# Biosynthesis of Fatty Acids

By

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# Fatty Acids Definition

Fatty acids are comprised of hydrocarbon chains terminating with carboxylic acid groups. Fatty acids and their associated derivatives are the primary components of lipids. The length and degree of saturation of the hydrocarbon chain is highly variable between each fatty acid, and dictates the associated physical properties (e.g., melting point and fluidity). Moreover, fatty acids are responsible for the hydrophobic properties (insoluble in water) exhibited by lipids.

# What are essential fatty acids?

are fatty acids which cannot be synthesized *de novo* by human body , but by plants and microorganisms, such as bacteria, fungi and whose deficiency can be reversed by dietary addition.

There are two essential fatty acids: linoleic acid or LA and α-linolenic acid or ALA , polyunsaturated fatty acids (PUFAs) with 18 carbon atoms, belonging to omega-6 and omega-3 families, respectively.

# Function of Fatty Acids

1) signal-transduction pathways .

2) cellular fuel sources .

3) the modification of proteins .

4) energy storage within adipose tissue (specialized fat cells) in the form of triacylglycerols.

# THE MAIN PATHWAY FOR DE NOVO SYNTHESIS OF FATTY ACIDS (LIPOGENESIS) OCCURS IN THE CYTOSOL

This system is present in many tissues, including liver, kidney, brain, lung, mammary gland, and adipose tissue.

Its cofactor requirements include NADPH, ATP, $Mn^{2+}$, biotin, and $HCO_3^-$ (as a source of $CO_2$).

Acetyl-CoA is the immediate substrate, and free palmitate is the end product.

# Production of Malonyl-CoA Is the Initial & Controlling Step in Fatty Acid Synthesis

CHAPTER 21

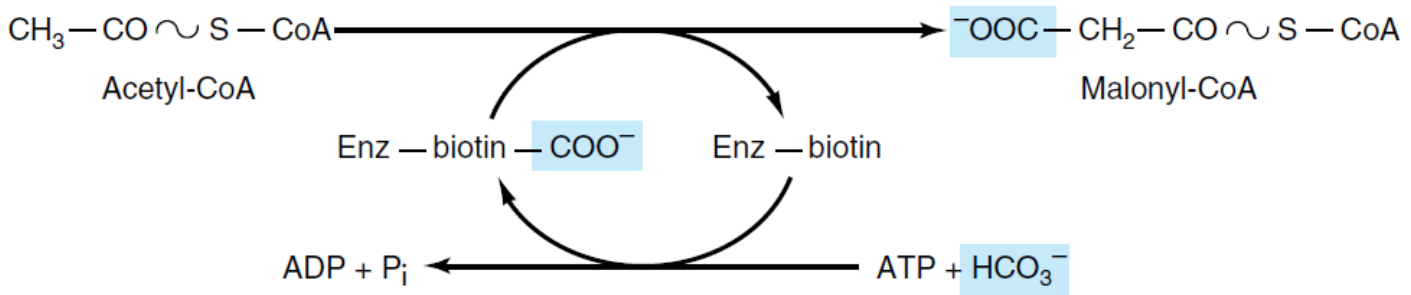


***Figure 21–1.*** Biosynthesis of malonyl-CoA. (Enz, acetyl-CoA carboxylase.)

athway. Its usual fate is esterification into
s, chain elongation or desaturation, or ester-
cholesteryl ester. In mammary gland, there
thioesterase specific for acyl residues of $C_8$,
which are subsequently found in milk

$$CH_2CO \cdot S \cdot CoA + 7HOOC \cdot CH_2CO \cdot S \cdot CoA + 14$$
$$\rightarrow CH_3(CH_2)_{14}COOH + 7CO_2 + 6H_2O + 8CoA$$

The acetyl CoA used as a primer

# The Fatty Acid Synthase Complex Is a Polypeptide Containing Seven Enzyme Activities

Is a dimer comprising two identical monomers, each containing all seven enzyme activities of fatty acid synthase (Figure 21–2).

