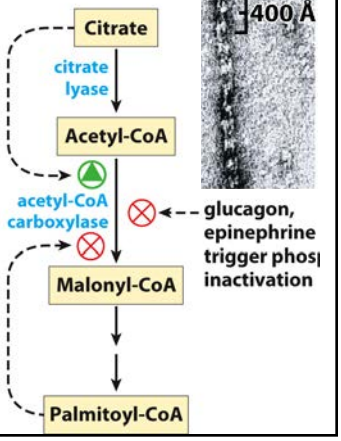
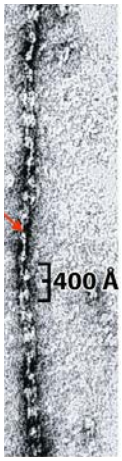
Fatty Acid Biosynthesis

Control of Fatty-Acid Synthesis

- **Acetyl CoA carboxylase (ACC) catalyzes the committal step.**
- **Allosteric Control**
  - Inhibited when energy is needed, fatty acids are acylated for degradation, and inhibit ACC.
    - ACC is feedback-inhibited by **palmitoyl-CoA**.
  - ACC is *activated* by **citrate**.
    - Citrate is made from acetyl-CoA in mitochondria (acetyl-CoA^{mt}).
    - Citrate signals excess energy to be converted to fat.
  - When [acetyl-CoA]^{mt} ↑ it is converted to citrate… citrate is exported to cytosol.
- **Hormonal Control**
  - Glucagon and epinephrine: leads to activation of AMP-dependent Protein Kinase (AMPK)
    - Phosphorylation inactivates ACC
    - Phosphorylation reverses the polymerization → monomers (inactive)
  - Insulin: leads to activation of Protein Phosphatase 2A
    - Dephosphorylation activates ACC
    - When dephosphorylated, ACC polymerizes into long filaments (active)
- **Changes in gene expression**
  - example: excess of certain polyunsaturated fatty acids (eicosanoids) bind to transcription factors called peroxisome proliferator-activated receptors (PPARS)





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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 Thromboxane
- Triacylglycerides

Membrane lipids
- Glycerophospholipids
- Sphingolipids

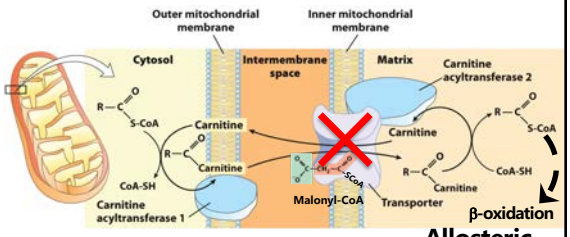
Isoprene lipids: **Cholesterol**

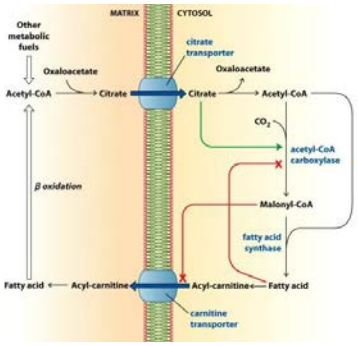
ANABOLISM II: Biosynthesis of Fatty Acids & Lipids

Fatty Acid Biosynthesis

Recall how β-oxidation starts: Acyl-Carnitine/Carnitine Transport:

- β oxidation of fatty acids occurs in mitochondria.
- If fatty acyl-CoAs are not transported in, they cannot be degraded
- Transport is via carnitine transporter.
- Blocking β oxidation with initial committed product of fatty-acid synthesis: malonyl-CoA





