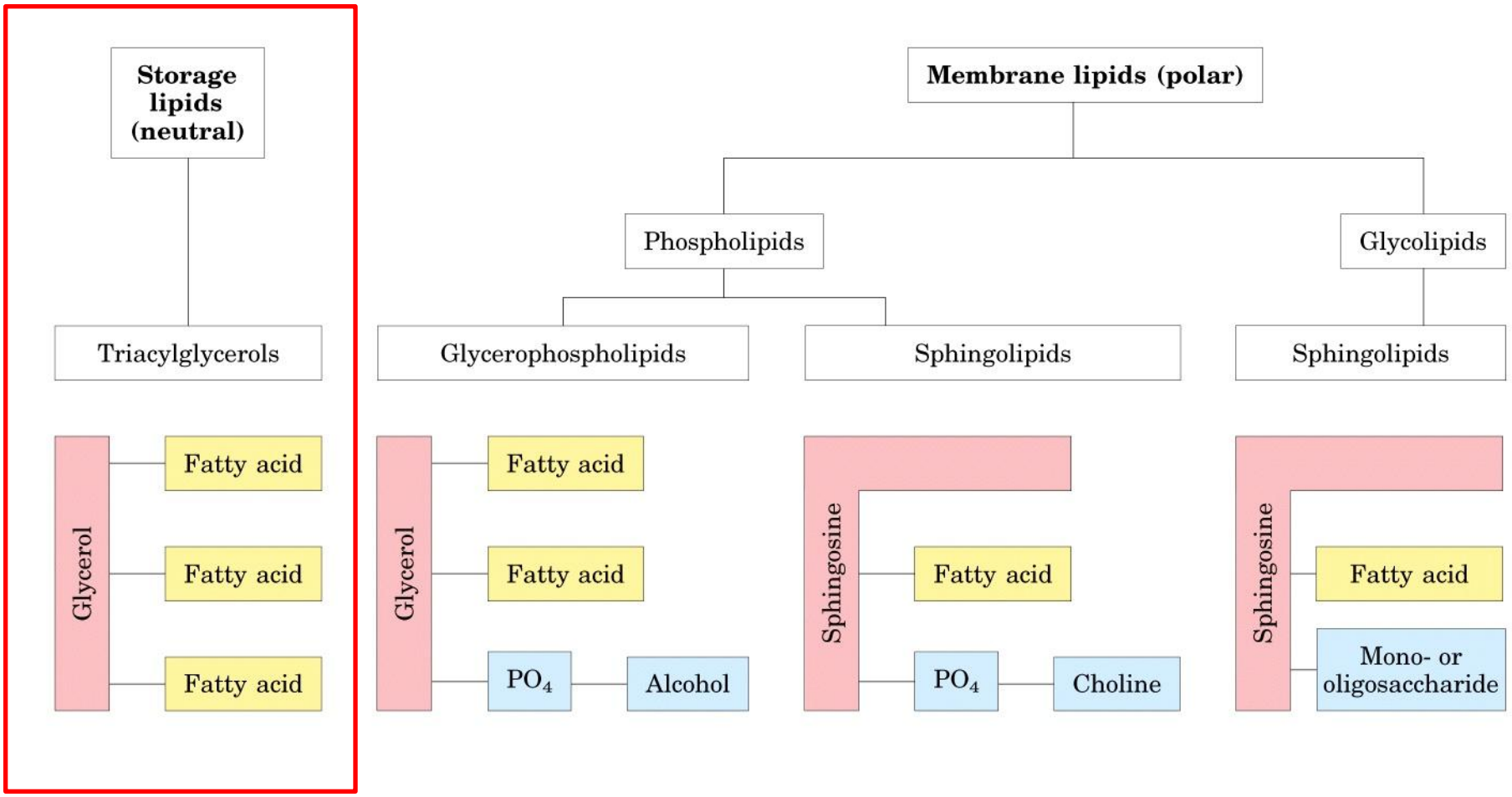
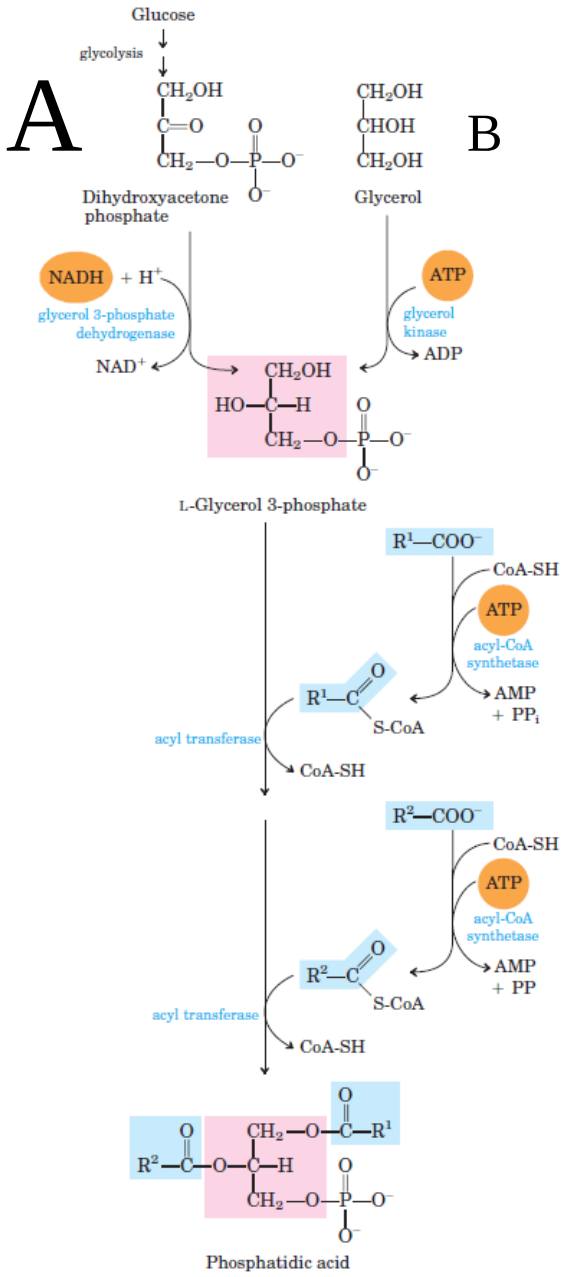
BIOSYNTHESIS OF LIPIDS

