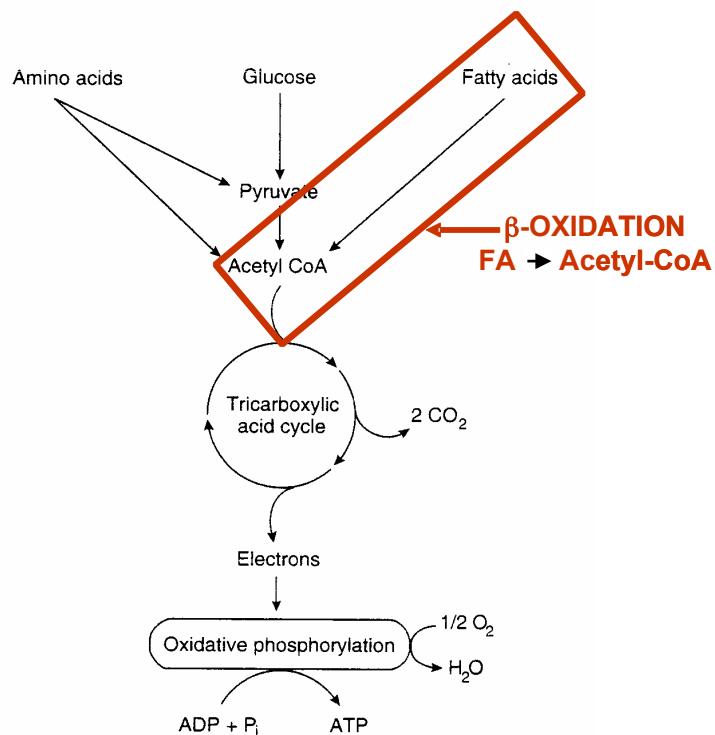


Lipid Metabolism



- **Triacylglycerols (TAGs)** and **glycogen** are the two major forms of **stored energy** in vertebrates
- Glycogen can supply ATP for muscle contraction for less than an hour
- Glycogen stores depleted 12-15 h after eating and shorter if exercising
- **Fats** are the most **highly concentrated** form of **stored biological energy**
- Long-term storage solution!
- Important for migratory birds who fly incredibly long distances
- Ruby-throated hummingbird winters in Central America and nests in southern Canada – often flies non-stop! Store large amounts of TAGs
% dry-weight body fat = 70% when migration begins; 30% or less for non-migratory birds
- Sustained work is fueled by metabolism of **TAGs** which are **very efficient energy stores** because:
 - (1) They are stored in an **anhydrous** form (no water present)
 - (2) Their fatty acids are **more reduced** than monosaccharides. Must go through many more oxidation steps than carbohydrates before completely broken down to CO_2

Table 20.5
Storage of metabolic fuel in humans^a

Tissue/fuel Type	Approximate Fuel Reserve (kJ) ^b	Estimated Time Fuel Would Last		
		Starvation ^c (days)	Walking ^d (days)	Marathon ^e (min)
Adipose/triacylglycerols	337,000	34	11	4012
Liver/glycogen	1500	0.15	0.05	18
Muscle/glycogen	6000	0.6	0.2	71
Free glucose (blood, etc.)	320	0.03	0.01	4
Total body protein	150,000	15	5	1786

^a Adapted from *Biochemistry for the Medical Sciences* by E. Newsholme and A. Leech (1983), John Wiley & Sons, Chichester, UK, and *Human Nutrition and Dietetics* by Davidson et al. (1979), 7th edition, Churchill Livingstone, Edinburgh, UK.

^b One nutritional Calorie (one kcal) is equal to 4.184 kJ.

^c Assuming an energy expenditure of about 10,000 kJ per day.

^d Assuming an energy expenditure of about 30,000 kJ per day.

^e Assuming an energy expenditure of about 84 kJ per minute.

Table 20-5 Concepts in Biochemistry, 3/e
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- Long chain fatty acids are the ideal storage fuel: hold more calories, and body has a virtually unlimited capacity to store fat; 70 kg man with 11% body fat has over 100,000 kcal stored as fat in abdominal cavity; only about 600 kcal in glycogen
- Fats can support body for long time: 60-90 days; obese people can survive for over a year without food.

How is this stored energy used?

- Fatty acids released from TAGs, transported to cytoplasm and then mitochondria of peripheral tissues (muscle cells) for degradation
- Catabolized by process called β -oxidation
 - 4 step process
 - Yields Acetyl-CoA units that feed into the TCA cycle
- When too much fuel is around, fatty acids are made, linked to glycerol (TAGs are made) and stored in adipocytes.
- LOCALIZATION OF PROCESSES:**
 - Degradation = mitochondrial matrix
 - Synthesis = cytosol

METABOLISM OF FATS: Adsorption and Mobilization of Fatty Acids

- Fatty acids need to be delivered to cells for β -oxidation to occur – how?
- Two major sources for fatty acids (FA) and glycerol for metabolic fuels are obtained from triacylglycerols:

(1) In the diet

(2) Stored in adipocytes (fat storage cells)

Free fatty acids occur only in trace amounts in cells

Storage and Mobilization of Fatty Acids in Fat Cells

- TAGs are stored in adipocytes, and fatty acids are released to supply energy demands
- Liberation of fatty acids from TAGs in adipose tissue is regulated by **hormones**
 - Epinephrine
 - Glucagon
 - Released into blood stream when there are low glucose levels in blood

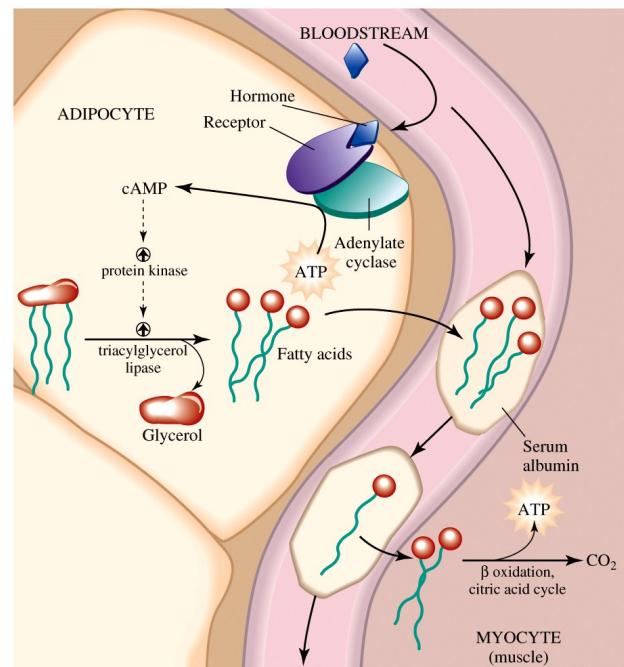
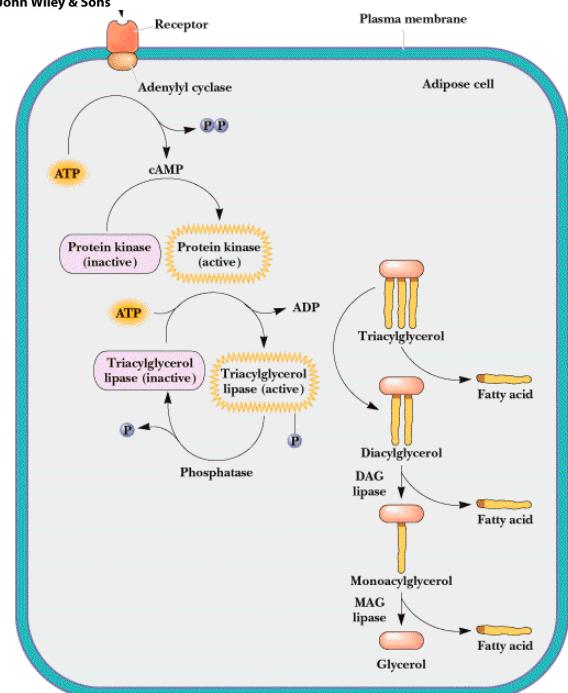


Figure 18-3 Concepts in Biochemistry, 3/e
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- At low carbohydrate and insulin concentrations, TAG hydrolysis is stimulated by increased epinephrine (binds to β -adrenergic receptors, and activates cAMP-dependent protein kinases)
- Hormones bind to **receptors** on adipocyte cell surface
- Binding starts a process that generates **cAMP** (a nucleotide derivative)
- cAMP acts as an intracellular messenger that activates hormone-sensitive **triacylglycerol lipase**
 - Lipase catalyzes hydrolysis of stored TAGs to free fatty acids and glycerol
- FAs exported from the cell into the blood stream (either by transporter or diffusion)
 - Bind to blood protein = serum albumin and transported to muscle cells via capillaries, enter cells, get transported into the mitochondrial matrix and undergo β -oxidation.
 - Glycerol is gluconeogenic

Absorption of Dietary Lipids

- On average, fat makes up 37% of calories in American diet
- Most diet lipids of mammals are TAGs
- 90% of the fat we eat is TAG; rest: cholesterol esters, phospholipids, essential unsaturated fatty acids (Linoleic acid (LA) (omega-6) 18:2^{9,12} and linolenic acid (omega-3) 18:3^{9,12,15}), and fat soluble vitamins A, D, E, and K
- In normal individuals, 95% of fat consumed is absorbed and most transported to adipose for storage.
- General principle of dietary lipid assimilation is to hydrolyze large non-absorbable molecules into smaller units.

