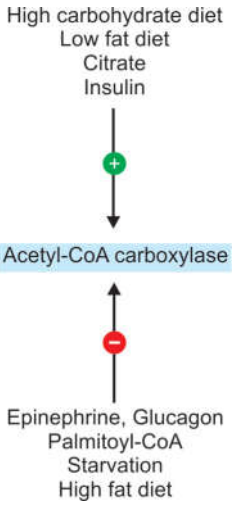

Figure 13.20: Regulation of fatty acid synthesis

TRIACYLGLYCEROL METABOLISM

Triacylglycerols are esters of the alcohol glycerol and fatty acids. Fatty acids derived from endogenous synthesis or from the diet are stored in the adipose tissue in the form of triacylglycerol, called *"neutral fat."*

Triacylglycerol serves as the body's major fuel storage reserve.

Biosynthesis of Triacylglycerols

In both liver and adipose tissue, triacylglycerols are synthesized **(Figure 13.21).**

- First fatty acids are activated to acyl-CoA (**see Figure 13.3).**
- Then two molecules of acyl-CoA combine with glycerol-3-phosphate to form phosphatidic acid (1,2-diacylglycerol phosphate) via formation of lysophosphatidic acid.
- Phosphatidic acid is the common precursor in the biosynthesis of the triacylglycerols and many glycerophospholipids and cardiolipin.
- Dephosphorylation of phosphatidic acid produces diacylglycerol.
- A further molecule of acyl-CoA is esterified with diacylglycerol to form triacylglycerol.
- The sources of glycerol-3-phosphate, which provides the glycerol moiety for triacylglycerol synthesis, differ in liver and adipose tissue.
- In liver glycerol-3-phosphate is produced from the phosphorylation of glycerol by ***glycerol kinase*** or from the reduction of dihydroxyacetone phosphate (DHAP), derived from glycolysis.
- Adipose tissue lacks glycerol kinase and can produce glycerol-3-phosphate only from glucose via DHAP.

Fate of Triacylglycerol Formed in Liver and Adipose Tissue

The fate of triacylglycerol in liver and adipose tissue is different.

- In the liver, little triacylglycerol is stored; instead most is exported in the form of very low density lipoprotein (VLDL). Once released into the blood stream, triacylglycerol of VLDL is hydrolyzed by ***lipoprotein lipase*** enzyme, which is located on the walls of blood capillaries. It clears the triacylglycerol in VLDL, forming free fatty acids and glycerol.
- In adipose tissue triacylglycerol is stored in the cells. It serves as *"depot fat"* ready for mobilization when the body requires it for fuel.

PHOSPHOLIPID METABOLISM

Phospholipids are the major class of ***membrane lipids.*** There are two classes of phospholipids:

1. Those that have glycerol, a 3-carbon alcohol, as a backbone, called ***glycerolphospholipids*** or ***phosphoglycerides,*** **e.g.**
   - phosphatidylserine
   - phosphatidylinositol
   - phosphatidylcholine (Lecithin)
   - phosphatidylethanolamine (Cephalin)
   - cardiolipin
   - plasmalogens
2. Those that contain **sphingosine,** a more complex amino alcohol called ***sphingophospholipid,*** **e.g.**
   - Sphingomyelin.

Biosynthesis of Glycerophospholipids

The initial steps in the synthesis of glycerophospholipids are similar to those of triacylglycerol synthesis **(see Figure 13.21).** Phosphatidate (diacylglycerol-3-phosphate) is a common intermediate in the synthesis of glycerophospholipids and triacylglycerols.

