Fatty Acid Degradation

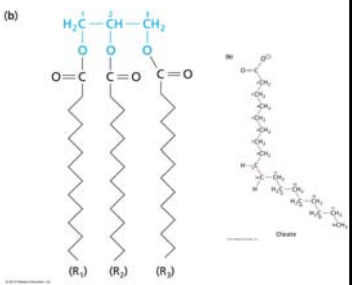
Chapter 27, Stryer Short Course

Catabolism Overview

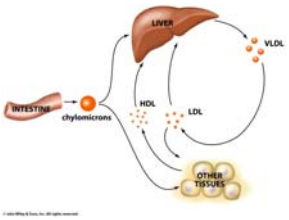
- Lipids as a fuel source—diet
- Beta oxidation
  - saturated
  - Unsaturated
  - Odd-chain
- Ketone bodies as fuel
- Physiology

TAG and FA

- High energy
  - More reduced
  - Little water content
  - 9 Cal/g vs 4 Cal/g for carbs
- Unsaturated FA
- Glycerol



Lipoprotein Review



- Liver is the packaging center
- VLDL are sent out of liver
- Constant cycling of LDL in blood
- Genetic cholesterol problem: no LDL receptors in non-liver cells
- HDLs are "good cholesterol"

Utilization Stage 1: Mobilization

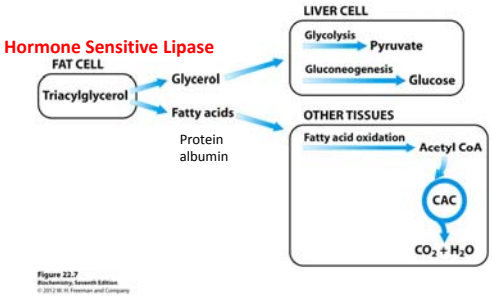
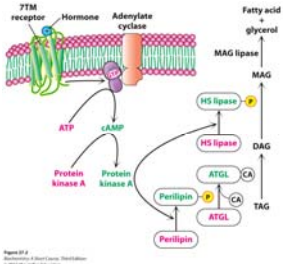


Figure 22.7
Biochemistry, Seventh Edition
© 2012 W. H. Freeman and Company

You don't need to know the details!



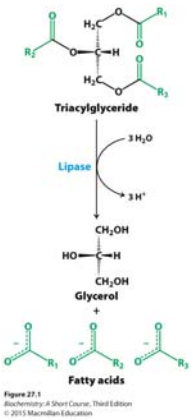
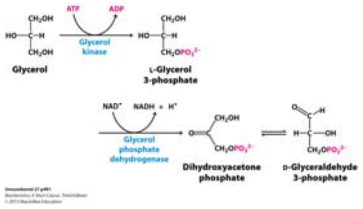


Figure 27.1
Biochemistry: A Short Course, Third Edition
© 2015 Macmillan Education

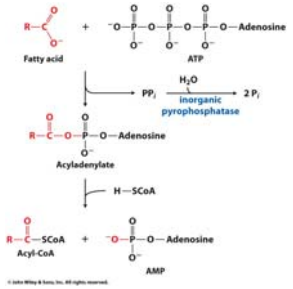
Glycerol: Glucogenic

- Taken to liver
- Three carbon unit
- Prepared for glycolysis/ gluconeogenesis
- What happens to fatty acids?



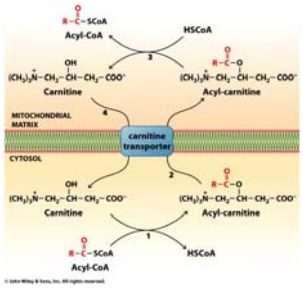
Utilization Stage 2: Activation and Transport into Matrix

- FA must be attached to CoA
- High energy bond
- Costs ATP→ AMP (2 ATP equivalents)



Utilization Stage 2: Transport into Matrix

- Matrix is site of fatty acid breakdown
  - Goes into citric acid cycle
- Carnitine ester: another high energy bond
- Transporter: Major site of regulation of FA degradation

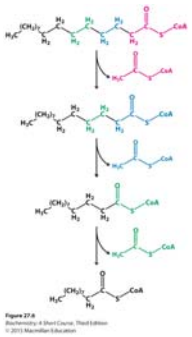


Pathological Applications

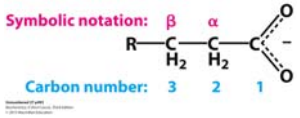
- A deficiency of carnitine results in muscle cramps, which are exacerbated by fasting or exercise. Give a biochemical explanation for the muscle cramping, and explain why cramping increases during fasting and exercise.

