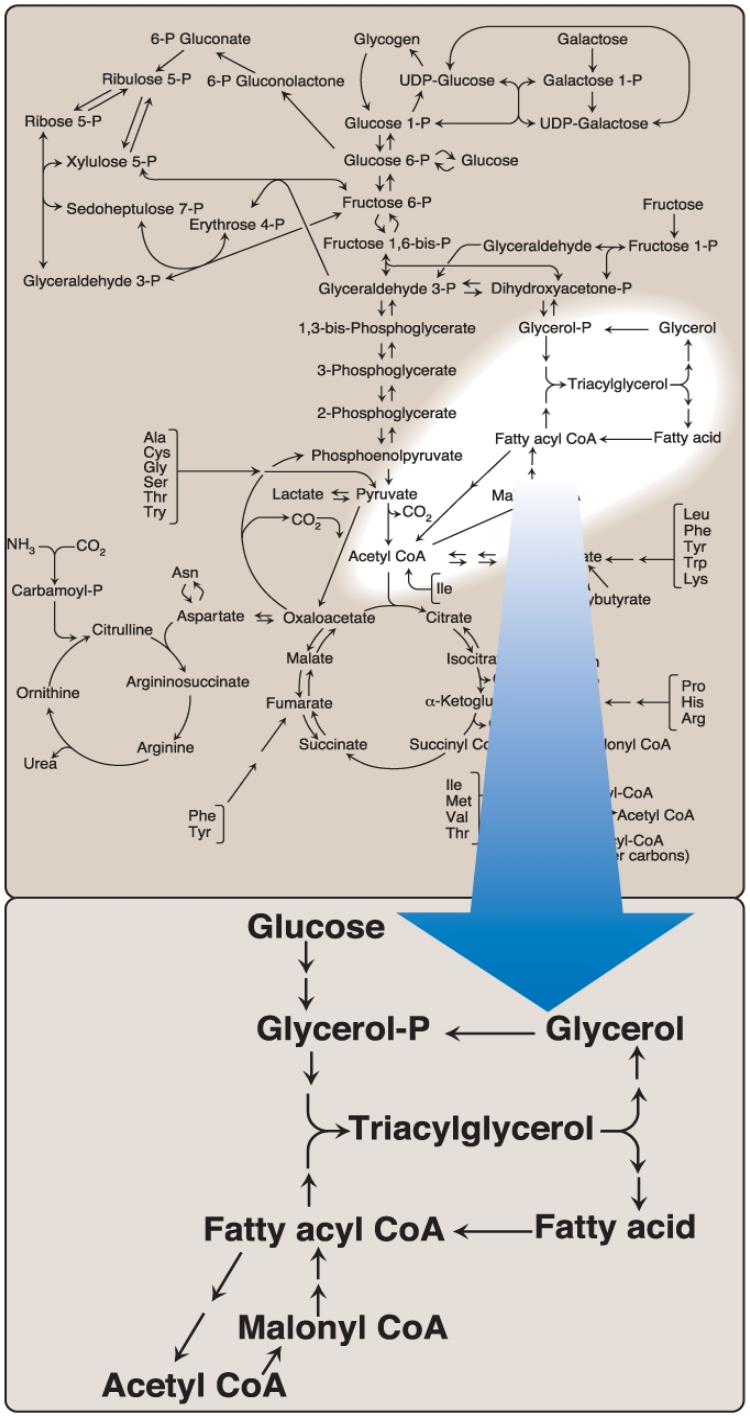


Fatty acids exist in the body free (unesterified) or as acyl ester in more complex molecules. Esterified fatty acids in the form of triacylglycerol serve as the major energy reserve of the body. The metabolic pathways of fatty acids synthesis and degradation and relation to carbohydrate metabolism is shown above.

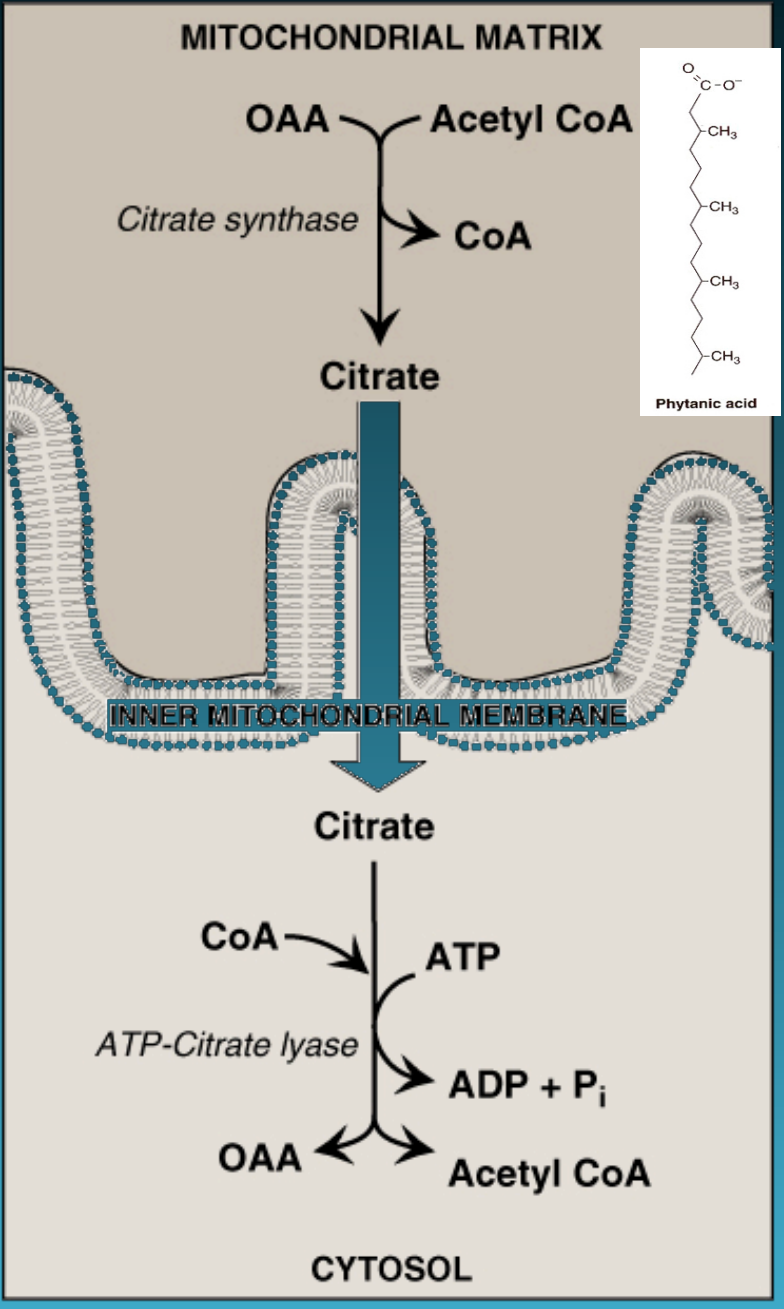


Figure 16.6
Production of cytosolic acetyl CoA.

Most of the fatty acids in mammals are of straight line however branched fatty acids do exist in nature for example Phytanic acid which is found in many dairy products. Inability to brake this fatty acid results in Refsum's disease (accumul. of lipid in plasma and tissues.

In humans synthesis of fatty acids occurs mainly in liver and in mammary glands. The process incorporates acetyl CoA into the growing fatty acid chain using ATP and NADPH. The first step is the transfer of acetyl CoA from the mitochondria to the cytosol.This is done in the form of citrate (acetyl CoA + OAA = citrate). Citrate lyase converts citrate back to OAA + acetyl CoA.

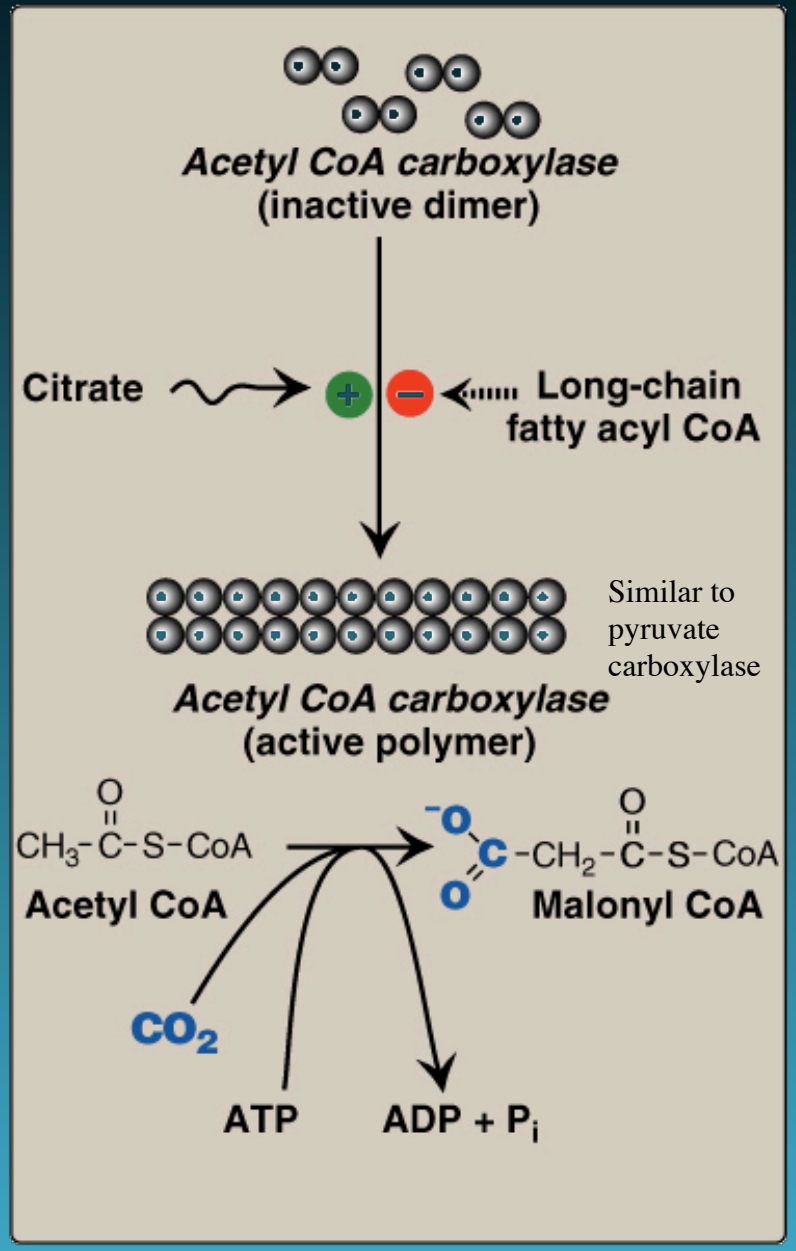


Figure 16.7

Allosteric regulation of malonyl CoA synthesis by *acetyl CoA carboxylase*. The carboxyl group contributed by dissolved CO_2 is shown in blue.

