BI/CH 422/622

ANABOLISM OUTLINE:

Photosynthesis
Carbon Assimilation – Calvin Cycle
Carbohydrate Biosynthesis in Animals
- Gluconeogenesis
- Glycogen Synthesis
- Pentose-Phosphate Pathway
- Regulation of Carbohydrate Metabolism
- Anaplerotic reactions

Biosynthesis of Fatty Acids and Lipids
- Fatty Acids
  - contrasts
  - location & transport
  - Synthesis
    - acetyl-CoA carboxylase
    - fatty acid synthase
      - ACP priming
      - 4 steps
  - Control of fatty acid metabolism
    - ACC
    - Reciprocal control of β-ox
- Diversification of fatty acids
  - Eicosanoids
  - Prostaglandins and Thromboxanes
- Triacylglycerides
- Membrane lipids
  - Glycerophospholipids
  - Sphingolipids
  - Isoprene lipids:
    - Ketone Bodies
    - **Cholesterol**

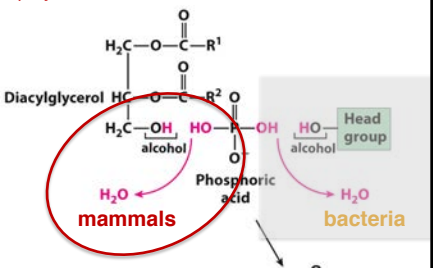
Lipid Biosynthesis

Biosynthesis of Membrane Phospholipds

Glycerophospholipid Biosynthesis requires Activation by CTP

- 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

Attach head group by condensation here:



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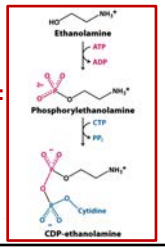
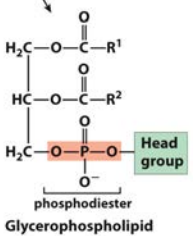
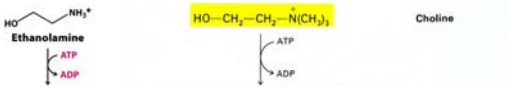
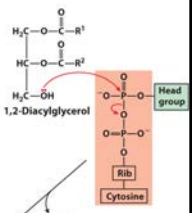


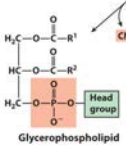




Lipid Biosynthesis

Synthesis of Phosphatidyl-choline, -ethanolamine, and -serine and in Mammals

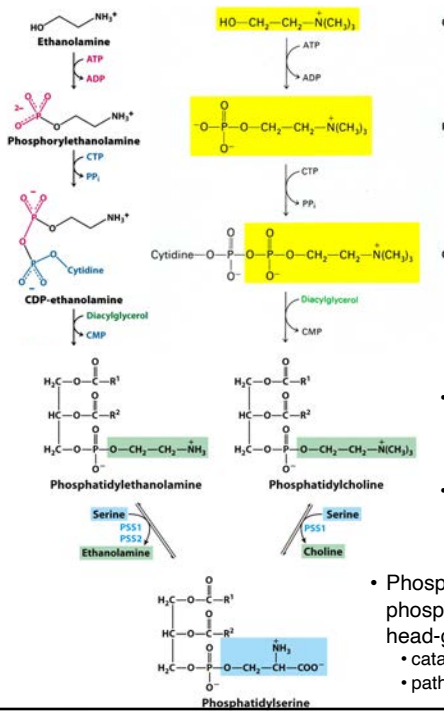




Mammals use CDP-alcohol

- 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



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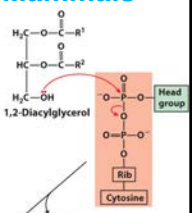