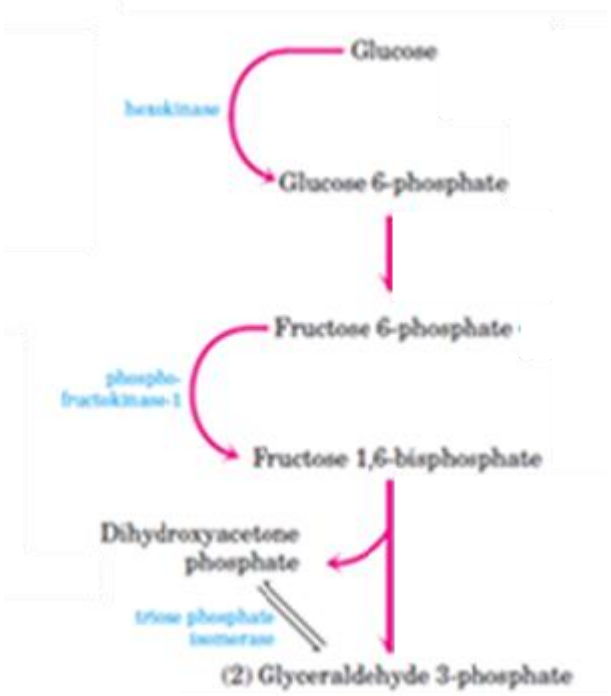
BIOSYNTHESIS OF TRIACYLGLYCEROLS

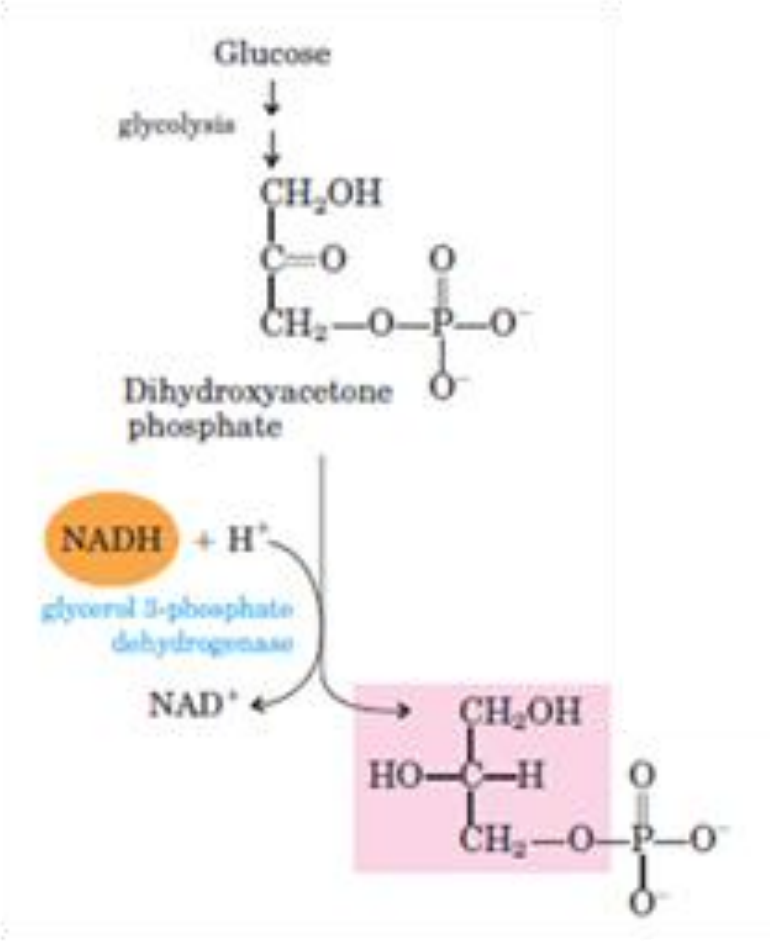


Biosynthesis of phosphatidic acid

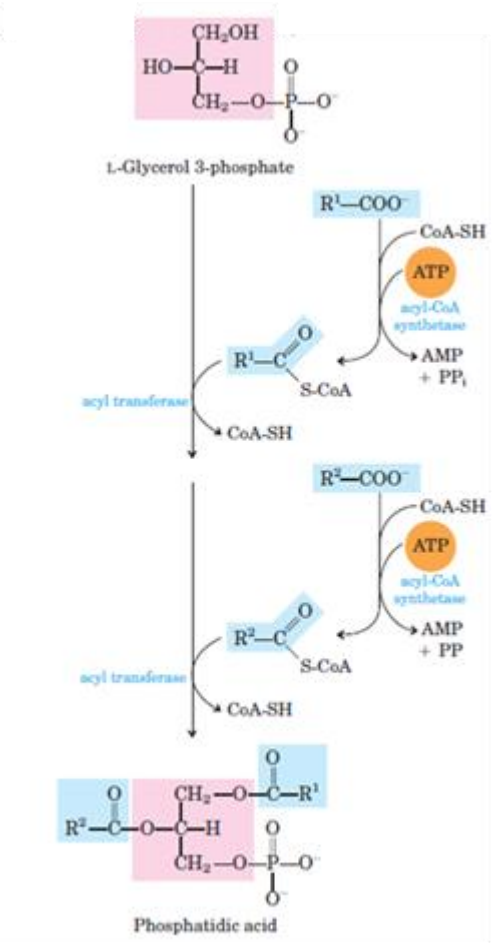
A fatty acyl group is activated by formation of the fatty acyl–CoA, then transferred to ester linkage with L-glycerol 3-phosphate, formed in either of the two ways shown. Phosphatidic acid is shown here with the correct stereochemistry at C-2 of the glycerol molecule.







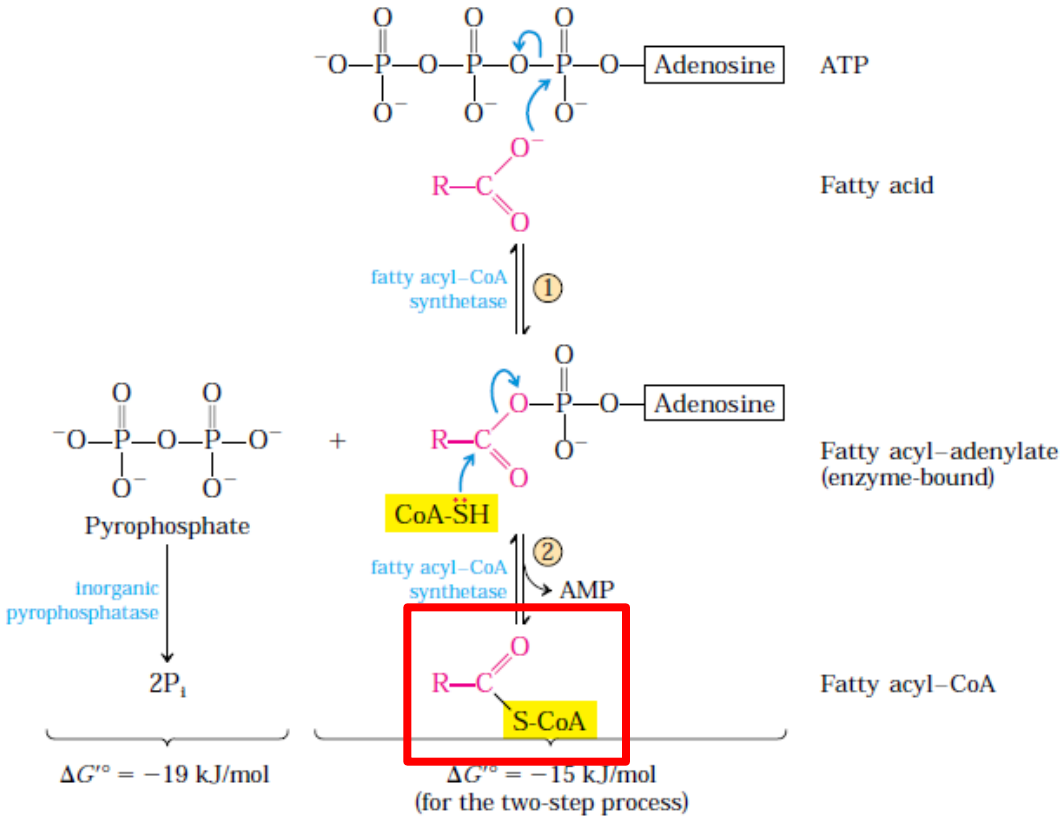
L-glycerol 3-phosphate



=

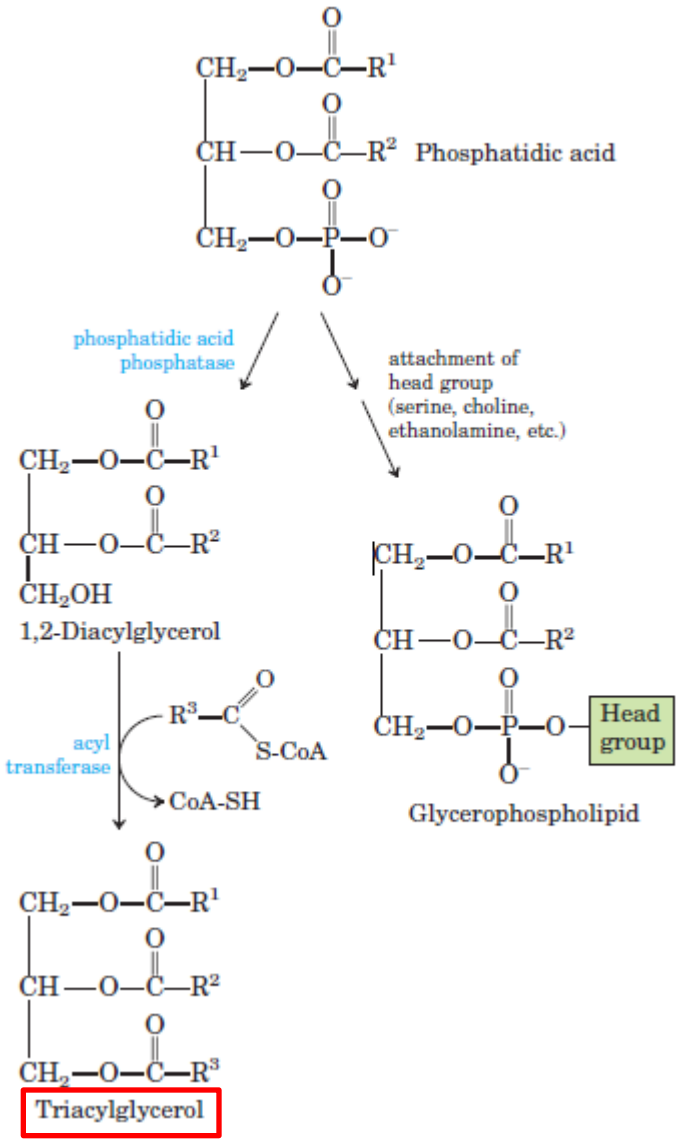
Diacylglycerol 3-phosphate

The **conversion of a fatty acid to a fatty acyl–CoA** is catalyzed by fatty acyl–CoA synthetase and inorganic pyrophosphatase. Fatty acid activation by formation of the fatty acyl–CoA derivative occurs in two steps. In step 1 , the carboxylate ion displaces the outer two (and) phosphates of ATP to form a fatty acyl–adenylate, the mixed anhydride of a carboxylic acid and a phosphoric acid. The other product is PPi, an excellent leaving group that is immediately hydrolyzed to two Pi, pulling the reaction in the forward direction. In step 2 , the thiol group of coenzyme A carries out nucleophilic attack on the enzyme-bound mixed anhydride, displacing AMP and forming the thioester fatty acyl–CoA. The overall reaction is highly exergonic.



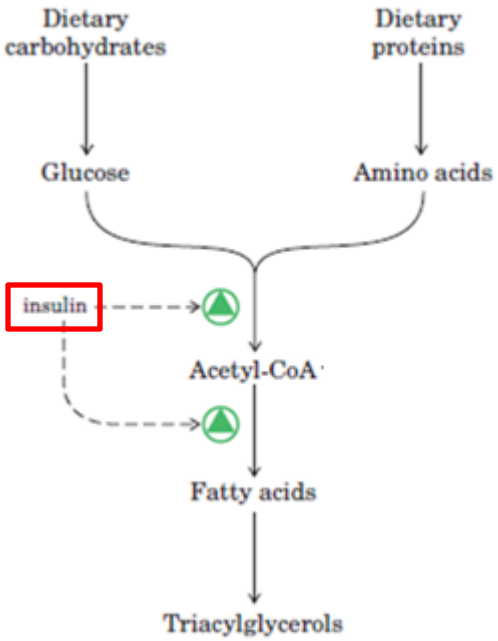
Phosphatidic acid in lipid biosynthesis.

Phosphatidic acid is the precursor of both **triacylglycerols** and glycerophospholipids.