Allosteric Control of Fatty Acid Metabolism

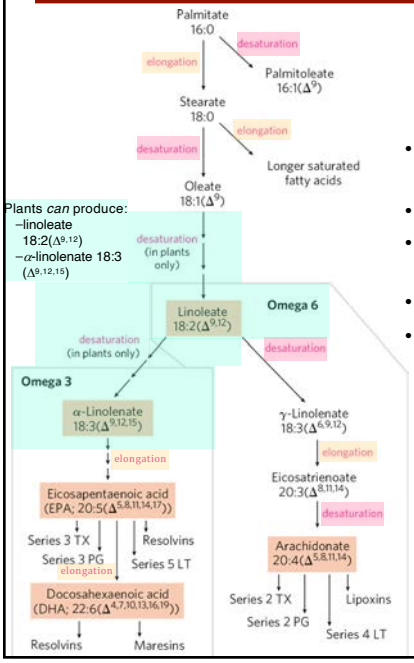
Inhibition

Activation

Reciprocal Control of Fatty-Acid Degradation *versus* Fatty-Acid Synthesis

ensures that fat synthesis and oxidation don't occur simultaneously

Fatty Acid Biosynthesis



Diversification of Palmitate: Elongation

Fatty Acid Elongation Systems

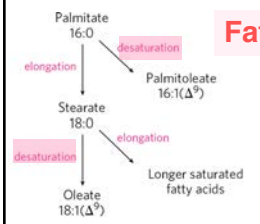
- Elongation systems in the endoplasmic reticulum and mitochondria create longer fatty acids.
- Use CoA derivatives
- As in palmitate synthesis, each step adds units of 2 C. Use malonyl-CoA.
- Stearate (18:0) is the most common product.
- Plants make linoleate (Ω6) and α-linolenate (Ω3), animals can't; But they can elongate these ingested essential FA
  - These fatty acids are "essential" to humans.
    - –Polyunsaturated fatty acids (PUFAs) help control membrane fluidity.
    - –PUFAs are precursors to eicosanoids
  - The ratio of omega-6 to omega-3 fatty acids in the diet, if too high, can lead to cardiovascular disease

Eicosanoids

PG = Prostaglandins
TX = Thromboxanes
LT = Leukotrienes

Fatty Acid Biosynthesis

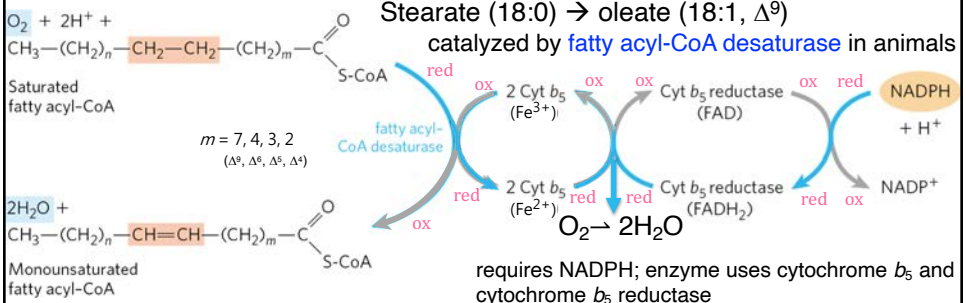
Diversification of Palmitate: Desaturation



Fatty Acyl-CoA Desaturase

- Looks like a mixed-function oxidase: OXIDASE
- Humans have Δ^4, Δ^5, Δ^6, and Δ^9 desaturases but *cannot* desaturate beyond Δ^9.

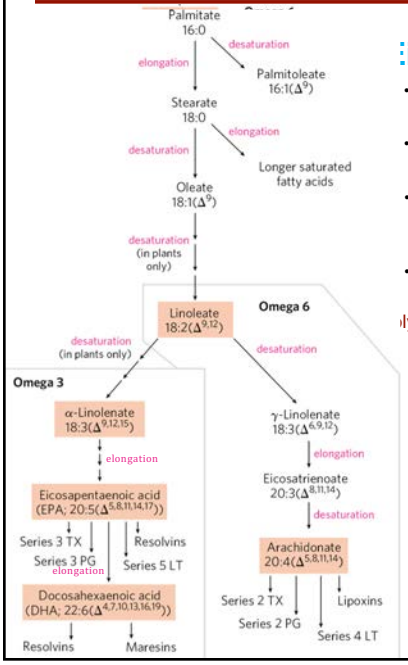
FOR EXAMPLE: for a *Δ^9-desaturation*
Palmitate(16:0) → palmitoleate(16:1, Δ^9)
Stearate (18:0) → oleate (18:1, Δ^9)
catalyzed by fatty acyl-CoA desaturase in animals



requires NADPH; enzyme uses cytochrome b_5 and cytochrome b_5 reductase
Both donate electrons to O_2 (total of 4)

In plants & bacteria the desaturases work on PL, not fatty-acyl CoA; needed for rapid changes in fluidity

