

ANABOLISM II:

Biosynthesis of Fatty Acids & Lipids

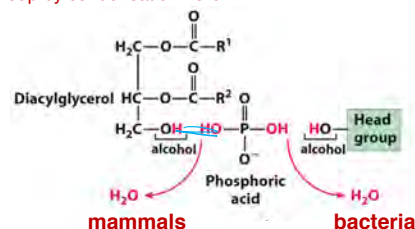
Lipid Biosynthesis

Biosynthesis of Membrane Phospholipids

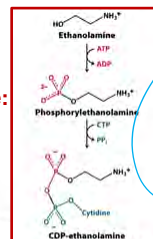
Glycerophospholipid Biosynthesis requires
Activation by CTP

Attach head group by condensation here:

- Begin with **phosphatidic acid** (microorganisms) or **1,2 Diacylglycerol** (mammals)
- Both activate precursors using CTP
- Bacteria use phosphatidate and attach head group to C-3 phosphate group
 - Make CDP-diacylglycerol from CTP and phosphatidic acid
- Mammals use CDP-alcohol and attach head group to diacylglycerol
 - Make CDP-alcohol from CTP and choline or ethanolamine



Example:



Lipid Biosynthesis

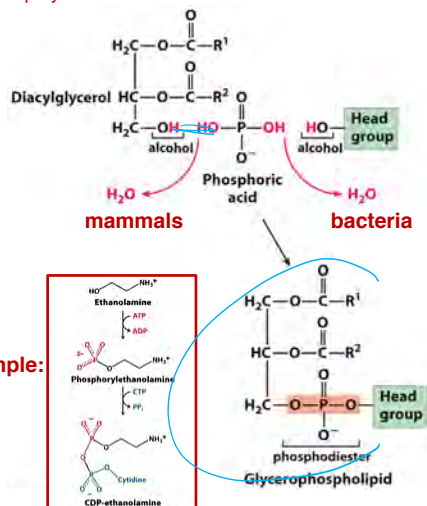
Biosynthesis of Membrane Phospholipids

Glycerophospholipid Biosynthesis requires

Activation by CTP

Attach head group by condensation here:

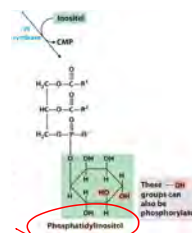
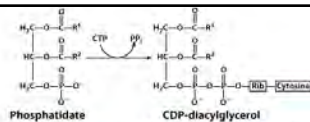
- Begin with **phosphatidic acid** (microorganisms) or **1,2 Diacylglycerol** (mammals)
- Both activate precursors using **CTP**
- Bacteria use phosphatidate and attach head group to C-3 phosphate group
 - Make CDP-diacylglycerol from CTP and phosphatidic acid
- Mammals use CDP-alcohol and attach head group to diacylglycerol
 - Make CDP-alcohol from CTP and choline or ethanolamine



Lipid Biosynthesis

Glycerophospholipid Synthesis in *E. coli*

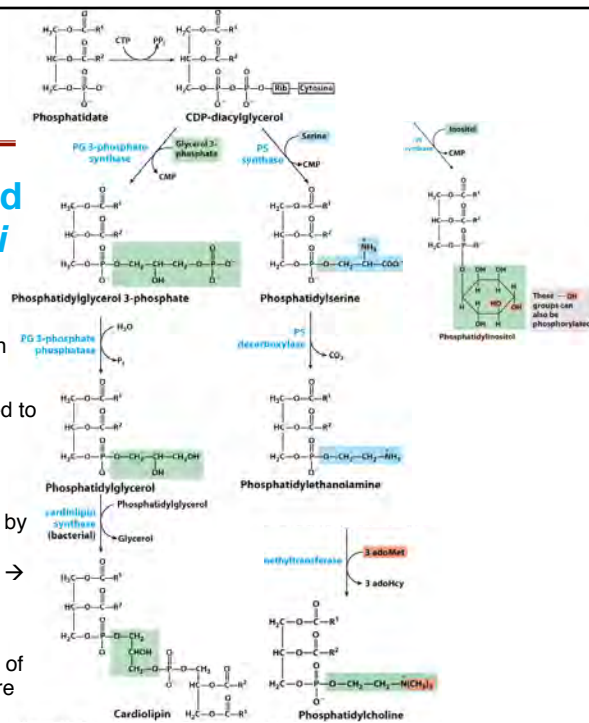
- For **Phosphatidylserine** and **phosphatidylinositol**, the free alcohol does a nucleophilic attack on the CDP-activated **phosphatidate**.
- Phosphatidylserine is decarboxylated to **phosphatidylethanolamine**.
 - enzyme is phosphatidylserine decarboxylase
- Phosphatidylethanolamine acted on by **S-adenosylmethionine (SAM)** adds three methyl groups to amino group → **phosphatidylcholine (lecithin)**.
 - catalyzed by methyltransferase
- **Cardiolipin** is from the condensation of two phosphatidyl glycerols, which are formed from glycerol 3-phosphate.