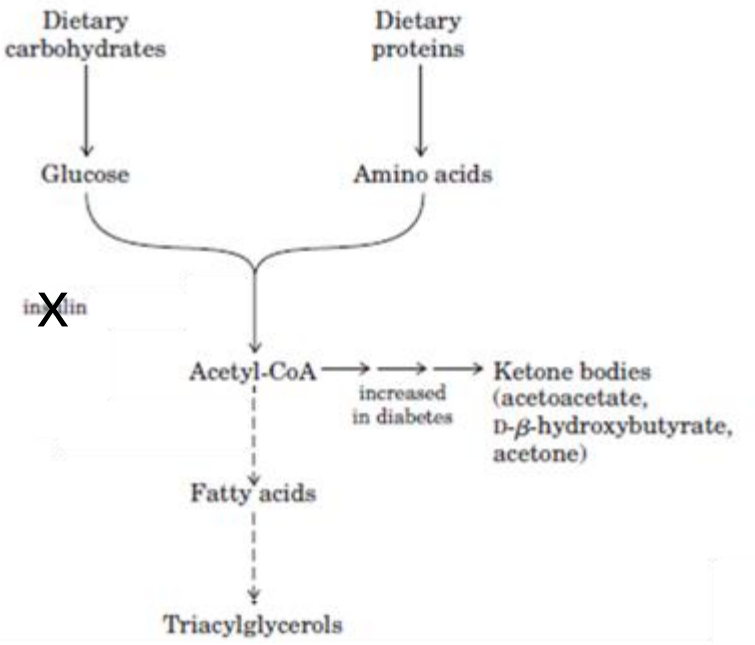
Regulation of triacylglycerol synthesis by insulin

Insulin stimulates conversion of dietary carbohydrates and proteins to fat.



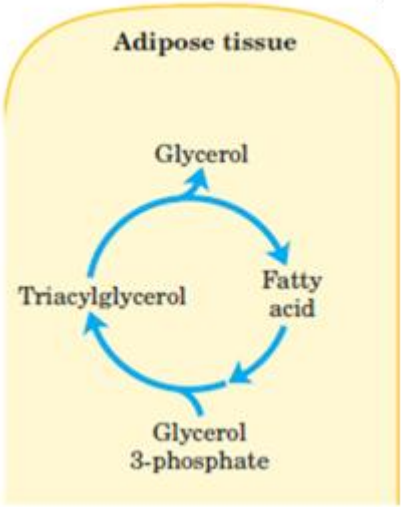
Individuals with diabetes mellitus lack insulin

In uncontrolled disease, this results in diminished fatty acid synthesis, and the acetyl-CoA arising from catabolism of carbohydrates and proteins is shunted instead to ketone body production.



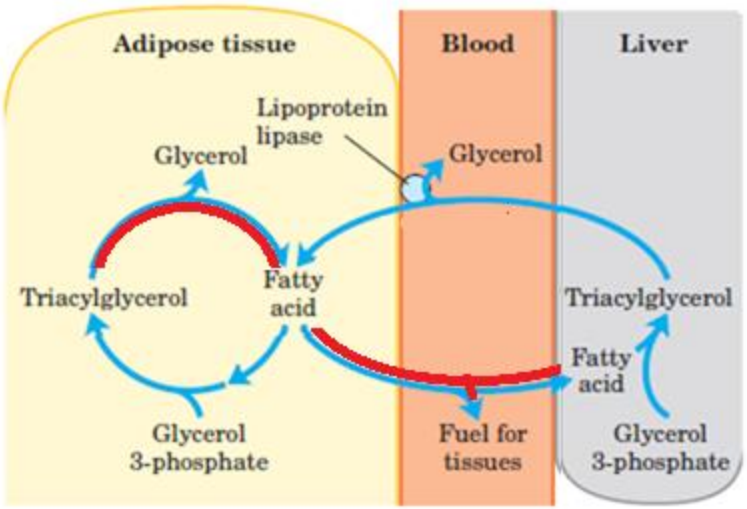
The triacylglycerol cycle

During starvation in mammals, triacylglycerol molecules are broken down and resynthesized in a triacylglycerol cycle.



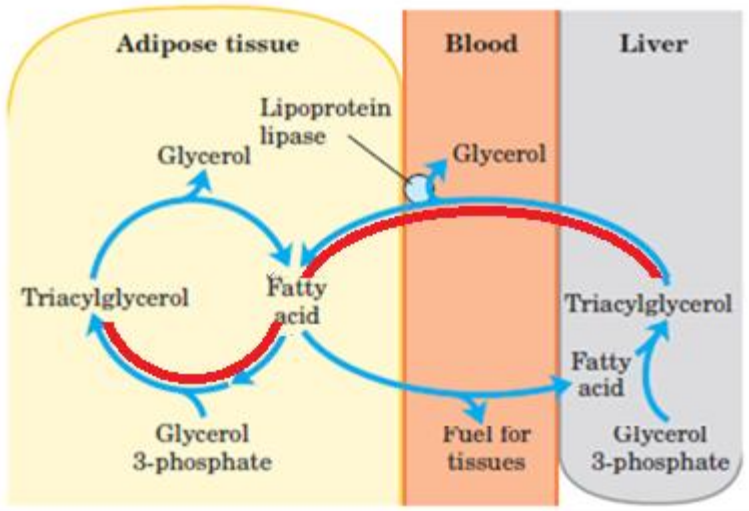
The triacylglycerol cycle

Some of the fatty acids released by lipolysis of triacylglycerol in adipose tissue pass into the bloodstream. Some of the fatty acids released into the blood are used for energy (in muscle, for example), and some are taken up by the liver and used in triacylglycerol synthesis.



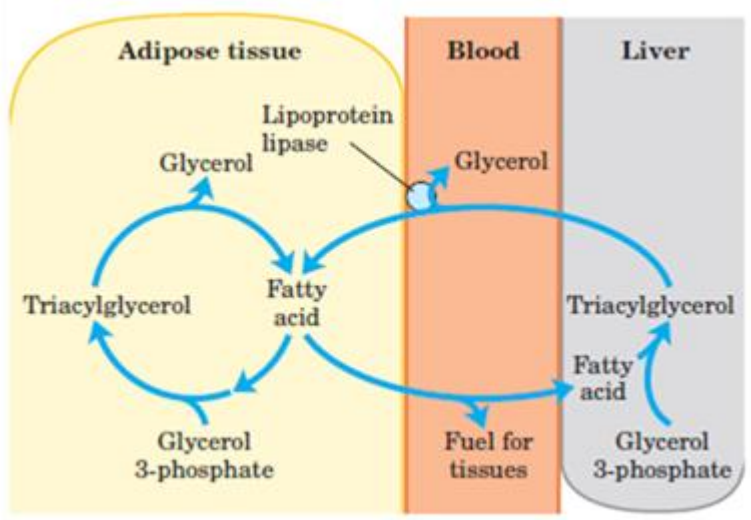
The triacylglycerol cycle

The triacylglycerol formed in the liver is transported in the blood back to adipose tissue, where the fatty acid is released by extracellular lipoprotein lipase, taken up by adipocytes, and reesterified into triacylglycerol.



The triacylglycerol cycle

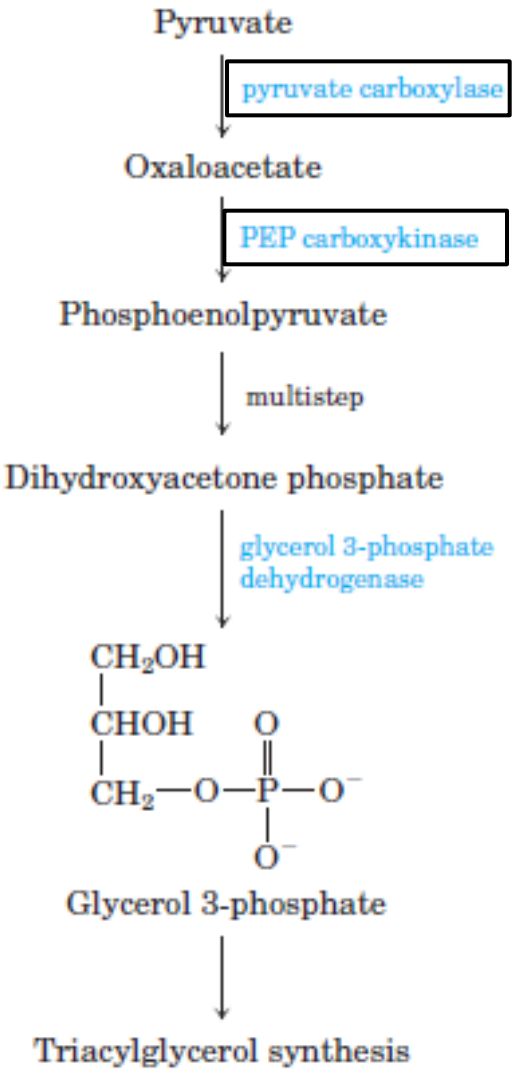
Fatty acid reconverted to triacylglycerol rather than be oxidized as fuel could represent an energy reserve in the bloodstream during fasting, that would be more rapidly mobilized in a “fight or flight” emergency than would stored triacylglycerol.