Fatty Acid Biosynthesis



Animals can do, plants can do

Eicosanoids: Synthesis and Classes

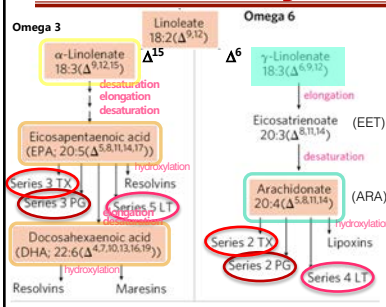
- Linoleate (18:2($\Delta^{9,12}$) gets desaturated on both sides = γ-linolenate (18:3($\Delta^{6,9,12}$) & α-linolenate (18:3($\Delta^{9,12,15}$).
- Elongation to C20, and further desaturation of γ-linolenate (18:3($\Delta^{6,9,12}$) gives Arachidonate, 20:4($\Delta^{5,8,11,14}$)
- Elongation to C20, and TWO further desaturation of α-linolenate (18:3($\Delta^{9,12,15}$) gives EPA, 20:5($\Delta^{5,8,11,14,17}$). More of the same gets DHA, 22:6($\Delta^{4,7,10,13,16,19}$)
- These desaturations are all going closer to the carboxylate and can be accomplished by animals.

lyunsaturated fatty acids (PUFAs)) bioactive paracrine

PG = Prostaglandins
TX = Thromboxanes
LT = Leukotrienes

- Created from the arachidonate or EPA, which are incorporated into membranes phospholipids.
- In response to stimuli (hormone, etc.), phospholipase A_2 is activated
- The unsaturated C-2 fatty acid is released

Fatty Acid Biosynthesis



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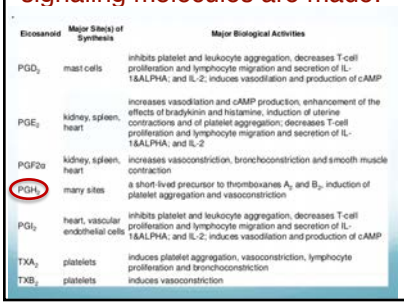
From these Eicosanoids (20C Polyunsaturated fatty acids (PUFAs)) bioactive paracrine signaling molecules are made:



Eicosanoid	Major Site(s) of Synthesis	Major Biological Activities
PGD_2	mast cells	inhibits platelet and leukocyte aggregation, decreases T-cell proliferation and lymphocyte migration and secretion of IL-1&ALPHA; and IL-2; induces vasodilation and production of cAMP
PGE_2	kidney, spleen, heart	increases vasodilation and cAMP production, enhancement of the effects of bradykinin and histamine, induction of uterine contractions and of platelet aggregation; decreases T-cell proliferation and lymphocyte migration and secretion of IL-1&ALPHA; and IL-2
PGF2α	kidney, spleen, heart	increases vasoconstriction, bronchoconstriction and smooth muscle contraction
PGH_2	many sites	a short-lived precursor to thromboxanes A_2 and B_2; induction of platelet aggregation and vasoconstriction
PGI_2	heart, vascular endothelial cells	inhibits platelet and leukocyte aggregation, decreases T-cell proliferation and lymphocyte migration and secretion of IL-1&ALPHA; and IL-2; induces vasodilation and production of cAMP
TXA_2	platelets	induces platelet aggregation, vasoconstriction, lymphocyte proliferation and bronchoconstriction
TXB_2	platelets	induces vasoconstriction

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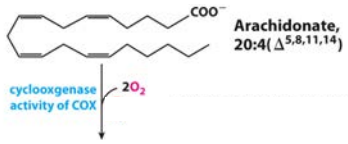
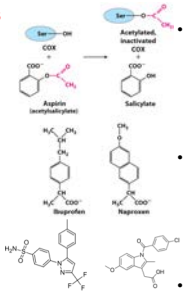
Fatty Acid Biosynthesis

Eicosanoids: Cyclic Pathway



- PGH_2 synthase (cyclooxygenase, or COX) has isozymes
- COX-1 is ubiquitous and catalyzes synthesis of prostaglandins that regulate *gastric mucin secretion and other smooth muscle functions*
- COX-2 is inducible (except in brain) by immune response and acts at the sites of inflammation. It catalyzes synthesis of prostaglandins that mediate *pain, inflammation, and fever.*

Nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit COX isozymes



- Aspirin (acetylsalicylate) is an irreversible inhibitor.
  - acetylates a Ser in active site
  - blocks active site in both COX isozymes
- Ibuprofen, naproxen, and indomethacin are competitive inhibitors.
  - resemble substrate; also block active site in both isozymes
- Celebrex and Vioxin are specific for COX-2

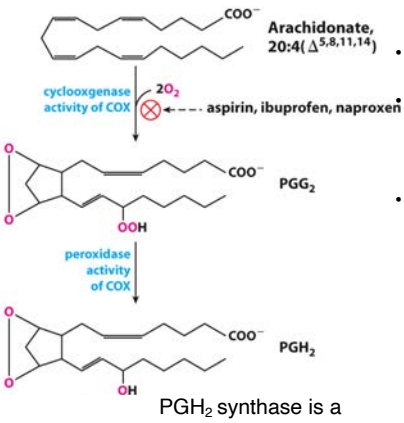
Bengt Samuelsson
Nobel Prize 1982

PGH_2 synthase is a cyclooxygenase/peroxidase enzyme that functions in the smooth ER.

- Step 1: PGH_2's cyclooxygenase activity adds 2 O_2 to form PGG_2.
- Step 2: PGH_2's peroxidase activity converts peroxide to alcohol, creates PGH_2.

Fatty Acid Biosynthesis

Eicosanoids: Cyclic Pathway



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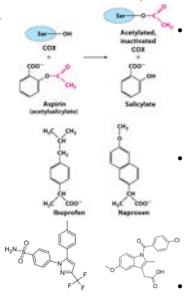

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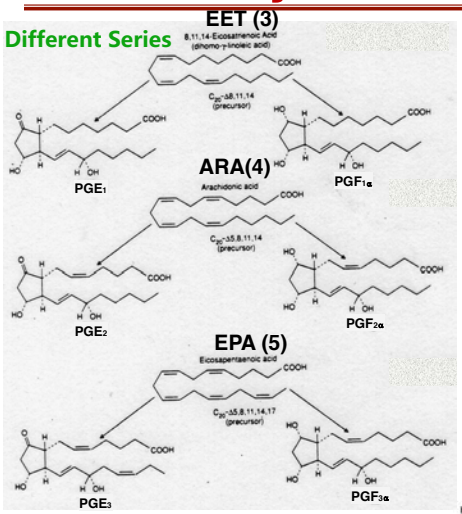
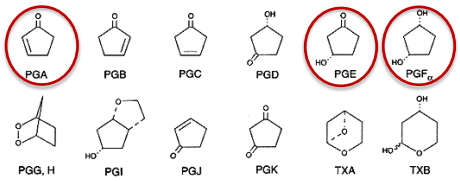
Fatty Acid Biosynthesis