Lipid Biosynthesis

Glycerophospholipid Synthesis in *E. coli*

- For **Phosphatidylserine** and **phosphatidylinositol**, the free alcohol does a nucleophilic attack on the CDP-activated **phosphatide**.
- Phosphatidylserine is decarboxylated to **phosphatidylethanolamine**.
 - enzyme is phosphatidylserine decarboxylase
- Phosphatidylethanolamine acted on by **S-adenosylmethionine (SAM)** adds three methyl groups to amino group → **phosphatidylcholine (lecithin)**.
 - catalyzed by methyltransferase
- Cardiolipin** is from the condensation of two phosphatidyl glycerols, which are formed from glycerol 3-phosphate.



Lipid Biosynthesis

Synthesis of Phosphatidylcholine, -ethanolamine, and -serine and in Mammals

$\text{HO}-\text{CH}_2-\text{CH}_2-\text{NH}_3^+$
Ethanolamine
 $\xrightarrow[\text{ADP}]{\text{ATP}}$

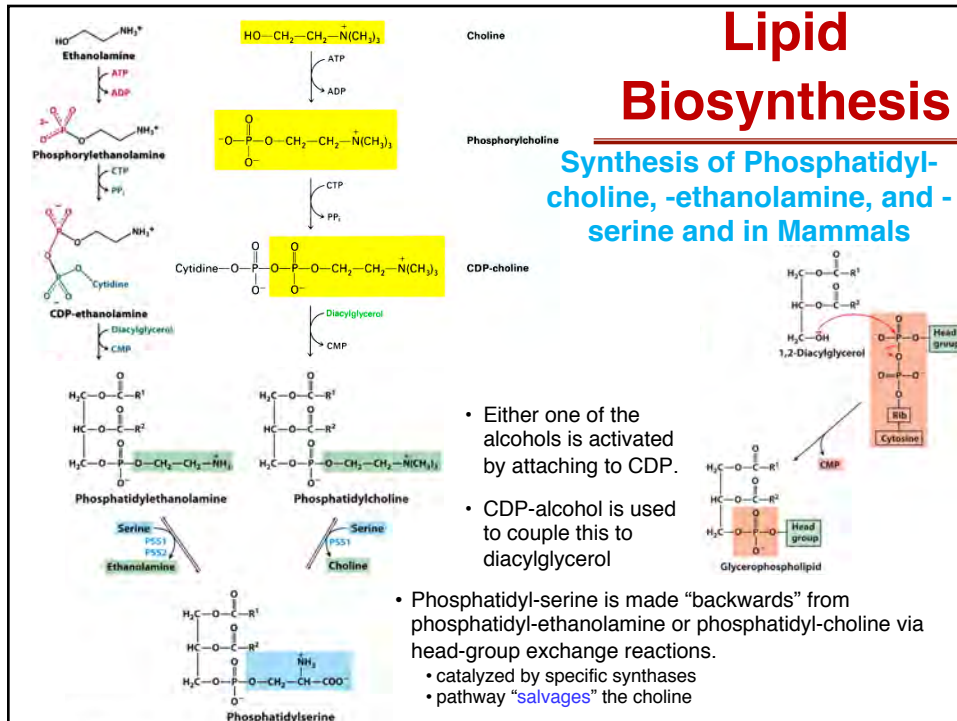
$\text{HO}-\text{CH}_2-\text{CH}_2-\text{N}(\text{CH}_3)_3$
Choline
 $\xrightarrow[\text{ADP}]{\text{ATP}}$

The diagram shows the synthesis of phospholipids in mammals. It begins with the activation of an alcohol (ethanolamine or choline) to form CDP-alcohol. This CDP-alcohol then reacts with 1,2-diacylglycerol to form a glycerophospholipid. The head group of the resulting phospholipid is shown as either ethanolamine or choline. A note indicates that phosphatidyl-serine is made 'backwards' from phosphatidyl-ethanolamine or phosphatidyl-choline via head-group exchange reactions, catalyzed by specific synthases, and that this pathway 'salvages' the choline.