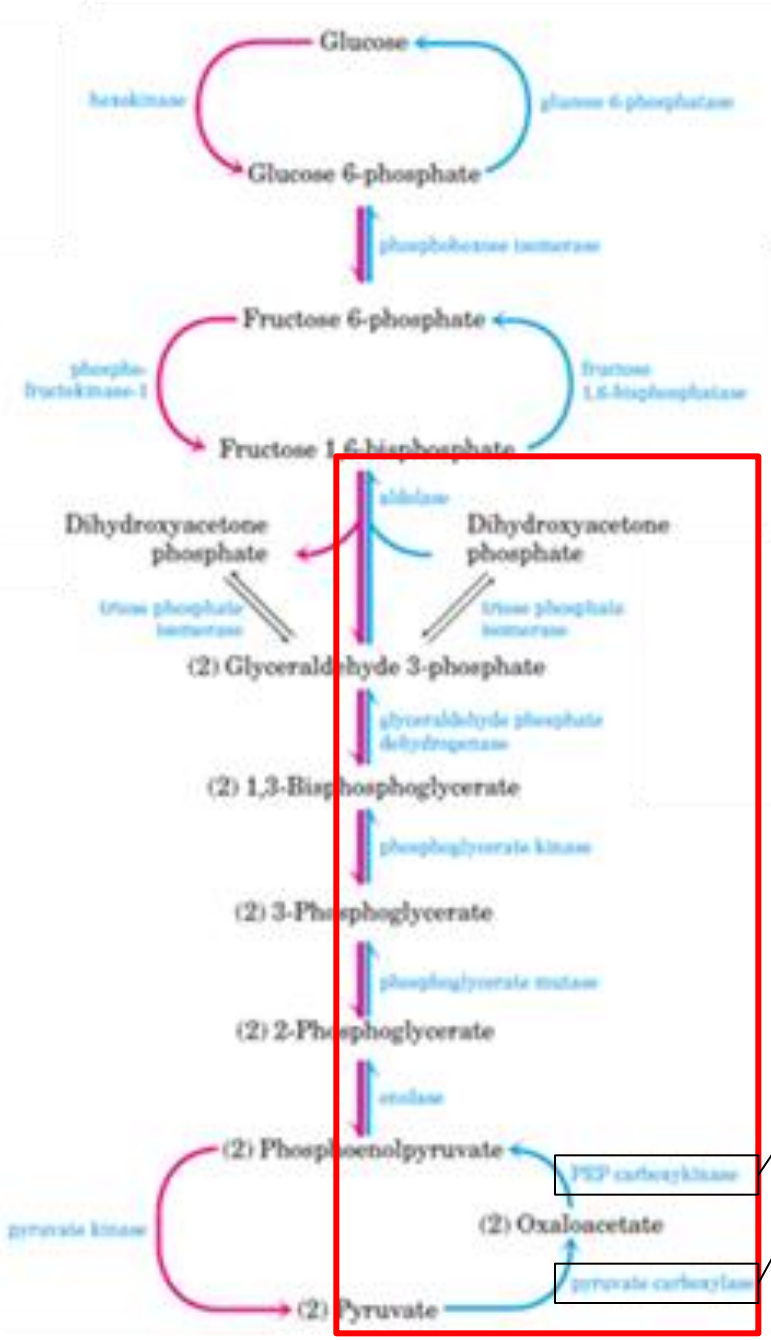


However the constant recycling of triacylglycerols in adipose tissue even during starvation raises a question:
what is the source of the glycerol 3-phosphate required for this process?

Indeed, glycolysis is suppressed in these conditions by the action of glucagon and epinephrine, so that little DHAP is available.
Moreover, glycerol released during lipolysis cannot be converted directly to glycerol 3-phosphate in adipose tissue, because these cells lack glycerol kinase.

Glyceroneogenesis is essentially an abbreviated version of gluconeogenesis, from pyruvate to dihydroxyacetone phosphate (DHAP), followed by conversion of DHAP to glycerol 3-phosphate, which is used for the synthesis of triacylglycerol.

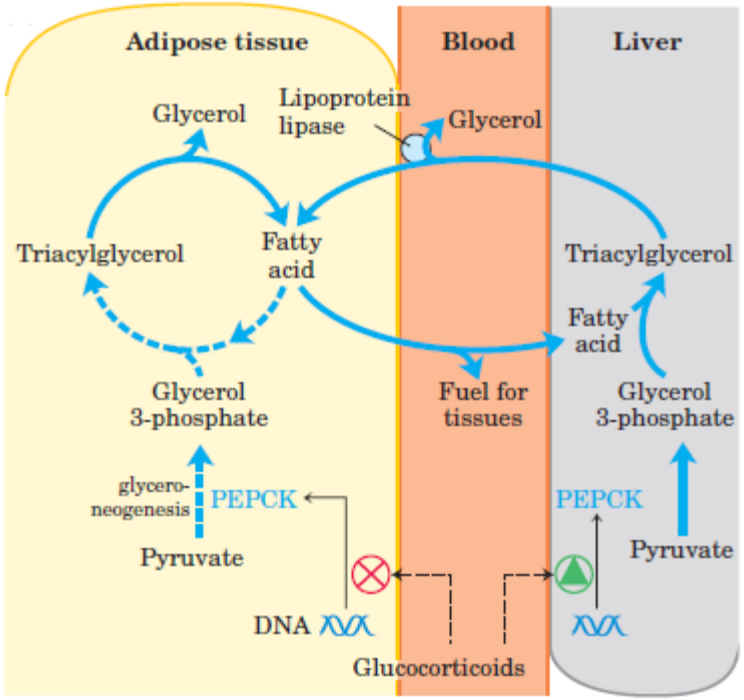




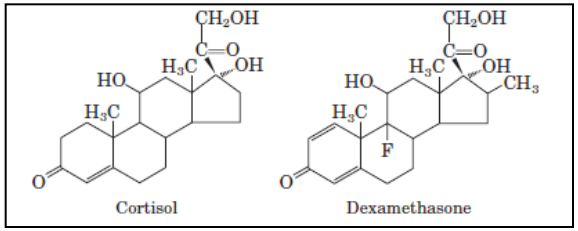
These enzymes are present in adipose tissue, where glucose is not synthesized

Regulation of glyceroneogenesis

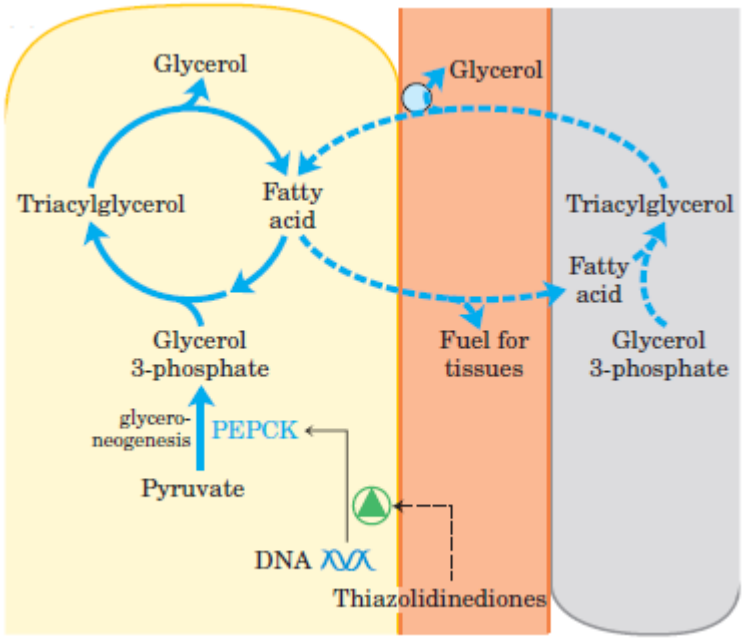
Glucocorticoid hormones *
stimulate glyceroneogenesis and gluconeogenesis in the liver, while suppressing glyceroneogenesis in the adipose tissue (by reciprocal regulation of the gene expressing PEP carboxykinase (PEPCK) in the two tissues); this increases the flux through the triacylglycerol cycle. The glycerol freed by the breakdown of triacylglycerol in adipose tissue is released to the blood and transported to the liver, where it is primarily converted to glucose, although some is converted to glycerol 3-phosphate by glycerol kinase.