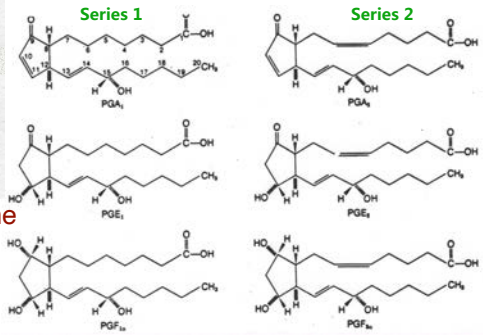
Different Series



Prostaglandin & Thromboxane: Synthesis and Classes

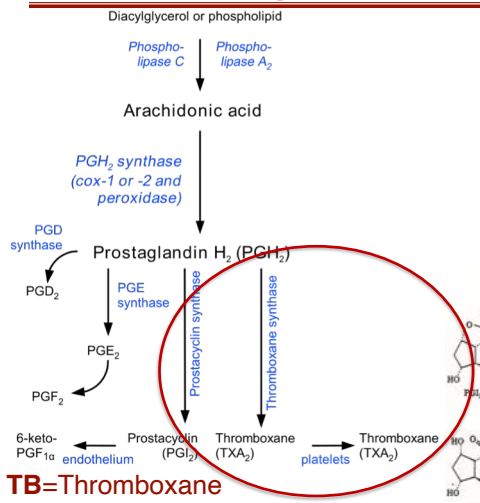


Different Classes

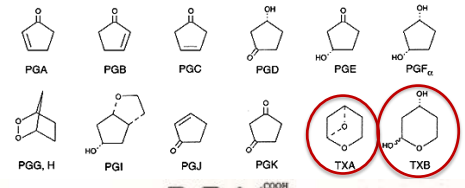


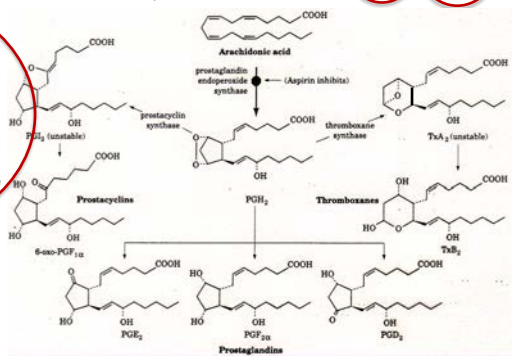
PG = Prostaglandins/**TB**=Thromboxane
–letters-after are for number and oxidation state of oxygens and ring
–subscript is the number of double bonds

Fatty Acid Biosynthesis



Thromboxane: Synthesis and Classes





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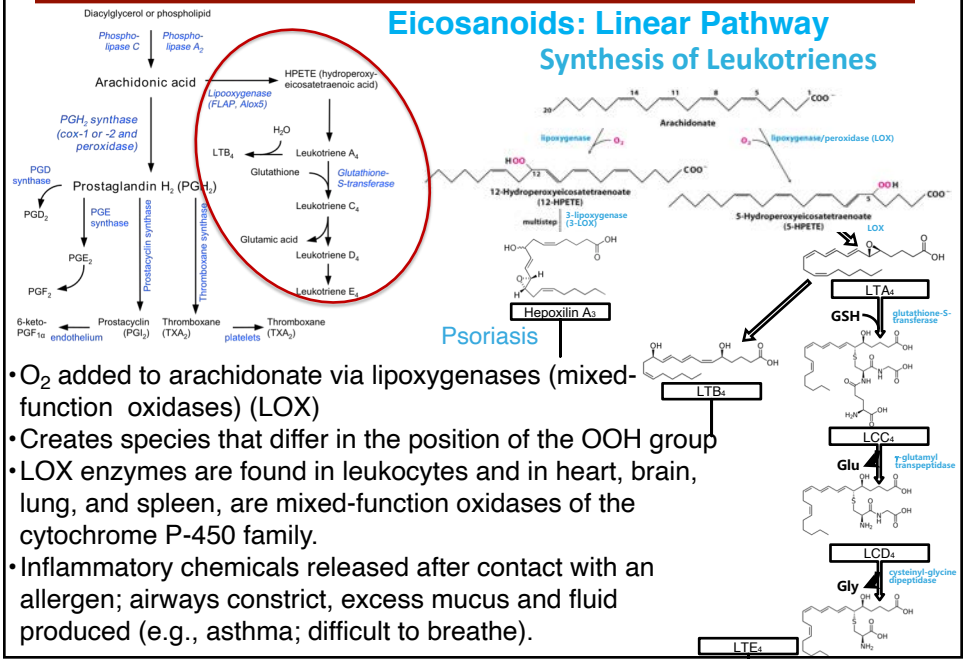
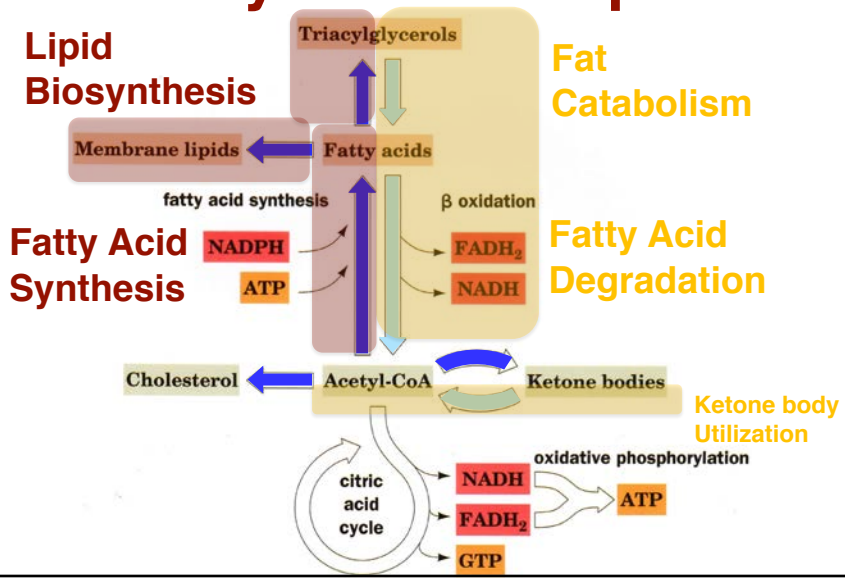
Platelet aggregation and wound healing