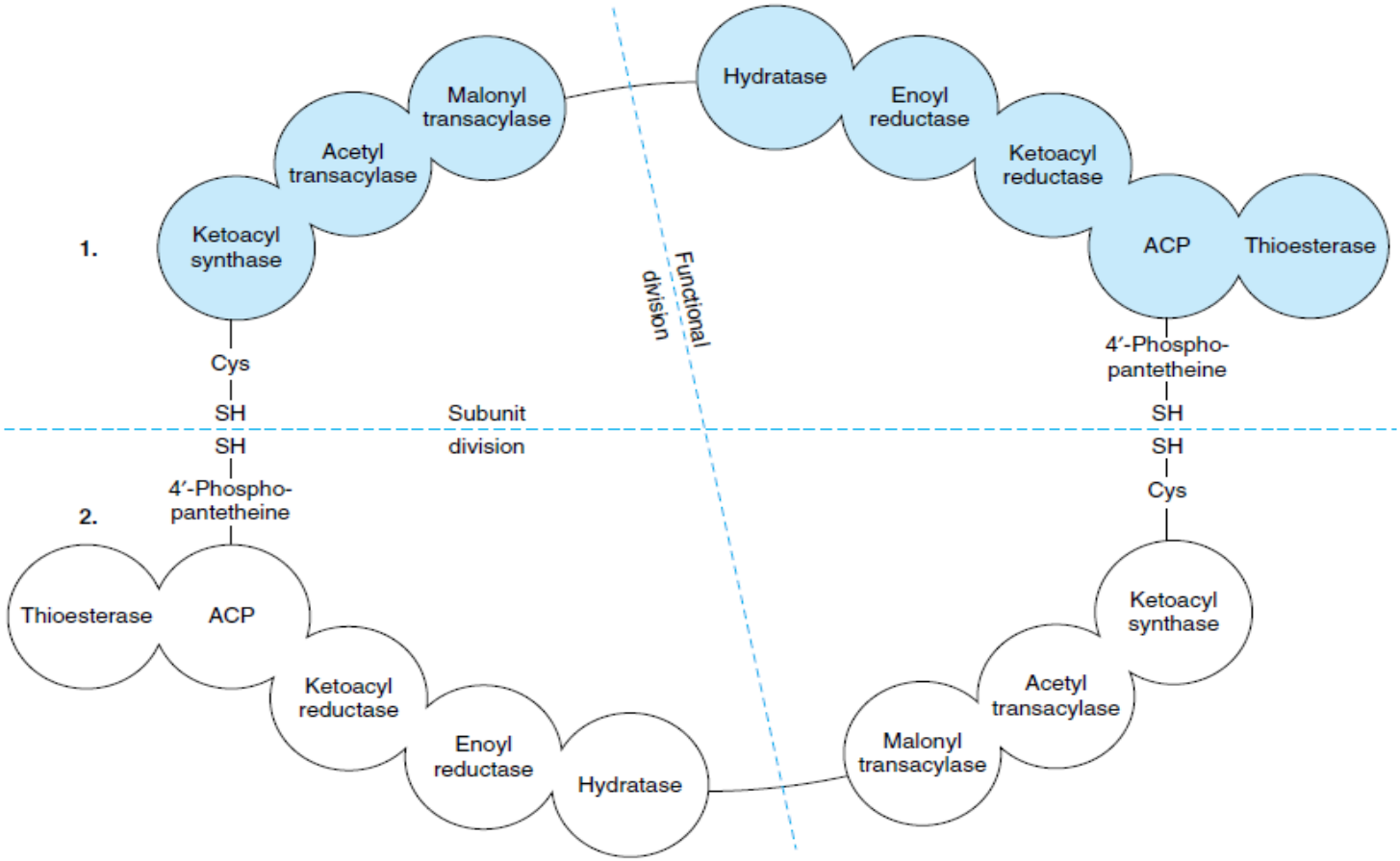


***Figure 21–2.*** Fatty acid synthase multienzyme complex. The complex is a dimer of two identical polypeptide monomers, 1 and 2, each consisting of seven enzyme activities and the acyl carrier protein (ACP). (Cys—SH, cysteine thiol.) The —SH of the 4′-phosphopantetheine of one monomer is in close proximity to the —SH of the cysteine residue of the ketoacyl synthase of the other monomer, suggesting a "head-to-tail" arrangement of the two monomers. Though each monomer contains all the partial activities of the reaction sequence, the actual func-

