BI/CH 422/622

OUTLINE:

Introduction and review
Transport
Glycogenolysis
Glycolysis
Other sugars
Pasteur: Anaerobic vs Aerobic

Exam-1 material

Exam-2 material

Fermentations
Pyruvate
- pyruvate dehydrogenase (ox-decarbox; S-ester)

Krebs' Cycle
- How did he figure it out?
- Overview
- 8 Steps
  - Citrate Synthase (C-C)
  - Aconitase (=, -OH)
  - Isocitrate dehydrogenase (ox-decarbox; =O)
  - Ketoglutarate dehydrogenase (ox-decarbox; S-ester)
  - Succinyl-CoA synthetase (sub-level phos)
  - Succinate dehydrogenase (=)
  - Fumarase (-OH)
  - Malate dehydrogenase (=O)
- Energetics
- Regulation
- Summary

Oxidative Phosphorylation
- Energetics (-0.16 V needed for making ATP)
- Mitochondria
- Transport (2.4 kcal/mol needed to transport H^+ out)
- Electron transport
  - Discovery
  - Four Complexes
    - Complex I: NADH → $CoQH_2$
    - Complex II: Succinate → $CoQH_2$
    - Complex III: $CoQH_2$ → Cytochrome C (Fe^{2+})
    - Complex IV: Cytochrome C (Fe^{2+}) → H_2O
- Chemiosmotic theory: Phosphorylation
  - ATPase
  - Mitchell Hypothesis
  - Binding-Change Model
  - Connection to the proton motive force
  - Net ATP production
  - Regulation

Exam-3 material

Lipid Degradation (Catabolism)
- FOUR stages in the catabolism of lipids:
  - Mobilization from adipose tissues
  - Activation of fatty acids
  - Transport
  - Oxidation

Lipid Degradation

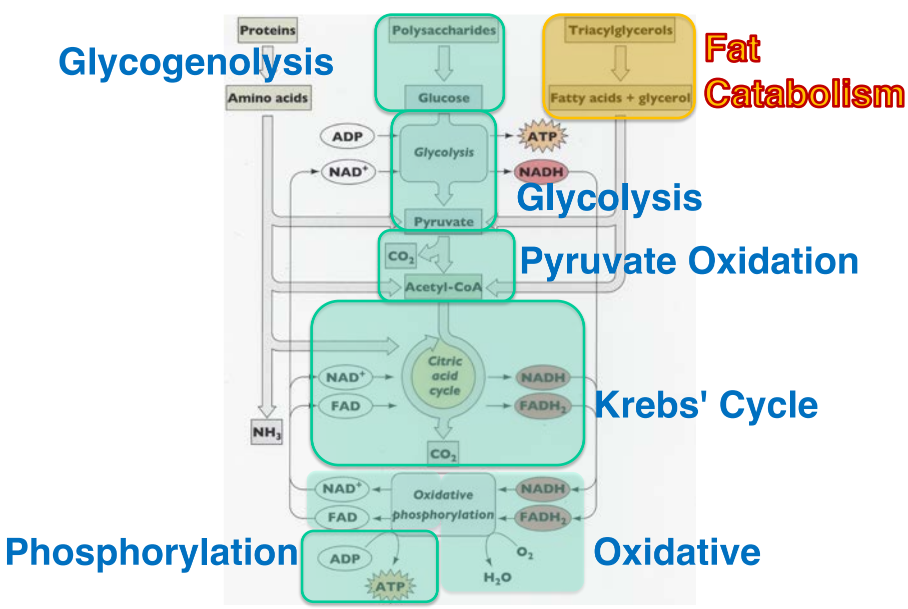
Lipid Catabolism

OUTLINE:

Fat Catabolism
- diet
- storage

Fatty-Acid Catabolism
- Mobilization
- Activation
- Transport
- Oxidation
  - Saturated FA
    - β-oxidation
    - energetics
  - Unsaturated FA
  - Odd-chain FA
  - Ketone Bodies