*



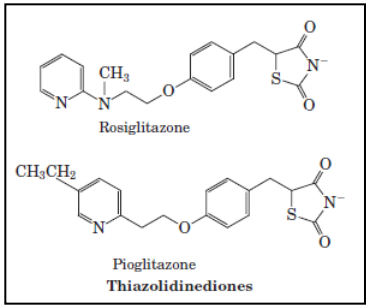
Regulation of glyceroneogenesis



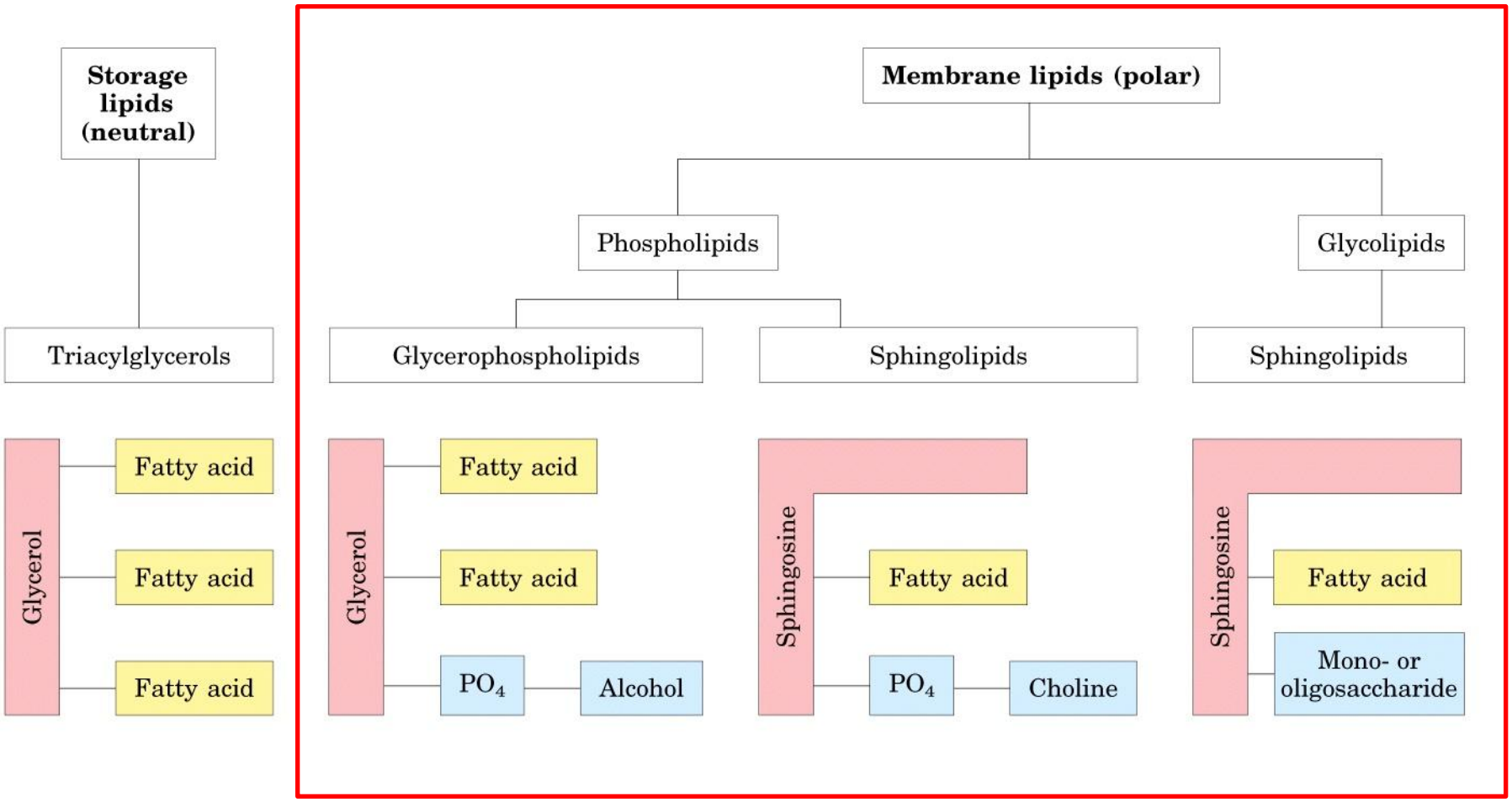
A class of drugs called **thiazolidinediones** * are now used to treat type 2 diabetes.

In this disease, high levels of free fatty acids in the blood interfere with glucose utilization in muscle and promote insulin resistance. Thiazolidinediones activate a nuclear receptor called peroxisome proliferator-activated receptor (PPAR), which induces the activity of PEP carboxykinase. Therapeutically, thiazolidinediones increase the rate of glyceroneogenesis, thus increasing the resynthesis of triacylglycerol in adipose tissue and reducing the amount of free fatty acid in the blood.

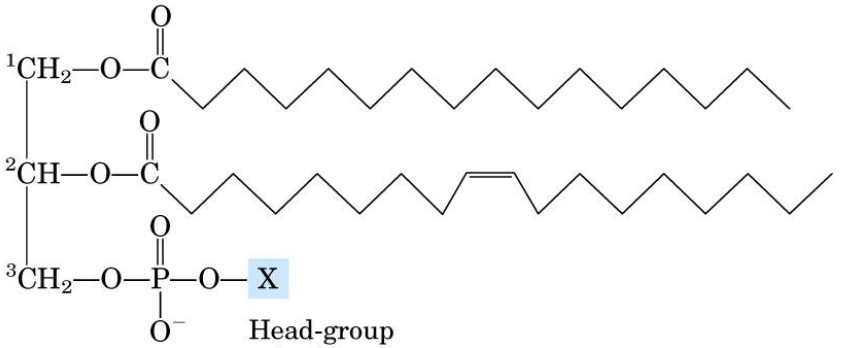
*

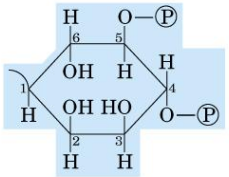
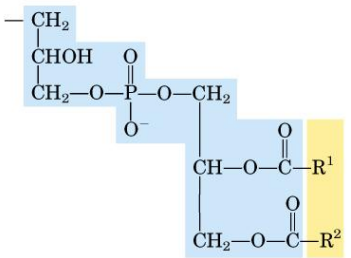


BIOSYNTHESIS
OF MEMBRANE PHOSPHOLIPIDS



Glycerophospholipid (general structure)

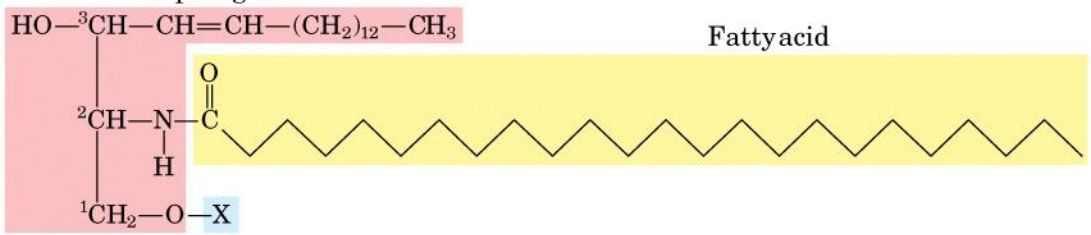


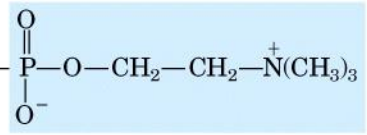
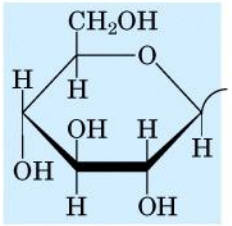
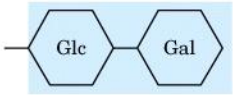
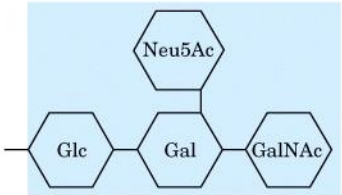
Name of glycerophospholipid	Name of X	Formula of X	Net charge (at pH 7)
Phosphatidic acid	—	— H	−1
Phosphatidylethanolamine	Ethanolamine	— CH_2—CH_2—$\overset{+}{N}H_3$	0
Phosphatidylcholine	Choline	— CH_2—CH_2—$\overset{+}{N}(CH_3)_3$	0
Phosphatidylserine	Serine	— CH_2—$CH(\overset{+}{N}H_3)$—COO^-	−1
Phosphatidylglycerol	Glycerol	— CH_2—$CH(OH)$—CH_2—OH	−1
Phosphatidylinositol 4,5-bisphosphate	*myo*-Inositol 4,5-bisphosphate		−4
Cardiolipin	Phosphatidyl-glycerol		−2

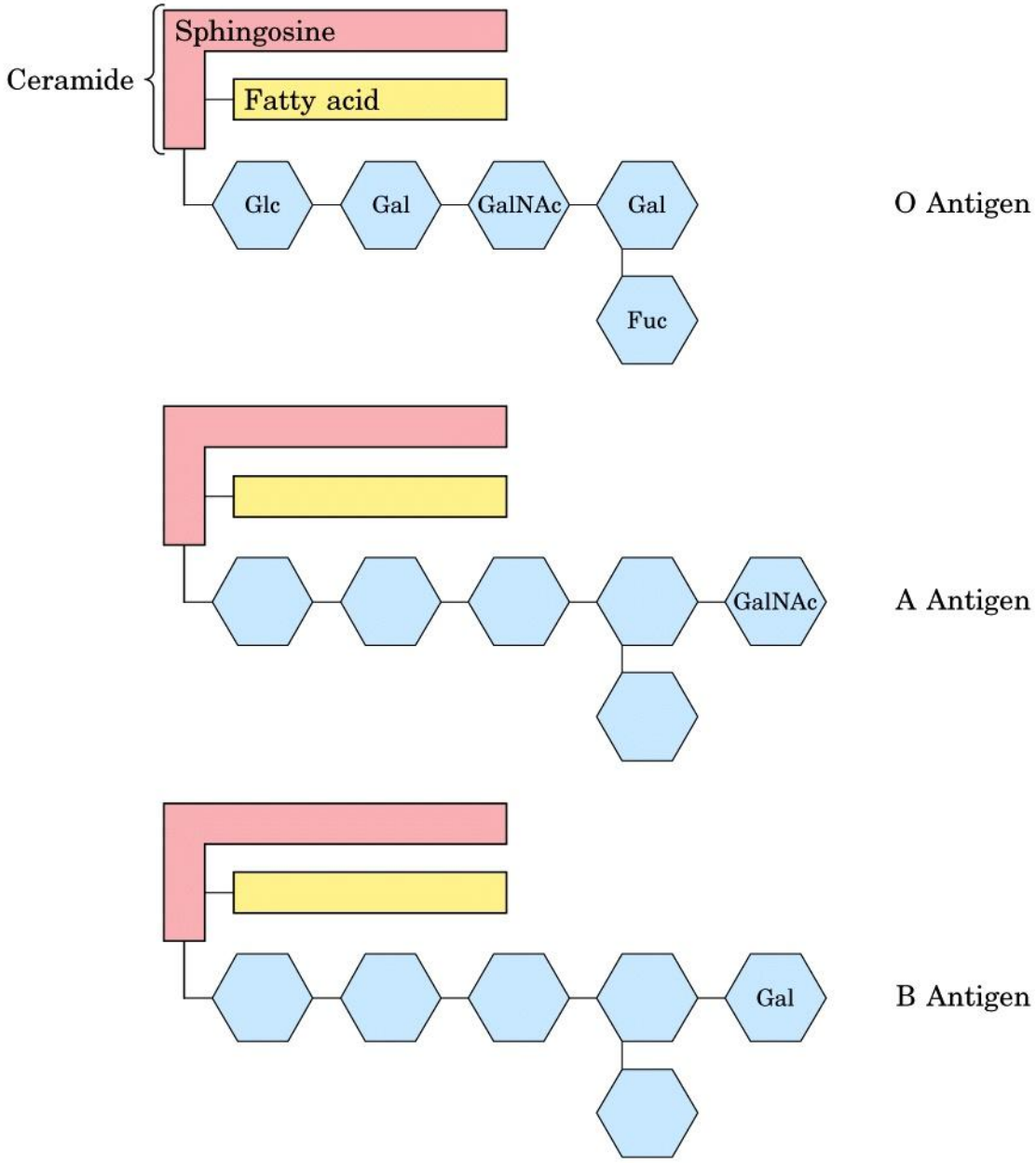
Sphingosine

Fatty acid

Sphingolipid (general structure)