Acetyl CoA is carboxylated to form malonyl CoA in the cytoplasm by Acetyl CoA carboxylase. This rx requires ATP and the coenzyme biotin. The carboxylase enzyme is activated by citrate which induces the polymerization of the protomer. On the other hand this enzyme is inhibited by malonyl CoA or palmitoyl CoA. This enzyme can also be phophorylated by the presence of epinephrine and inactivated. In the presence of insulin it is dephosphorylate and thereby activated.

High carbohydrate diet will induce the carboxylase enzyme synthesis and hence fatty acid synthesis while high fat diets will reduce fatty acid synthesis by reducing Acetyl CoA carboxylase synthesis.

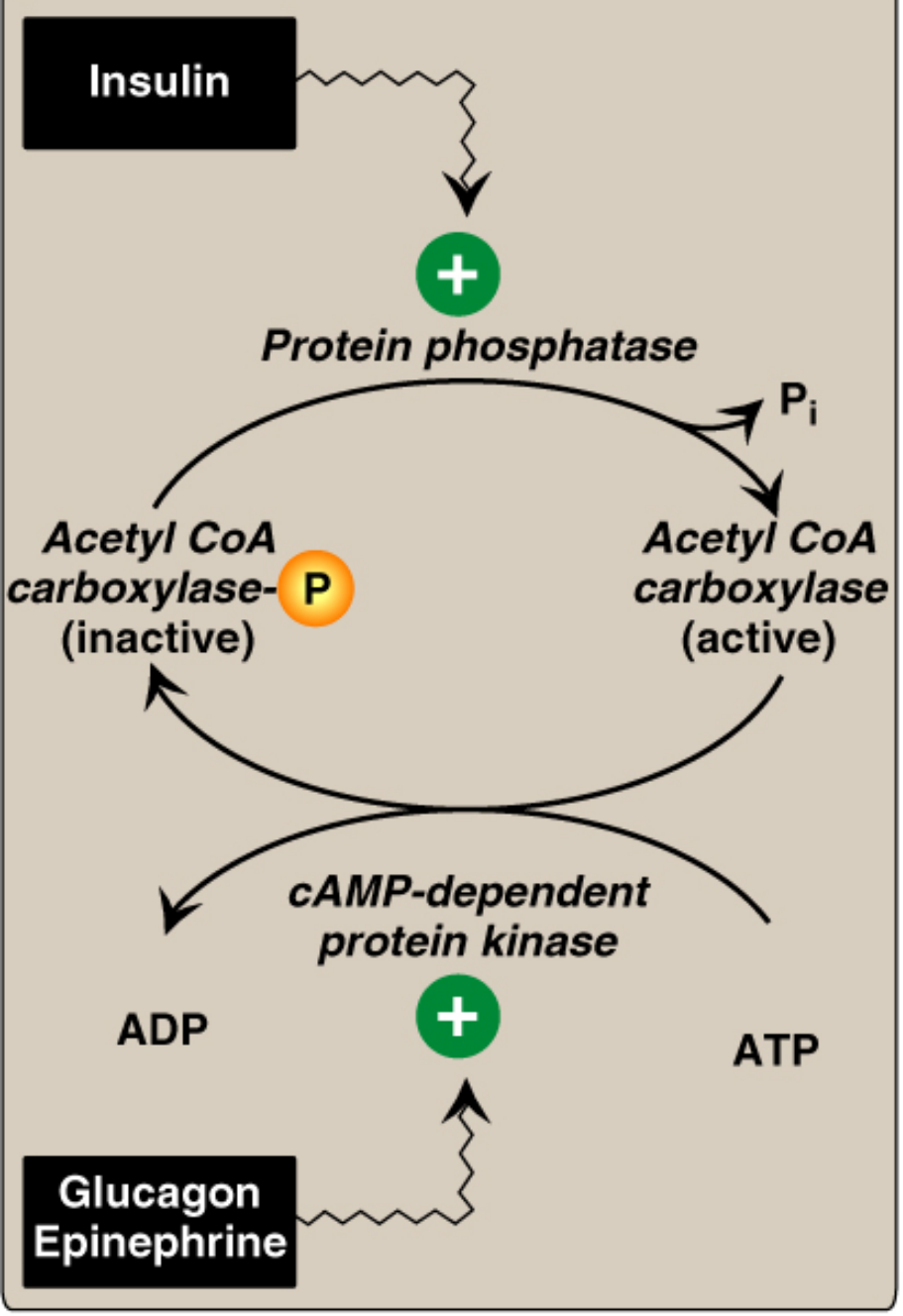


Figure 16.8
Hormone-mediated, covalent regulation of *acetyl CoA carboxylase*.

Fatty acid synthase is a multienzyme complex (dimer each monomer has seven enzymic activities) regulated similarly as the acetyl CoA carboxylase. It has a domain that covalently binds a molecule of 4'-phosphopantetheine (it carries acetyl and acyl units on its terminal thiol (SH) group.

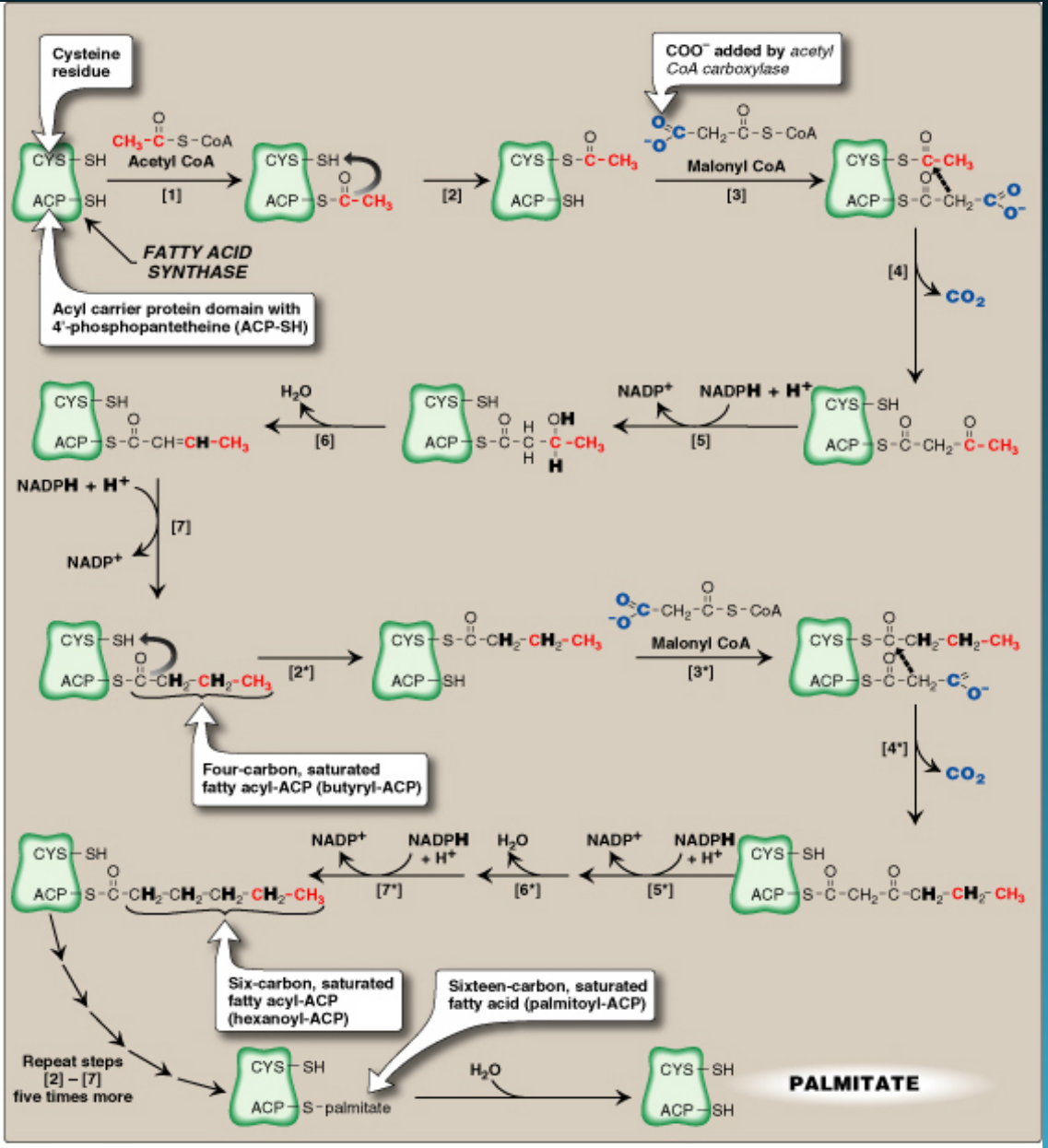


Figure 16.9
Synthesis of palmitate (16:0) by the *fatty acid synthase* complex. [Note: Numbers in brackets correspond to bracketed numbers in the text. A second repetition of the steps is indicated by numbers with an asterisk (*). Carbons provided directly by acetyl CoA are shown in red.]