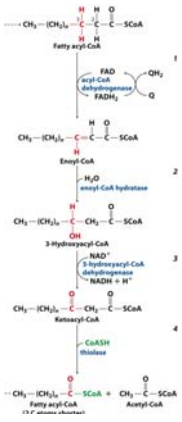
Utilization Stage 3: Beta Oxidation

- Four step process by which fatty acids cleaved into 2-carbon acetylCoA
- Oxidation leads to formation of
  - QH_2
  - NADH



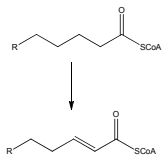
- Four steps
- Steps 1-3 resemble three steps in _____ pathway
- Step 4 breaks C-C





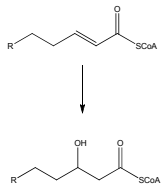
Step 1: Acyl CoA Dehydrogenase

- Similar to succinate DH from citric acid cycle
- Prosthetic FAD/$FADH_2$
- High energy electrons passed on to QH_2
- 1.5 ATP



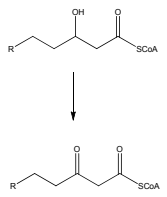
Step 2: Enoyl CoA Hydratase

- Similar to fumarate hydratase from citric acid cycle
- Addition of water
- No energy cost/production



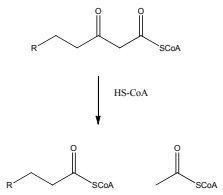
Step 3: 3-hydroxyacyl CoA DH

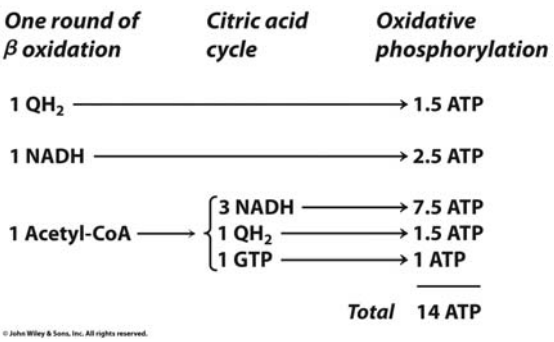
- Similar to malate DH from citric acid cycle
- Oxidation of secondary alcohol to ketone
- NADH production
- 2.5 ATP



Step 4: Thiolase

- CoA is used as a nucleophile in a "nucleophilic acyl substitution"
- FA shortened by 2 carbons
- Acetyl CoA produced



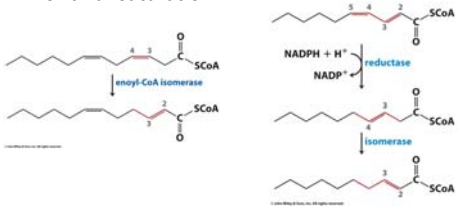


ATP Accounting

- How much ATP is netted from palmitate (16 carbons)?
  - Cost 2 ATP to activate to palmitate CoA
  - Run through beta oxidation SEVEN times
    - 7 QH2 = 10.5 ATP
    - 7NADH = 17.5 ATP
  - 8 acetyl CoA produced = 80 ATP
- Total: 106 ATP, or 6.625 ATP per carbon
- Compare to glucose, which is 5.33 ATP per C

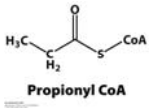
Processing Other FA

- Unsaturated and trans fatty acids
  - Trans is natural intermediate
  - Produce 1.5 ATP less for unsaturation, 4 ATP less for di-unsaturation