Synthesis of Phosphatidylserine and Phosphatidylinositol (Figure 13.21)

- Synthesis of phosphatidylserine and phosphatidylinositol starts with the formation of cytidine diacylglycerol (CDP-diacylglycerol) an activated phosphatidyl unit, from phosphatidate and cytidine triphosphate (CTP).
- The activated phosphatidyl unit then reacts with the hydroxyl group of alcohol.
  - If alcohol is serine, it forms **phosphatidylserine**
  - Likewise if the alcohol is inositol, the product is **phosphatidylinositol.**

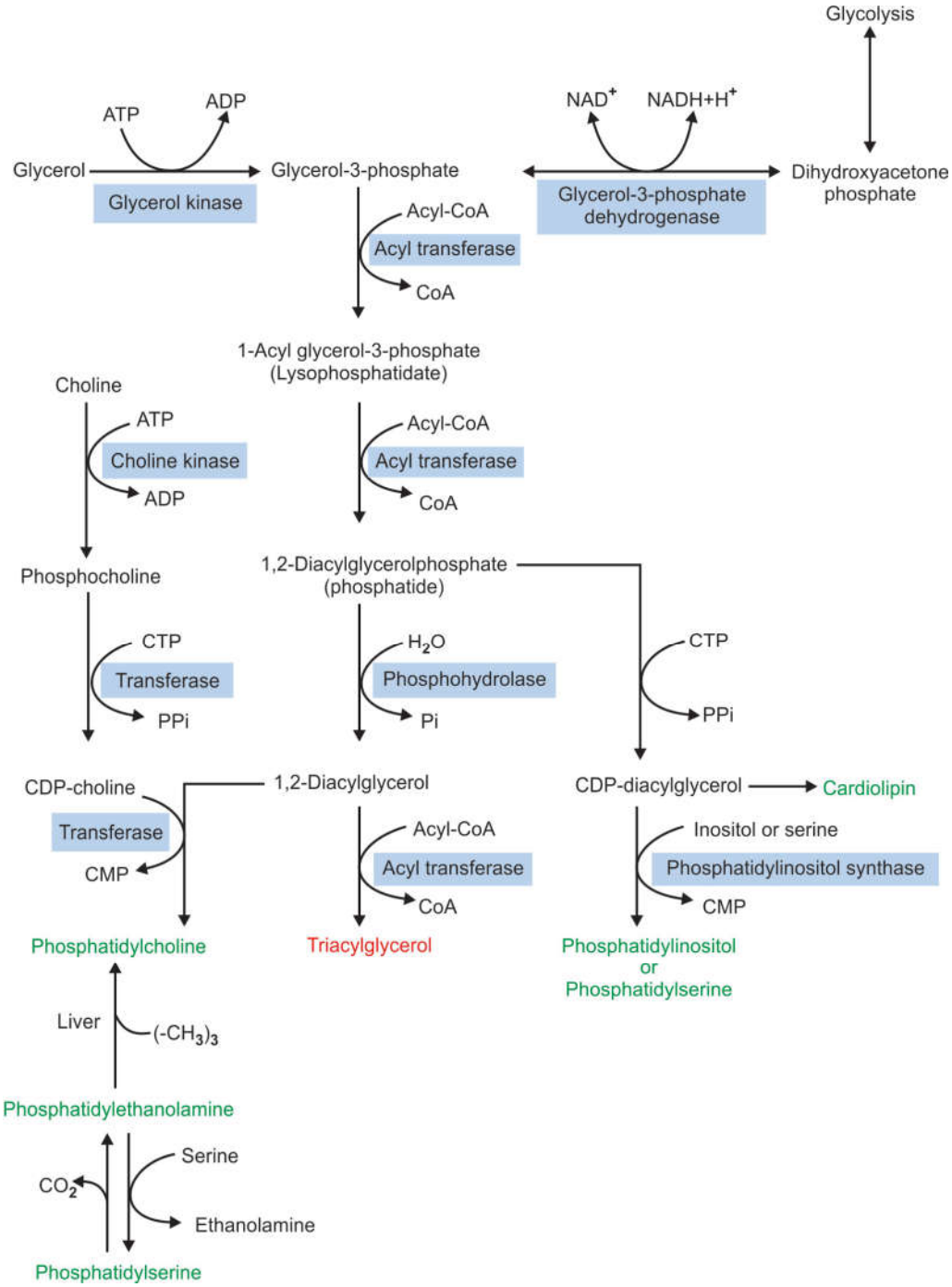

Figure 13.21: Synthesis of triacylglycerol and glycerophospholipids

- Phosphatidylserine can also be formed from phosphatidylethanolamine directly by reactions with serine.