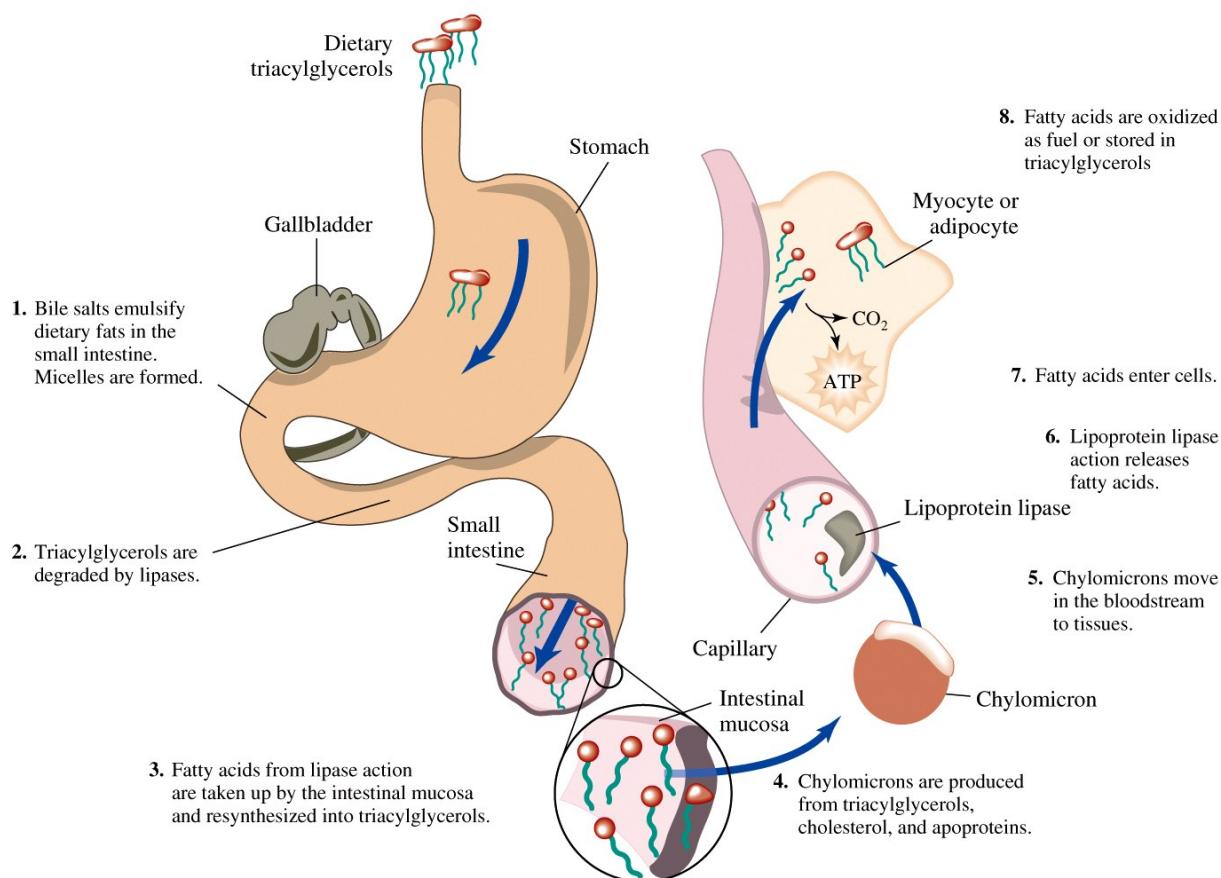


Figure 18-1 Concepts in Biochemistry, 3/e
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1. Emulsification starts in the stomach and continues in the lumen of the small intestine

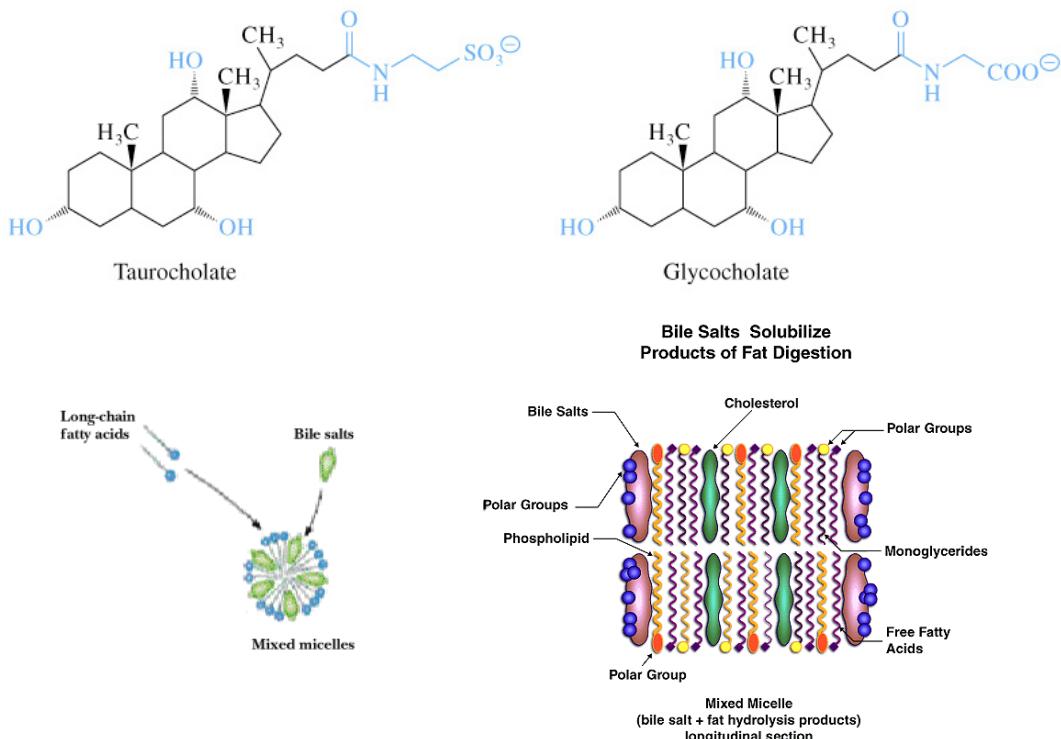
- Starts as a big glob of hydrophobic fat – has limited surface area to attack
- In the stomach the fat is heated to liquify, peristaltic movements help emulsify (like a washing machine) (mixer making mayonnaise)

2. In the small intestine, fat particles are coated with bile salts and digested by pancreatic lipases

Bile salts: Biological Detergents

Bile salts are amphipathic: synthesized in liver, stored and secreted by gall bladder to intestine. Made from cholesterol: retain the ring structure but have more hydroxyl groups and a polar side chain – can act as **DETERGENTS** - Serve to convert water-insoluble lipids to dispersible micellar aggregates

- They **emulsify** fat globules into smaller micelles, increasing the surface area accessible to lipid-hydrolyzing enzymes. Aid in lipid digestion and are essential for the absorption of lipid digestion products
- Also required for efficient intestinal absorption of lipid-soluble vitamins A, D, E, and K
 - Taurocholate** and **glycocholate** (cholesterol derivatives) are the most abundant bile salts
 - Amphipathic:** hydrophilic (blue), hydrophobic (black)



• Form MICELLES

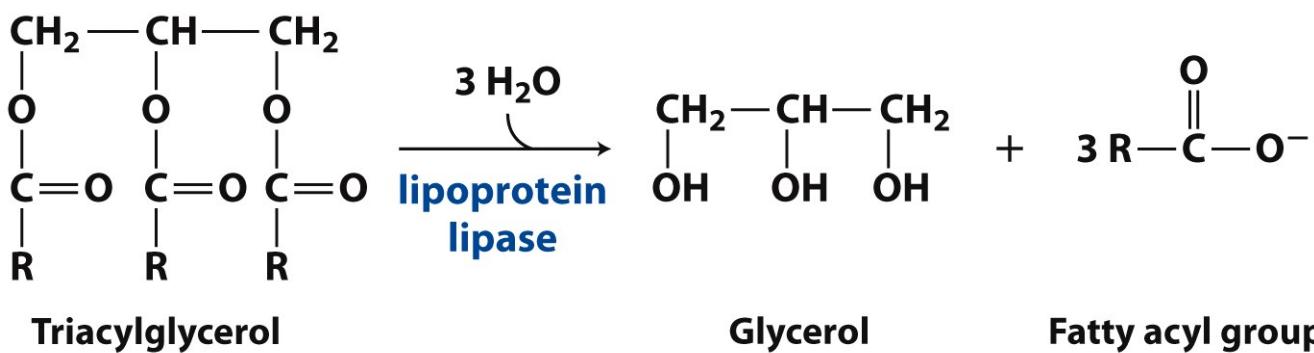
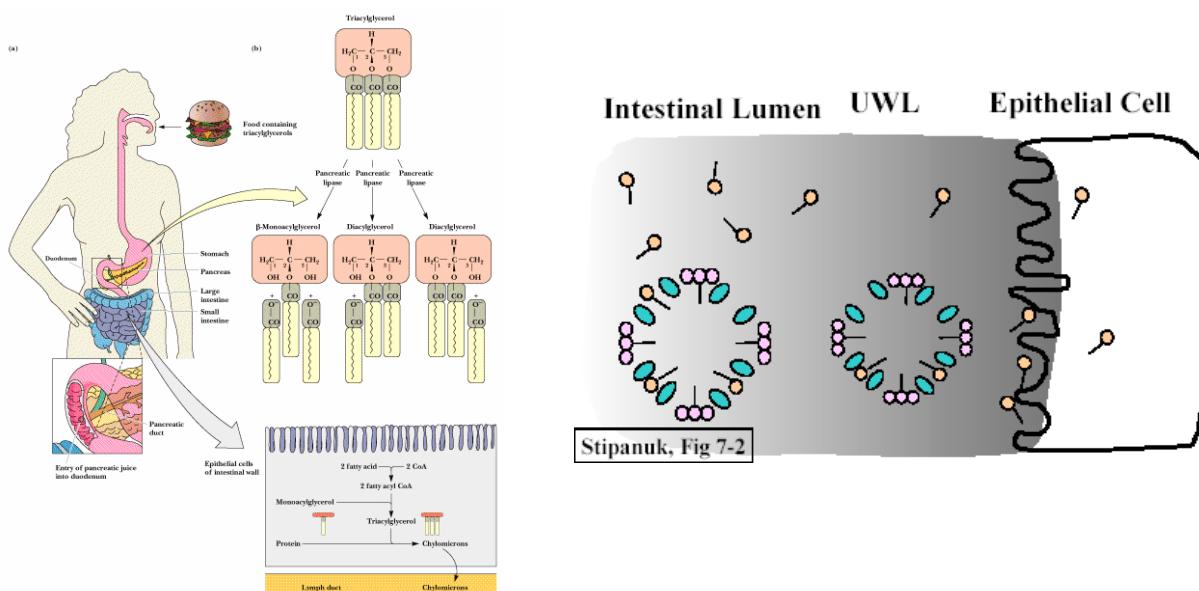
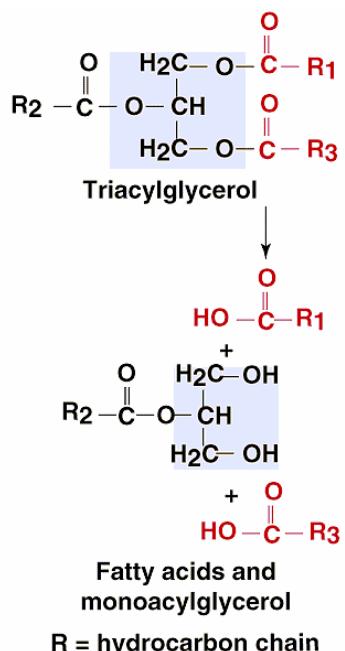
- Hydrophobic portions interact with lipids while the hydrophilic groups remain exposed to water
- Disc-like shapes - **free fatty acids and bile**
- Recycled through hepatic portal vein from intestine back to liver

LIPASES: Action of pancreatic lipase

- Duct at the junction of pancreas and duodenum enters pancreatic juice – contains lipases (among other things, including **colipase**: small protein that the lipase needs around to keep it active with all the bile salts around).
 - Lipases degrade TAGs to **free fatty acids (FA)** and a **2-monoacylglycerol (MAG)** by hydrolysis at the C-1 and C-3 positions
 - Dietary phospholipids are degraded by phospholipases

Dietary cholesterol

- Most dietary cholesterol is unesterified
 - Any Cholesteryl esters are hydrolyzed by an intestinal esterase to yield free cholesterol
 - Free cholesterol is solubilized by bile-salt micelles for absorption