- Either one of the alcohols is activated by attaching to CDP.
- CDP-alcohol is used to couple this to diacylglycerol
- Phosphatidyl-serine is made "backwards" from phosphatidyl-ethanolamine or phosphatidyl-choline via head-group exchange reactions.
 - catalyzed by specific synthases
 - pathway "salvages" the choline

Lipid Biosynthesis

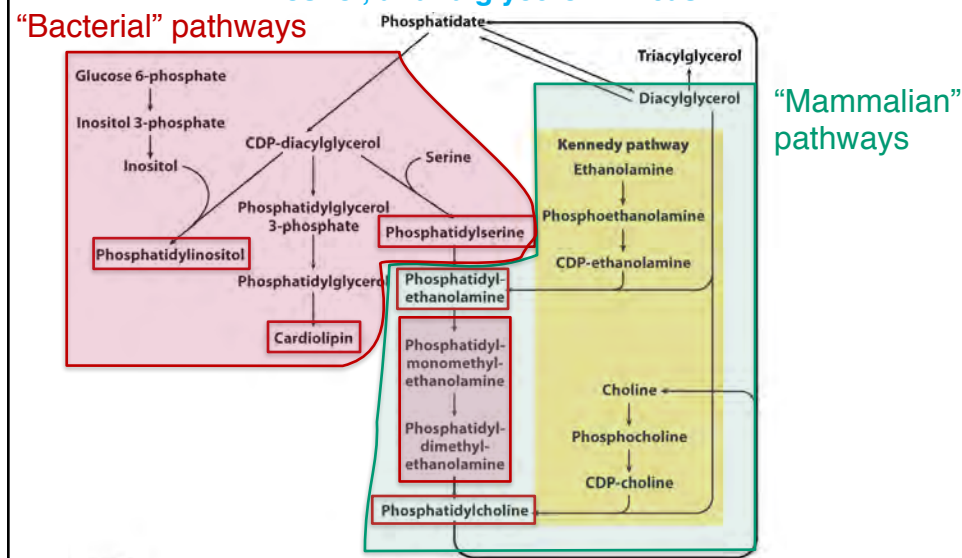
Synthesis of Phosphatidylcholine, -ethanolamine, and -serine and in Mammals



Lipid Biosynthesis

Synthesis of Phosphatidylcholine, -ethanolamine, -serine, -inositol, and -diglycerol in Yeast

“Bacterial” pathways



$$\begin{array}{c}
 \text{O} \\
 \parallel \\
 \text{CoA-S} - \text{C} - (\text{CH}_2)_{14} - \text{CH}_3 \\
 \downarrow \text{Serine} \\
 \text{CoA-SH} + \text{CO}_2
 \end{array}$$

Palmitoyl-CoA

Lipid Biosynthesis

Synthesis of Sphingolipids

- Sphingosine comes from amino acids + fatty acids; serine + palmitate
- Condensation of palmitoyl-CoA and serine, forms β -ketosphinganine
- Reduction, acylation, oxidase yields N-acyl-sphinganine (a ceramide).

$$\begin{array}{c}
 \text{O} \\
 \parallel \\
 \text{CoA-S} - \text{C} - (\text{CH}_2)_{14} - \text{CH}_3 \\
 \downarrow \text{Serine} \\
 \text{CoA-SH} + \text{CO}_2 \\
 \downarrow \\
 \text{H}_2\text{N}-\text{CH}(\text{CH}_2\text{OH})-\text{C}(=\text{O})-\text{CH}_2-\text{OH} \\
 \beta\text{-Ketosphinganine} \\
 \downarrow \text{NADPH} + \text{H}^+ \rightarrow \text{NADP}^+ \\
 \text{HO}-\text{CH}(\text{CH}_2\text{OH})-\text{CH}_2-\text{OH} \\
 \text{Sphinganine} \\
 \downarrow \text{Fatty acyl-CoA} \\
 \text{HO}-\text{CH}(\text{CH}_2\text{OH})-\text{C}(=\text{O})-\text{CH}_2-\text{OH} \\
 \text{N-Acylsphinganine} \\
 \downarrow \text{dihydroceramide desaturase 1} \\
 \text{HO}-\text{CH}(\text{CH}_2\text{OH})-\text{CH}=\text{CH}-(\text{CH}_2)_{12}-\text{CH}_3 \\
 \text{Ceramide} \\
 \downarrow \text{head-group attachment} \\
 \text{HO}-\text{CH}(\text{CH}_2\text{OH})-\text{CH}=\text{CH}-(\text{CH}_2)_{12}-\text{CH}_3 \\
 \text{Sphingomyelin}
 \end{array}$$

Lipid Biosynthesis

Synthesis of Sphingolipids

- Sphingosine comes from amino acids + fatty acids; serine + palmitate
- Condensation of palmitoyl-CoA and serine, forms β -ketosphinganine
- Reduction, acylation, oxidase yields N-acyl-sphinganine (a ceramide).