1) Molecule of acetate is transferred from acetyl CoA to the SH group of ACP acetyl CoA-ACP transacylase 2) this two carbon fragment is transferred to a cystein residue as a holding site 3) the vacant ACP site accepts a 3 carbon malonate unit from malonyl CoA (ACP acetyl CoA-ACP transacylase) 4) the acetyl group attacks the malonyl group which loses CO_2 (β-ketoacyl-ACP synthase) the next 3 rxs convert the β-ketoacyl group to corresponding saturated acyl group by reductions and dehydration steps
5) the keto group is converted to alcohol (β-ketoacyl-ACP reductase) 6) water is removed double bond introduced 7) second reduction step occurs

The result of these seven reactions is the production of four carbons compound with 3 terminal carbons saturated attached to ACP. This cycle of rxs is repeated seven times, each time incorporating a two carbon unit (from malonyl CoA) once it reaches a length of 16 carbons the process is terminated. Result a palmitate saturated molecule (16:0). Overall rx is 8 Acetyl CoA+ 14 NADPH +4H+ 7ATP Palmitic acid + 8 CoA +

14 NADP +7 ADP + 7 Pi + 7 H2O

The major source of NADPH for fatty acid synthesis comes from the HMP (12 NADPH/ glucose molecule oxidized) The cytosolic conversion of malate to pyruvate also contributes to the pool of NADPH.

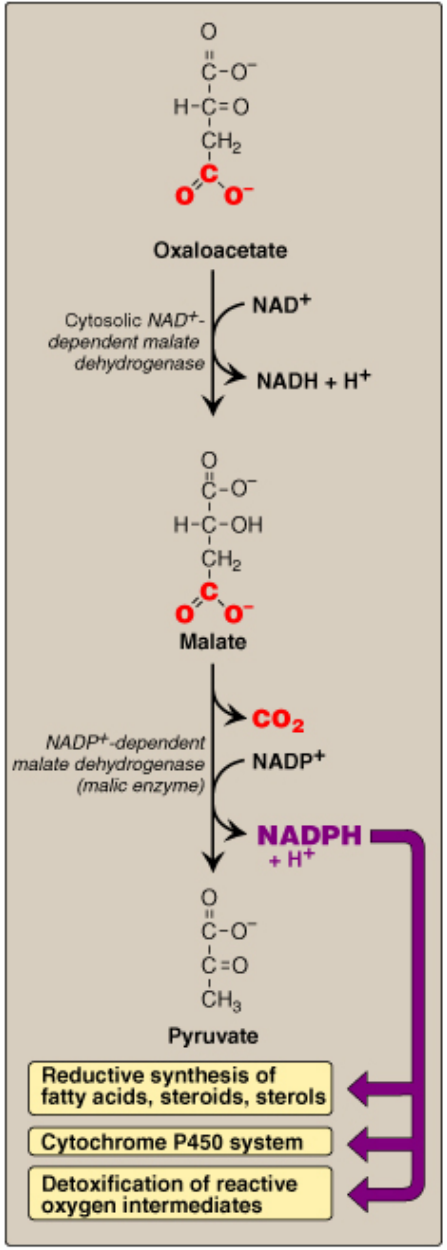
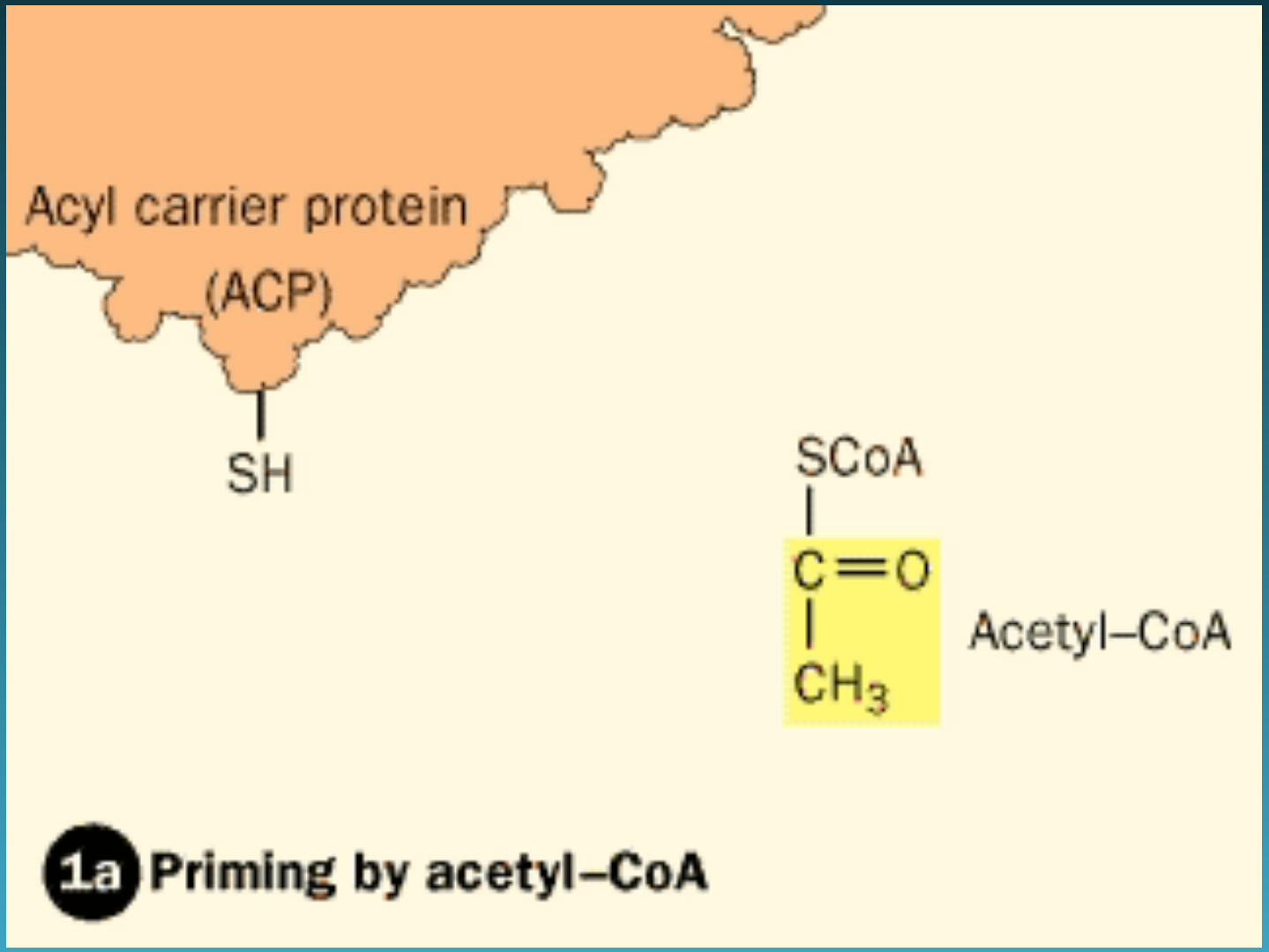


Figure 16.10
Cytosolic conversion of oxaloacetate to pyruvate with the generation of NADPH.