# Biosynthesis of long-chain fatty acids

Step1 : Initially, a priming molecule of acetyl-CoA combines with a cysteine □SH group catalyzed by **acetyl transacylase** (Figure 21–3, reaction 1a). Malonyl-CoA combines with the adjacent □SH on the 4’-phosphopantetheine of ACP of the other monomer, catalyzed by **malonyl transacylase (reaction 1b), to form acetyl (acyl)-malonyl enzyme.**

# Biosynthesis of long-chain fatty acids

Step 2: The acetyl group attacks the methylene group of the malonyl residue, catalyzed by **3-ketoacyl synthase, and liberates CO2, forming 3-ketoacyl enzyme** (acetoacetyl enzyme) (reaction 2), freeing the cysteine □SH group.

# Biosynthesis of long-chain fatty acids

The 3-ketoacyl group is reduced, dehydrated, and reduced again (steps 3, 4, 5) to form the corresponding saturated acyl-S enzyme.

# Biosynthesis of long-chain fatty acids

A new malonyl-CoA molecule combines with the □SH of 4’-phosphopantetheine, displacing the saturated acyl residue onto the free cysteine □SH group.

The sequence of reactions is repeated six more times until a saturated 16-carbon acyl radical (palmityl) has been assembled. It is liberated from the enzyme complex by the activity of a seventh enzyme in the complex, **thioesterase (deacylase).**

# The equation for the overall synthesis of palmitate from acetyl-CoA and malonyl-CoA is:

:oA. (Enz, acetyl-CoA carboxylase.)

$$CH_2CO \cdot S \cdot CoA + 7HOOC \cdot CH_2CO \cdot S \cdot CoA + 14NADPH + 14H^+$$

$$\rightarrow CH_3(CH_2)_{14}COOH + 7CO_2 + 6H_2O + 8CoA \cdot SH + 14NADP^+$$

The acetyl-CoA used as a primer forms carbon atoms 15 and 16 of palmitate. The addition of all the subsequent $C_2$ units is via malonyl-CoA. Propionyl-CoA acts as primer for the synthesis of long-chain fatty