3. Free FA and cholesterol from bile salt mixed micelles are taken up through the intestinal wall

Micelle = free fatty acids and bile

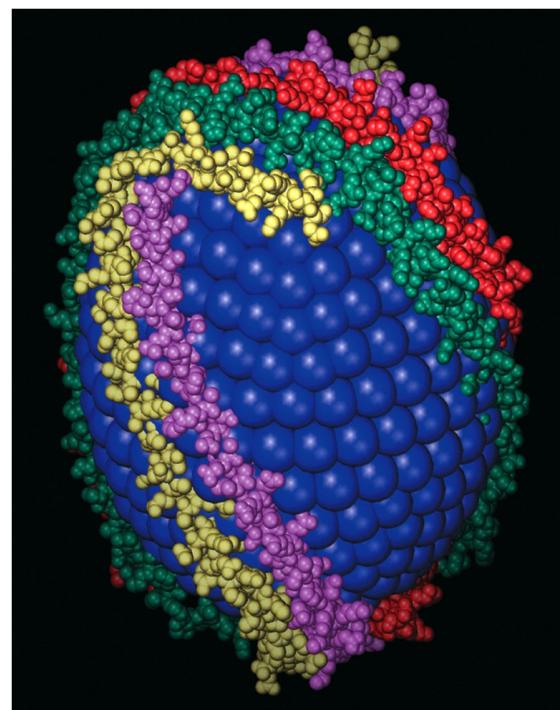
Micelle can interact with brush border and is the form in which lipids are absorbed

4. Once inside intestinal cells, cholesteroyl acyl-CoA esters are formed and FA are resynthesized into triacylglycerols (TAGs)

5. TAGs, cholesterol and apoproteins are packaged into a chylomicron (lipoprotein) and exported into blood for use

- TAGs, cholesterol and cholesterol esters are **insoluble** in water and cannot be transported in blood or lymph as free molecules
- These lipids assemble with phospholipids and apoproteins (apolipoproteins) to form spherical particles called **lipoproteins** with:
 - Hydrophobic cores: TAGs, cholesteroyl esters
 - Hydrophilic surfaces: cholesterol, phospholipids, apolipoproteins
- **Chylomicrons** are the largest **lipoproteins**
- **Make fats SOLUBLE**
- They deliver TAGs from the intestine (via lymph and blood) to tissues (muscle for energy, adipose for storage)
- They are present in blood only after feeding
- Cholesterol-rich chylomicron remnants deliver cholesterol to the liver

6. Lipoprotein lipase on cells lining capillary wall adjacent to ADIPOSE and MUSCLE tissue promotes release of fatty acids; The chylomicrons dock with lipoprotein lipases



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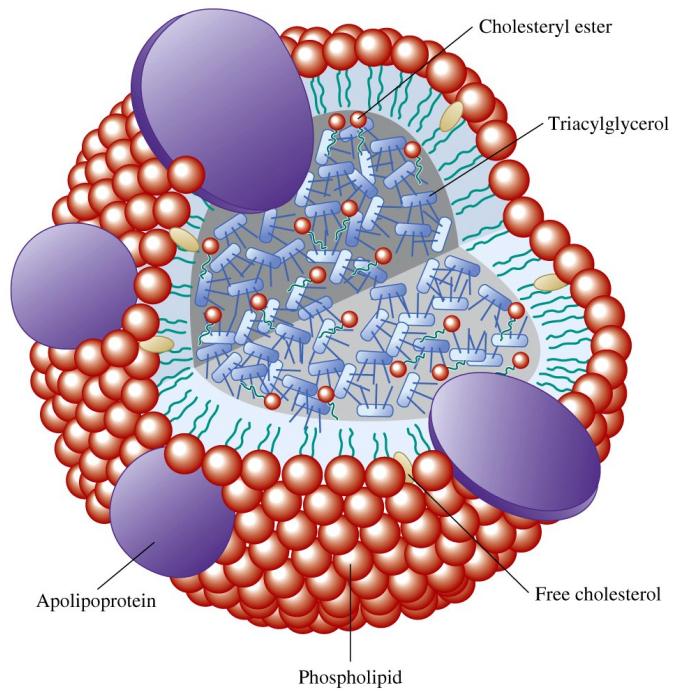
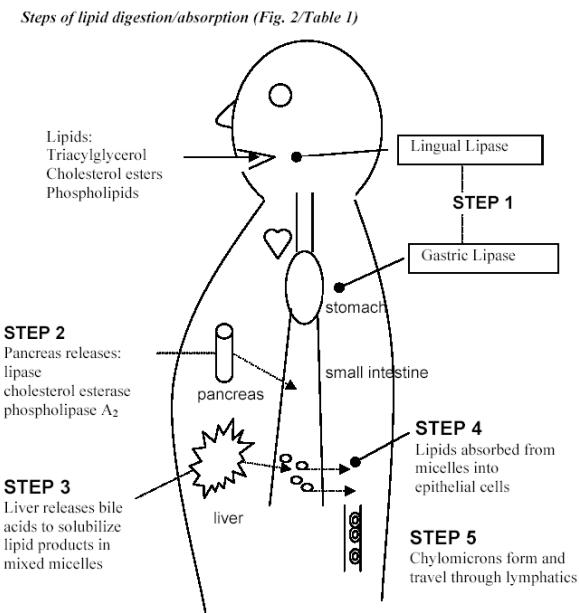
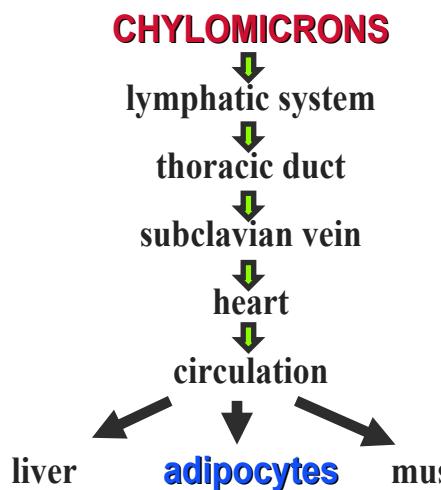


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7. Fatty acids are taken up and degraded by β -oxidation in mitochondrial matrix



Fatty Acid Oxidation

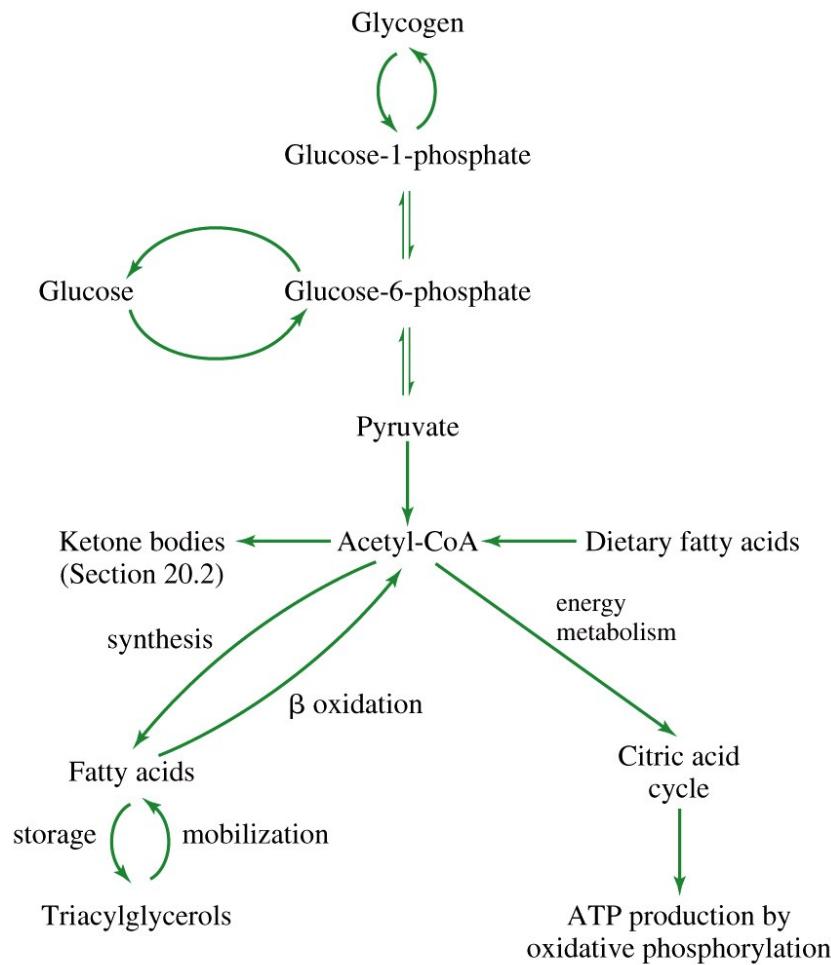
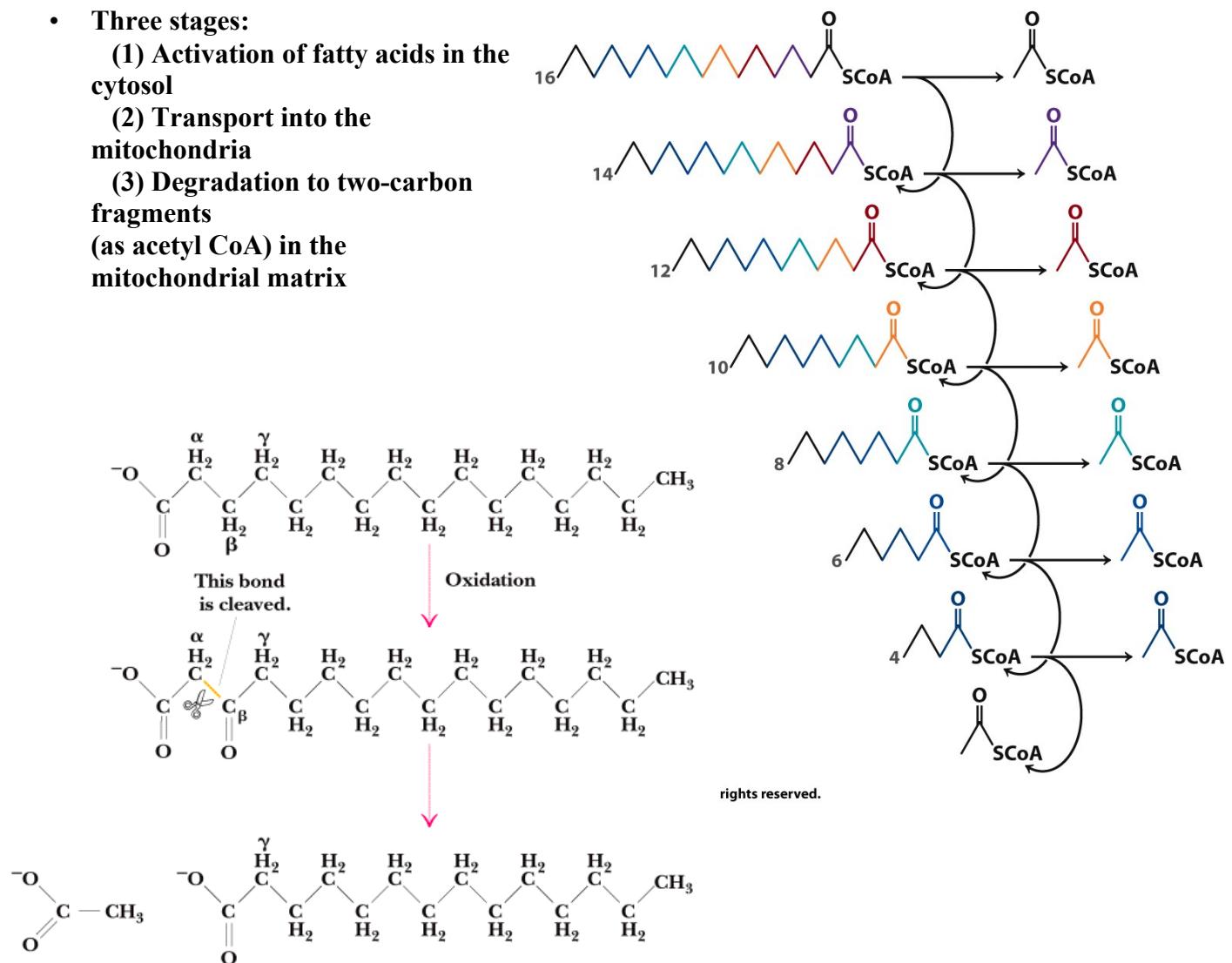