Animation of fatty acid synthesis



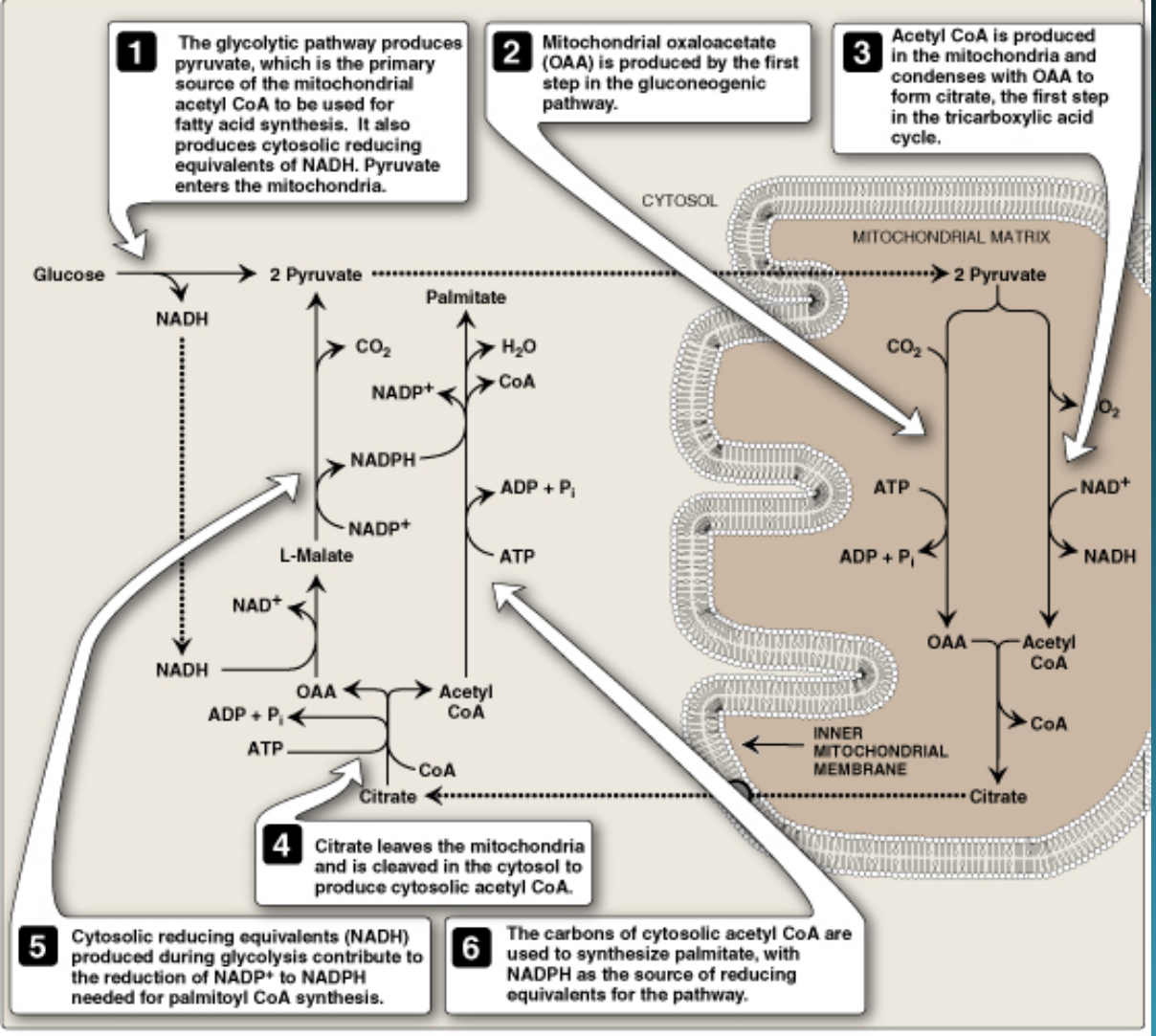
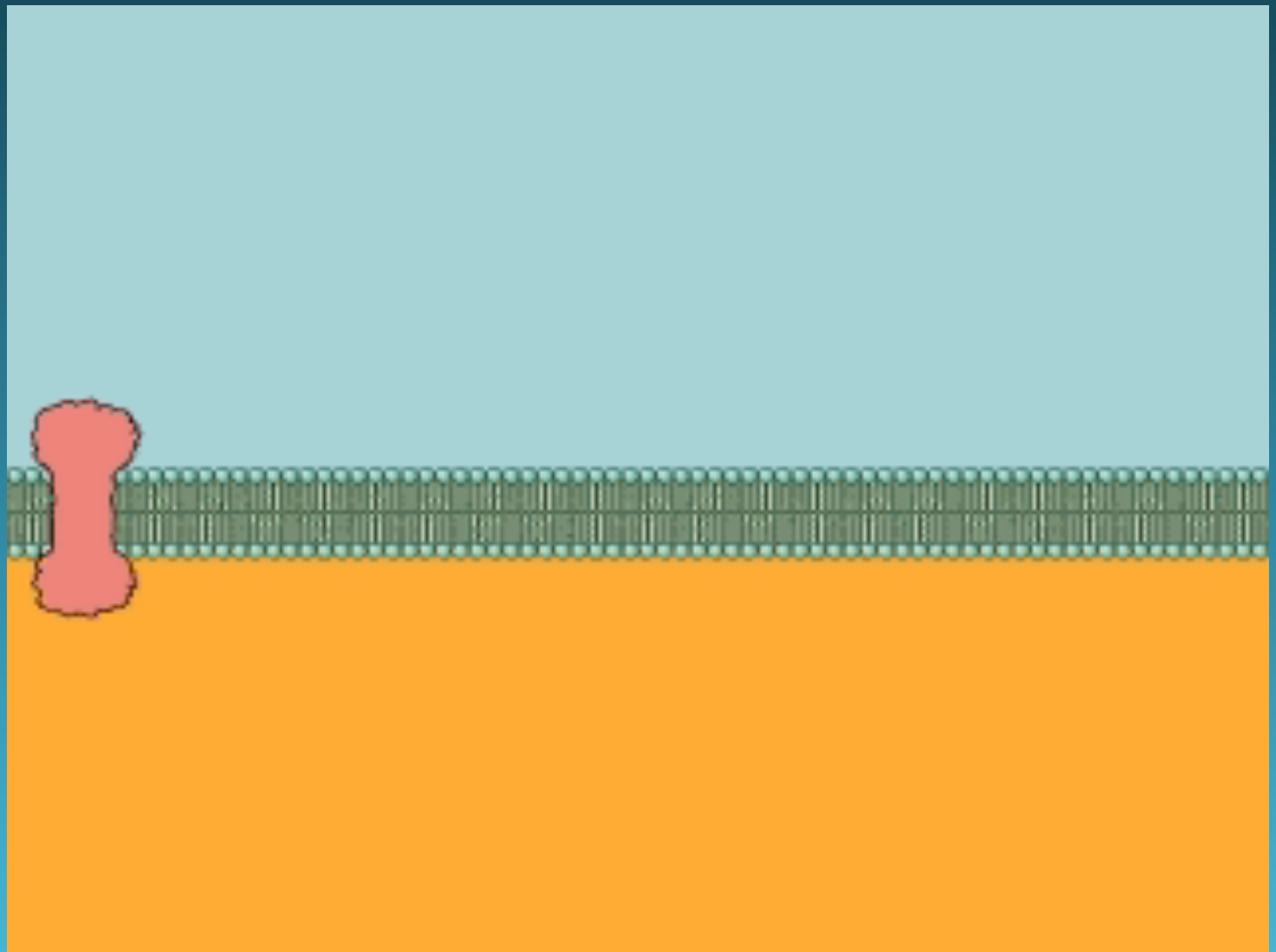
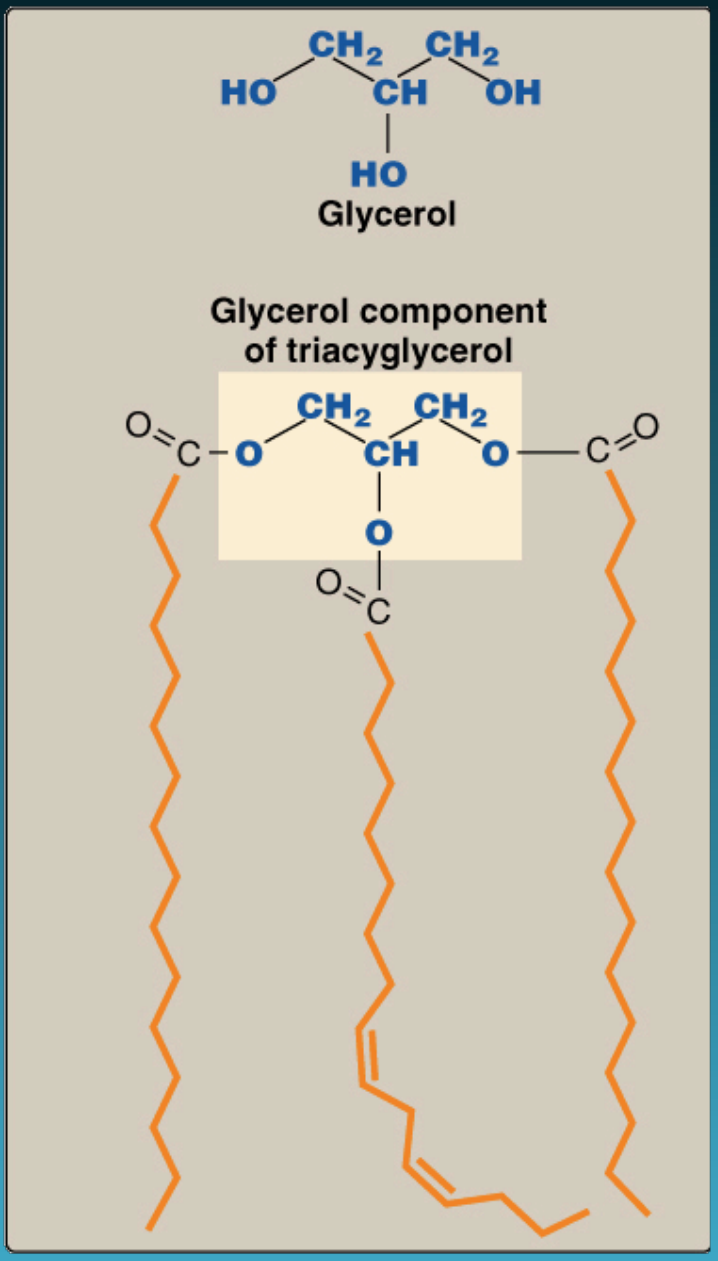


Figure 16.11
Interrelationship between glucose metabolism and palmitate synthesis.

This figure summarizes the interrelationship between glucose metabolism and palmitate synthesis. Note that in step one Glucose is converted to pyruvate by the glycolysis pathway generating NADH. This NADH is used to generate NADPH through the convertion of malate to pyruvate. Pyruvate is the primary source of mitochondrial acetyl CoA to be used in fatty acid synthesis. OAA is also produced from pyruvate as first step in gluconeogenesis. Acetyl CoA is produced in mitochondria and condensed with OAA to citrate which is exported out of the mitochondria and reconverted to Acetyl CoA and OAA. Acetyl CoA can know be used in fatty acid synthesis and OAA converted to malate to generate NADPH for the fatty acid synthesis.

Movement of Acetyl CoA and OAA from the mitochondria to the cytosol and pyruvate back in to the mitochondria to replenish OAA





Further elongation of palmitate (16:0) or desaturation can occur by separate enzymatic processes. It occurs in the mitochondria and in the ER. Humans lack the ability to add double bonds beyond carbons 9 to 10 and therefore must have the polyunsaturated linoleic and linolenic acids provided in the diet as essential fatty acids. Fatty acids are esterified through their carboxyl groups losing their negative charge and becoming neutral.The fatty acids on the glycerol molecule are not the same type. Carbon 1 is usually saturated, carbon 2 is usually unsaturated and 3 can be either. Glycerol phosphate is the initial acceptor of fatty acids.

There are two pathways for the production of Glycerol-P. this occurs in both liver and adipose tissues.