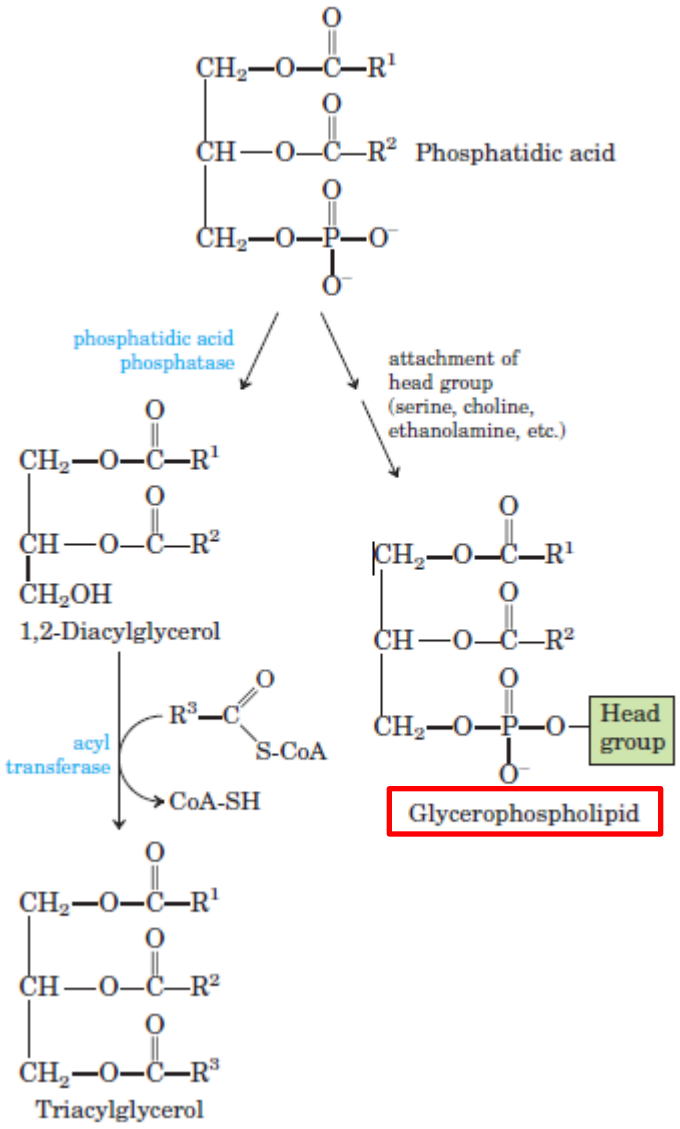


Name of sphingolipid	Name of X	Formula of X
Ceramide	—	—H
Sphingomyelin	Phosphocholine	
Neutral glycolipids Glucosylcerebroside	Glucose	
Lactosylceramide (a globoside)	Di-, tri-, or tetrasaccharide	
Ganglioside GM2	Complex oligosaccharide	


Ceramide
Sphingosine
Fatty acid
Glc
Gal
GalNAc
Gal
Fuc
O Antigen
GalNAc
A Antigen
Gal
B Antigen

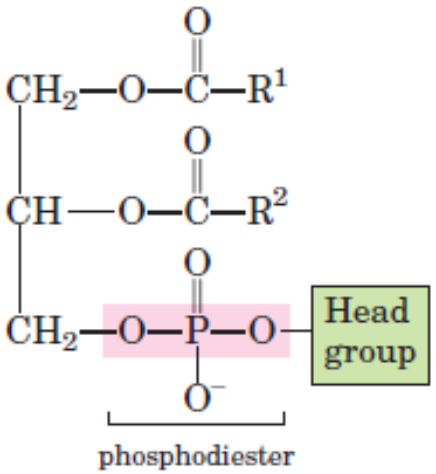
Phosphatidic acid in lipid biosynthesis.

Phosphatidic acid is the precursor of both triacylglycerols and **glycerophospholipids**.

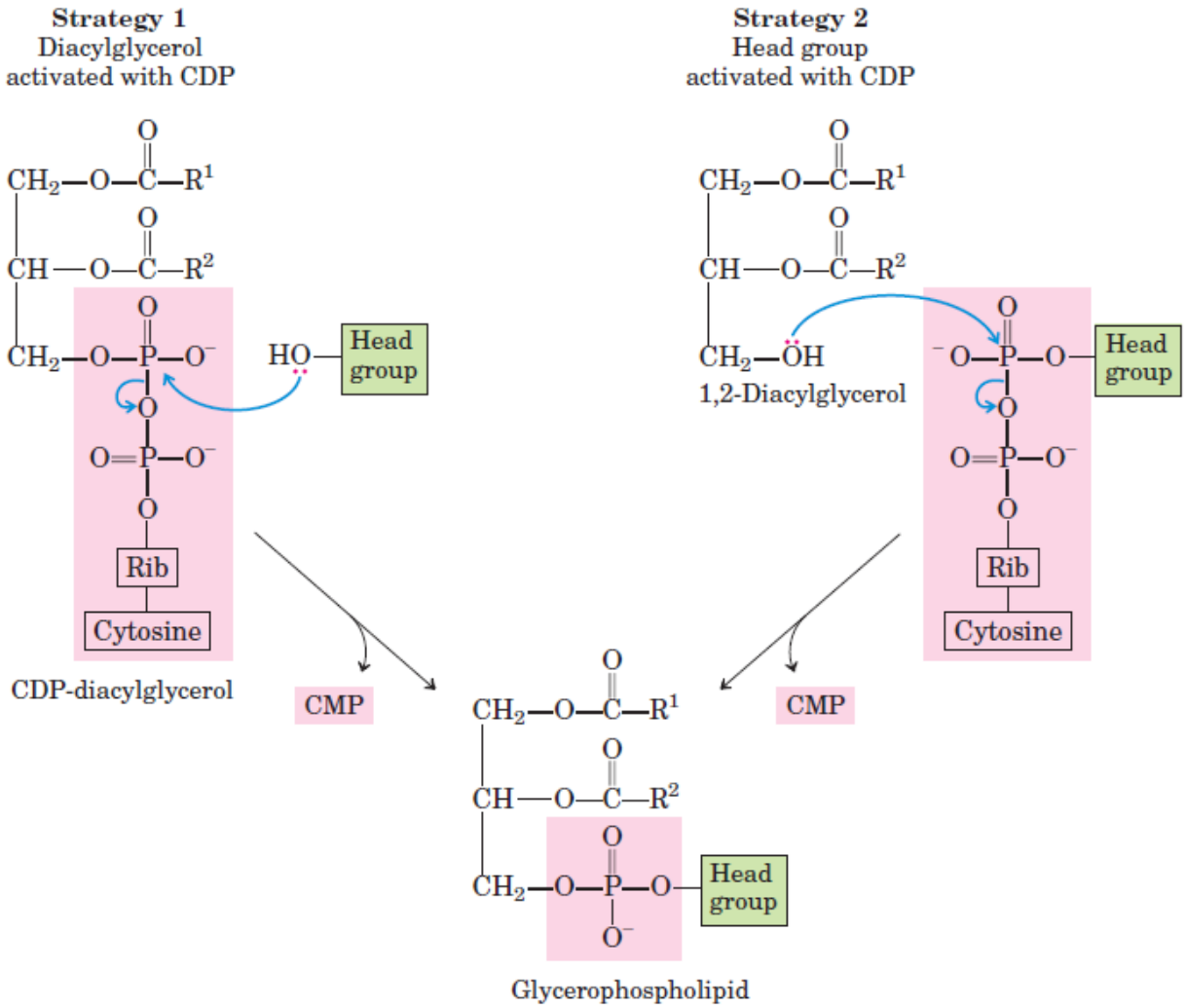


Head-group attachment

The phospholipid head group is attached to a diacylglycerol by a phosphodiester bond, formed when phosphoric acid condenses with two alcohols, eliminating two molecules of H_2O.