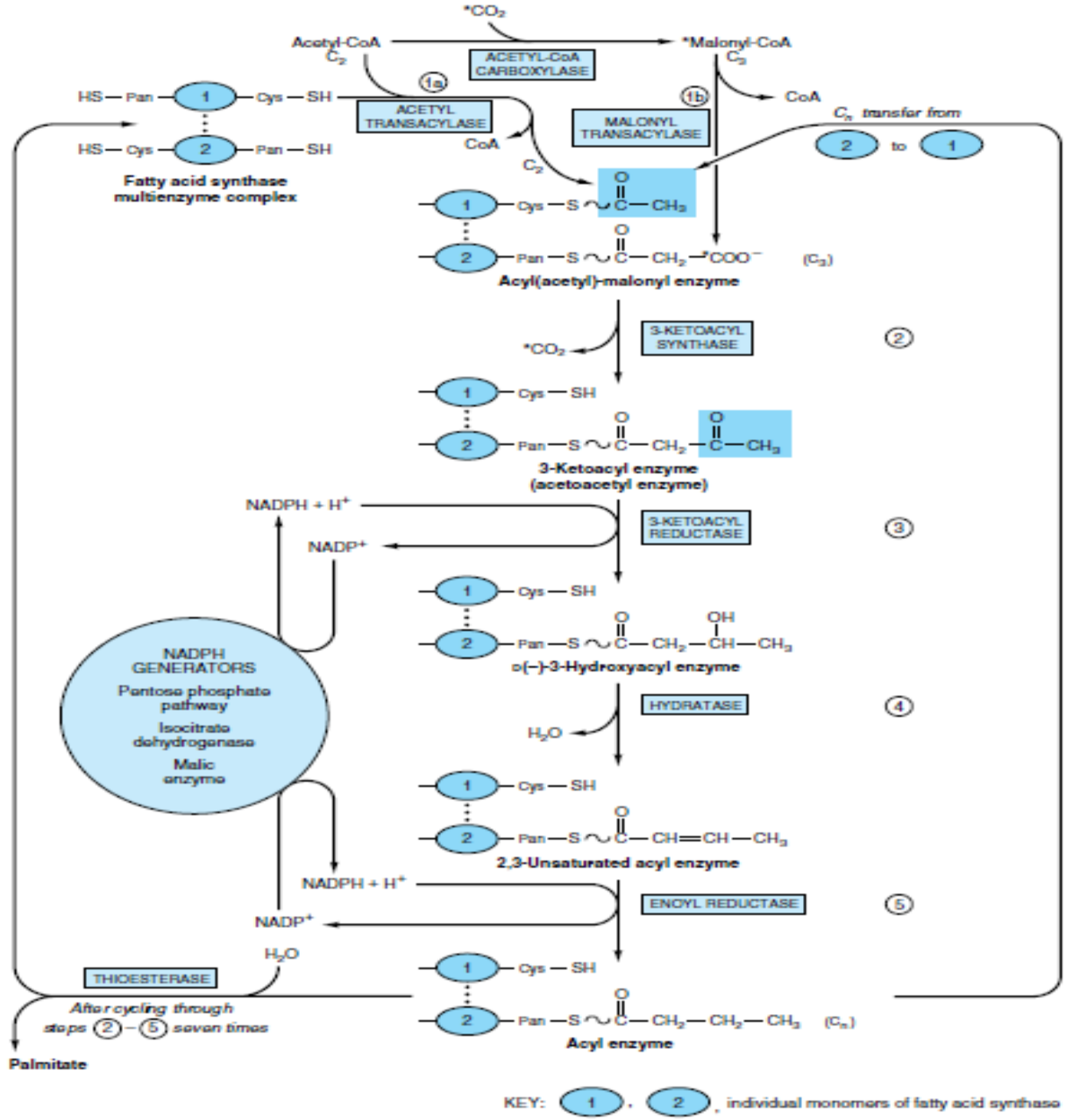


***Figure 21–3.*** Biosynthesis of long-chain fatty acids. Details of how addition of a malonyl residue causes the acyl chain to grow by two carbon atoms. (Cys, cysteine residue; Pan, 4′-phosphopanto

# The Main Source of NADPH for Lipogenesis Is the Pentose Phosphate Pathway

The oxidative reactions of the pentose phosphate pathway (PPP) are the chief source of the hydrogen required for the reductive synthesis of fatty acids. Significantly, tissues specializing in active lipogenesis—ie, liver, adipose tissue, and the lactating mammary gland—also possess an pentose phosphate pathway. active

Other sources of NADPH include the reaction that converts malate to pyruvate catalyzed by the **“malic enzyme” (NADP malate dehydrogenase) (Figure** 21–4) and the extramitochondrial **isocitrate dehydrogenase** reaction .

