**LIPID BIOSYNT**

**Energy Storage**

Fatty acid synthesis is regulated, both in plants and animals. Excess carbohydrate and protein in the diet are converted into fat. Only a relatively small amount of energy is stored in animals as glycogen or other carbohydrates, and the level of glycogen is closely regulated.

Protein storage doesn’t take place in animals. Except for the small amount that circulates in the cells, amino acids exist in the body only in muscle or other protein-containing tissues. If the animal or human needs specific amino acids, they must either be synthesized or obtained from the breakdown of muscle protein. Adipose tissue serves as the major storage area for fats in animals. A normal human weighing 70 kg contains about 160 kcal of usable energy. Less than 1 kcal exists as glycogen, about 24 kcal exist as amino acids in muscle, and the balance-more than 80 percent of the total-exists as fat. Plants make oils for energy storage in seeds. Because plants must synthesize all their cellular components from simple inorganic compounds, plants-but usually not animals-can use fatty acids from these oils to make carbohydrates and amino acids for later growth after germination.

**Fatty Acid Biosynthesis**

The biosynthetic reaction pathway to a compound is usually not a simple opposite of its breakdown. Chapter 12 of Volume 1 discusses this concept in regard to carbohydrate metabolism and gluconeogenesis. In fatty acid synthesis, acetyl-CoA is the direct precursor only of the methyl end of the growing fatty acid chain. All the other carbons come from the acetyl group of acetyl-CoA but only after it is modified to provide the actual substrate for fatty acid synthase, malonyl-CoA.

Malonyl-CoA contains a 3-carbon dicarboxylic acid, malonate, bound to Coenzyme A. Malonate is formed from acetyl-CoA by the addition of CO2 using the biotin cofactor of the enzyme acetyl-CoA carboxylase.

HCO3

– Acetyl-CoA + HCO3

– + ATP Malonyl-CoA + ADP + Pi

Formation of malonyl-CoA is the commitment step for fatty acid synthesis, because malonyl-CoA has no metabolic role other than serving as a precursor to fatty acids.

Fatty acid synthase (FAS) carries out the chain elongation steps of fatty acid biosynthesis. FAS is a large multienzyme complex. In mammals, FAS contains two subunits, each containing multiple enzyme activities. In bacteria and plants, individual proteins, which associate into a large complex, catalyze the individual steps of the synthesis scheme.

**Initiation**

Fatty acid synthesis starts with acetyl-CoA, and the chain grows from the “tail end” so that carbon 1 and the alpha-carbon of the complete fatty acid are added last. The first reaction is the transfer of the acetyl group to a pantothenate group of acyl carrier protein (ACP), a region of the large mammalian FAS protein. (The acyl carrier protein is a small, independent peptide in bacterial FAS, hence the name).

The pantothenate group of ACP is the same as is found on Coenzyme A, so the transfer requires no energy input: Acetyl~S-CoA + HS-ACP® HS-CoA + Acetyl~S-ACP.

In the preceding reaction, the S and SH refer to the thio group on the end of Coenzyme A or the pantothenate groups. The ~ is a reminder that the bond between the carbonyl carbon of the acetyl group and the thio group is a “high energy” bond (that is, the activated acetyl group is easily donated to an acceptor). The second reaction is another transfer, this time, from the pantothenate of the ACP to cysteine sulfhydral (–SH) group on FAS.

Acetyl~ACP + HS-FAS ® HS-ACP + Acetyl~S-FAS

Note that at this point, the FAS has two activated substrates, the acetyl group bound on the cysteine –SH and the malonyl group bound on the pantothenate –SH. Transfer of the 2-carbon acetyl unit from

Acetyl~S-cysteine to malonyl-CoA has two features:

Release of the CO2 group of malonyic acid that was originally

put on by acetyl-CoA carboxylase

Generation of a 4-carbon b-keto acid derivative, bound to the pantothenate of the ACP protein

The ketoacid is now reduced to the methylene (CH2) state in a

three-step reaction sequence.

The elongated 4-carbon chain is now ready to accept a new 2-carbon unit from malonyl-CoA. The 2-carbon unit, which is added to the growing fatty acid chain, becomes carbons 1 and 2 of hexanoic acid (6-carbons).

**Release**

The cycle of transfer, elongation, reduction, dehydration, and reduction continues until palmitoyl-ACP is made. Then the thioesterase activity of the FAS complex releases the 16-carbon fatty acid palmitate from the FAS.

Note that fatty acid synthesis provides an extreme example of the phenomenon of metabolic channeling: neither free fatty acids with more than four carbons nor their CoA derivatives can directly participate in the synthesis of palmitate. Instead they must be broken down to acetyl-CoA and reincorporated into the fatty acid.

Fatty acids are generated cytoplasmically while acetyl-CoA is made in the mitochondrion by pyruvate dehydrogenase.This implies that a shuttle system must exist to get the acetyl-CoA or its equivalent out of the mitochondrion. The shuttle system operates in the following:

way: Acetyl-CoA is first converted to citrate by citrate synthase in the TCA-cycle reaction. Then citrate is transferred out of the mitochondrion by either of two carriers, driven by the electroosmotic

gradient: either a citrate/phosphate antiport or a citrate/malate antiport as shown in Figure 2-2.