Synthesis of Phosphatidylcholine (Lecithin) and Phosphatidylethanolamine (Cephalin)

Phosphatidylcholine is synthesized by a pathway that utilizes choline obtained from the diet.

- Choline must first be converted to active choline. This is a stage process, first is the phosphorylation with ATP to form phosphocholine, which then reacts with CTP to form CDP-choline (active form).
- The phosphorylcholine unit of CDP-choline is then transferred to a diacylglycerol to form phosphatidylcholine **(see Figure 13.21).**
- Likewise phosphatidylethanolamine can be synthesized from ethanolamine by forming a CDP-ethanolamine intermediate by analogous reactions.
- Phosphatidylserine may form phosphatidylethanolamine by decarboxylation.
- An alternative pathway in liver enables phosphatidylethanolamine to give rise directly to phosphatidylcholine by methylation of the ethanolamine residue utilizing S-adenosyl-methionine (SAM) as the methyl donor.

Synthesis of Cardiolipin (Figure 13.22)

In the synthesis of cardiolipin first CDP-diacylglycerol combines with glycerol-3-phosphate to form phosphatidyl glycerol which, in turn, reacts with another molecule of CDP-diacylglycerol to produce cardiolipin (diphosphatidyl-glycerol).

Synthesis of Plasmalogens

Plasmalogens differ from other glycerophospholipids in that the fatty acid at carbon 1 of glycerol bound by an ether linkage instead of ester linkage. The biosynthesis of plasmalogen occurs in peroxisomes and is shown in **(Figure 13.23).**