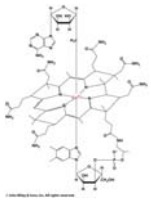


Processing Other FA

- Odd chain fatty acids
  - Rare, but do occur in diet
  - One of 2 requirements for Vitamin B_{12} (cobalamine) in human diet



Propionyl CoA



Production of Succinate

- Carboxylase (biotin)
- Rearrangement (vitamin B12-radical)
- Net glucose can be produced

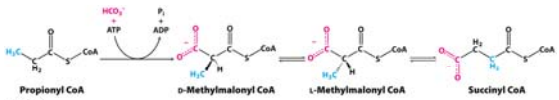
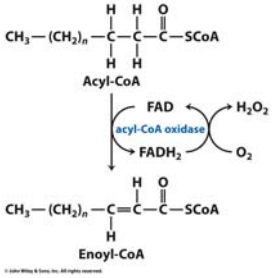


Figure 27.9
Biochemistry: A Short Course, Third Edition
© 2015 Macmillan Education

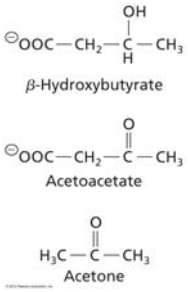
Review: Peroxisome

- Handles long fatty acids
  - Chain shortening
- Branched fatty acids
- Chemistry of first oxidation is different



Alternate Fate of Acetyl CoA: Ketone Bodies

- Water soluble form of lipids
- Less potential energy than FA
- Main energy source of brain in starvation
- Also used in muscle and intestine



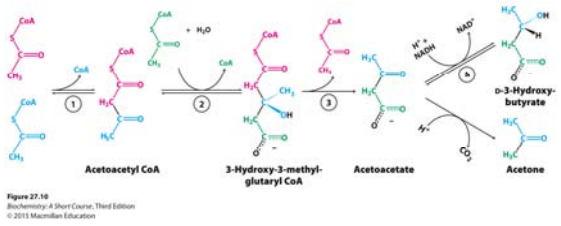
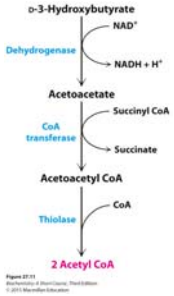


Figure 27.10
Biochemistry: A Short Course, Third Edition
© 2015 Macmillan Education

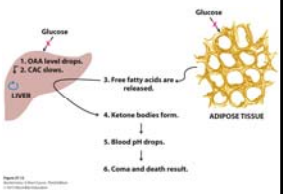
Ketone Bodies Serve as Fuel

- Normal condition
  - Feeds heart
  - Regulation marker: high blood levels turns off fatty acid release from adipose
- Can reach abnormal levels in diabetes, starvation



Diabetes

- No glucose uptake by liver
  - Glycolysis is down, gluconeogenesis is up
  - Oxaloacetate depleted
  - Citric acid cycle has diminished capacity
  - Acetyl CoA levels build up
- No inhibition of fatty acid mobilization from adipose
  - Acetyl CoA levels build up
- Ketone bodies are formed



Starvation

- Fuel Usage: About 7000 kJ/day minimum
- Storage: About 700,000 kJ
  - Fats and muscle protein: 1-3 months
  - Glucose: 7000 kJ (1 day)
- Glucose is essential for brain

Table 27.2 Fuel reserves in a typical 70-kg (154-lb) man

Organ	Available energy in kilojoules (kcal)					
	Glucose or glycogen		Triacylglycerols		Mobilizable proteins	
Blood	250	(60)	20	(45)	0	(0)
Liver	1,700	(400)	2,000	(450)	1,700	(400)
Brain	30	(8)	0	(0)	0	(0)
Muscle	5,000	(1,200)	2,000	(450)	100,000	(24,000)
Adipose tissue	330	(80)	560,000	(135,000)	170	(40)

Metabolic Priority

- Early starvation: convert protein to glucose (cannot convert fat to glucose)
- Later starvation
  - Preserve muscle
  - Muscle uses fat as fuel; buildup of acetyl CoA shuts down pyruvate→ acetyl CoA
  - Low [OAA] means acetyl CoA buildup
  - Ketone bodies produced
  - Brain uses KB, glucose is conserved