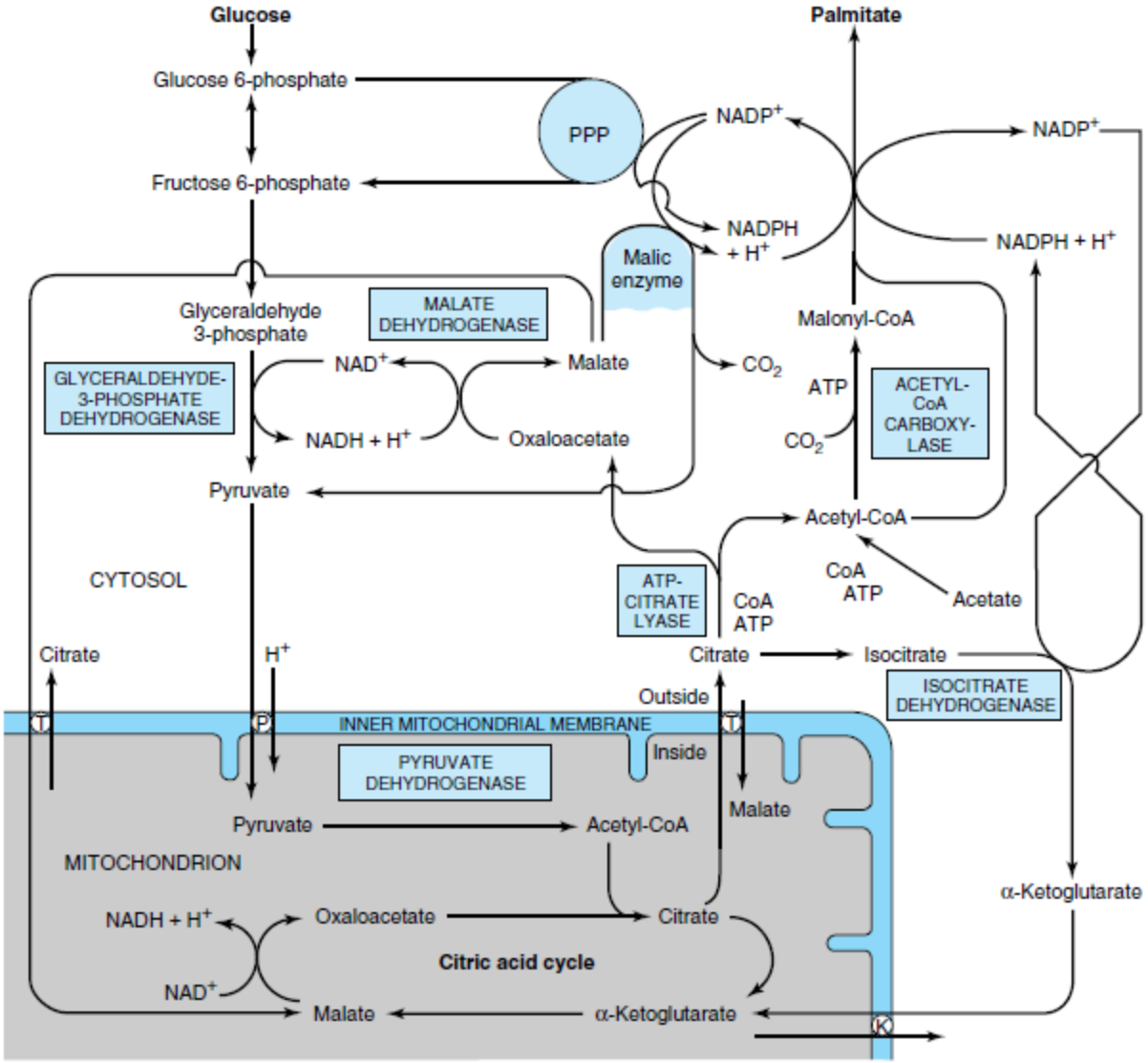


***Figure 21–4.*** The provision of acetyl-CoA and NADPH for lipogenesis. (PPP, pentose phosphate pathway; T, tricarboxylate transporter; K, α-ketoglutarate transporter; P, pyruvate transporter.)

# Acetyl-CoA Is the Principal Building Block of Fatty Acids

Acetyl-CoA is formed from glucose via the oxidation of pyruvate within the mitochondria. However, it does not diffuse readily into the extramitochondrial cytosol, the principal site of fatty acid synthesis.

Citrate, formed after condensation of acetyl-CoA with oxaloacetate in the citric acid cycle within mitochondria, is translocated into the extramitochondrial compartment via the tricarboxylate transporter, where in the presence of CoA and ATP it undergoes cleavage to acetyl-CoA and oxaloacetate catalyzed by **ATP-citrate lyase, which increases** in activity in the well-fed state.

The acetyl-CoA is then available for malonyl-CoA formation and synthesis to palmitate

# Elongation of Fatty Acid Chains Occurs in the Endoplasmic Reticulum

This pathway (the “microsomal system”) elongates saturated and unsaturated fatty acyl-CoAs (from C10 upward) by two carbons, using malonyl-CoA as acetyl donor and NADPH as reductant, and is catalyzed by the microsomal **fatty acid elongase system of enzymes** (Figure 21–5).