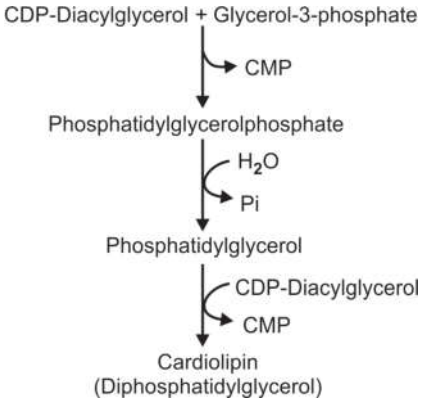

Figure 13.22: Synthesis of cardiolipin

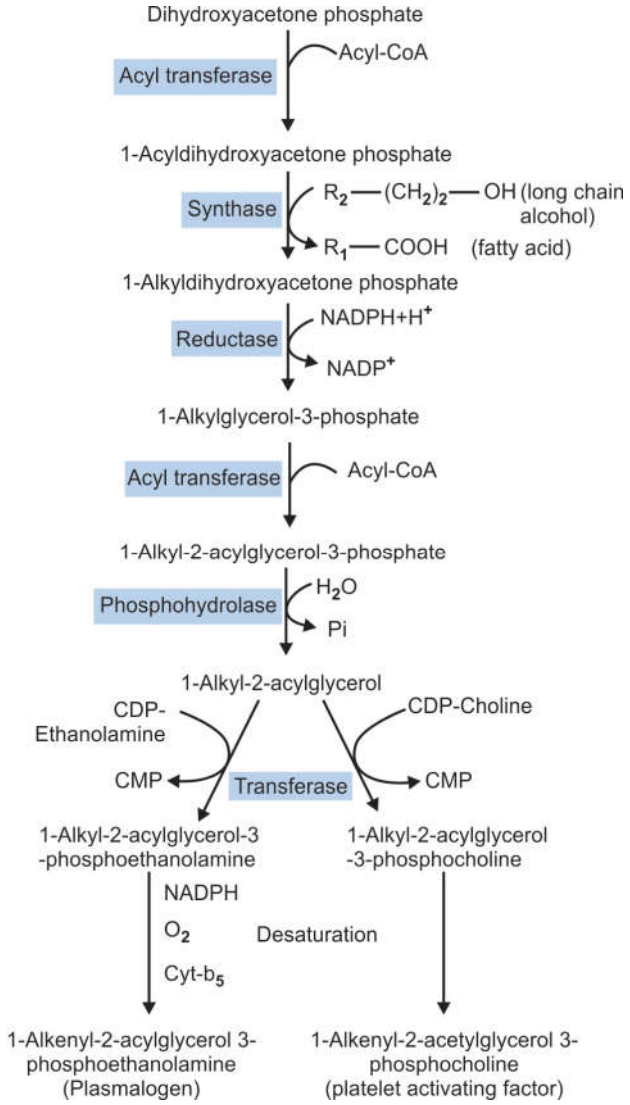

Figure 13.23: Synthesis of plasmalogen and platelet activating factor

Biosynthesis of Sphingomyelin

- These phospholipids contain a complex amino alcohol **sphingosine** instead of glycerol.
- Palmitoyl-CoA and serine condense to form 3-keto-sphinganine. The enzyme catalyzing this reaction requires **pyridoxal phosphate.**
- 3-ketosphinganine is then converted to sphingosine.
- In all sphingolipids, a long chain acyl-CoA reacts with sphingosine to form **ceramide.**
- Ceramide reacts with phosphatidylcholine to form sphingomyelin **(Figure 13.24).**

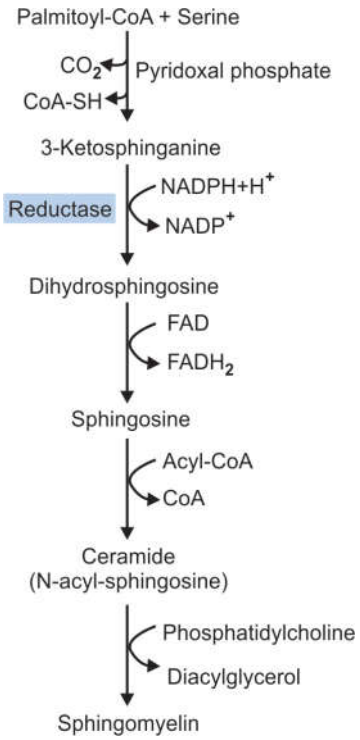

Figure 13.24: Synthesis of sphingomyelin

Degradation of Glycerophospholipids

Phospholipases located in cell membranes or in lysosomes degrade glycerophospholipids. Several specific phospholipases have been isolated which are designated as A_1, A_2, B, C and D. The bonds hydrolyzed by phospholipases ***A_1, A_2, B, C*** and **D** are shown in **(Figure 13.25).**

- **Phospholipase-A_1** removes the fatty acyl group on C_1 of the glycerol moiety.
- **Phospholipase-A_2** catalyzes the hydrolysis of the ester bond in position 2 of glycerophospholipids to form a free fatty acid and lysophospholipid, which is attacked by lysophospholipase removing the remaining 1-acyl group.
- ***Phospholipase-B*** hydrolyzes both acyl groups on C_1 and C_2.
- ***Phospholipase-C*** cleaves the bond, between phosphate and glycerol of phospholipids.
- The bond between the phosphate and the nitrogen base is cleaved by ***phospholipase-D***.

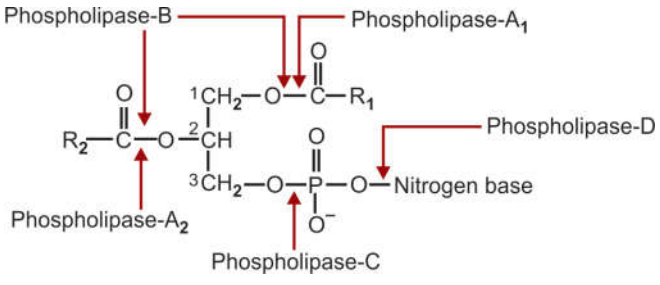

Figure 13.25: Sites of hydrolytic cleavage of glycerophospholipid by phospholipases

Degradation of Sphingomyelin

The sphingomyelins are hydrolyzed by lysosomal enzyme **sphingomyelinase** to ceramide and phosphorylcholine. The ceramide so formed is further hydrolyzed by another lysosomal enzyme **ceramidase** into sphingosine and free fatty acid.