Lipid Degradation



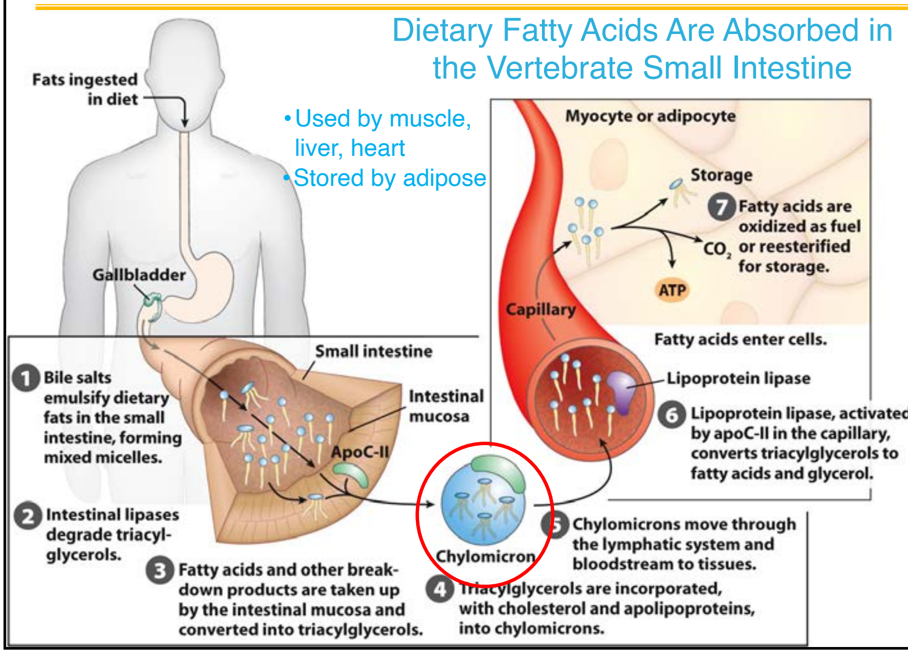
Fat Catabolism

- Fat as a fuel; ingestion of the “chunks”
- How fats are mobilized and transported in animal tissues
- COMPARTMENTATION
  - o How fats are oxidized in mitochondria
    - – Glycerol
    - – Saturated Fatty Acids
    - – Un-saturated Fatty Acids
    - – Odd-chain Fatty Acids
  - o Blocks to oxidation in mitochondria: How “ketone bodies” are utilized
  - o Fatty-acid metabolism in other organelles

Fat Catabolism

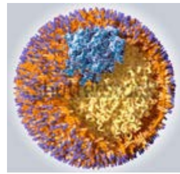
Dietary Fatty Acids Are Absorbed in the Vertebrate Small Intestine

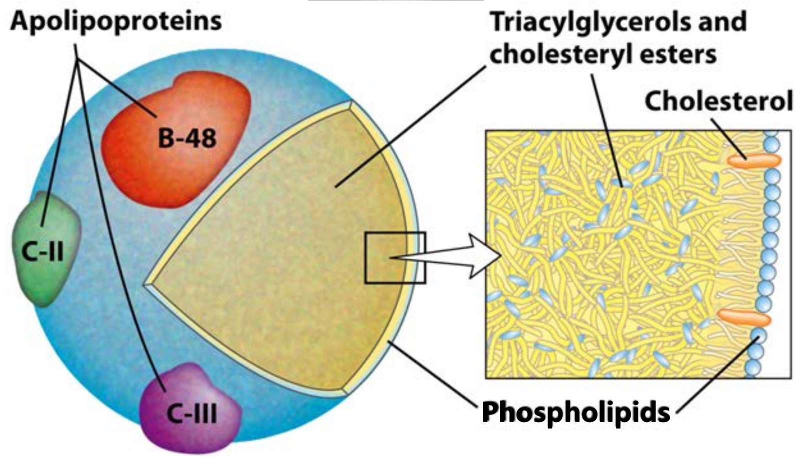
- Used by muscle, liver, heart
- Stored by adipose