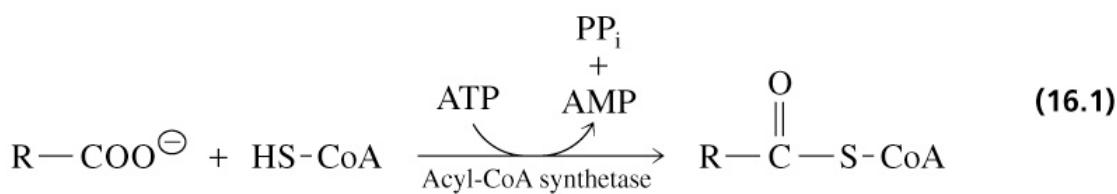
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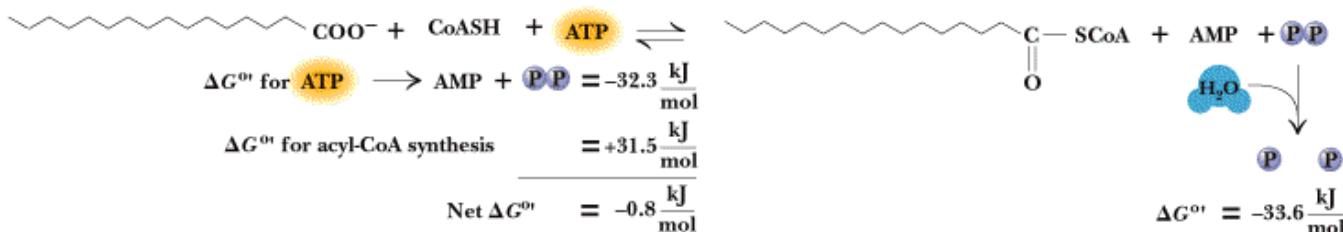
- The β -oxidation pathway degrades fatty acids two carbons at a time
- Skeletal muscle, liver, kidney, heart can use FA directly
- Three stages:**
 - Activation of fatty acids in the cytosol
 - Transport into the mitochondria
 - Degradation to two-carbon fragments (as acetyl CoA) in the mitochondrial matrix



Activation of Fatty Acids

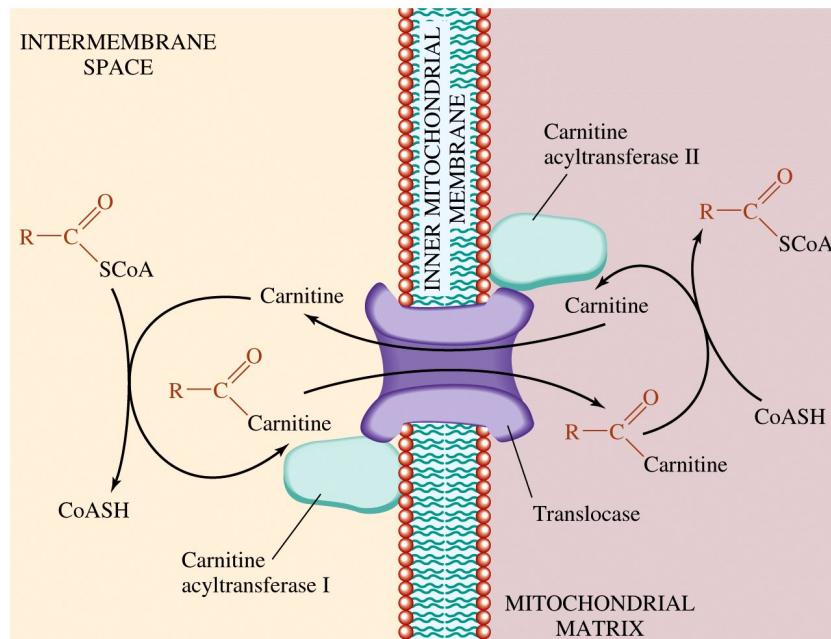
- Fatty acids in the cytosol are **activated** by conversion to CoA thioesters by **acyl-CoA synthetase** (ATP dependent)
- Fatty acid attached to CoA-SH
- The PPi released is hydrolyzed by a pyrophosphatase to 2 Pi
- Net of **two ATP equivalents** are **consumed** to activate **one fatty acid to a thioester**





2. Transport of Fatty Acyl CoA into Mitochondria

- Activated acyl-CoA freely diffuses through OMM into intermembrane space, however cannot pass IMM to be brought into mitochondrial matrix
- The **carnitine shuttle system** transfers fatty acyl CoA from the cytosol into the mitochondria
- Fatty acyl CoA is first converted to acylcarnitine (which can enter the mitochondria) and then back to fatty acyl CoA
- The β -oxidation cycle enzymes (mitochondrial) can then degrade the fatty acyl CoA

Figure 18-6 Concepts in Biochemistry, 3/e
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Sequence of Events:

- At IMM, acyl group transferred to **carnitine**, a small organic molecule that carries the fatty acyl group into the mitochondrial matrix. Used as a SHUTTLE for fatty acyl groups.
Compound = **acylcarnitine**
Enzyme = **carnitine acyltransferase I**
- Acylcarnitine is transported across IMM via **protein translocase**
- Once in the matrix, acyl group is transferred back to CoA-SH by **carnitine acyltransferase II**
- Carnitine transported back to intermembrane space via translocase to get another molecule of acyl
- Keep pools of CoA-SH separate
 - Cytosolic CoA-SH used for synthesis
 - Mitochondrial CoA-SH used for degradation

ANIMATION:

http://www.brookscole.com/chemistry_d/templates/student_resources/shared_resources/animations/carnitine/carnitine1.html

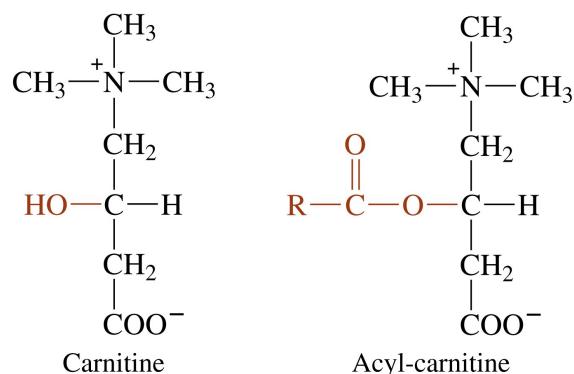
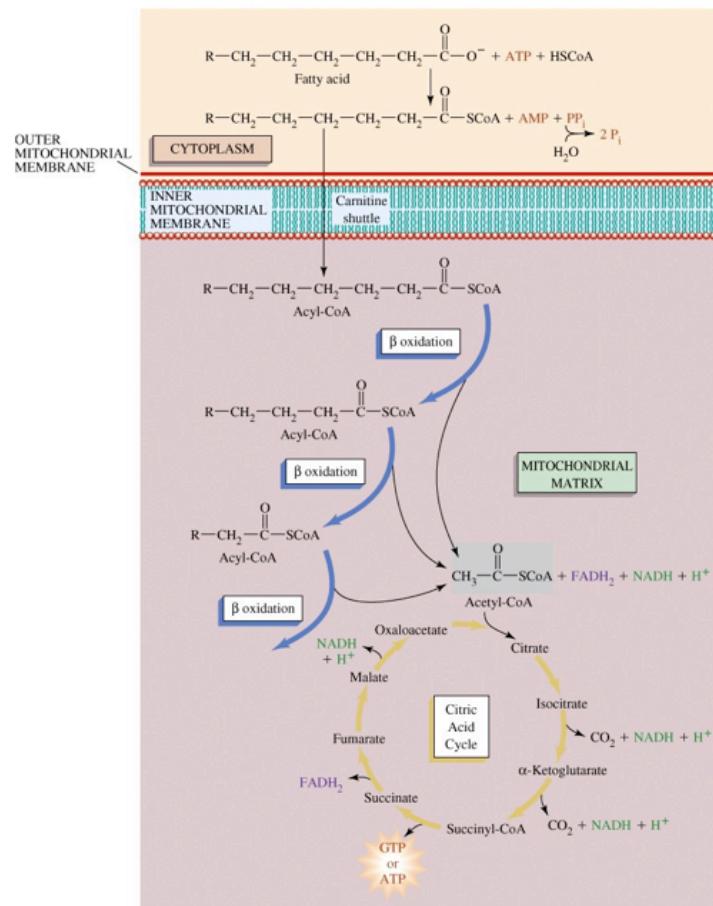
CARNITINE:

- Diet: red meat, dairy, poultry, fish
- Body: made in liver and kidneys
- Enters cells by specific transporter

- Carnitine deficiencies:

- **Symptoms:**
 - Poor muscle tone
 - Muscle weakness
 - Brain dysfunction
 - Heart dysfunction

- **Primary Deficiency:** Rare disorder due to faulty transporter that allows carnitine into cells
- **Secondary Deficiency:** Poor dietary intake or metabolic diseases that deplete or limit stores
- **Treatment:** Pharmaceutical administration of carnitine to supplemental stores in the body; Can flood system and enough carnitine can enter if due to a faulty transporter
- **NOTE:** NO evidence exists that if normal, taking more supplements of carnitine does anything. Not bad – excess carnitine is not harmful but not necessarily beneficial.