Fatty Acid Biosynthesis



- O_2 added to arachidonate via lipoxygenases (mixed-function oxidases) (LOX)
- Creates species that differ in the position of the OOH group
- LOX enzymes are found in leukocytes and in heart, brain, lung, and spleen, are mixed-function oxidases of the cytochrome P-450 family.
- Inflammatory chemicals released after contact with an allergen; airways constrict, excess mucus and fluid produced (e.g., asthma; difficult to breathe).

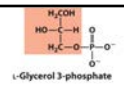
ANABOLISM II: Biosynthesis of Fatty Acids & Lipids



Lipid Biosynthesis

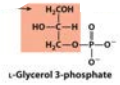
Biosynthesis of Triacylglycerol

Fat (Triacylglycerol) and Phospholipids in Animals, Plants, and Bacteria have a common intermediate:
Phosphophatidic Acid



Usually saturated

Usually u



- Animals and plants store fat for fuel.
  - plants: in seeds, nuts
  - typical 70-kg human has ~15 kg fat
    - enough to last 12 weeks
    - compare with 12 hours worth of glycogen in liver and muscle
- All organisms make glycerophospholipids for membranes.
- Both molecules contain glycerol from Glycerol 3-P
- Most Glycerol 3-P comes from **dihydroxyacetone phosphate** (DHAP) in glycolysis.
  - via glycerol 3-phosphate dehydrogenase
- Minor amount from glycerol (liver and kidney).
  - via glycerol kinase
- **Phosphatidic acid** is the precursor to fat and glycerophospholipids.
  - fatty acids attached by acyl transferases
  - releases CoA

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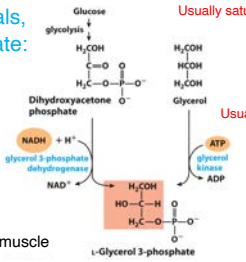

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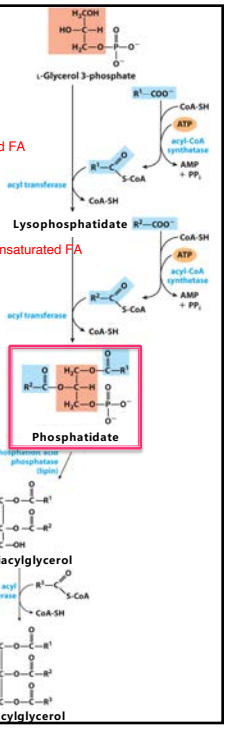

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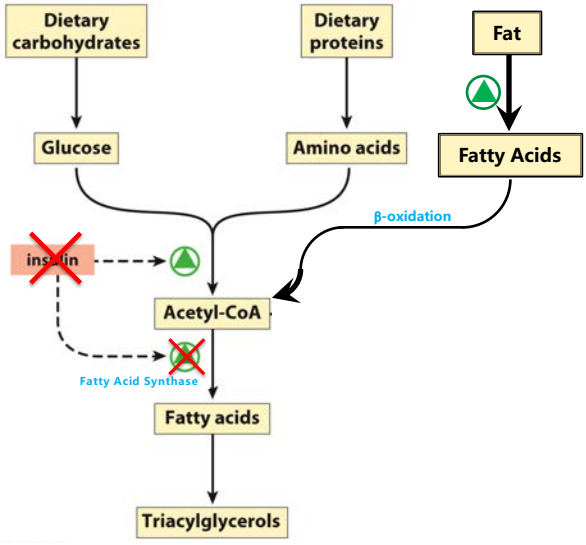
Lipid Biosynthesis