Fat Catabolism

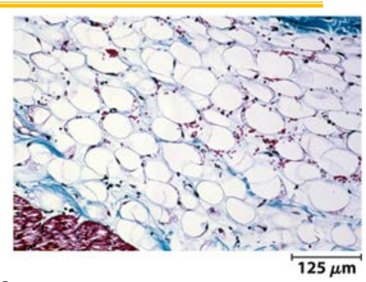
Chylomicrons

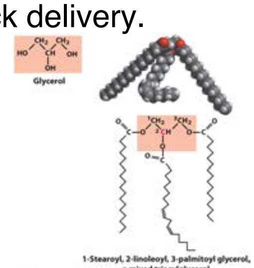


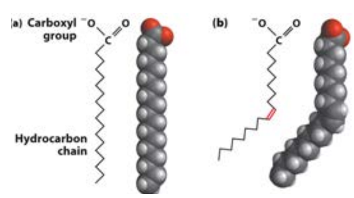


Fat Catabolism

- Fuel Storage of Fat is efficient
- The advantage of fats over polysaccharides:
  - Fatty acids carry more energy per carbon because they are more reduced.
  - Fatty acids complex or carry less water because they are nonpolar.
- Glucose and glycogen are for short-term energy needs and quick delivery.
- Fats are for long-term (months) energy needs, storage, and have slow delivery.







- How are fat stores accessed?

Fatty acids come in all types: ± double bonds, long & short, odd & even, etc.

Lipid Degradation: Fatty Acids

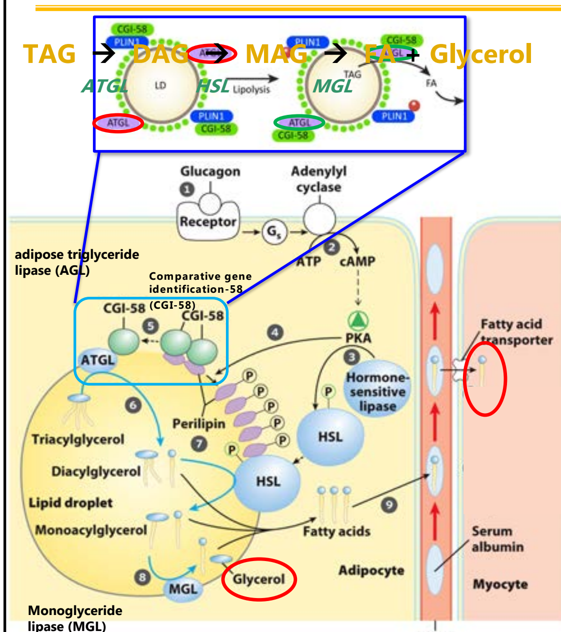
- Fatty Acid Oxidation is a Major Energy Source
- About one-third of human energy needs comes from dietary triacylglycerols (fat).
- There are differences in tissue utilization. About 80% of energy needs of mammalian heart and liver are met by oxidation of fatty acids.
- Many hibernating animals, such as grizzly bears, rely almost exclusively on fats as their source of energy.

There are FOUR stages in the catabolism of fatty acids:

1) Mobilization from tissues (mostly adipose)
2) Activation of fatty acids
3) Transport
4) Oxidation

Fatty Acid Degradation

Mobilization



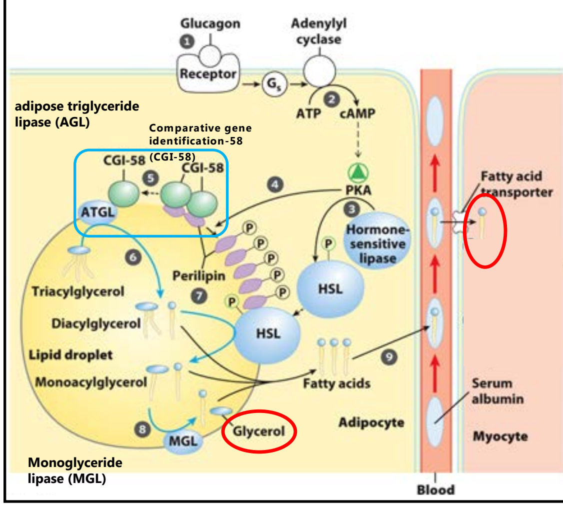
- Stored Triacylglycerides are released in response to Hormone signals
- Hormones trigger a mobilization "cascade" that activates lipases
- Lipases are activated by hormones glucagon and epinephrine. ❶ ❷❸❹
- In the case of glucagon, Protein Kinase A (**PKA**) is activated, ❺❼ which leads to the progressive activation of 3 lipases, one for each position on glycerol. ❸❻❽
- Fats are degraded into fatty acids and glycerol in the cytoplasm of adipocytes. ❽❾
- Fatty acids are transported to other tissues through the blood.