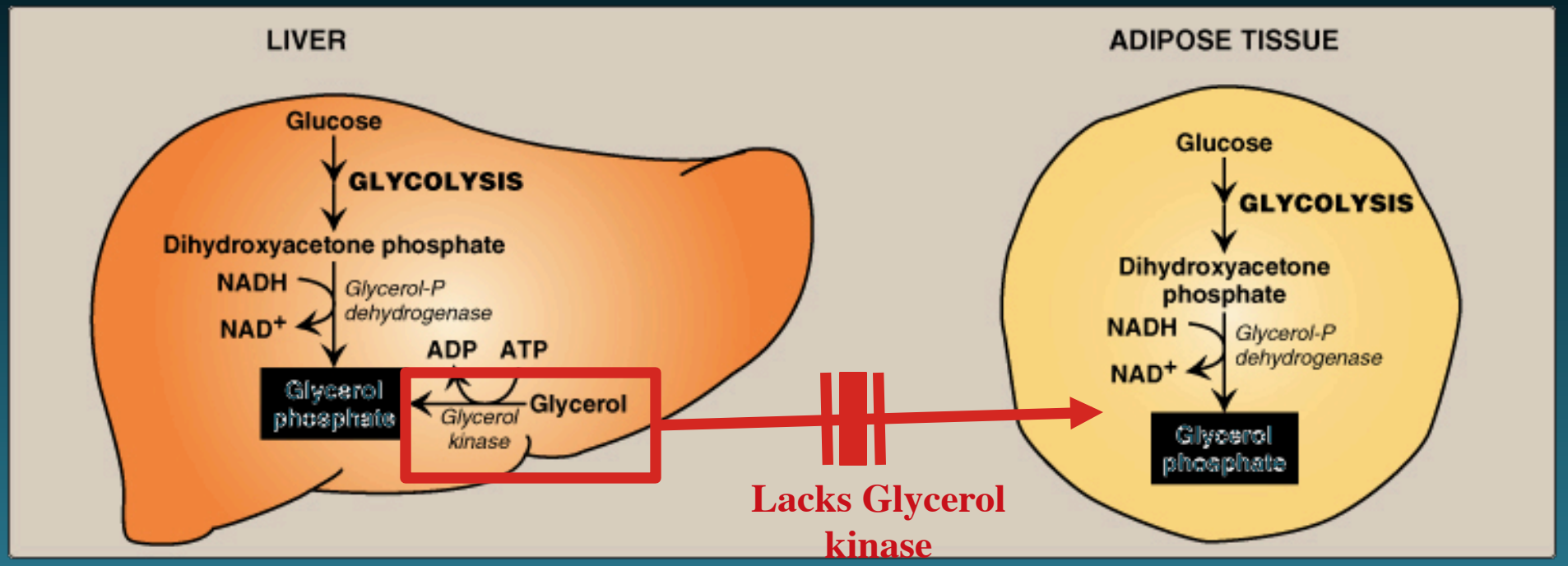


Figure 16.13
Pathways for production of glycerol phosphate in liver and adipose tissue.

Glycerol-P can be produced from glucose through glycolysis rx's to produce dihydrohyacetone-P (DHAP) then to glycerol-P by glycerol phosphate dehydrogenase. A second patway found in the liver but NOT in adipose tissues, is the formation of glycerol-P from glycerol by glycerol kinase. Triacylglycerol is stored in adipose tissue in the cytosol as depot fat and in the liver most of the triacylglycerol is exported as VLDL (apoB-100, triacylglycerol, cholesteryl esters, cholesterol, phospholipids and protein).

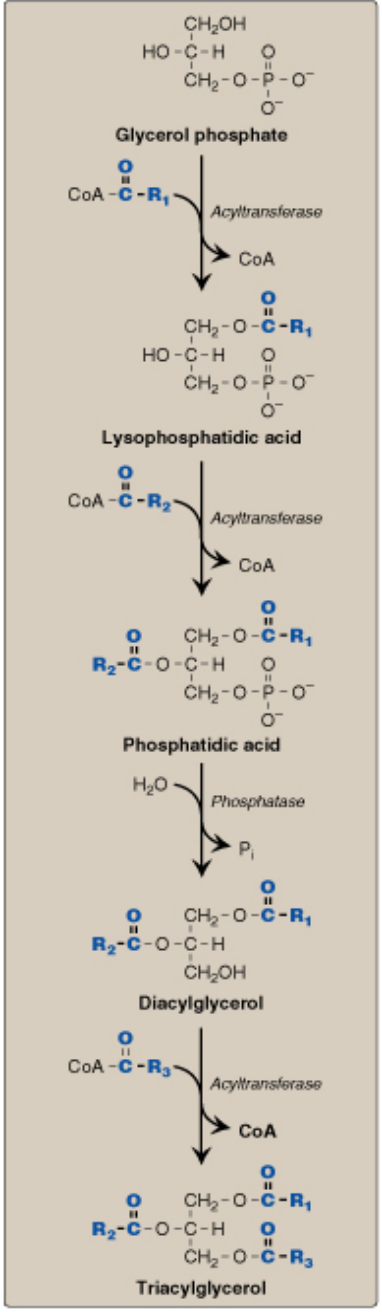
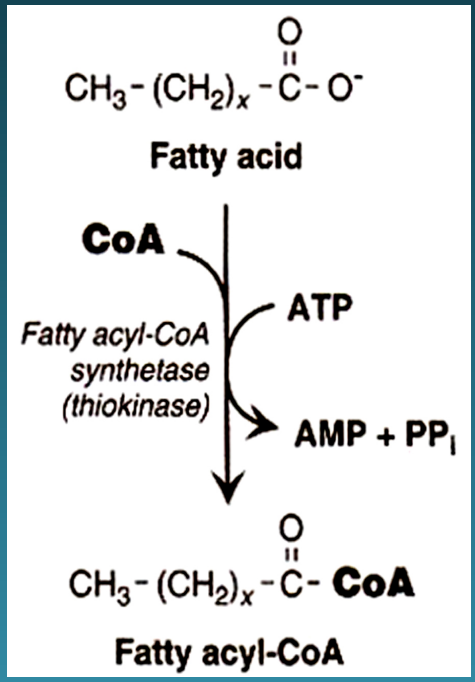


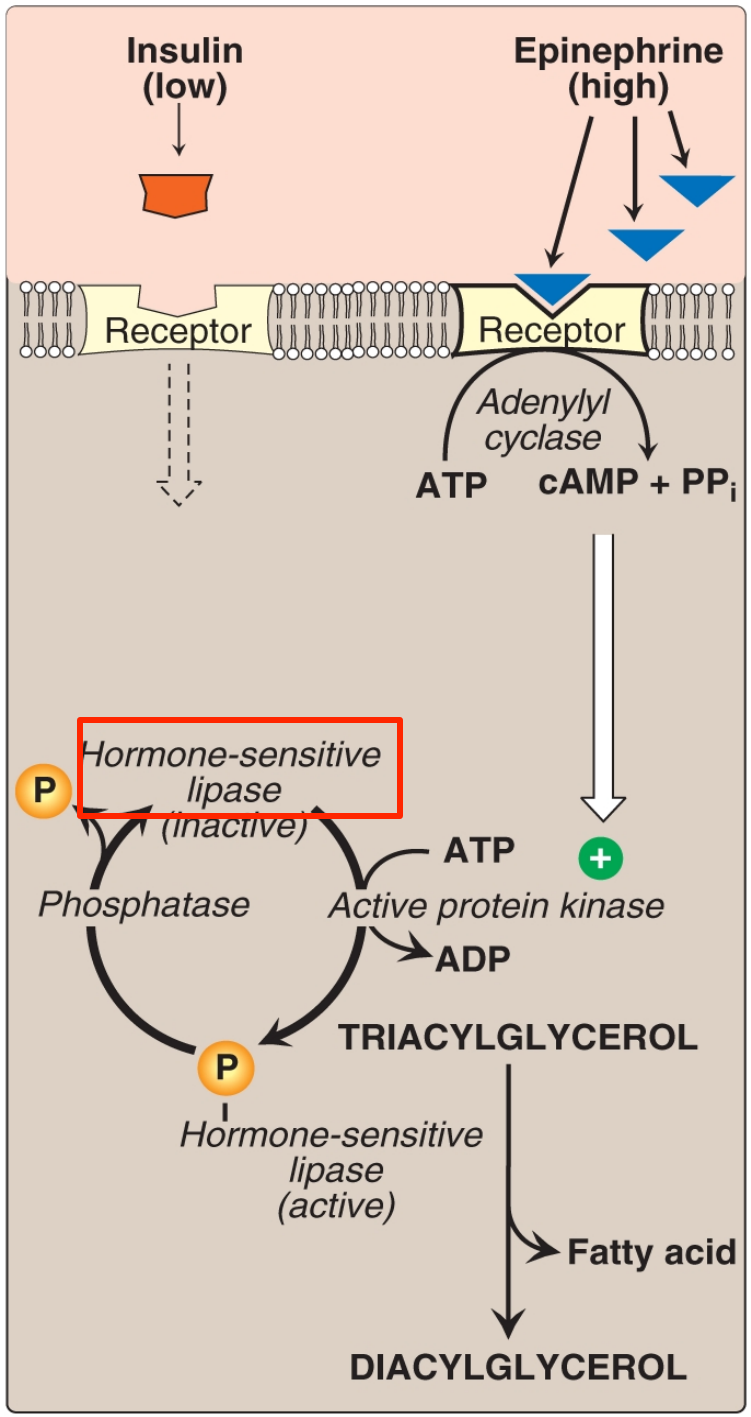
Figure 16.14
Synthesis of triacylglycerol.

Synthesis of Triacylglycerol from Glycerol-P

Activation of free fatty acids to fatty acyl CoA derivatives is required by fatty acyl CoA synthetase



The four rx's for the synthesis of triacylglycerol. The first acyl group is added to carbon 1, the second is added to carbon 2 and the third to carbon 3 after the dephosphorylation by the phosphatase. The acyl groups are added by acyltransferases. With the formation of lysophosphatidic acid followed by phosphatidic acid . Diacylglycerol to triacylglycerol.



Release of fatty acids from triacylglycerol is initiated by hormone sensitive lipase which removes a fatty acid from either carbon 1 or 3. This enzyme is activated when phosphorylated by 3' 5' cyclic AMP-dependent protein kinase. This is activated by epinephrine which activates adenylate cyclase. Acetyl CoA carboxylase (formation of malonyl CoA) is inhibited by hormone directed phosphorylation. In addition Glycogen synthase is also inactivated. Why? Explain, reasoning (low energy environment). Thus if cAMP cascade is activated fatty acid synthesis is turned off, whereas triacyglycerol breakdown is turned on and glucose is not being stored. Insulin and glucose will inactivate hormone-sensitive lipase as it is dephosphorylated.