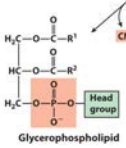

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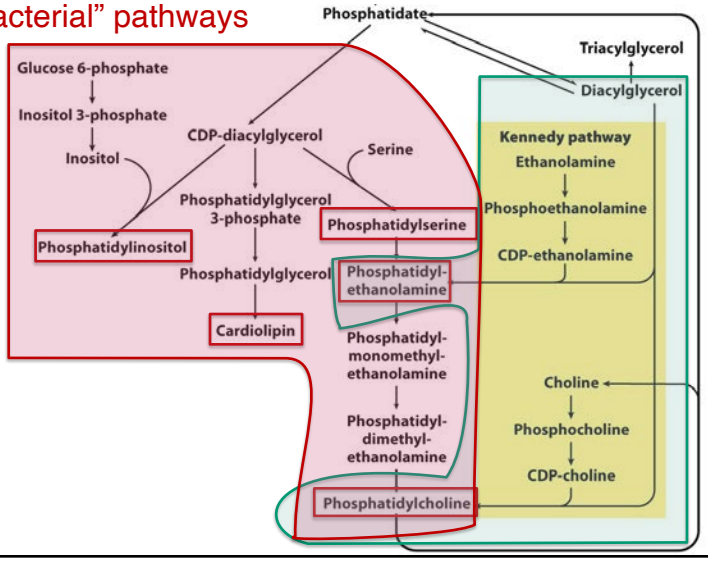
Lipid Biosynthesis

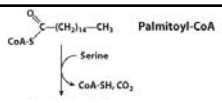
Synthesis of Phosphatidyl-choline, -ethanolamine, -serine, -inositol, and -diglycerol in Yeast

"Bacterial" pathways



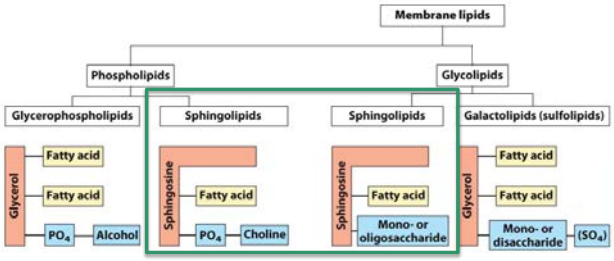
"Mammalian" pathways

Head-group exchange reactions that interconvert PE, PS, & PC in mammals are not shown.



Lipid Biosynthesis

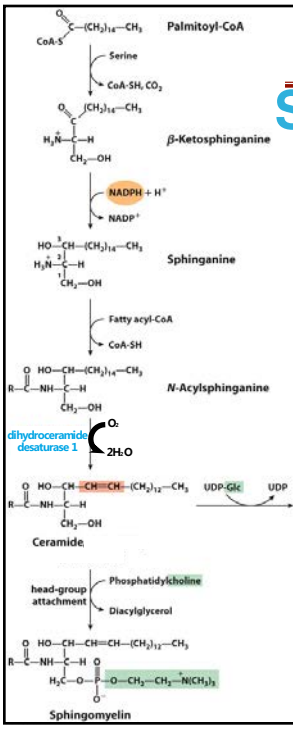
Synthesis of Sphingolipids

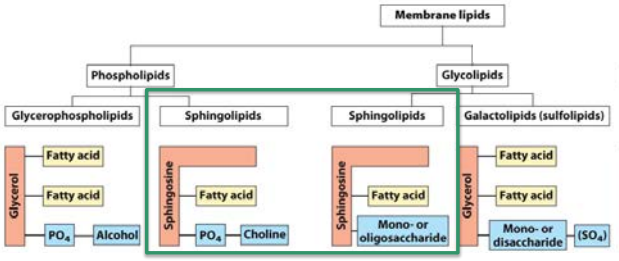


- Sphingosine comes from amino acids + fatty acids; serine + palmitate
- Condensation of palmitoyl-CoA and serine, forms β-ketosphinganine
- Reduction, acylation, oxidase yields N-acyl-sphinganine (a ceramide).

Lipid Biosynthesis

Synthesis of Sphingolipids





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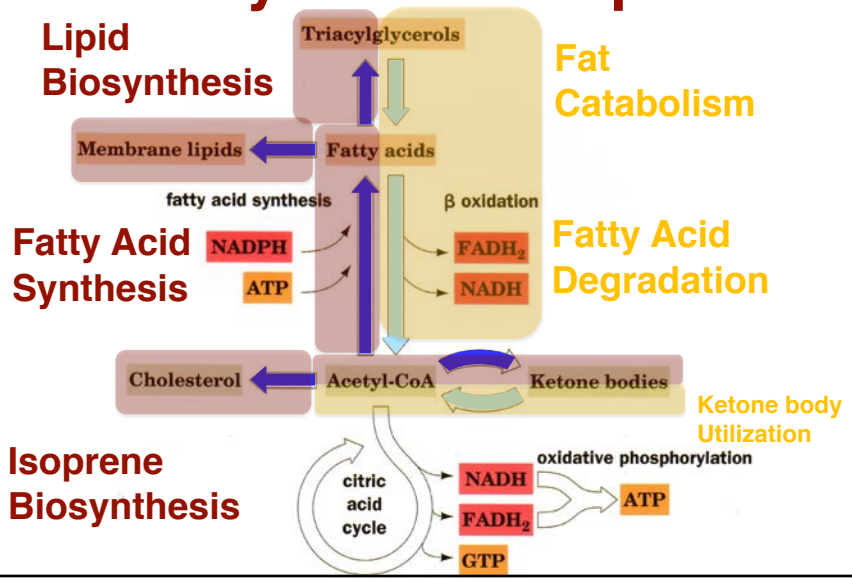
ANABOLISM II: Biosynthesis of Fatty Acids & Lipids