Figure 18-5 Concepts in Biochemistry, 3/e
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The Reactions of β -oxidation

- One round of β -oxidation: 4 enzyme steps produce **acetyl CoA** from fatty acyl CoA
- Each round generates one molecule each of:
 - 1 FADH₂ – oxidative phosphorylation**
 - 1 NADH – oxidataive phosphorylation**
 - 1 Acetyl CoA – enters TCA cycle**
 - Fatty acyl CoA** (2 carbons shorter each round)

Process continues until acyl-CoA is completely broken down to Acetyl-CoA groups

- Cleavage occurs between the α and β carbons of the acyl-CoA (between 1st and 2nd C next to carbonyl)
- # of acetyl-CoA made = $\frac{1}{2}$ the number of Carbons in the original fatty acid
- # of cycles of β -oxidation = # of acetyl-CoAs made minus 1
- Example:**
 - Palmitic acid = 16:0**
 - 8 moles of acetyl-CoA (enter TCA cycle)**
 - 7 rounds of β -oxidation**

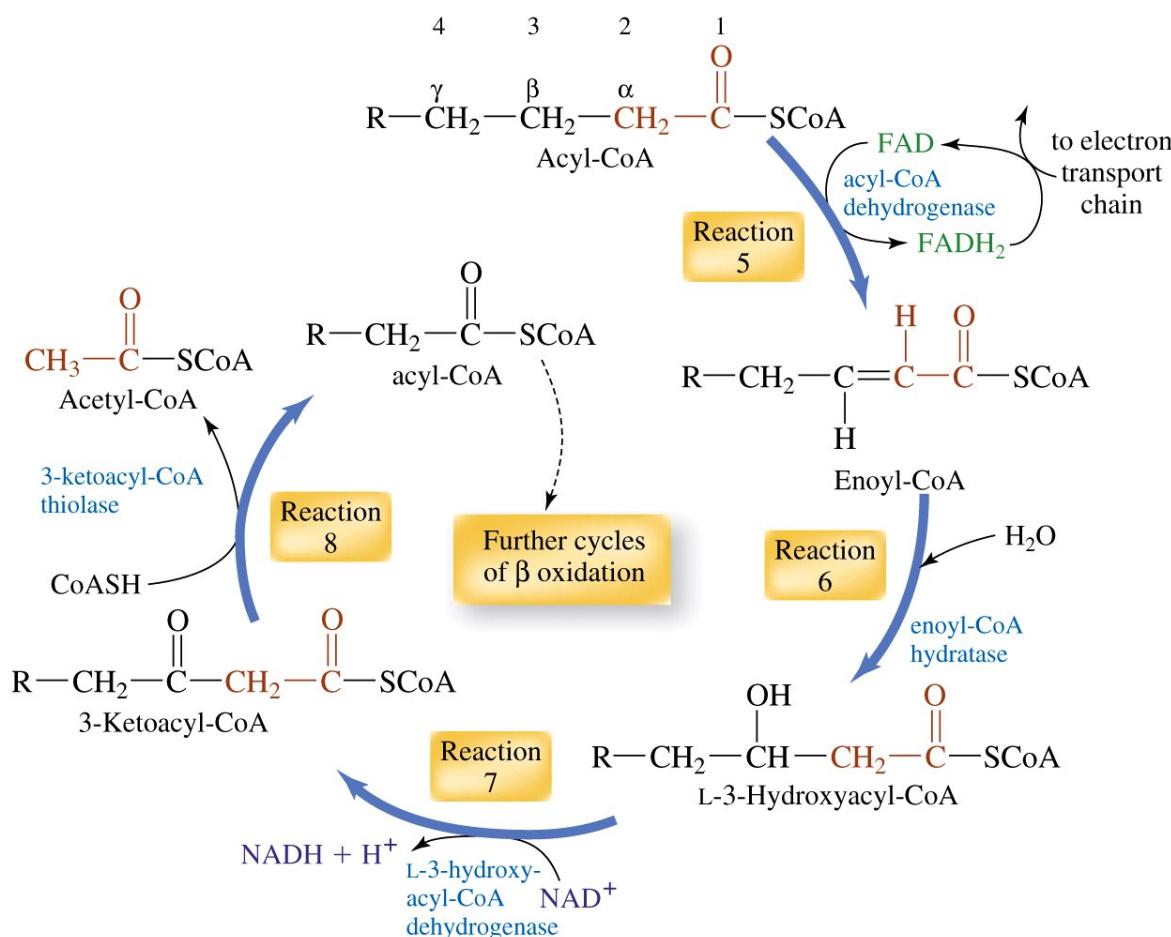


Figure 18-8 Concepts in Biochemistry, 3/e
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β-OXIDATION, A SPIRAL PATHWAY:**Reaction 1:** Oxidation-reduction reaction catalyzed by *Acyl-CoA Dehydrogenase*

- Generates FADH₂
- Produces a double bond between carbon atoms 2 and 3

Reaction 2: Hydration reaction catalyzed by *Enoyl-CoA Hydratase*

- Catalyzes stereospecific **hydration** of the trans double bond produced in the 1st step of the pathway
- Forms 3-L-Hydroxyacyl-CoA

Reaction 3: Oxidation-reduction reaction catalyzed by *3-L-Hydroxyacyl-CoA Dehydrogenase*

- Generates NADH
- Oxidation of the hydroxyl in the β position (C3) to a ketone

Reaction 4: Bond cleavage reaction catalyzed by *Thiolase*

- Requires CoA-SH (Coenzyme A)
- Releases Acetyl-CoA – which enters the TCA cycle
- Acyl-CoA (2 carbons shorter) re-enters β-oxidation

Table 18.1

Reactions for fatty acid activation, transport, and the β-oxidation spiral

Reaction Number	Reaction	Enzyme	Reaction ^a Type
1	Fatty acid + CoASH + ATP \rightleftharpoons acyl-CoA + AMP + PP _i	Acyl-CoA synthetase	6
2	PP _i + H ₂ O \rightleftharpoons 2 P _i	Pyrophosphatase	3
3	Carnitine + acyl-CoA \rightleftharpoons acyl-carnitine + CoASH (intermembrane space)	Carnitine acyltransferase I	2
4	Acyl-carnitine + CoASH \rightleftharpoons acyl-CoA + carnitine (mitochondria)	Carnitine acyltransferase II	2
5	Acyl-CoA + E-FAD \rightleftharpoons trans-Δ ² -enoyl-CoA + E-FADH ₂ ^b	Acyl-CoA dehydrogenase	1
6	trans-Δ ² -Enoyl-CoA + H ₂ O \rightleftharpoons L-3-hydroxyacyl-CoA	Enoyl-CoA hydratase	4
7	L-3-Hydroxyacyl-CoA + NAD ⁺ \rightleftharpoons 3-ketoacyl-CoA + NADH + H ⁺	Hydroxyacyl-CoA dehydrogenase	1
8	3-Ketoacyl-CoA + CoASH \rightleftharpoons acetyl-CoA + acyl-CoA ^c	β-Ketothiolase	4

^aReaction type: 1, oxidation-reduction; 2, group transfer; 3, hydrolysis; 4, nonhydrolytic cleavage (addition or elimination); 5, isomerization-rearrangement; 6, bond formation coupled to ATP cleavage.

^bE-FAD and E-FADH₂ refer to the cofactor flavin adenine dinucleotide covalently linked to the enzyme.

^cAcyl-CoA product is shortened by a C₂ unit.

Table 18-1 Concepts in Biochemistry, 3/e

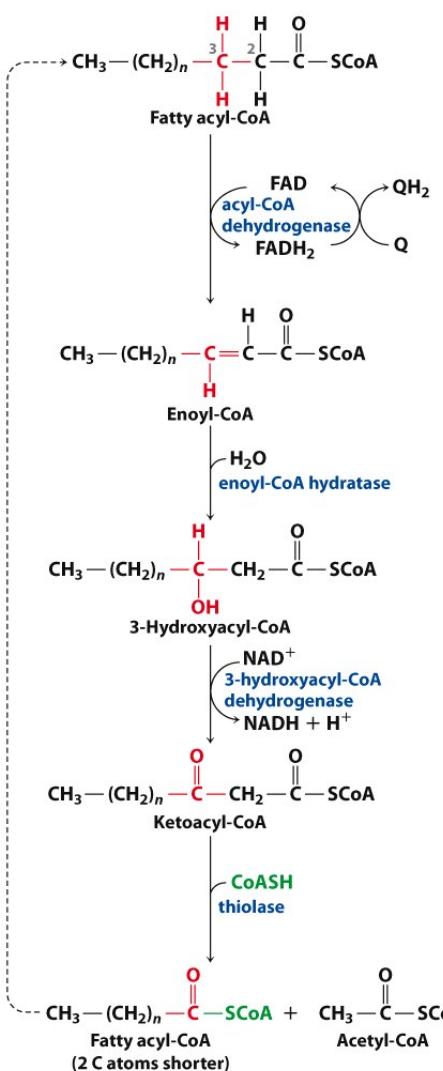
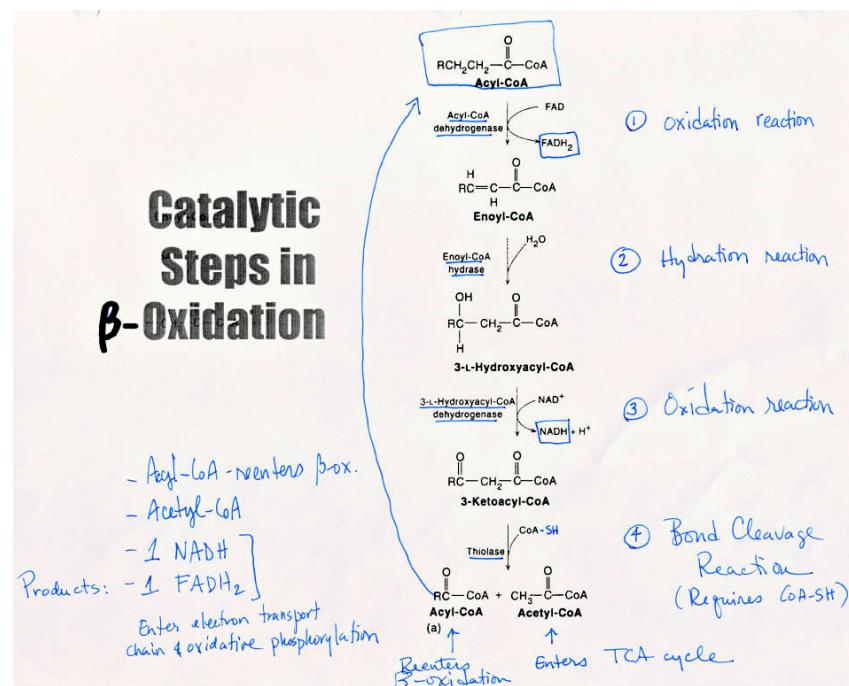
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ANIMATION: <http://www.wiley.com/college/fob/anim/>

Fig. 19-9 -- The β-Oxidation Pathway of Fatty Acyl-CoA

SUMMARY OF THE PRODUCTS OF EACH CYCLE:

- Acyl-CoA which re-enters β -oxidation
- 1 Acetyl-CoA which enters TCA
- 1 FADH₂
- 1 NADH

