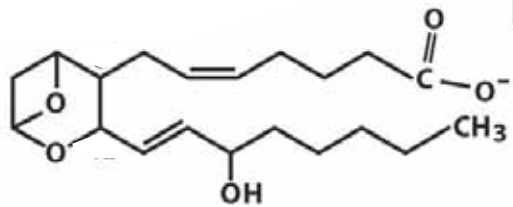
Eicosanoids are 20-carbon lipids that act locally to stimulate a variety of processes



Prostaglandin E_1

Prostaglandins:

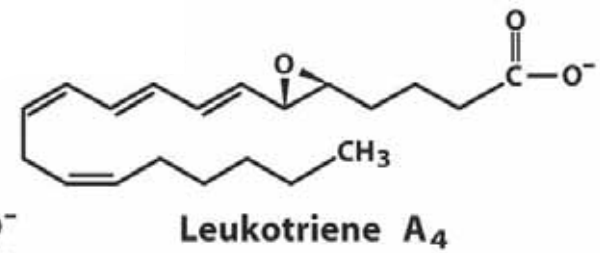
act through cAMP; stimulate contraction of smooth muscle, affect blood flow, elevate body temperature, or cause inflamation & pain



Thromboxane A_2

Thromboxanes:

produced by platelets; act in formation of blood clots & reduction of blood flow at the site of a clot

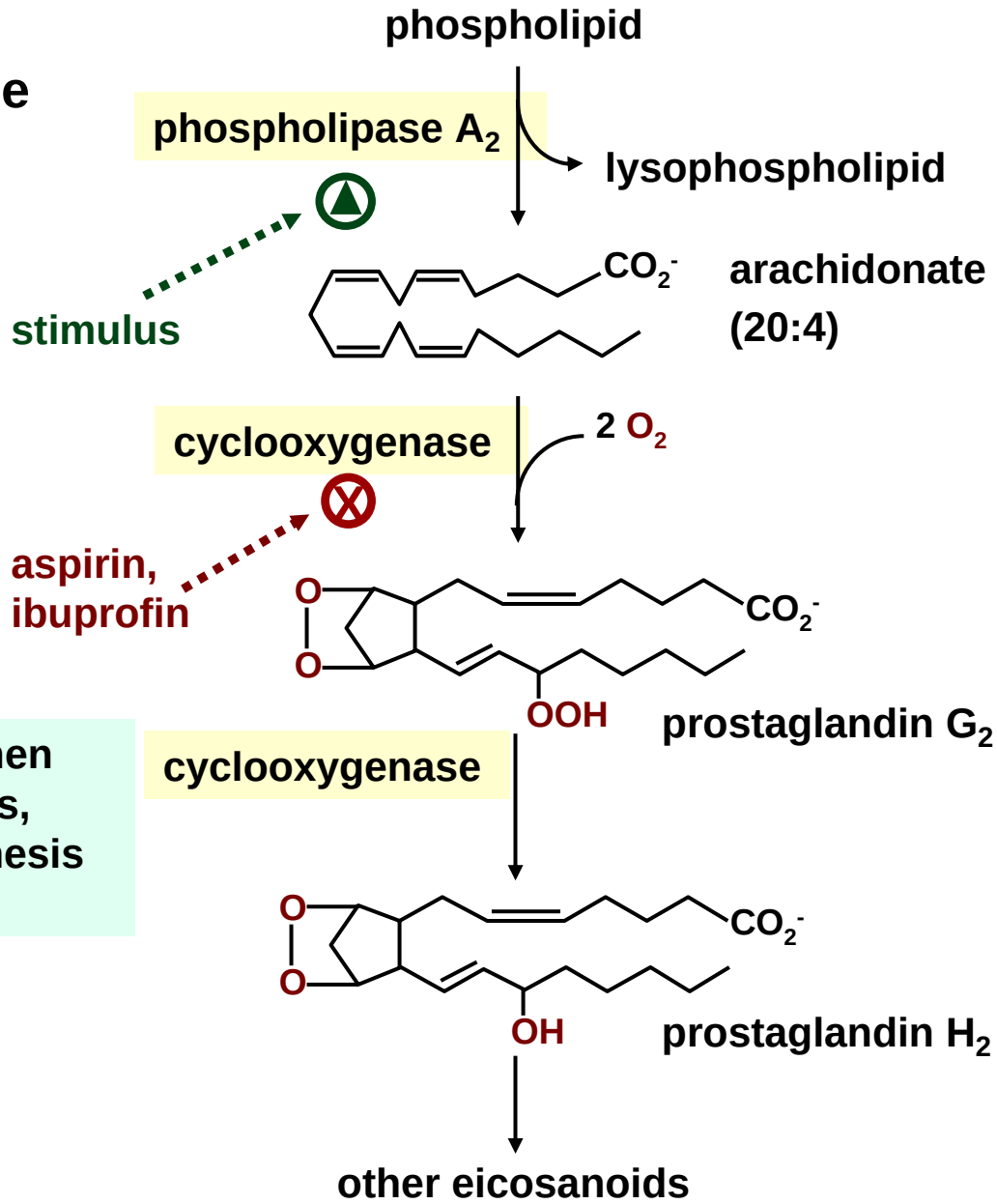


Leukotriene A_4

Leukotrienes:

induce contraction of muscle lining airways to the lungs.