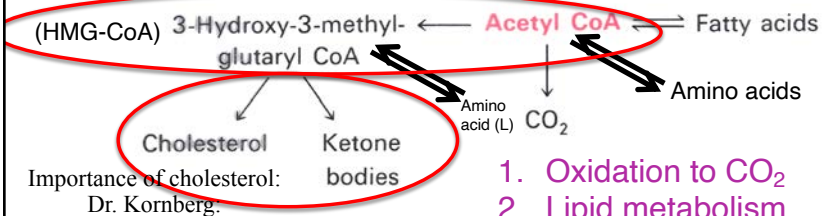


ANABOLISM II: Biosynthesis of Fatty Acids & Lipids

1. Biosynthesis of fatty acids
2. Regulation of fatty acid degradation and synthesis
3. Assembly of fatty acids into triacylglycerol and phospholipids
4. Metabolism of isoprenes
   a. Ketone bodies and Isoprene biosynthesis
   b. Isoprene polymerization
      i. Cholesterol
      ii. Steroids & other molecules
      iii. Regulation
      iv. Role of cholesterol in human disease

Cholesterol and Steroid Biosynthesis

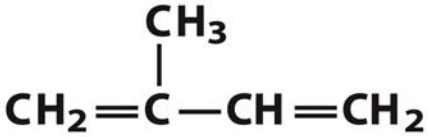
Fates of Acetyl CoA



Importance of cholesterol:
Dr. Kornberg:
Lecture 04.05.17 (12:01-17:12) 5 min

1. Oxidation to CO_2
2. Lipid metabolism
3. Amino acid metabolism

- Nearly all the remaining lipids have a chemical relationship, and their biosynthesis are built on, the 5-carbon **isoprene unit**
- Isoprene is made through the intermediate, mevalonate

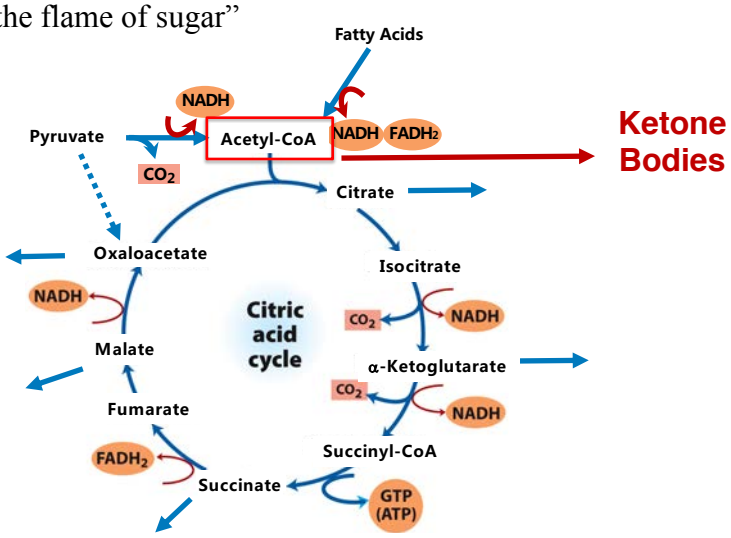


Isoprene

1912-2000
Nobel Prize 1964

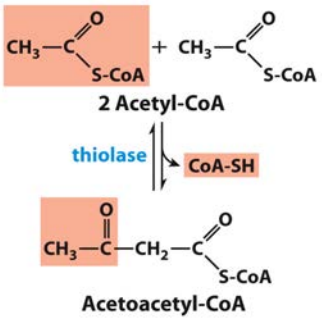
Cholesterol and Steroid Biosynthesis

"Fat burns in the flame of sugar"