GLYCOLIPID METABOLISM

Glycolipids, as their name implies, are sugar containing lipids. Glycolipids like sphingomyelin are derived from sphingosine. Sphingosine reacts with acyl-CoA to form **ceramide.** ***Cerebroside*** and ***gangliosides*** are the different types of glycolipids.

Biosynthesis of Glycolipids

Cerebroside is the simplest glycosphingolipid. In a cerebroside, glucose or galactose is linked to the terminal hydroxyl group of ceramide to form ***glucocerebroside*** or ***galactocerebroside.***

Galactocerebroside is a major lipid of myelin, whereas glucocerebroside is the major glycolipid of extraneural tissues and a precursor of most of the more complex glycolipids.

- Ceramide reacts with UDP-glucose or UDP-galactose to form ***glucocerebroside*** or ***galactocerebroside*** respectively.
- **Gangliosides** are the more complex glycolipids, contain a branched chain oligosaccharide of as many as seven sugar residues.
- Gangliosides are produced from ceramide by the stepwise addition of activated sugar, e.g. UDP-glucose, UDP-galactose and sialic acid usually N-acetylneuraminic acid (NANA) **(Figure 13.26).**

Degradation of Glycolipids

- The glucocerebrosides and galactocerebrosides are hydrolyzed by lysosomal enzymes β-**glucocerebrosidase** (β-glucosidase) and **β-galactocerebrosidase** (β-glactosidase), respectively to ceramide and hexose residues. The ceramide so formed is further cleaved by another lysosomal enzyme **ceramidase** to sphingosine and free fatty acid.

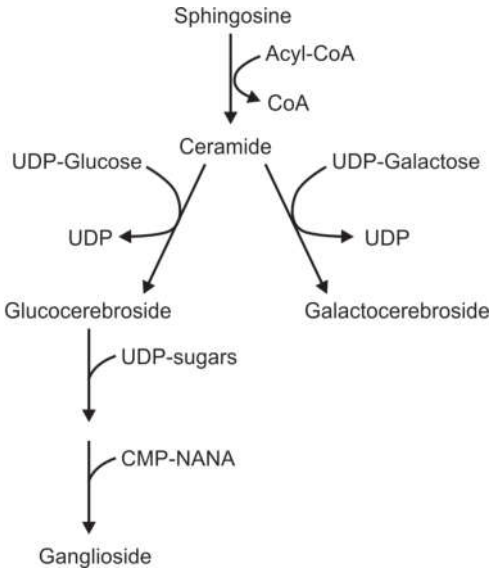

Figure 13.26: Biosynthesis of Glycolipids
where, CMP-NANA: Cytidine monophosphate-N-acetyl neuraminic acid

- The different gangliosides are degraded by a set of lysosomal enzymes, **β-glucosidase, β-hexosaminidase, β-galactosidase, neuraminidase,** etc.

Sphingolipidoses (Table 13.1) (Sphingolipid Storage Disease)

- Spingolipidoses are a group of inherited diseases that result from defective degradation and accumulation of any one of the sphingolipids (sphingomyelins or glycolipids).
- Depending on the enzyme affected several types of sphingolipidoses have been recognized. Some major types of sphingolipidoses are discussed here **(Figure 13.27).**