Mammalian cells synthesize eicosanoids from arachidonic acid



Arachidonic acid is released by breakdown of phospholipids in response to cell damage or hormonal stimuli.

Aspirin, ibuprofin and acetaminophen (nonsteroidal anti-inflamatory drugs, NSAIDS) block prostaglandin synthesis by inhibiting cyclooxygenase.

Non-steroidal anti-inflamatory drugs (NSAIDs) have been used widely to treat osteoarthritis and rheumatoid arthritis.

Aspirin, taken regularly in small amounts, decreases the risk of atherosclerosis.

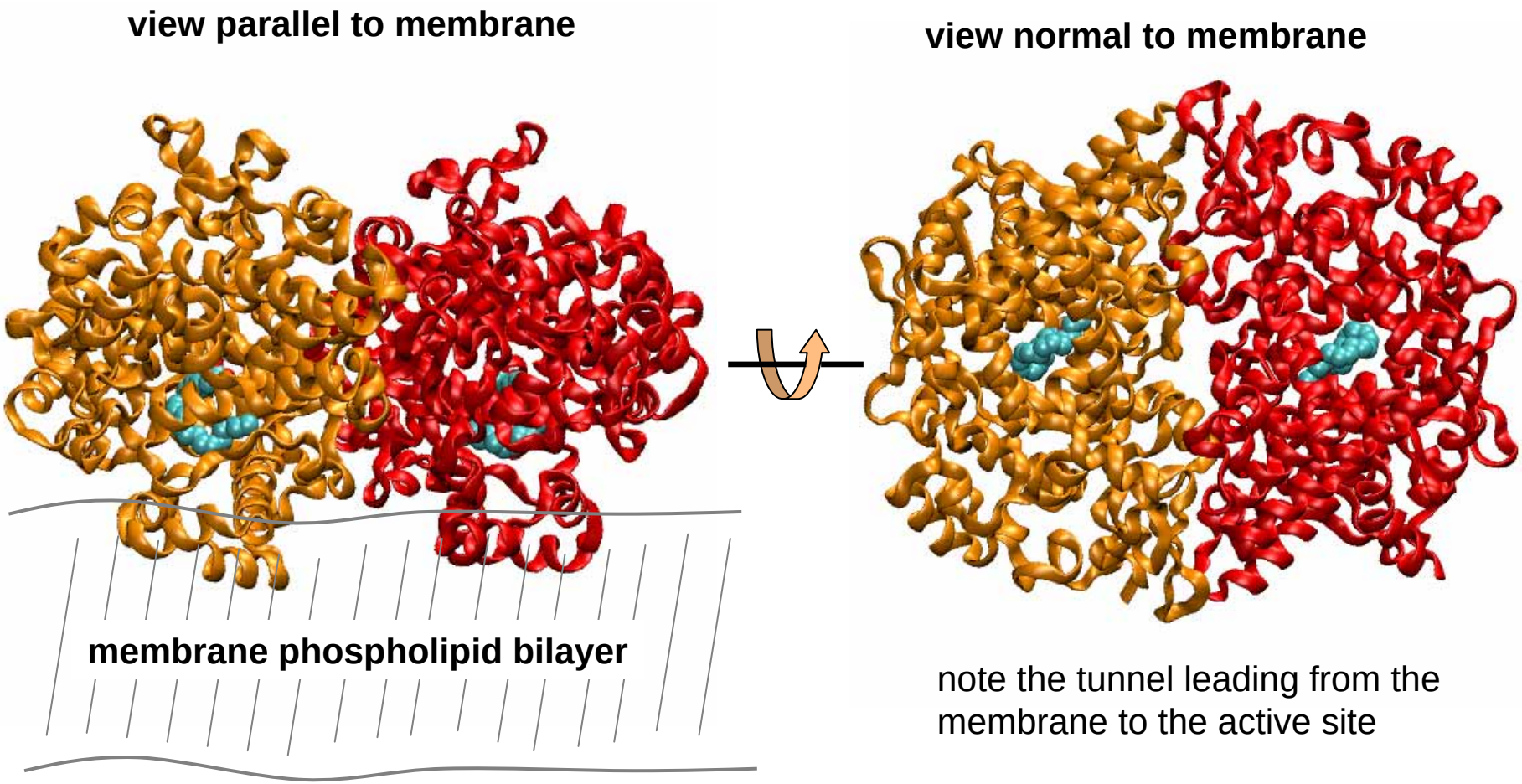
Mammals have two isozymes of cyclooxygenase -- COX-1 & COX-2. The prostaglandins produced by COX-1 participate in some "house-keeping" functions such as secretion of gastric mucin; those produced by COX-2 play larger roles in inflamation.