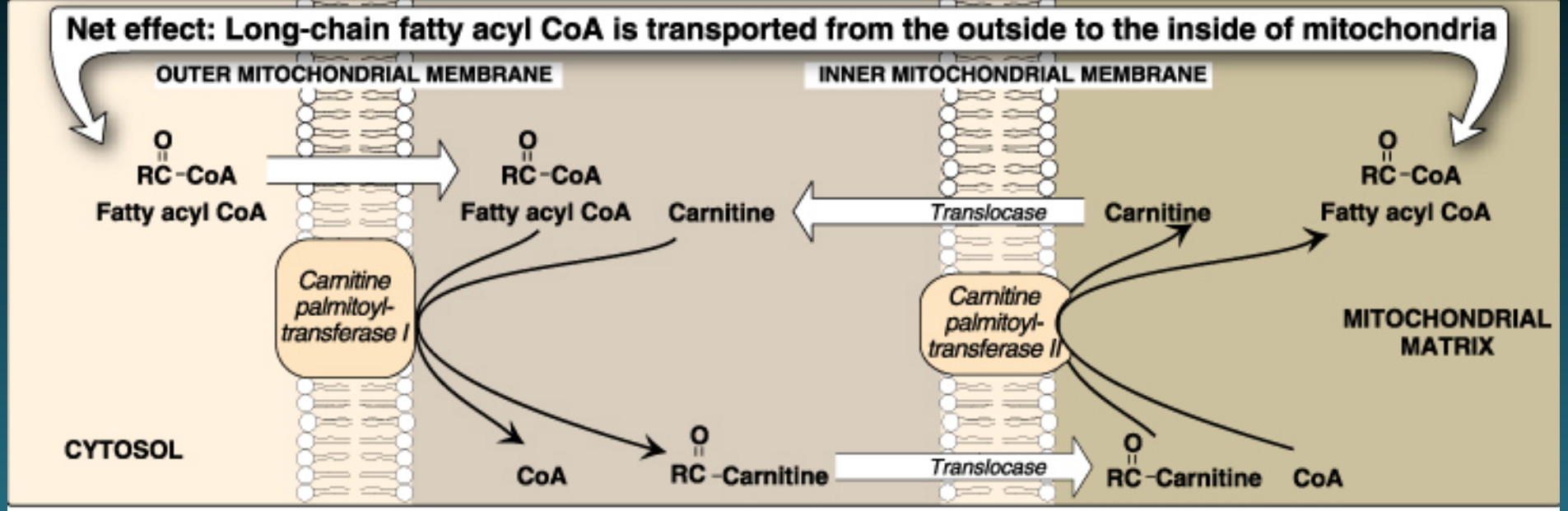
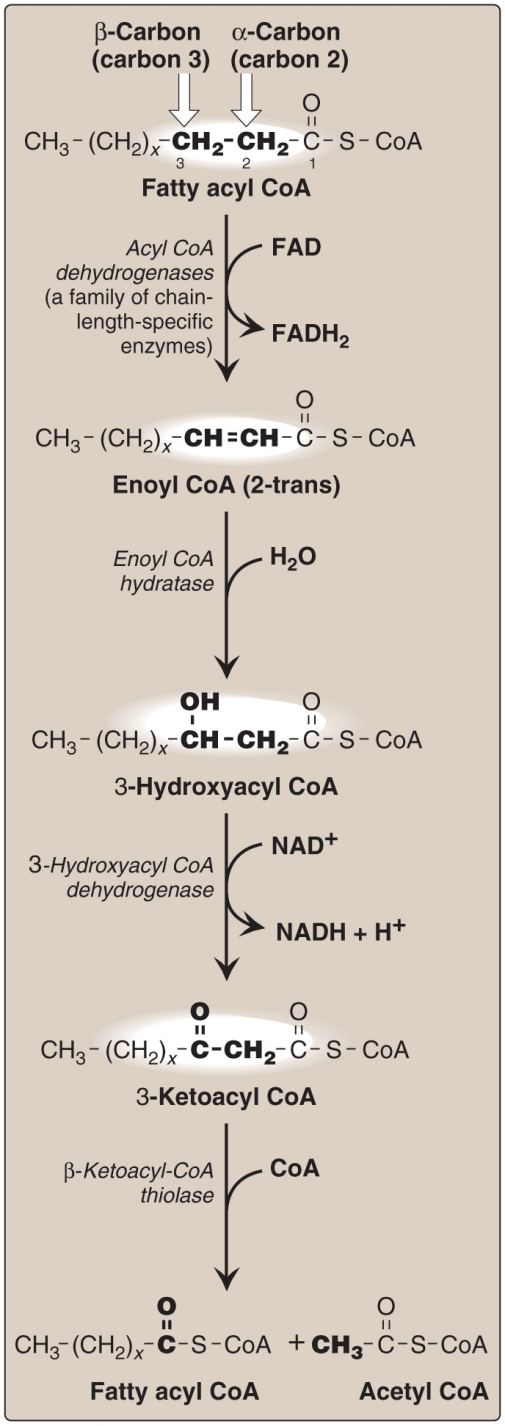


Figure 16.16
Carnitine shuttle.

In order to degrade the fatty acid by β-oxidation the fatty acids needs to cross the mitochondrial membrane since β-oxidation occurs in the mitochondrial matrix. This is accomplished by the Carnitine Shuttle process using Carnitine as the carrier. The acyl group is transferred to the carrier by carnitine palmitoyl transferase I (outer surface of the membrane) forming O-acylcarnitine. After transporting the acyl group to the inner matrix of the mitochondria it is transferred to another molecule of CoA by carnitine palmitoyl transferase II. Malonyl CoA inhibits carnitine transferase I (therefore when synthesis is occurring in the cytoplasm transport of fatty acids into the mitochondria is halted. Genetic defects of on carnitine transferase I results in the inability to use long chain fatty acids (myoglobinemia, weakness following exercise.