1. **Niemann Pick disease:** The degradation of sphingomyelins is impaired in Niemann Pick disease due to inherited deficiency of **sphingomyelinase.** As a result sphingomyelins accumulate in liver, brain and spleen. The clinical findings are:
   - Enlarged liver and spleen
   - Mental retardation and death may occur in early childhood.
2. **Tay-Sach's disease:** It is due to inherited deficiency of **hexosaminidase A** required for the degradation of ganglioside GM_2. Since degradation of GM_2 of ganglioside is impaired, the GM_2 accumulates in brain and nervous tissues.
   - The infants with Tay-Sach's disease suffer from muscular weakness, mental retardation, blindness and death occur in early childhood.
3. **Gaucher's disease:** The inherited deficiency **β-glucosidase** impairs the hydrolysis of glucocerebrosides, which results in accumulation of glucocerebrosides in brain, liver, spleen, and bone marrow.
   - This disorder is associated with mental retardation and enlargement of liver and spleen.
4. **Krabbes' disease:** The inherited deficiency of the enzyme **β-galactosidase** impairs the hydrolysis of galactocerebrosides, which results in accumulation of galactocerebrosides in brain and other nervous tissues.
   - There is almost complete absence of myelin in nervous tissue. The clinical features include mental retardation, blindness and deafness. Krabbe's disease is fatal in early life.
5. **Farber's disease:** The inherited deficiency of enzyme **ceramidase** impairs the hydrolysis of ceramides which results in accumulation of ceramides in the body tissue.
   - The symptoms include skeletal deformities, and mental retardation. The disease is fatal and death occurs in early childhood.

Table 13.1: Common form of sphingolipidoses

Disease	*Lipid accumulation*	*Enzyme deficiency*	*Clinical symptoms*
Niemann Pick	Sphingomyelin	Sphingomyelinase	Enlarged liver and spleen, mental retardation in infants
Gaucher's	Glucocerebroside	β-Glucosidase	Same as Niemann-Pick disease
Tay-Sach's	GM_2—Ganglioside	Hexosaminidase	Mental retardation, blindness, muscular weakness
Krabbe's	Galactocerebroside	β-Galactosidase	Mental retardation, blindness and deafness, myelin almost absent
Farber's	Ceramide	Ceramidase	Mental retardation, skeletal deformities

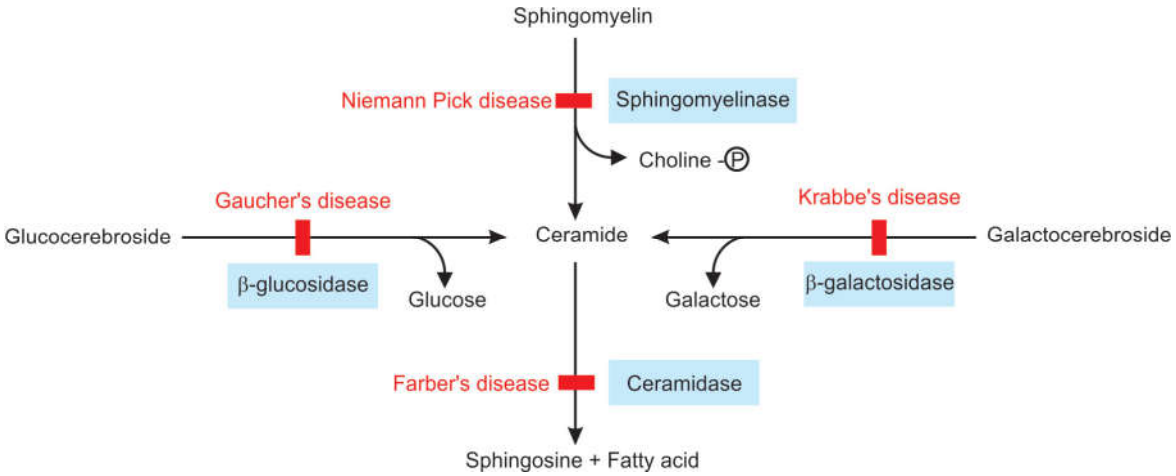

Figure 13.27: Degradation of sphingomyelin and cerebroside