Fatty Acid Degradation

Mobilization

TAG → DAG → MAG → 3FA + Glycerol

ATGL *HSL* *MGL*



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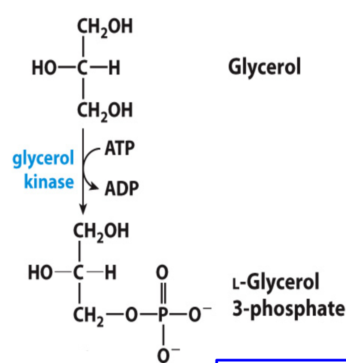
Fatty Acid Degradation

- Glycerol is a sugar alcohol and is converted to a glycolytic intermediate
- Glycerol kinase activates glycerol at the expense of ATP.
- Subsequent reactions recover more than enough ATP to cover this cost.
- Allows limited anaerobic catabolism of fats
- A redox reaction is required to convert the alcohol to a ketone. Done by glycerol-3-phosphate dehydrogenase
- We'll see this reaction again in lipid synthesis



Same cytosolic enzyme as used by the Glycerol-3-Phosphate Shuttle

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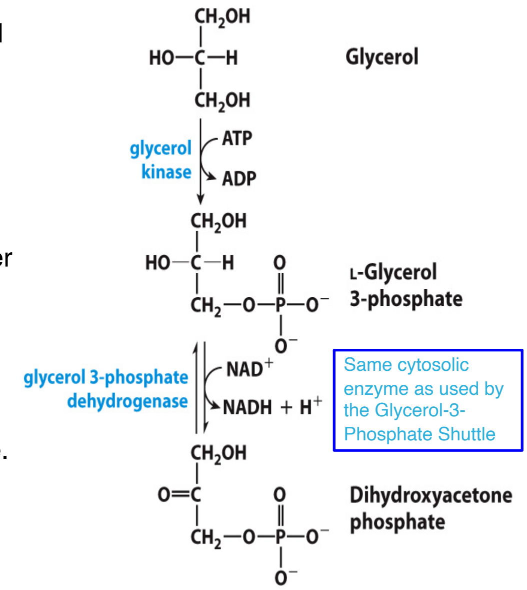


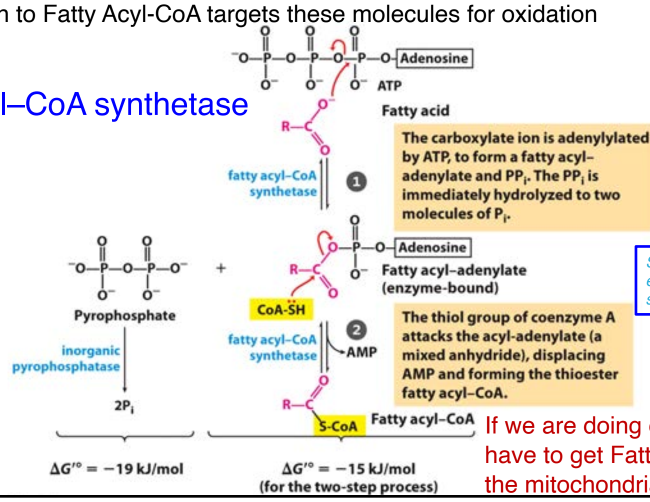
Same cytosolic enzyme as used by the Glycerol-3-Phosphate Shuttle

Fatty Acid Degradation

Activation

- Like the activation of sugars by phosphorylation, fatty acids must also be activated.
- Not having any alcohol groups, esterification of the carboxylate is the only chemistry available.
- A thio-ester is a higher energy bond than a simple ester: use Coenzyme A.
- Conversion to Fatty Acyl-CoA targets these molecules for oxidation

Fatty acyl–CoA synthetase



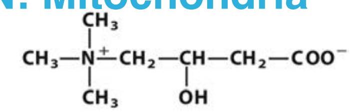
Similar to TCA-enzyme succinyl-CoA synthetase in reverse

If we are doing catabolism, we have to get Fatty-acyl CoA into the mitochondria.