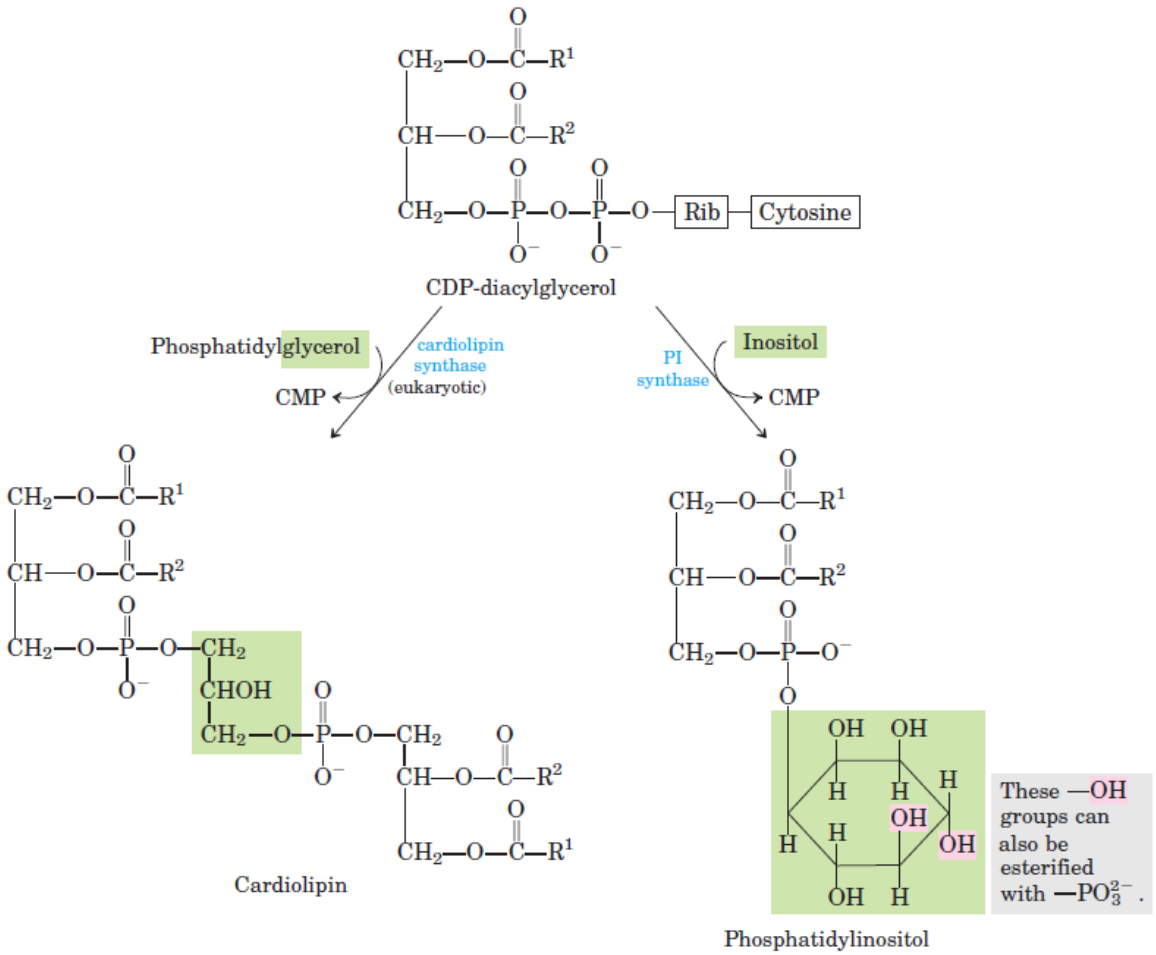


Glycerophospholipid



Two general strategies for forming the phosphodiester bond of phospholipids

In both cases, CDP supplies the phosphate group of the phosphodiester bond.



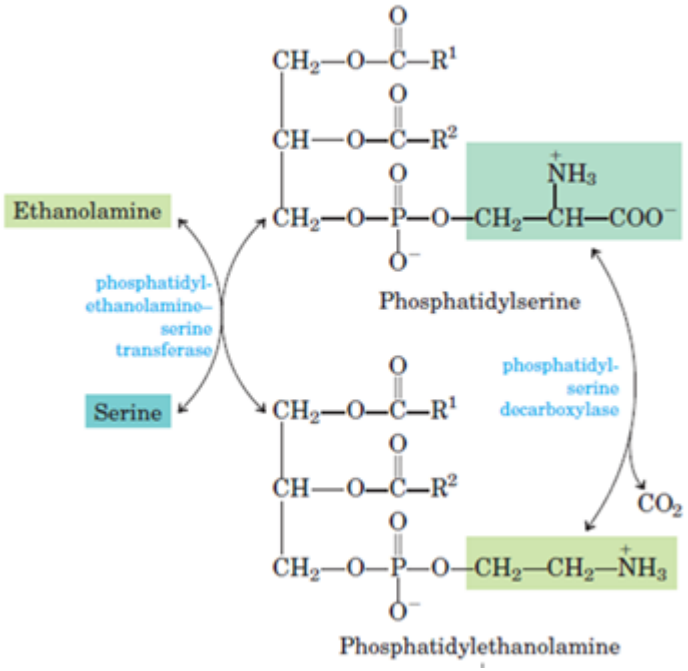
Synthesis of cardiolipin and phosphatidylinositol in eukaryotes

These glycerophospholipids are synthesized using strategy 1

From phosphatidylserine to phosphatidylethanolamine

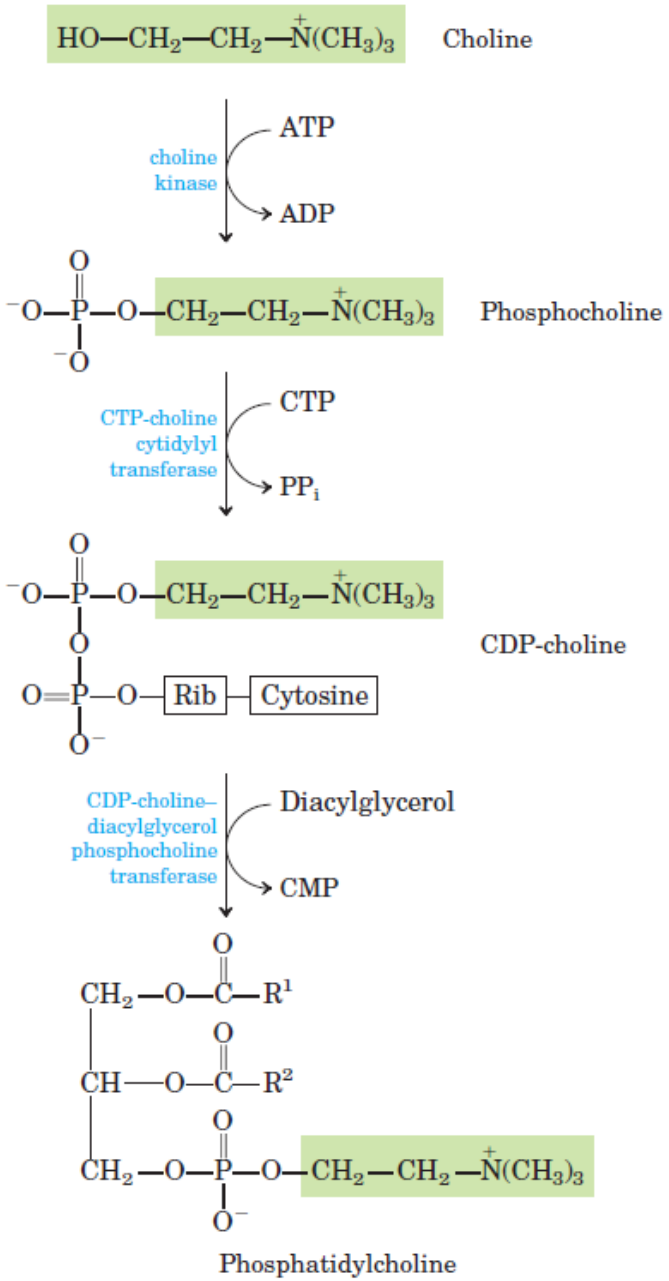
Phosphatidylserine and phosphatidylethanolamine are interconverted by a reversible head-group exchange reaction.

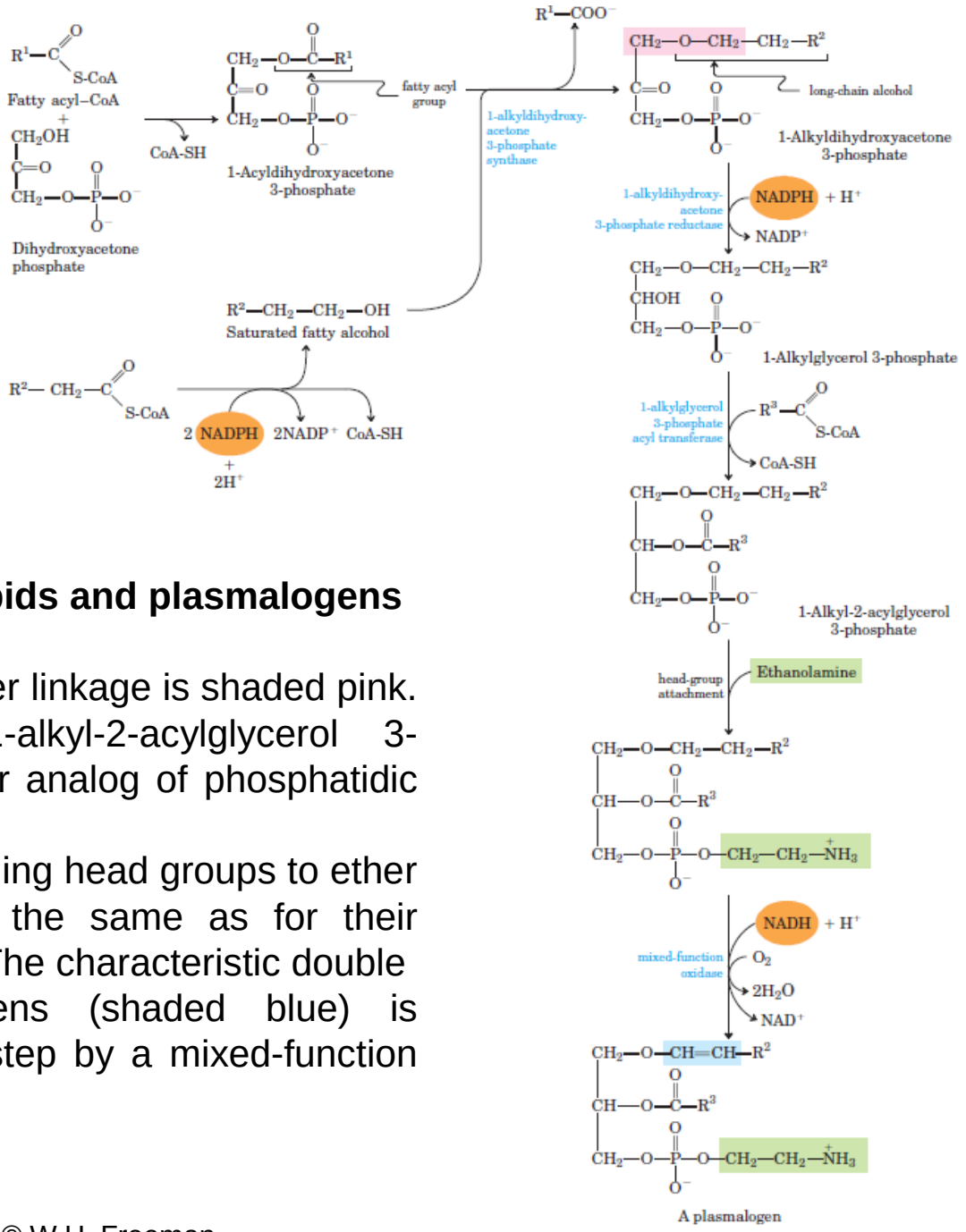
In mammals, phosphatidylserine is derived from phosphatidylethanolamine by a reversal of this reaction.