Cholesterol and Steroid Biosynthesis

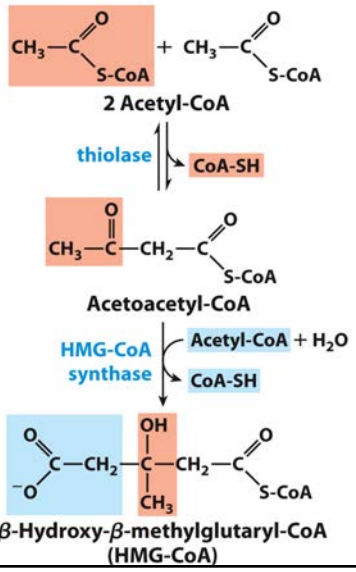
Ketone Body Biosynthesis



- The first step is reverse of the last step in the β oxidation: thiolase reaction joins two acetate units.
- A second step incorporates a third acetyl-CoA.
- Together, two CoASH are freed from three acetyl-CoA.
- In the liver, this synthesis occurs regardless of excess acetyl-CoA
- HMG-CoA is a metabolic junction

Cholesterol and Steroid Biosynthesis

Ketone Body Biosynthesis



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Cholesterol and Steroid Biosynthesis

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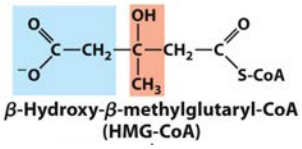
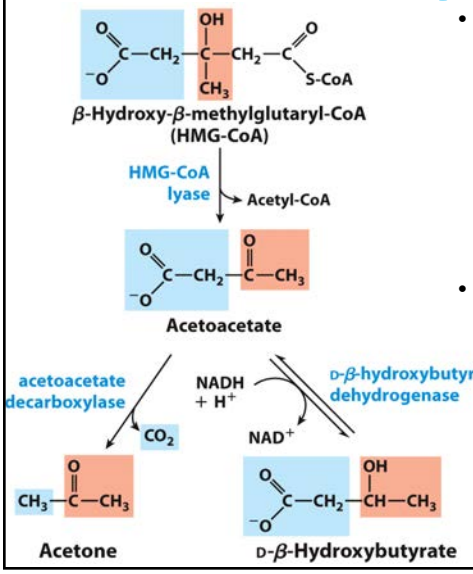


- In order to traffic to other tissues, CoA must be removed. This is done by removing as acetyl-CoA leaving Acetoacetate. This along with Acetone and β-hydroxybutyrate can then travel through the blood to other tissues for energy (catabolism).
  - In the mitochondria
- Acetone is removed as a gas and exhaled (although some species or tissues can metabolize acetone), but acetoacetate and β-hydroxybutyrate can traffic to the heart, kidney, muscle, and adapted brain for use in energy production.

HMG-CoA & ketone bodies:
Dr. Kornberg:
Lecture 03.01.17 (27:35-32:16) 4.5 min

Cholesterol and Steroid Biosynthesis

Ketone Body Biosynthesis



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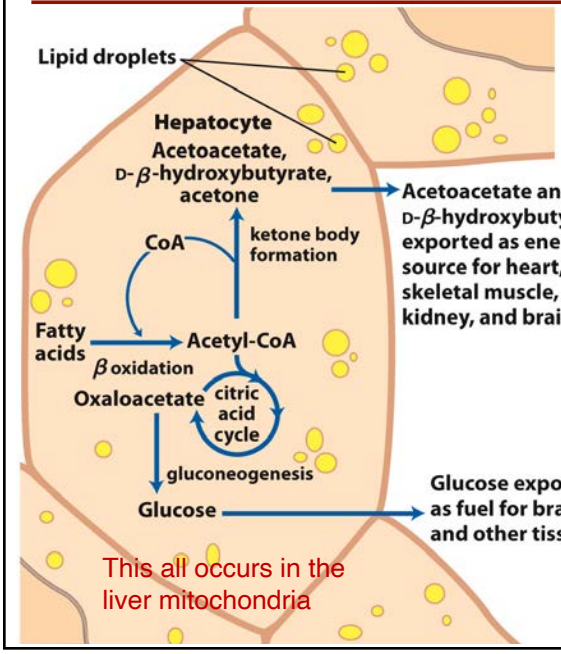
HMG-CoA & ketone bodies:
Dr. Kornberg:
Lecture 03.01.17 (27:34-32:16) 4.5 min