Fatty Acid Degradation

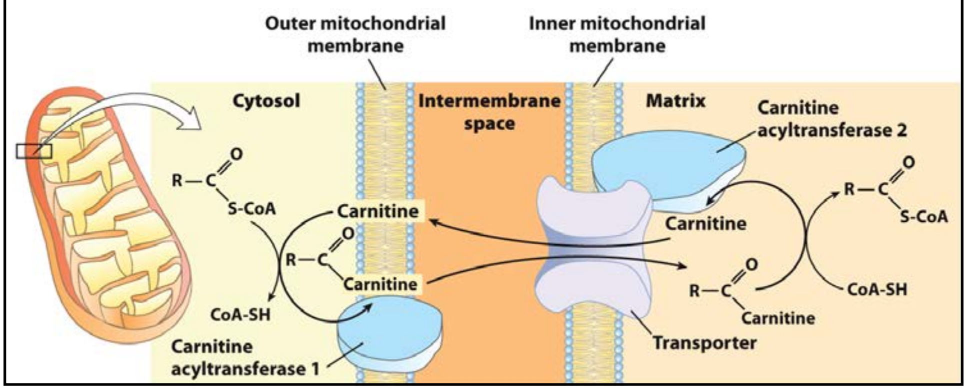
COMPARTMENTATION: Mitochondria

Acyl-Carnitine/Carnitine Transport



Carnitine

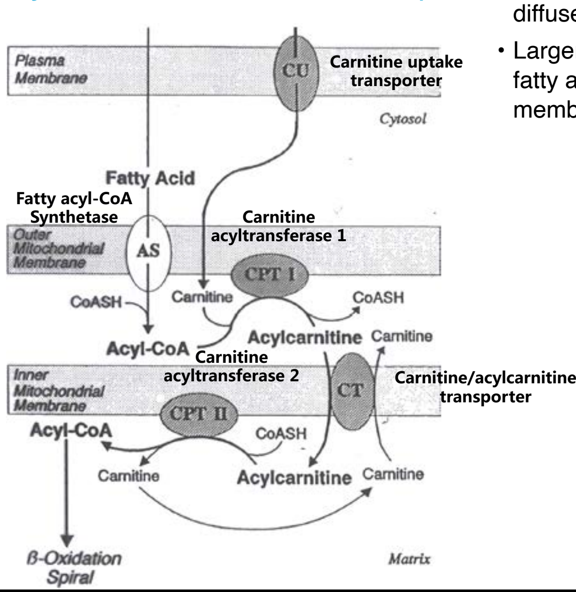
- β oxidation of fatty acids occurs in mitochondria.
- Fatty acyl-CoAs are transported via acyl-carnitine/carnitine transporter (anti-porter).



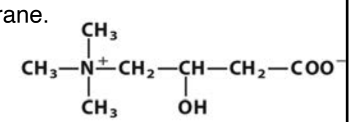
Fatty Acid Degradation

Transport

Acyl-Carnitine/Carnitine Transport



- Small (< 12 carbons) free fatty acids diffuse freely across membranes.
- Larger fatty acids are transported via fatty acid transporters on the plasma membrane.



Carnitine

- Fatty-acyl-CoA Synthetase is attached to the OUTER mitochondrial membrane.
- Recent evidence shows that its associated with an integral membrane transporter: Fatty-acyl Transporter Protein I
- Together, they are indicated on the figure as AS.

Lipid Degradation: Fatty Acids

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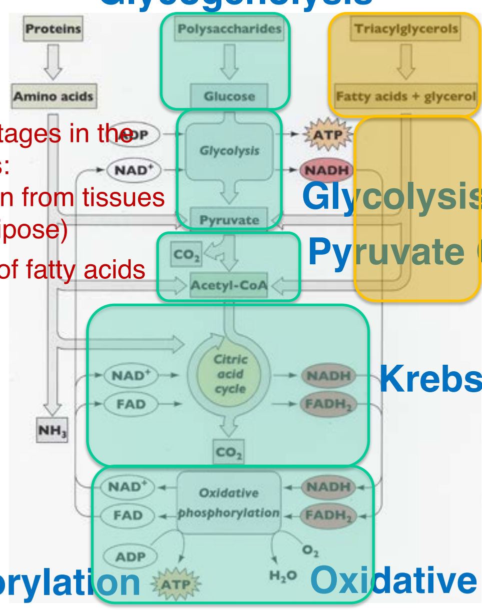
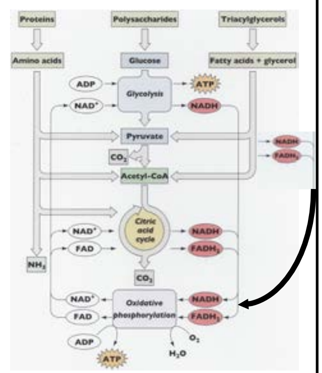