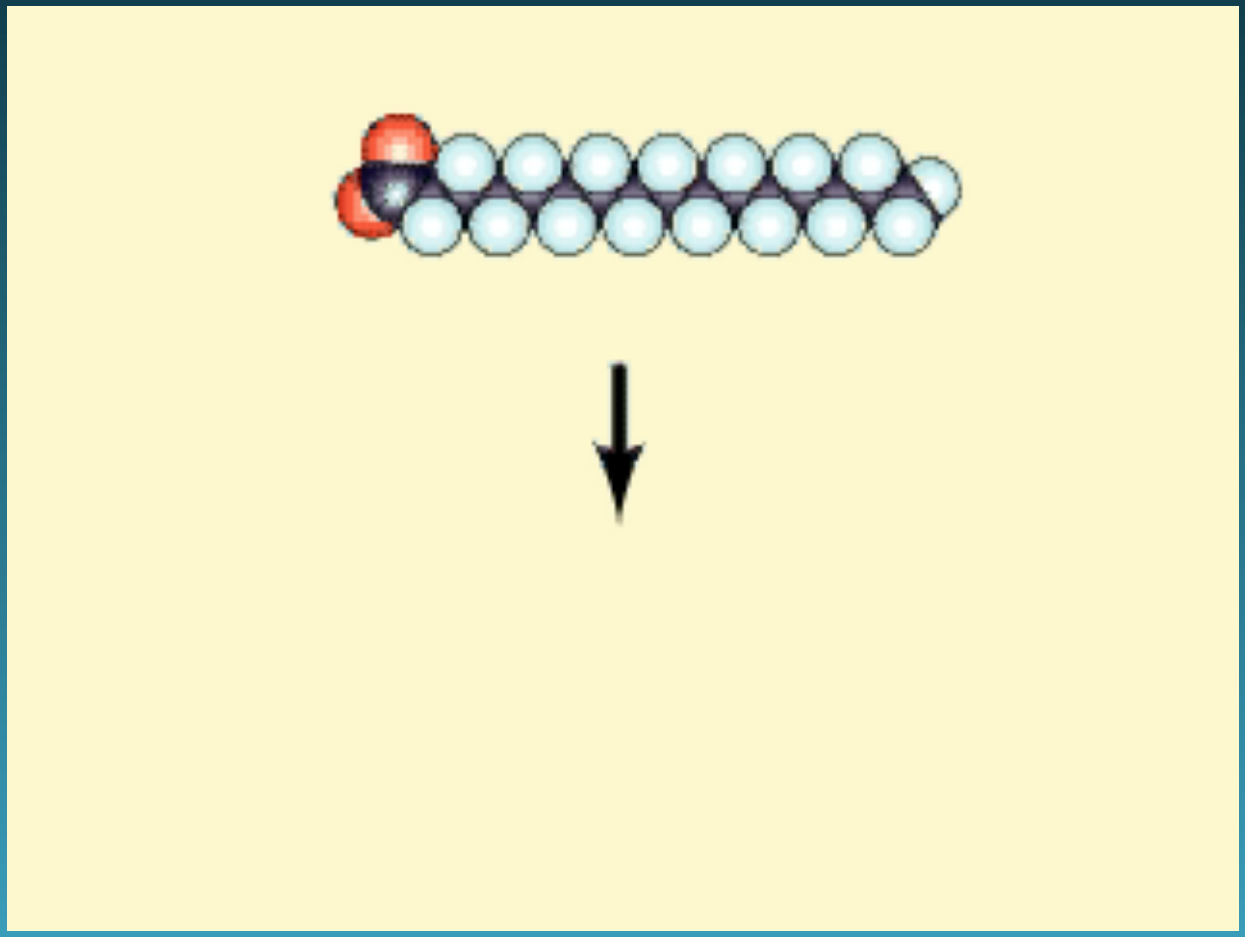


Reactions of β-oxidation

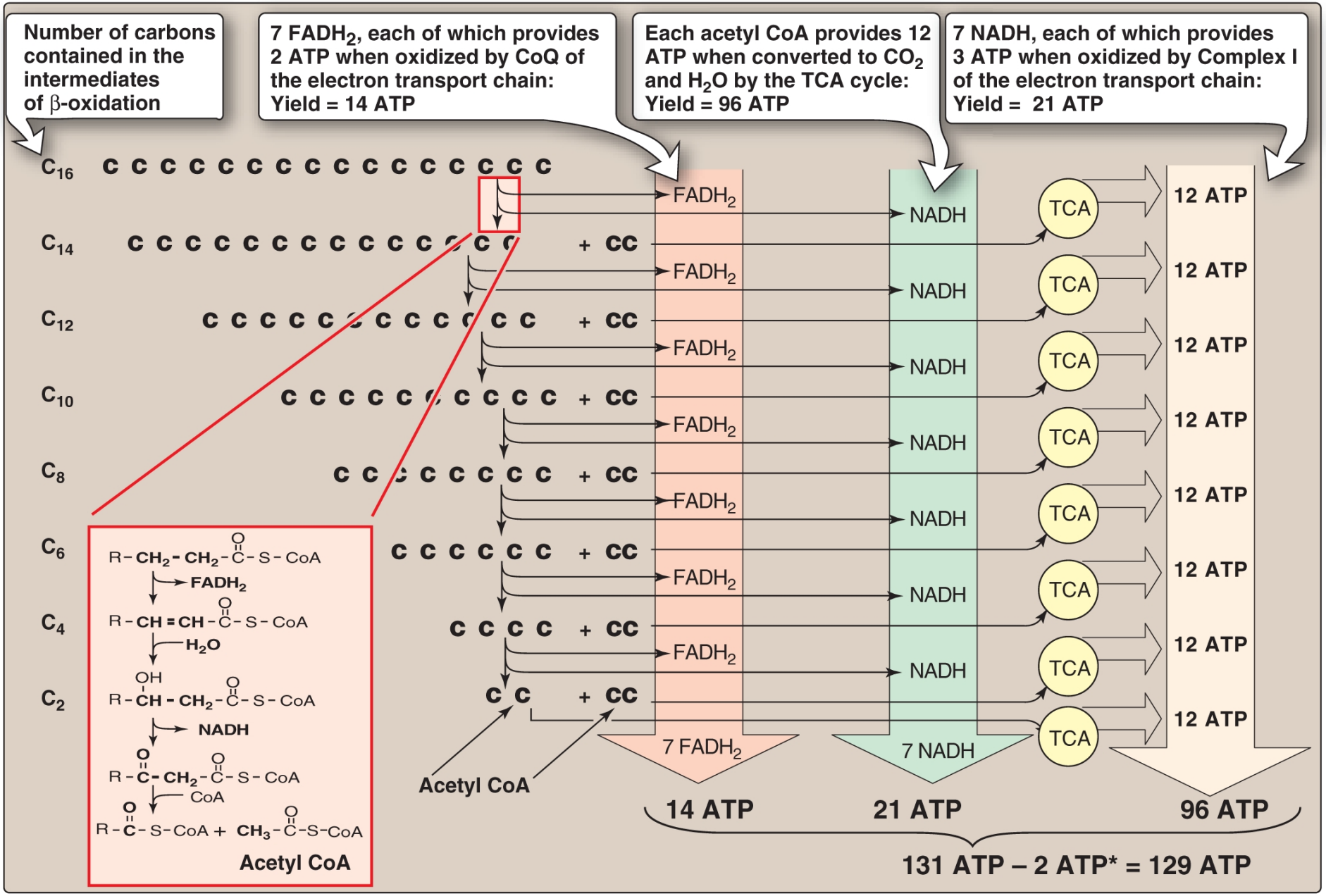
The major pathway of catabolism of saturated fatty acids is known as β-oxidation. Two carbon fragments are successively removed from the carboxyl end of the fatty acyl CoA producing acetyl CoA. The first cycle of this process is shown on this figure. It is called the β-oxidation because the cleavage is performed at the β-carbon. An oxidation that produces $FADH_2$, hydration, a second oxidation that produces NADH, and a thiolic cleavage that releases acetyl CoA. The four steps are repeated for saturated fatty acids. For even number of carbon chains (n/2)-1. The final thiolytic cleavage produces 2 acetyl CoA groups. (FEHK) Feel Enough His Kisses.

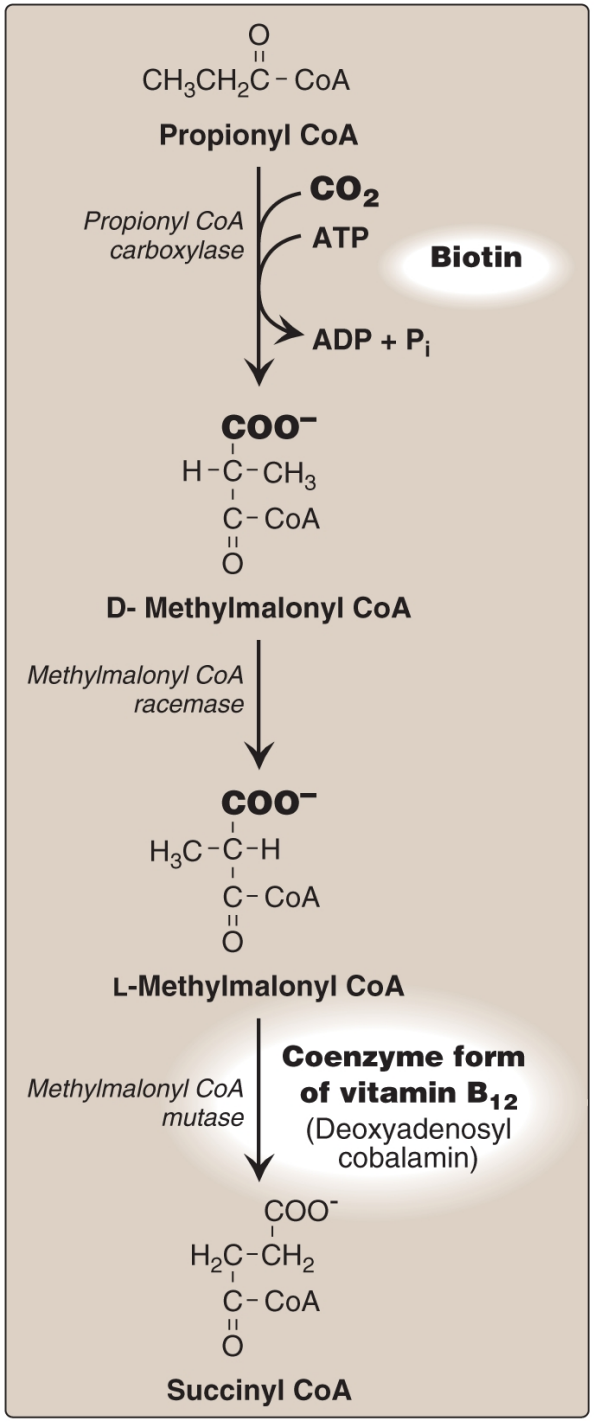
The β-oxidation cycle, degradation of even carbon number fatty acid chains

Energy yield from fatty acid oxidation from palmitoyl CoA is 131



When starting from palmitate the ATP required for the production of palmytoyl CoA must be taken into consideration, two ATPs are consumed therefore the production of energy is 129 ATPs



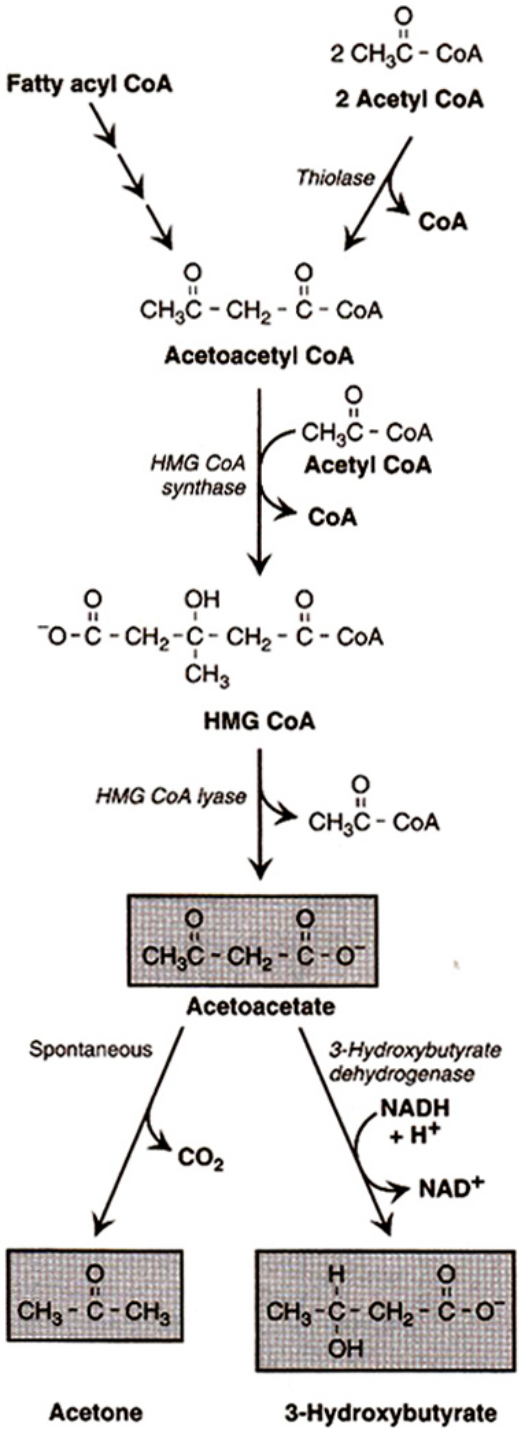


Oxidation of fatty acid with an odd number of carbons proceeds through the same route as the even until it reaches the three final carbons (propionyl CoA). The formula for determining the number of beta oxidations and number of acetyl CoA formed is given by the formula (n-3)/2. Propionyl CoA is metabolized as shown in the adjacent figure. Methylmalonyl CoA is synthesized followed by succynyl CoA which can now enter the tricarboxylic acid cycle.

The oxidation of unsaturated fatty acids provides less energy than that of the saturated equivalent because they are less highly reduced.