Elongation of stearyl-CoA in brain increases rapidly during myelination in order to provide C22 and C24 fatty acids for sphingolipids

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## THE NUTRITIONAL STATE REGULATES LIPOGENESIS

Excess carbohydrate is stored as fat in many animals in anticipation of periods of caloric deficiency such as starvation, hibernation, etc, and to provide energy for use between meals in animals, including humans, that take their food at spaced intervals. Lipogenesis converts surplus glucose and intermediates such as pyruvate, lactate, and acetyl-CoA to fat, assisting the anabolic phase of this feeding cycle. The nutritional state of the organism is the main factor regulating the rate of lipogenesis. Thus, the rate is high in the well-fed animal whose diet contains a high proportion of carbohydrate. It is depressed under conditions of restricted caloric intake, on

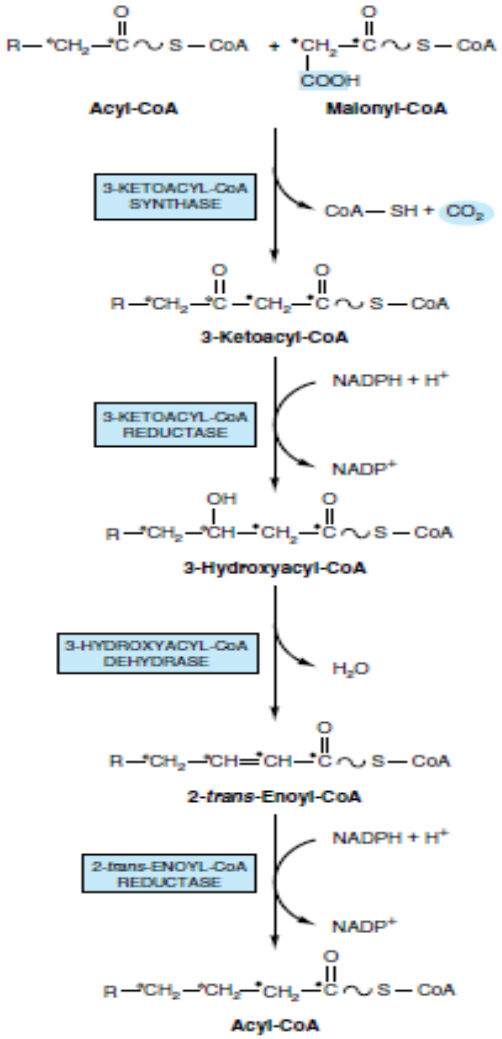


***Figure 21–5.*** Microsomal elongase system for fatty acid chain elongation. NADH is also used by the reductases, but NADPH is preferred.

a fat diet, or when there is a deficiency of insulin, as in diabetes mellitus. These latter conditions are associated with increased concentrations of plasma free fatty acids, and an inverse relationship has been demonstrated between hepatic lipogenesis and the concentration of serum-free fatty acids. Lipogenesis is increased when su-

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# Acetyl-CoA Carboxylase Is the Most Important Enzyme in the Regulation of Lipogenesis

Acetyl-CoA carboxylase is an allosteric enzyme and is activated by **citrate,** which increases in concentration in the well-fed state and is an indicator of a plentiful supply of acetyl-CoA.

Inactivation is promoted

by phosphorylation of the enzyme and by long chain acyl-CoA molecules, an example of negative feedback inhibition by a product of a reaction.

Thus, if acyl-CoA accumulates because it is not esterified quickly enough or because of increased lipolysis or an influx of free fatty acids into the tissue, it will automatically reduce the synthesis of new fatty acid.

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Acyl-CoA may also inhibit the mitochondrial **tricarboxylate transporter, thus preventing activation of the enzyme** by egress of **citrate** from the mitochondria into the cytosol.

Acetyl-CoA carboxylase is also regulated by hormones such as **glucagon, epinephrine, and insulin via** changes in its phosphorylation state (details in Figure ٢١–٦).

crose is fed instead of glucose because fructose bypasses the phosphofructokinase control point in glycolysis and floods the lipogenic pathway (Figure 20–5).