Degradation of Saturated Fatty Acids

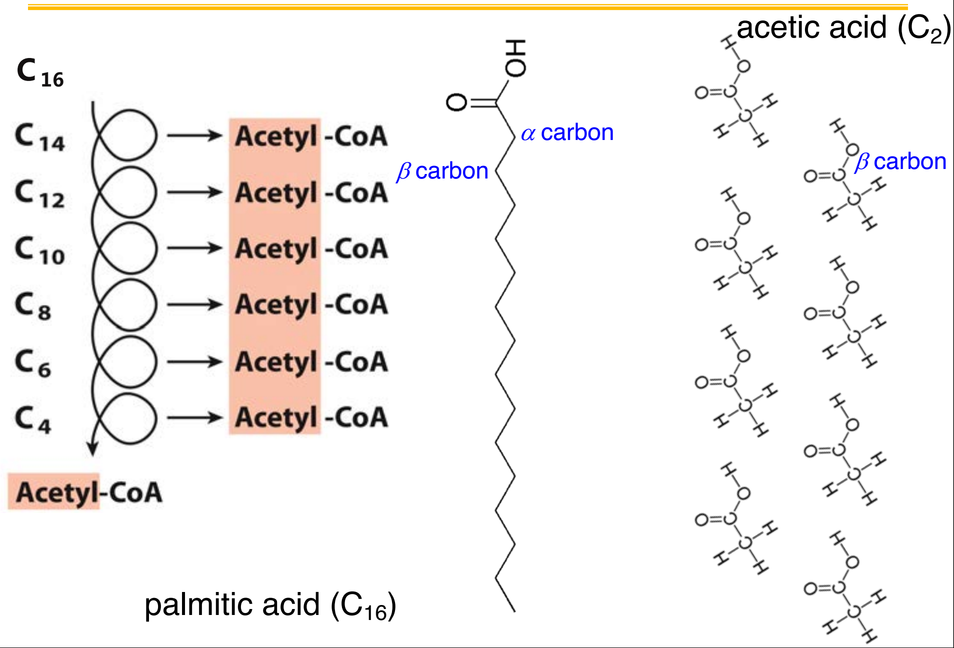
Fatty Acid Degradation

Oxidation

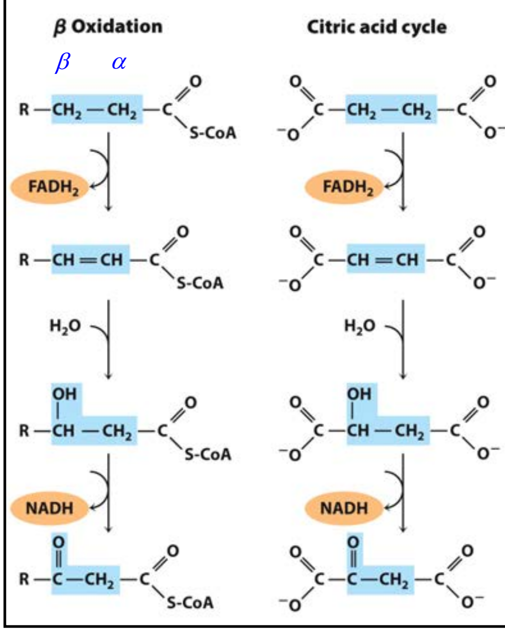
- Fatty Acid Oxidation consists of oxidative conversion of two-carbon units into acetyl-CoA at the β carbon of the fatty acid with concomitant generation of NADH and $FADH_2$.
  - –involves oxidation of β carbon to thioester of fatty acyl-CoA
  - –Concept of thiolysis; similar to phosphorolysis for polysaccharides
- The acetyl-CoA is converted into CO_2 via citric acid cycle with concomitant generation NADH and $FADH_2$. The NADH and $FADH_2$ are re-oxidized via the electron transport down the respiratory chain, and conversion into ATP.
- CONVERGENT PATHWAY with GLUCOSE.