Regulation of Triacylglycerol Synthesis by Insulin

- Secretion of Insulin results in stimulation of triacylglycerol synthesis.
- Lack of insulin results in:
  - –increased lipolysis
  - –increased fatty acid oxidation
    - And when citric acid cycle intermediates (oxaloacetate) are depleted (as in diabetes when glucose cannot get in), acetyl-CoA builds up and ketones bodies are made
  - –Repression of fatty acid synthase (PP2A)
  - –ACC is not active
  - –No malonyl-CoA means β-oxidation is active



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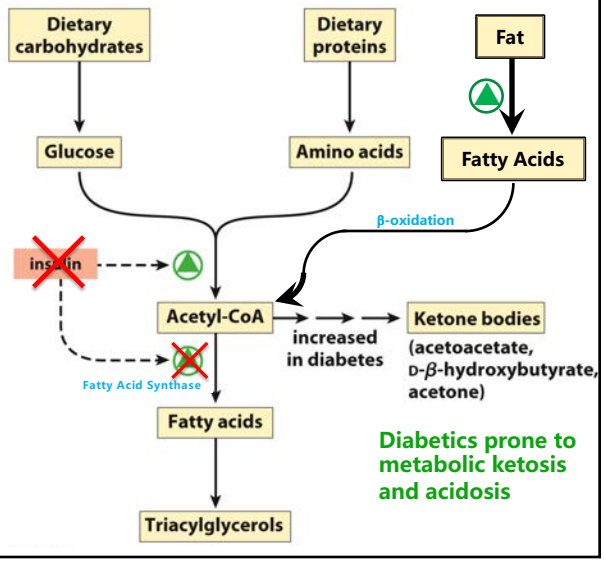


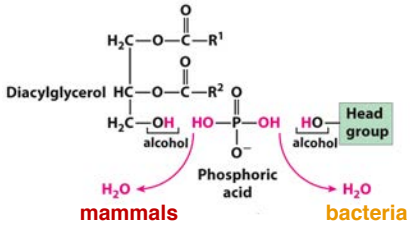
Lipid Biosynthesis

Biosynthesis of Membrane Phospholipds

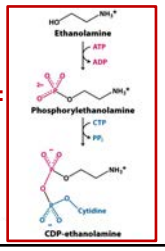
Glycerophospholipid Biosynthesis requires Activation by CTP

- 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:



Example:



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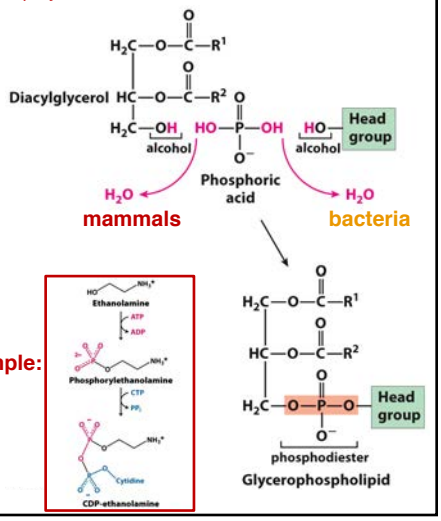
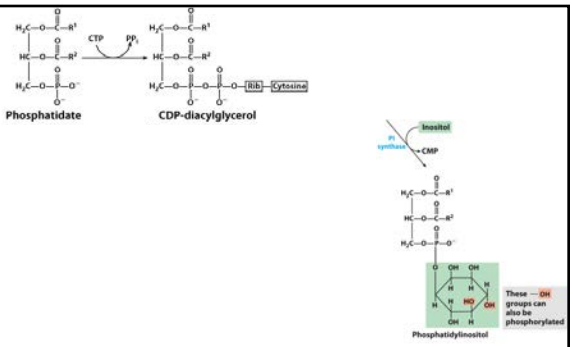


Example:

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 → ***phopshatidylcholine (lecithin).***
  - catalyzed by methyltransferase
- **Cardilipin** is from the condensation of two phosphatidyl glycerols, which are formed from glycerol 3-phosphate.



Lipid Biosynthesis

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