Phosphatidylcholine synthesis from choline in mammals

This glycerophospholipid is synthesized using strategy 2



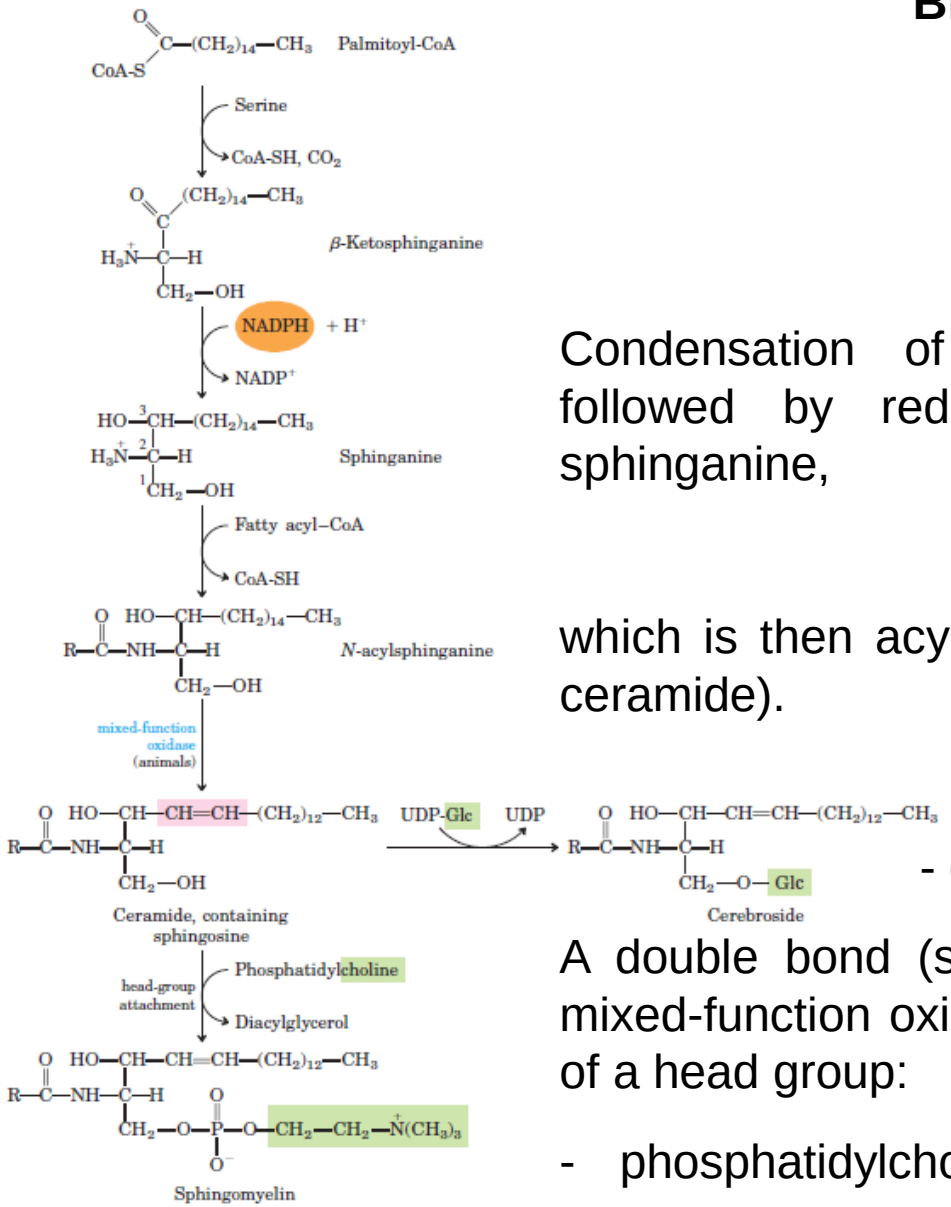


Synthesis of ether lipids and plasmalogens

The newly formed ether linkage is shaded pink. The intermediate 1-alkyl-2-acylglycerol 3-phosphate is the ether analog of phosphatidic acid.

Mechanisms for attaching head groups to ether lipids are essentially the same as for their ester-linked analogs. The characteristic double bond of plasmalogens (shaded blue) is introduced in a final step by a mixed-function oxidase system

Biosynthesis of sphingolipids



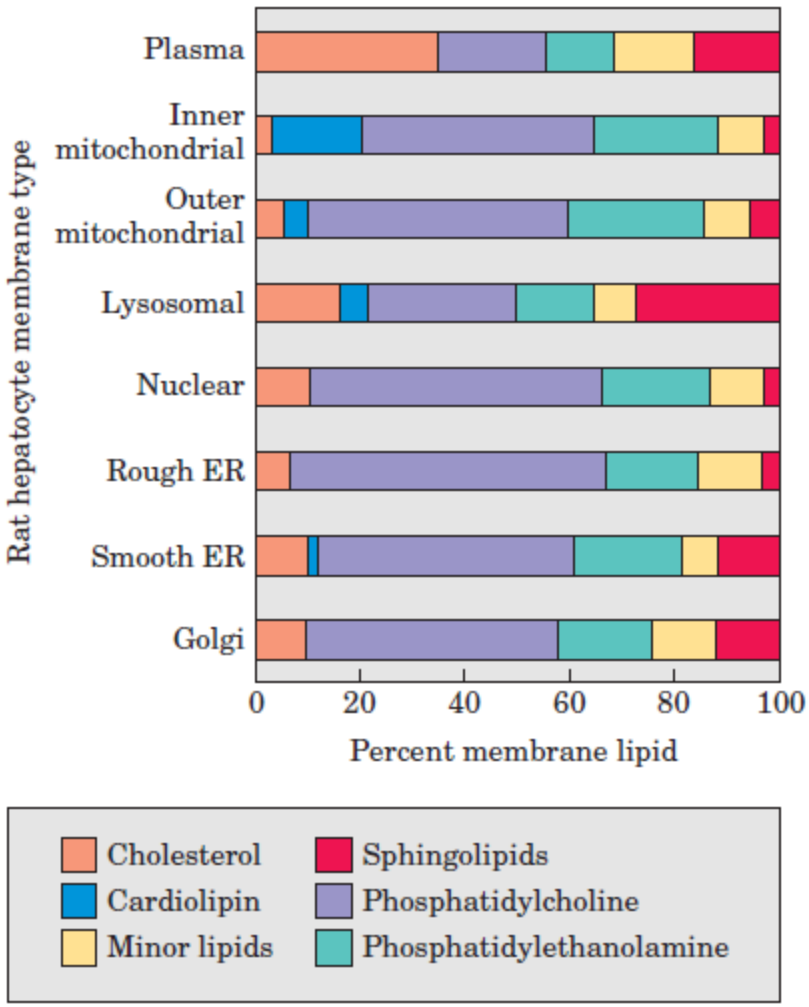
Condensation of palmitoyl-CoA and serine followed by reduction with NADPH yields sphinganine,

which is then acylated to *N*-acylsphinganine (a ceramide).

- glucose, to form a cerebroside

A double bond (shaded pink) is created by a mixed-function oxidase, before the final addition of a head group:

- phosphatidylcholine, to form sphingomyelin



Lipid composition of the plasma membrane and organelle membranes of a rat hepatocyte

The functional specialization of each membrane type is reflected in its unique lipid composition.

Cholesterol is prominent in plasma membranes but barely detectable in mitochondrial membranes.

Cardiolipin is a major component of the inner mitochondrial membrane but not of the plasma membrane.

Phosphatidylserine, phosphatidylinositol, and phosphatidylglycerol are relatively minor components (yellow) of most membranes but serve critical functions; phosphatidylinositol and its derivatives, for example, are important in signal transductions triggered by hormones.

Sphingolipids, phosphatidylcholine, and phosphatidylethanolamine are present in most membranes, but in varying proportions.

Glycolipids are virtually absent from animal cells.