Fatty acid biosynthesis (and most biosynthetic reactions) requires NADPH to supply the reducing equivalents. Oxaloacetate is used to generate NADPH for biosynthesis in a two-step sequence.

The first step is the malate dehydrogenase reaction found in the TCA cycle. This reaction results in the formation of NAD from NADH (the NADH primarily comes from glycolysis). The malate formed is a substrate for the malic enzyme reaction, which makes pyruvate, CO2, and NADPH. Pyruvate is transported into the mitochondria where pyruvate carboxylase uses ATP energy to regenerate oxaloacetate.

Palmitate is the starting point for other fatty acids that use a set of related reactions to generate the modified chains and head groups of the lipid classes. Microsomal enzymes primarily catalyze these chain modifications. Desaturation uses O2 as the ultimate electron acceptor to introduce double bonds at the nine, six, and five positions of an acyl-CoA.

Elongation is similar to synthesis of palmitate because it uses malonyl-CoA as an intermediate. See Figure 2-3.

**Synthesis of Triacylglycerols**

Glycerol accepts fatty acids from acyl-CoAs to synthesize glycerol lipids. Glycerol phosphate comes from glycolysis-specifically from the reduction of dihydroxyacetone phosphate using NADH as a cofactor. Then the glycerol phosphate accepts two fatty acids from fatty acyl-CoA. The fatty acyl-CoA is formed by the expenditure of two high-energy phosphate bonds from ATP.

**Cholesterol Biosynthesis and its Control**

Despite a lot of bad press, cholesterol remains an essential and important biomolecule in animals. As much as half of the membrane lipid in a cellular membrane is cholesterol, where it helps maintain constant fluidity and electrical properties. Cholesterol is especially prominent in membranes of the nervous system.

Cholesterol also serves as a precursor to other important molecules. Bile acids aid in lipid absorption during digestion. Steroid hormones all derive from cholesterol, including the adrenal hormones that maintain fluid balance; Vitamin D, which is an important regulator of calcium status; and the male and female sex hormones.

Although humans wouldn’t survive in one sense or another without cholesterol metabolites, cholesterol brings with it some well-known side effects. Doctors find cholesterol derivatives, being essentially insoluble in water, in the deposits (plaque) that characterize diseased arteries.

HMG CoA Reductase

HMG-CoA reductase is the committed and therefore the regulatory step in cholesterol biosynthesis. If HMG-CoA is reduced to mevalonate, cholesterol is the only product that can result. The reduction is a two-step reaction, which releases the Coenzyme A cofactor and converts the thiol-bound carboxylic group of HMG-CoA to a free alcohol. Two NADPH molecules supply the reducing equivalents because the thioester must first be reduced to the level of an aldehyde and then to an alcohol.

**Mevalonate Squalene**

Mevalonate molecules are condensed to a 30-carbon compound, squalene. The alcohol groups of mevalonate are first phosphorylated. Then they multiply phosphorylated mevalonate decarboxylates to make the two compounds isopentenyl pyrophosphate (IPP) and dimethylallyl pyrophosphate (DMAPP).

*mevalonate ® phosphomevalonate ® pyrophosphomevalonate*

First, the other hydroxyl group of mevalonate accepts a phosphate from ATP. The resulting compound rearranges in an enzyme-catalyzed reaction, eliminating both CO2 and phosphate. The 5-carbon compound that results, IPP, is rapidly isomerized with DMAPP.

In plants and fungi, IPP and DMAPP are the precursors to many so-called isoprenoid compounds, including natural rubber. In animals, they are mainly precursors to sterols, such as cholesterol. The first step is condensation of one of each to geranyl pyrophosphate, which then condenses with another molecule of IPP to make farnesyl pyrophosphate. Some important membrane-bound proteins have a farnesyl group added on to them; however, the primary fate of farnesyl pyrophosphate is to accept a pair of electrons from NADPH and condense with another molecule of itself to release both pyrophosphate groups.

The resulting 30-carbon compound is squalene; it folds into a structure that closely resembles the structure of the steroid rings, although the rings are not closed yet.

*Squalene ® Lanosterol*

The first recognizable steroid ring system is lanosterol; it is formed first by the epoxidation of the double bond of squalene that was originally derived from a DMAPP through farnesyl pyrophosphate, and then by the cyclization of squalene epoxide. The enzyme that forms the epoxide uses NADPH to reduce molecular oxygen to make the epoxide.

*Lanosterol ® Cholesterol*

This sequence of reactions is incompletely understood but involves numerous oxidations of carbon groups, for example, the conversion of methyl groups to carboxylic acids, followed bydecarboxylation. The end product, cholesterol, is the precursor to cholesterol esters in the liver and is transported to the peripheral tissues where it is a precursor to membranes (all cells), bile salts (liver), steroid hormones (adrenals and reproductive tissues), and vitamin D (skin, then liver, and finally kidney).

Cholesterol Transport, Uptake, and ControlCholesterol is expor ted to the peripheral tissues in LDL and VLDL (see Chapter 1). About 70 percent of the cholesterol molecules in LDL are esterified with a fatty acid (for example, palmitate) on the OH group (at Carbon 3; see Figure 2-5). Cells take up cholesterol from the LDL by means of LDL receptors in the outer cell membrane.