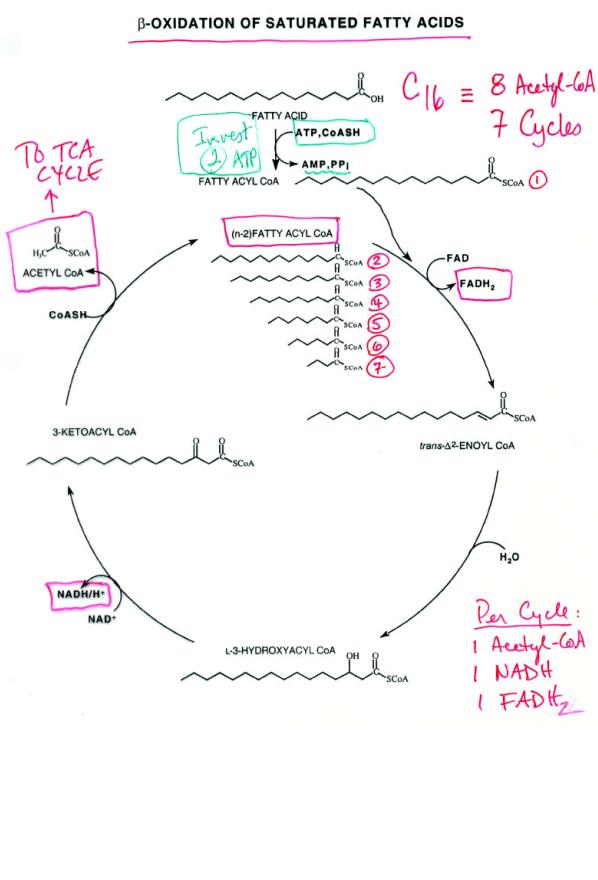
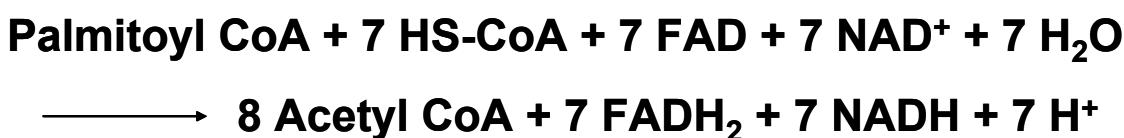


1. *Oxidation of acyl-CoA at the 2,3 position is catalyzed by an acyl-CoA dehydrogenase to yield a 2,3-enoyl-CoA. The two electrons removed from the acyl group are transferred to an FAD prosthetic group. A series of electron transfer reactions eventually transfers the electrons to ubiquinone (Q).*
2. *The second step is catalyzed by a hydratase, which adds the elements of water across the double bond produced in the first step.*
3. *The hydroxyacyl-CoA is oxidized by another dehydrogenase. In this case, NAD⁺ is the cofactor.*
4. *The final step, thiolysis, is catalyzed by thiolase and releases acetyl-CoA. The remaining acyl-CoA, two carbons shorter than the starting substrate, undergoes another round of the four reactions (dotted line).*

ATP Generation from Fatty Acid Oxidation

- Three things to keep in mind as sources of ATP
 - NADH and FADH₂ produced by β -oxidation cycles
 - Processing of Acetyl-CoA generated in β -oxidation cycles through TCA cycle and ox phos
 - How much ATP was USED in activating the FA for degradation
 - Remember – 2 ATP equivalents are used per mole of fatty acid; 1 ATP but 2 high energy bonds

The balanced equation for oxidizing one palmitoyl CoA by seven cycles of β -oxidation Net yield of ATP per palmitate oxidized to 16 CO₂



Each acetyl-CoA that enters TCA:

- 1 mole GTP
- 3 moles NADH
- 1 mole FADH₂

Therefore for palmitate: 80 ATP

- 8 GTP = 8 ATP
- 24 NADH = 60 ATP
- 8 FADH₂ = 12

ATP generated

8 acetyl CoA	80
7 FADH ₂	10.5
7 NADH	17.5
	108 ATP

ATP expended to activate palmitate -2

Net yield: 106 ATP

MUCH BETTER THAN GLUCOSE:

- Even for 3 glucose molecules, only get 96 ATP (18 carbons),
 - Palmitate (16:0) gives 106!
 - Fats are better energy stores than sugars/carbs!
- An important source of **metabolic water** for some animals:
 - Water is ultimately formed through the process of electron transport & oxidative phosphorylation
 - Gerbils, Killer Whales (do NOT drink sea water)
 - Camel – hump is essentially a large deposit of fat
 - Fatty acid metabolism from fat store provides metabolic energy as well as needed water during periods when food and drinking water is not available!!
 - It has been found for every half pound of fat metabolized, a pint of water is produced!
 - Water also stored in specialized places near the stomach.

Kangaroo rats

- exhibit many of the most common desert animal specializations
- speciose and abundant - very successful
- do not use evaporative cooling, so water budgets can be easily calculated
- small, easily studied in the lab
- pioneering studies of Knut Schmidt-Nielsen at Duke University
- drink no water

**Oxidation water**

Type of food	Water formed (g H ₂ O/g food)
starch* (carbohydrate)	0.56
fat	1.07
protein	0.39

*e.g. C₆H₁₂O₆ + 6 O₂ to 6 CO₂ + 6 H₂O

Water budget for a kangaroo rat

Water losses ml	Water gains ml
Urine 13.5	Oxidation 54.0
Feces 2.6	Absorbed water 6.0
Evaporation 43.9	
Total 60.0 ml	Total 60.0 ml

β Oxidation of Unsaturated Fatty Acids

- Unsaturated FA are common in nature
- Degradation requires two other enzymes in addition to the β -oxidation pathway enzymes:
 - (1) **Enoyl-CoA isomerase**
 - (2) **2,4-Dienoyl-CoA-reductase**

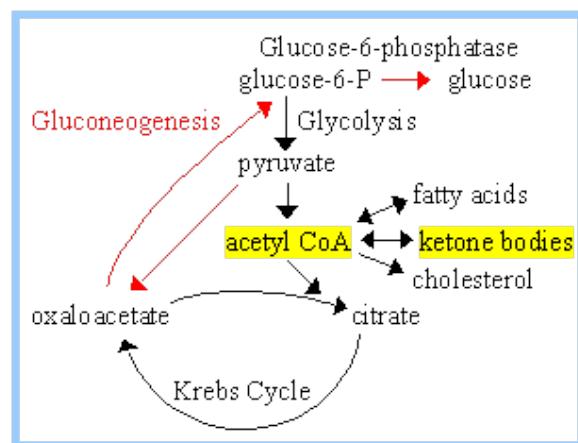
Ketone Bodies Are Fuel That Are Synthesized in the Liver

- Unbalanced metabolism of fats and carbohydrates changes the flow of nutrients in pathways
- Common factors in abnormal metabolic conditions
 - Lack of carbohydrates
 - Impaired use of carbohydrates
 - Fasting
 - Starvation
 - Untreated diabetes
 - Atkins' Diet

Response to a Fast and Starvation

The natural response to glucose and energy deficiency involves two metabolic processes. Firstly the adrenal cortex secretes glucocorticoids to stimulate **gluconeogenesis**. Secondly growth hormone is secreted to accelerate **lipolysis** in adipose tissue to **provide fatty acids for oxidation**.

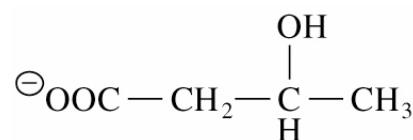
- Liver glycogen stores are depleted
- Fatty acids can be used by heart, kidney, skeletal muscle and liver
- Fatty acids are not used as fuel by the brain because they do not cross the blood-brain barrier
- Survival during starvation is mainly determined by the size of the stored triacylglycerol pool
- After several days of starvation, **acetyl-CoA** is made in abnormally high amounts:
 - Due to excessive fatty acid breakdown since glucose/glycogen is not available
 - Glucose is the primary source of fuel for the human brain, therefore the rate of gluconeogenesis has to increase
 - During fasting or carbohydrate starvation, **oxaloacetate** in liver is depleted from the TCA cycle because it is used for **gluconeogenesis** (making glucose for the brain)
 - Impedes entry of acetyl-CoA into the TCA cycle.



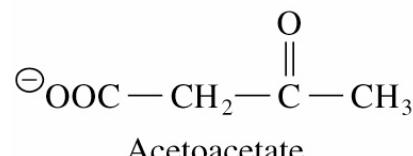
- Excessive Acetyl-CoA is converted in liver mitochondria to **ketone bodies**
 - Ketone bodies can be thought of as “soluble fats” – exported to cells that need it
They are transportable forms of fatty acids!
 - There is a limited amount of mitochondrial CoA-SH so need to regenerate it for further fatty acid catabolism

excess acetyl-CoA \longrightarrow D-3-hydroxybutyrate,
acetone

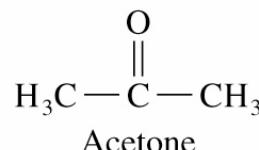
Ketone bodies



β -Hydroxybutyrate



Acetoacetate



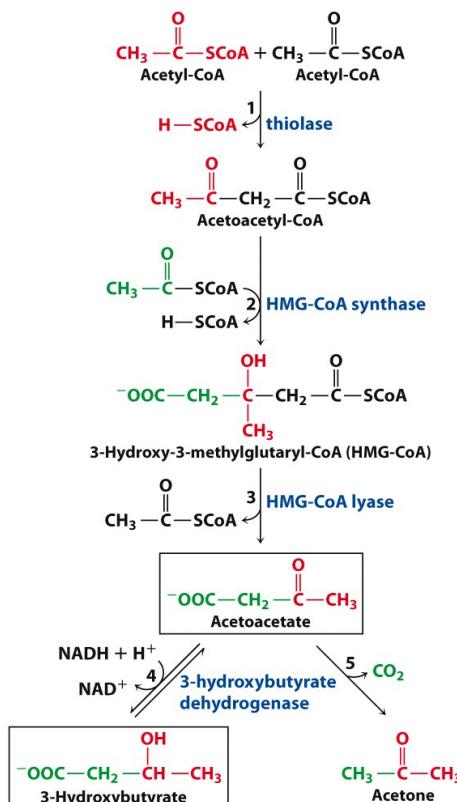
Acetone

- Ketone Bodies:**

- β -Hydroxybutyrate**
- Acetoacetate**
- Acetone** – expelled in breath
- Ketone bodies are **acids** – can cause lowering of blood pH leading to **acidosis (ketosis)**; untreated can lead to coma and death

- Ketone bodies can fuel brain cells during starvation**

- Use of ketone bodies minimizes protein breakdown
- Able to cross blood-brain barrier
- Major energy source for brain during starvation
- β -Hydroxybutyrate and acetoacetate used as fuel**
- Acetone – expelled in breath



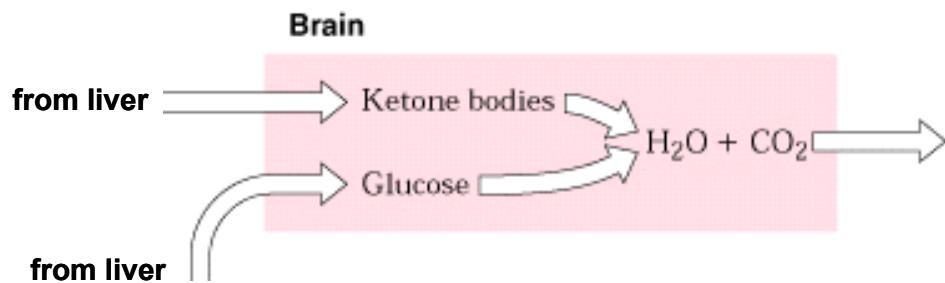
1. Two molecules of acetyl-CoA condense to form acetoacetyl-CoA. The reaction is catalyzed by a thiolase, which breaks a thioester bond.