Aspirin and other drugs that inhibit both COX-1 & COX-2 (e.g., ibuprofin, naproxin) have anti-inflamatory effects, but also decrease secretion of gastric mucin, causing stomach irritation.

Drugs that specifically inhibit COX-2 cause less stomach irritation. These include celecoxib (Celebrex) and rofecoxib (Vioxx).

But celecoxib, rofecoxib, valdecoxib (Bextra) and naproxin (Naprosin, Aleve) recently were found to increase the risk of heart attacks and stroke.

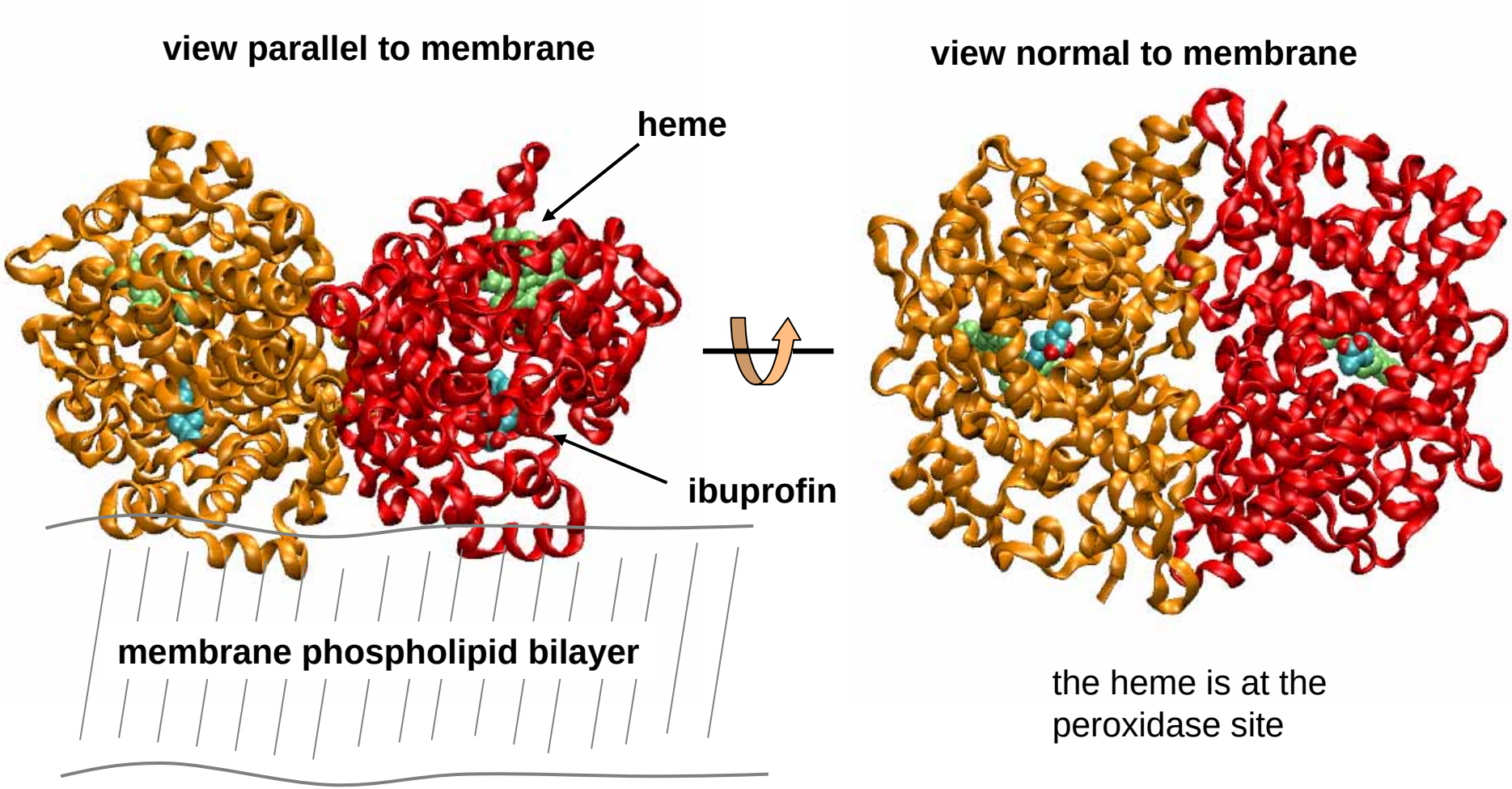
Phospholipase A_2 and cyclooxygenase operate on substrates in the plasma membrane



The cyclooxygenase-2 dimer with bound arachidonate, viewed from two perspectives

1cvu.pdb

Cyclooxygenase 1 is structurally very similar to cyclooxygenase 2



cyclooxygenase-1 dimer viewed from two perspectives 1eqg.pdf

Phosphatidylinositol participates in intracellular signaling