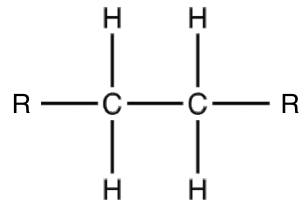


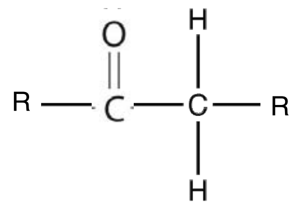
Fatty Acid Degradation



Fatty Acid Degradation

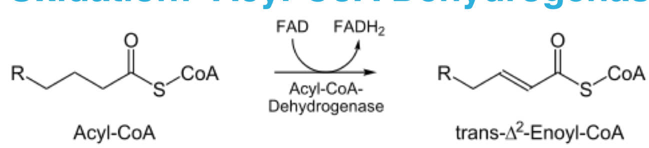




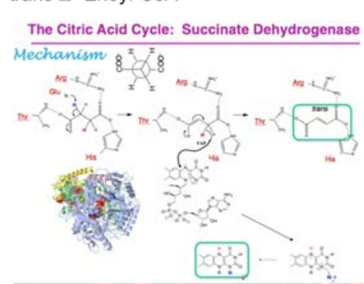


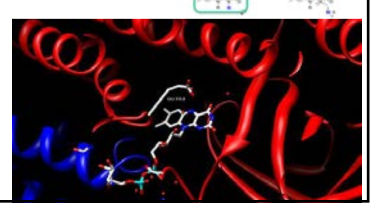
Fatty Acid Degradation

β-Oxidation: Acyl-CoA Dehydrogenase



- Catalyzed by isoforms of acyl-CoA dehydrogenase (AD) on the inner-mitochondrial membrane
  - very-long-chain AD (12–18 carbons)*
  - medium-chain AD (4–14 carbons)
  - short-chain AD (4–8 carbons)
- Results in trans double bond, different from naturally occurring unsaturated fatty acids
- Mechanism same as succinate dehydrogenase

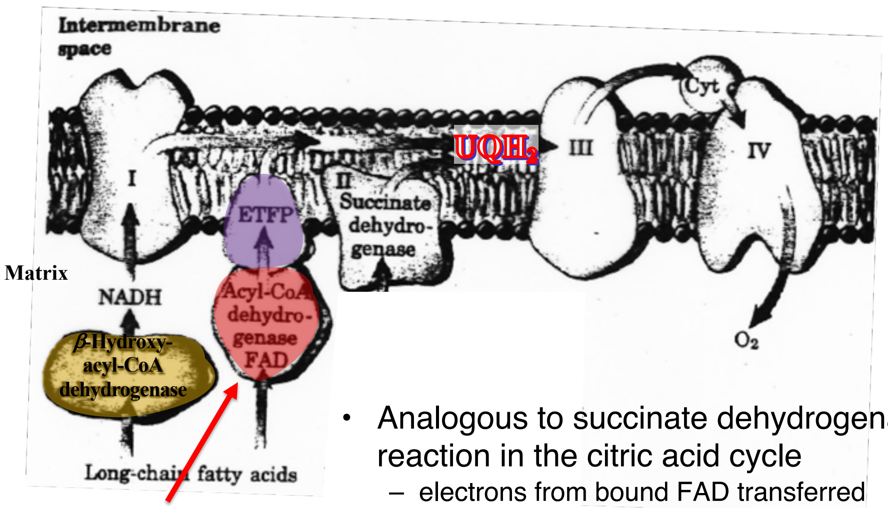




*Adrenoleukodystrophy (ALD)

Fatty Acid Degradation

β-Oxidation: Acyl-CoA Dehydrogenase



Different isozymes bind to same ETF

- Analogous to succinate dehydrogenase reaction in the citric acid cycle
  - electrons from bound FAD transferred directly to the electron- transport chain via electron-transferring flavoprotein (ETF)