2. The four-carbon acetoacetyl group condenses with a third molecule of acetyl-CoA to form the six-carbon 3-hydroxymethylglutaryl-CoA (HMG-CoA).

3. HMG-CoA is then degraded to the ketone body acetoacetate and acetyl-CoA.

4. Acetoacetate undergoes reduction to produce another ketone body, 3-hydroxybutyrate.

5. Some acetoacetate may also undergo nonenzymatic decarboxylation to acetone and CO_2 .



FORMATION OF KETONE BODIES:

1. **β -Ketothiolase**. The final step of the β -oxidation pathway runs backwards, condensing 2 acetyl-CoA to produce acetoacetyl-CoA, with release of one CoA.
2. **HMG-CoA Synthase** catalyzes condensation of a third acetate moiety (from acetyl-CoA) with acetoacetyl-CoA to form hydroxymethylglutaryl-CoA (HMG-CoA).
3. **HMG-CoA Lyase** cleaves HMG-CoA to yield **acetoacetate** plus acetyl-CoA.
4. **β -Hydroxybutyrate Dehydrogenase** catalyzes inter-conversion of the ketone bodies acetoacetate and β -hydroxybutyrate.

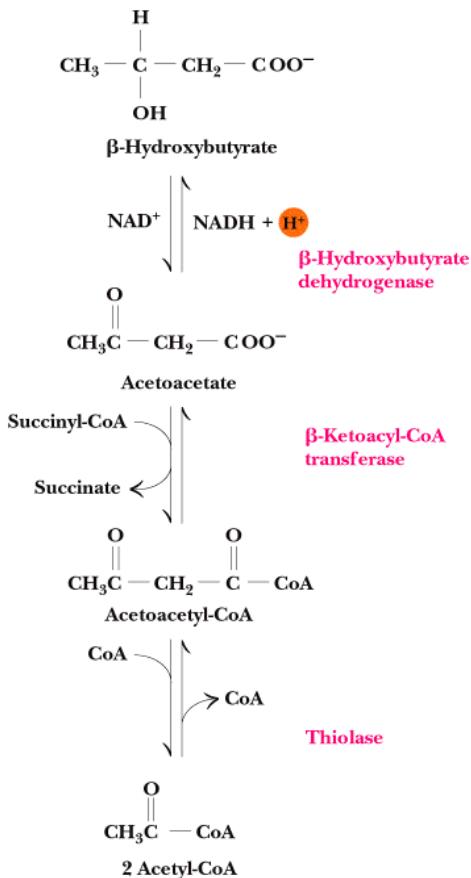
Ketone Bodies Are Oxidized in Mitochondria of many tissues OTHER than liver

- Liver **cannot** use ketone bodies because the activating enzyme required for ketone body utilization is absent in the liver.
- Acetyl-CoA regenerated and enter TCA cycle to make energy

DIABETES:

"Starvation of cells in the midst of plenty"

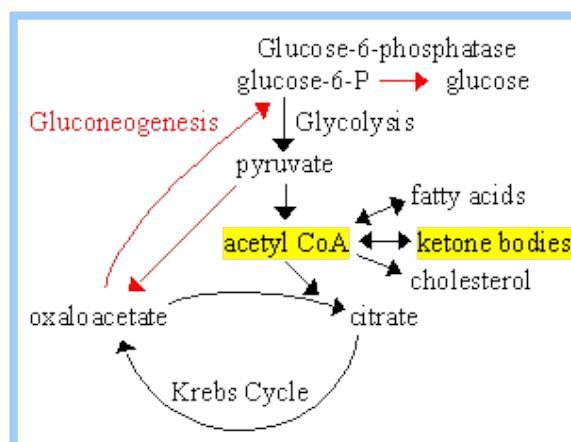
- Third leading cause of death in the U.S.
 - Two types: **Type 1 and Type 2**
- For glucose to get into cells, insulin must be present
- Causes of diabetes – Insufficient insulin is secreted or insulin does not stimulate its target cells
- Glucose builds up in the blood, overflows into urine, and passes out of body.
- Body loses main fuel source even though blood full of glucose
- **Consequences:**
 - Blood and urine [glucose] is **elevated**
 - Glucose is abundant in blood, but uptake by cells in muscle, liver, and adipose cells is low



- Cells, metabolically starved, turn to gluconeogenesis and fat/protein catabolism
 - Processes of TAG hydrolysis, fatty acid oxidation, gluconeogenesis accelerated
 - **OAA is low, due to excess gluconeogenesis, so Acetyl-CoA from fat/protein catabolism does not go to TCA, but rather to ketone body production**
- Blood levels of **ketone bodies** are elevated
 - Lowered pH of blood
 - Increased elimination of water and electrolytes, causing dehydration and lowered blood volume
 - Acetone can be detected on breath

ATKINS DIET

- High protein/High Fat/Low to no carbohydrate diets
- In a carbohydrate free diet, newly ingested fatty acids are immediately oxidized by all tissues except brain
- When diet contains carbohydrates, ingested fatty acids are transported to fat cells for storage (**Insulin** signals fat storage)
- **Effective** because **body fat is metabolized** for energy
- Also effective because lots of **water is lost** (excessive urination)
- BUT: No idea of what long term effects of being in constant ketosis are or other side-effects
- **Potentially Problematic Side Effects:**



- ❖ **Dehydration** – caused by excessive urination to rid body of acids
- ❖ **Electrolyte Imbalance** – Loss of Na^+ and K^+ in urine
- ❖ **Difficulty in Concentration** – Low fuel availability to brain
- ❖ **GI Problems** – No fiber
- ❖ **Bad Breath** – Acetone expulsion
- ❖ **Heartbeat Irregularities**
- ❖ **Kidney Stress or Damage**
 - Excessive urination to flush out toxins created by ketosis
 - Processes by-products of protein breakdown
- ❖ Excessive proteins can cause **Ca^{+2} loss from bones** which can lead to osteoporosis – esp. bad for women
- ❖ **Acidosis and Death**
- ❖ **Depression** – Lack of carbohydrates can result in lowered serotonin production – a mood stabilizing compound in the brain
- ❖ **Workouts suffer** – due to depleted energy stores

- Hard to stick with this diet – weight gain common afterwards

- If on this type of diet, be sure to drink lots of water and supplement with vitamins and salt
- **BE BALANCED!** Weight loss = Eat fewer calories and increase exercise
- 1 pound of fat = 3500 calories
 - o Cut 500 calories/day and lose 1 pound per week
 - o Safe weight loss that will last = 2 pounds per week
- **EVERYTHING IN MODERATION to keep body in balance – eat all food groups**

Integration of Metabolic Pathways:

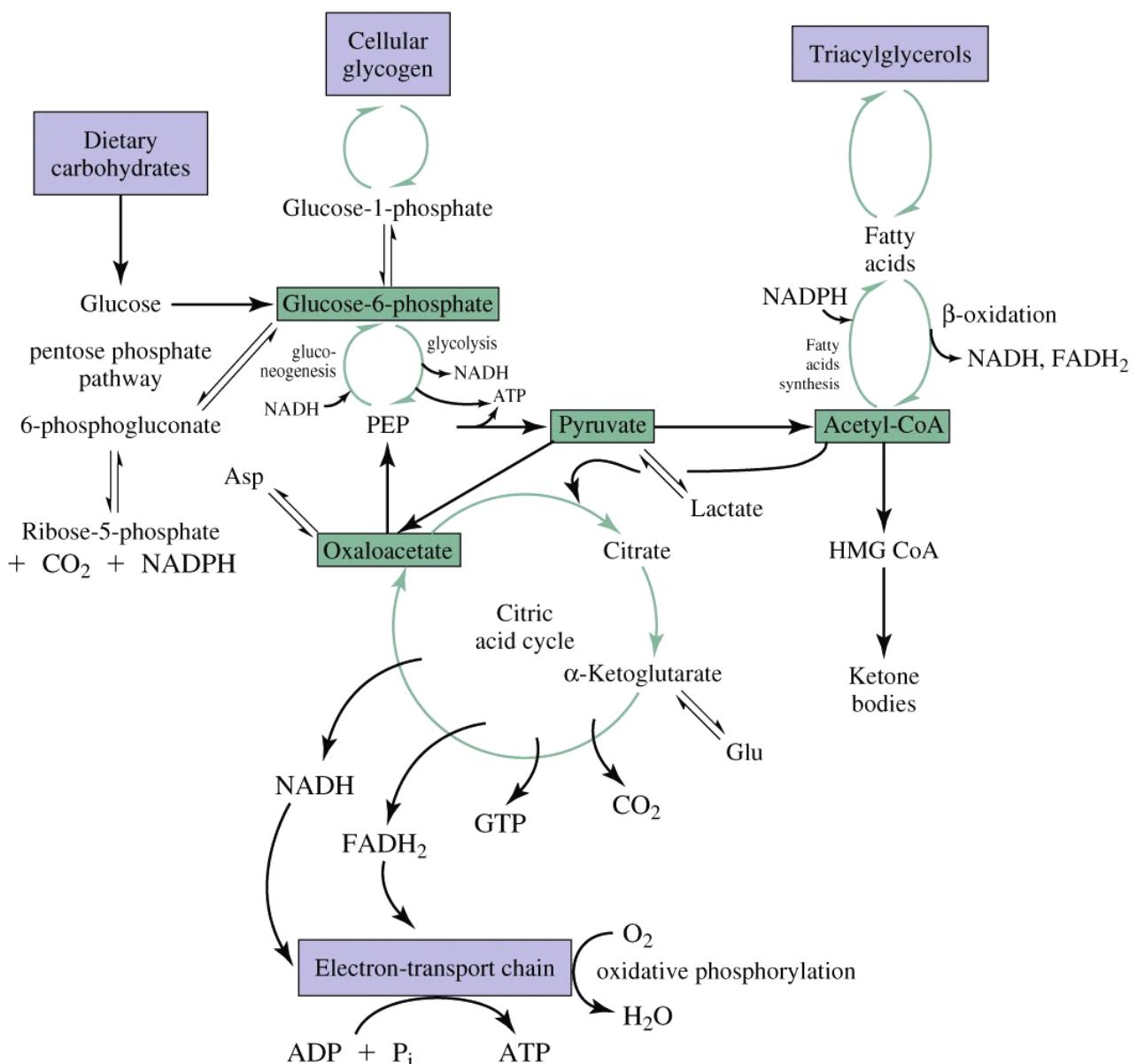


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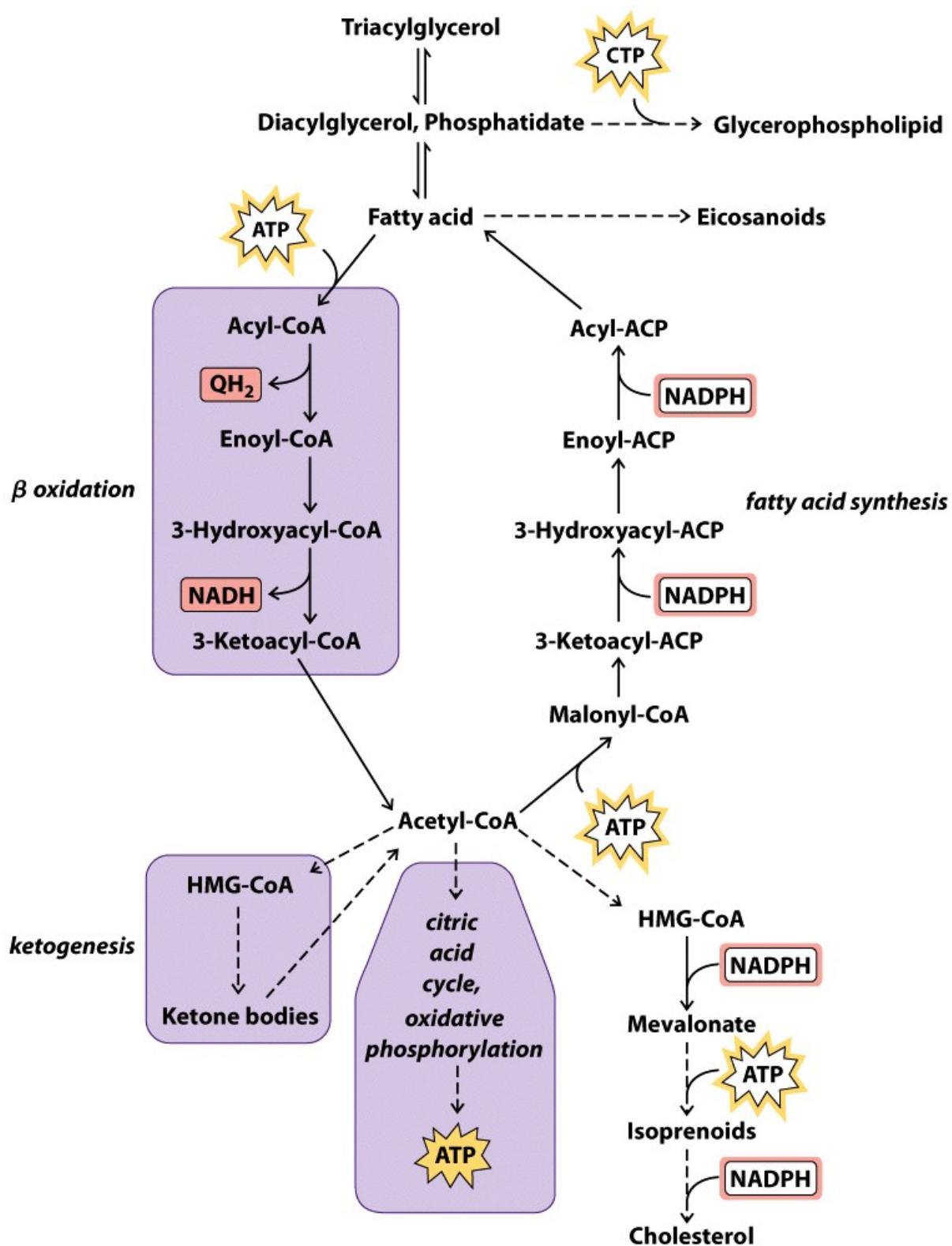


Table 20.2
Metabolic profiles of major organs

Tissue	Fuel Stored	Fuel Used	Fuel Molecules Exported
Brain	None	Glucose, ketone bodies	None
Skeletal muscle (at rest)	Glycogen	Fatty acids, glucose	None
Skeletal muscle (active)	None	Glucose, fatty acids, ketone bodies	Lactate, alanine
Heart muscle	None	Fatty acids, glucose, lactate, ketone bodies	None
Liver	Glycogen, triacylglycerols	Glucose, fatty acids, lactate, amino acids, glycerol	Fatty acids, glucose, ketone bodies
Adipose tissue	Triacylglycerols	Fatty acids, glucose	Fatty acids, glycerol

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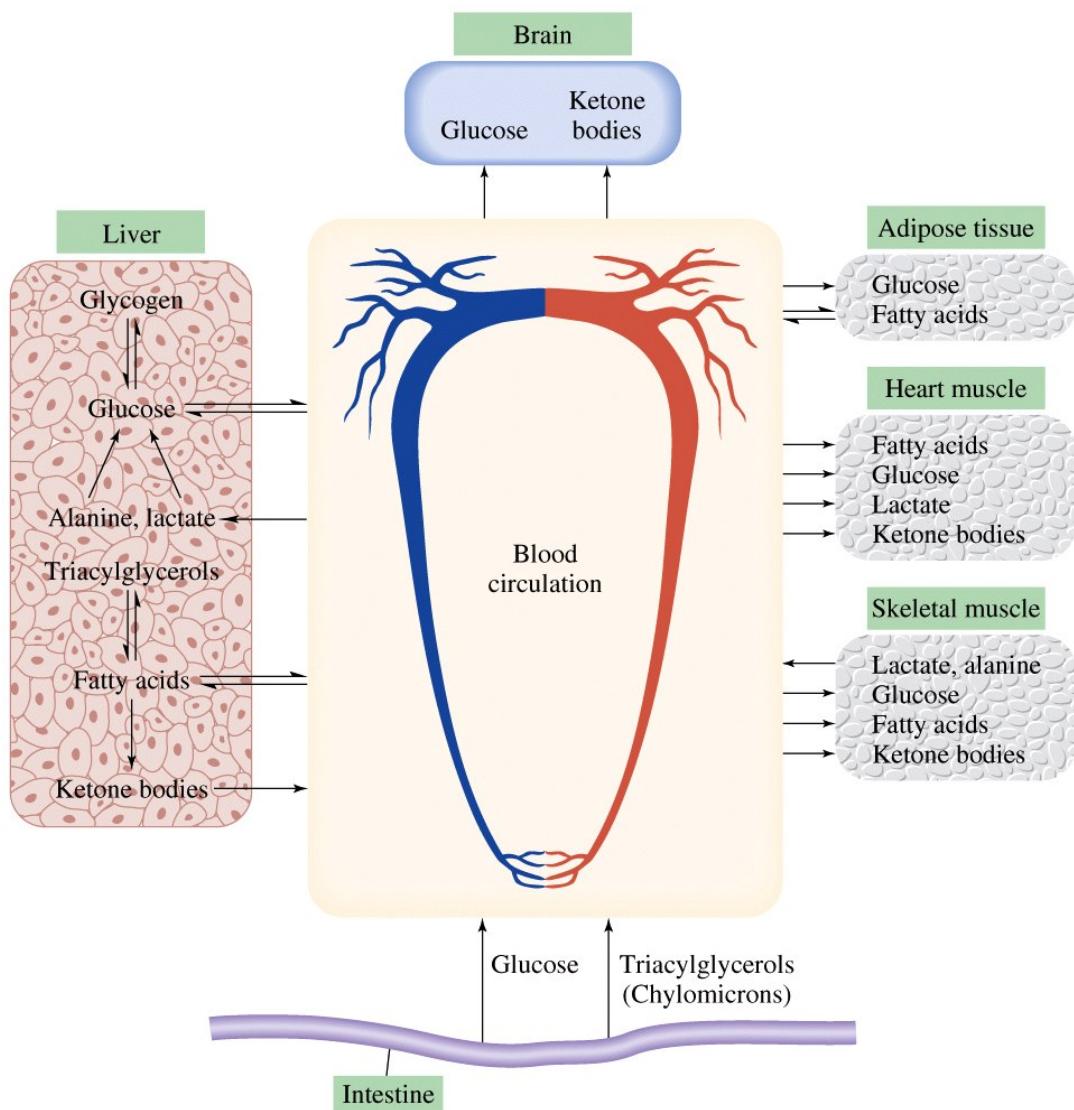


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EXTRA INFORMATION**DIABETES**

	Insulin-dependent diabetes mellitus	Non-insulin dependent diabetes mellitus
Synonym	Type I	Type II
Age of onset	During childhood or puberty	After age 35
Nutrition status at time of onset	Frequently undernourished	Obesity
Prevalence	10-20% of diagnosed diabetics	80-90% of diagnosed diabetics
Genetic predisposition	Moderate	Very strong
Defect or deficiency	Beta cells are destroyed	Insulin resistance; not enough Beta cells
Ketosis	Common	Rare
Plasma insulin	Low to absent	Normal to high
Acute complications	Ketoacidosis	Hyperosmolar coma
Oral hypoglycemia drugs	Unresponsive	Responsive
Treatment with insulin	Always	Usually not required

Type I (Insulin-Dependent) Diabetes (10% of cases)

- Formerly called **juvenile diabetes**
- Caused by slow **autoimmune destruction of insulin-secreting pancreatic β -cells**
- Patients **require insulin** to live
- Life spans reduced due to complications resulting from the crude metabolic control provided by insulin injections
- Hyperglycemia leads to blindness
 - Degeneration of the retina
 - Cataract formation due to protein glucosylation

Type II

- Comprises > 90% of the diagnosed cases
- Affects almost 20% of individuals over age 65
- Characterized by an insensitivity to insulin (impaired recognition of insulin)
- Insulin levels are elevated, but affected individuals have low numbers of or defects in insulin receptors
- Transport of glucose into muscle, liver and adipose tissue resumes significantly and despite abundant glucose, cells metabolically starved
- Respond by increased gluconeogenesis and catabolism of fat and protein

- **Causes of Insulin Resistance in type II Diabetics:**
 1. Defects in signal transduction
 2. Abnormal insulin or insulin receptors
 3. Defects in glucose transporters
 4. It is also thought that insulin resistance is caused by obesity as insulin response in type II diabetics dramatically improves with weight reduction.
 5. Postulated that in obese individuals there is a **constant elevated level of insulin** because of **high carbohydrate intake**.
 - Thought to cause beta cell destruction
 - Decrease the sensitivity of insulin receptors in the target organs
 - Increased insulin production resulting from overeating may suppress insulin receptor synthesis

Insulin Resistance**❖ Complication of obesity and type 2 diabetes**

- * Mildly increased plasma glucose
- * Normal or increased plasma insulin
 - Tissue insensitivity to insulin

❖ Several levels of defects

- * **Pre-receptor: rare**
 - Defect: insulin receptor antibodies, abnormal molecule
- * **Receptor:**
 - Decreased number or affinity of insulin receptors
- * **Post-receptor : Most probable site of insulin resistance in diabetes**
 - Defects in intracellular signal transduction, decreased activity of key enzymes such as pyruvate dehydrogenase or glycogen synthase
- * **Glucose transport: To be established**
 - Deficient or defective glucose transporters

- The **primary** treatment is exercise and diet.
 - The main goal with type II diabetes treatment is to keep the glucose concentration within the normal limits. In order to do this, the patient is asked to maintain a strict diet which is low in carbohydrates and weight reduction is encouraged by the doctor.
- **Prevention:**
 - Maintaining ideal body weight ([weight management](#)) and an active lifestyle may prevent the onset of type II [diabetes](#) in people at risk for the disease.

Drug Treatment:

1. **Sulfonylurea drugs** – enhance insulin secretion (e.g. glyburide)
2. **α -glucosidase inhibitors:** inhibits the digestion of ingested carbohydrates, thereby resulting in a smaller rise in blood glucose concentration following meals. Results in delayed glucose absorption Effect is additive to that of sulfonylureas when used in combination.