ANABOLISM II: Biosynthesis of Fatty Acids & Lipids

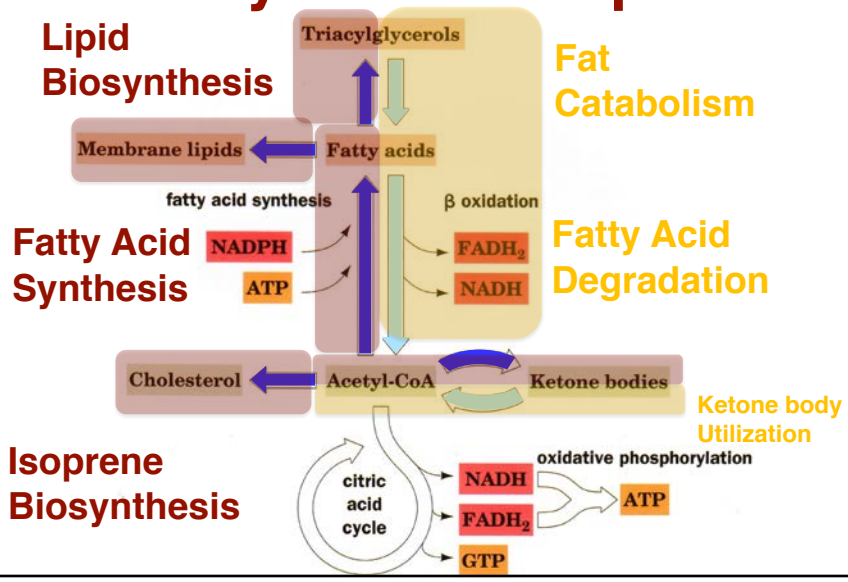
Cholesterol and Steroid Biosynthesis



Liver as a fuel source: Ketone Bodies & Glucose

- HMG CoA is present in both cytosol and mitochondria of liver
- Mitochondrial-ketogenesis
- Cytosolic – cholesterol synthesis

ANABOLISM II: Biosynthesis of Fatty Acids & Lipids

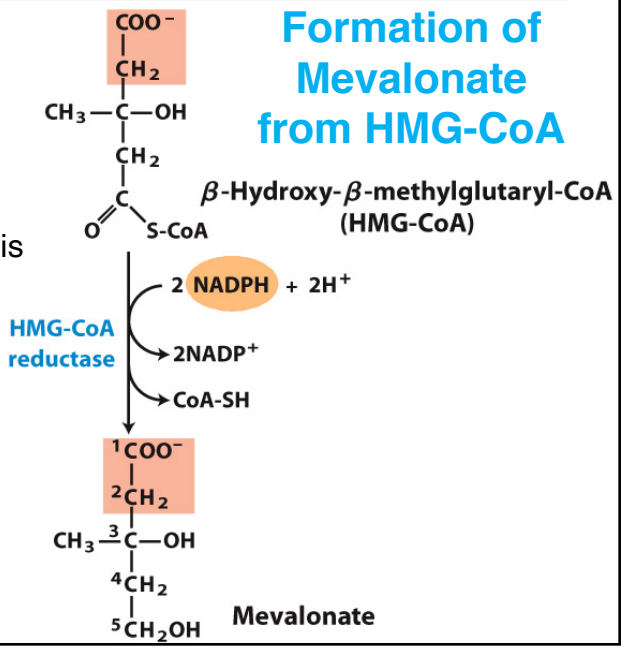


Cholesterol and Steroid Biosynthesis

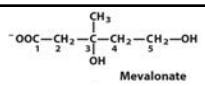
IN THE CYTOSOL

- HMG-CoA (from 3 acetyl-CoAs) is reduced to form mevalonate.
- *HMG-CoA reductase* is a common target of cholesterol-lowering drugs; called Statins

Formation of Mevalonate from HMG-CoA



Cholesterol and Steroid Biosynthesis



Mevalonate to Activated Isoprenes

- Two phosphates are transferred stepwise from ATP to mevalonate.
- A third phosphate from ATP is added at the hydroxyl, followed by decarboxylation and elimination catalyzed by pyrophospho-mevalonate decarboxylase creates a diphosphorylated 5-C product; *Δ^3-isopentyl pyrophosphate (IPP)* **(isoprene)**.
- Isomerization to a second isoprene *dimethylallylpyrophosphate (DMAPP)* gives two activated isoprene compounds that act as precursors for all of the other lipids in this class