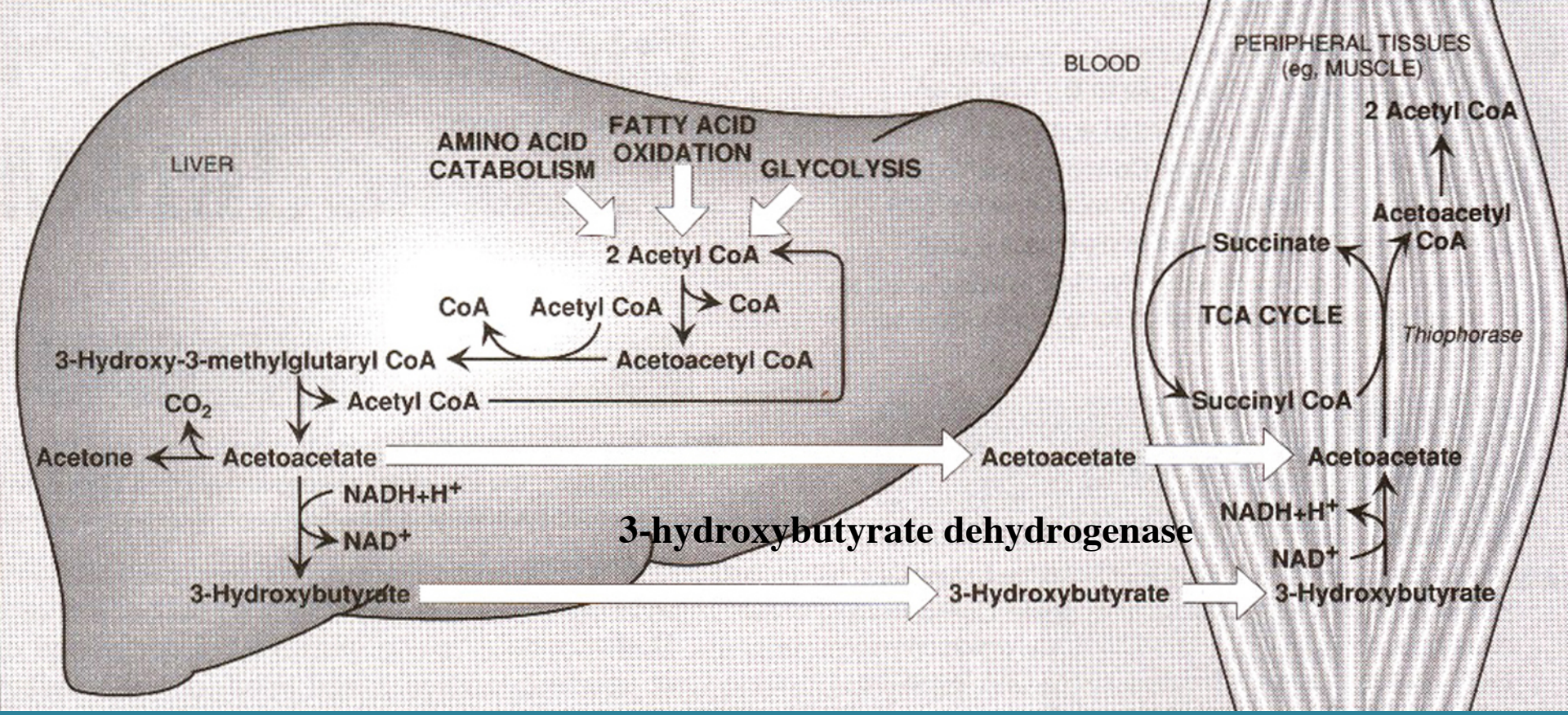
Comparison between fatty acid synthesis and degradation

	SYNTHESIS	DEGRADATION
Greatest flux through pathway	After carbohydrate-rich meal	In starvation
Hormonal state favoring pathway	High insulin/glucagon ratio	Low insulin/glucagon ratio
Major tissue site	Primarily liver	Muscle, liver
Subcellular location	Primarily cytosol	Primarily mitochondria
Carriers of acyl/acetyl groups between mitochondria and cytosol	Citrate (mitochondria to cytosol)	Carnitine (cytosol to mitochondria)
Phosphopantetheine-containing active carriers	Acyl carrier protein domain, coenzyme A	Coenzyme A
Oxidation/reduction coenzymers	NADPH (reduction)	NAD^+, FAD (oxidation)
Two-carbon donor/product	Malonyl CoA: donor of one acetyl group	Acetyl CoA: product of β-oxidation
Activator	Citrate	
Inhibitor	Long-chain fatty acyl CoA (inhibits *acetyl CoA carboxylase*)	Malonyl CoA (inhibits *carnitine palmitoyltransferase-I*)
Product of pathway	Palmitate	Acetyl CoA
Repetitive four-step process	Condensation, reduction dehydration, reduction	Dehydrogenation, hydration dehydrogenation, thiolysis



Ketone Bodies as fuel source.

Any excess of Acetyl CoA can be diverted into the formation of ketone bodies. Ketone bodies are acetoacetate, 3-hydroxybutyrate and acetone. They are transported to peripheral tissues where they can be reconverted to acetyl CoA and oxidized by the TCA cycle. They are soluble in aqueous solutions. They are produced in the liver when the oxidative capacity for acetyl CoA is exceeded. Used in skeletal muscle, renal, cardiac and brain. Acetoacetyl CoA can occur by one of two processes 1) incomplete breakdown of fatty acids or the reversal of thiolase rx of fatty oxidation. A third molecule of Acetyl CoA can combine with Acetoacetyl CoA to produce 3-hydroxy-3-methylglutaryl CoA (HMG CoA). The enzyme (HMG CoA synthase is the rate limiting step in the synthesis of ketone bodies. In the liver HMG CoA is cleaved to produce acetone and 3-hydroxybutyrate.



The liver produces ketone bodies but it can not reconvert acetoacetate to acetoacetyl CoA and therefore itself cannot use it as fuel. The liver lacks succinyl CoA-acetoacetate CoA transferase (thiophorase). The liver releases ketone bodies to the blood and to peripheral tissues where they are used as fuel when converted back to acetyl CoA. High levels of ketone bodies in the blood (ketonemia) and in the urine (ketonuria) can be found under starvation or in severe diabetis miellitus. Levels as high as 90mg/dL in the blood have been found.

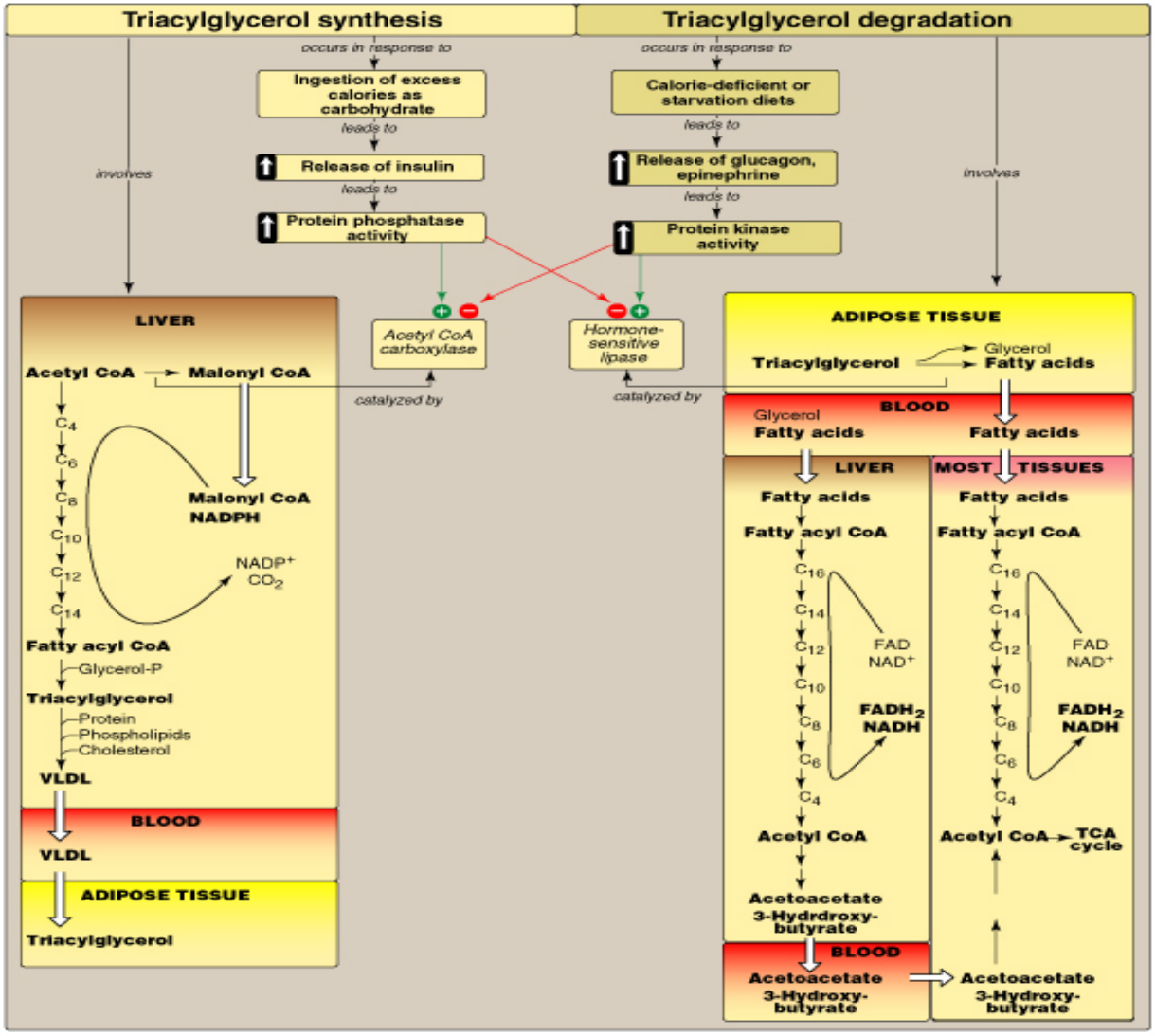


Figure 16.25
Key concept map for fatty acid and triacylglycerol metabolism.