## SHORT- & LONG-TERM MECHANISMS REGULATE LIPOGENESIS

Long-chain fatty acid synthesis is controlled in the short term by allosteric and covalent modification of enzymes and in the long term by changes in gene expression governing rates of synthesis of enzymes.

### Acetyl-CoA Carboxylase Is the Most Important Enzyme in the Regulation of Lipogenesis

Acetyl-CoA carboxylase is an allosteric enzyme and is activated by **citrate,** which increases in concentration in the well-fed state and is an indicator of a plentiful supply of acetyl-CoA. Citrate converts the enzyme from an inactive dimer to an active polymeric form, having a molecular mass of several million. Inactivation is promoted by phosphorylation of the enzyme and by long-chain acyl-CoA molecules, an example of negative feedback inhibition by a product of a reaction. Thus, if acyl-CoA accumulates because it is not esterified quickly enough or because of increased lipolysis or an influx of free fatty acids into the tissue, it will automatically reduce the synthesis of new fatty acid. Acyl-CoA may also inhibit the mitochondrial **tricarboxylate transporter,** thus preventing activation of the enzyme by egress of citrate from the mitochondria into the cytosol.

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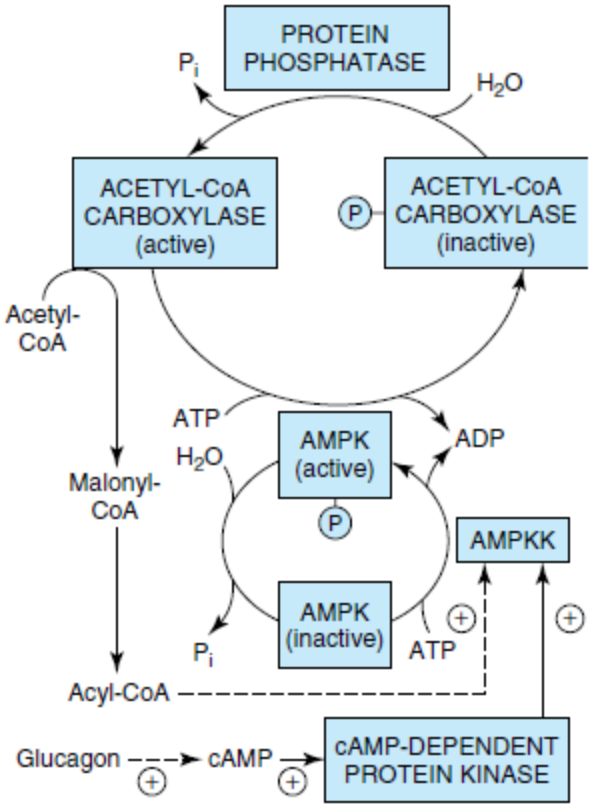


***Figure 21–6.*** Regulation of acetyl-CoA carboxylase by phosphorylation/dephosphorylation. The enzyme is inactivated by phosphorylation by AMP-activated protein kinase (AMPK), which in turn is phosphorylated and activated by AMP-activated protein kinase kinase (AMPKK). Glucagon (and epinephrine), after increasing cAMP, activate this latter enzyme via cAMP-dependent protein kinase. The kinase kinase enzyme is also believed to be activated by acyl-CoA. Insulin activates acetyl-CoA carboxylase, probably through an "activator" protein and an insulin-stimulated protein kinase.

# Pyruvate Dehydrogenase Is Also Regulated by Acyl-CoA

Acyl-CoA causes an inhibition of pyruvate dehydrogenase by inhibiting the ATP-ADP exchange transporter of the inner mitochondrial membrane, which leads to increased intramitochondrial [ATP]/[ADP] ratios and therefore to conversion of active to inactive pyruvate dehydrogenase , thus regulating the availability of acetyl-CoA for lipogenesis.

Furthermore, oxidation of acyl-CoA due to increased levels of free fatty acids may increase the ratios of [acetyl-CoA]/[CoA] and [NADH]/[NAD+] in mitochondria, inhibiting pyruvate dehydrogenase.

# Insulin Also Regulates Lipogenesis by Other Mechanisms

Insulin stimulates lipogenesis by several other mechanisms as well as by increasing acetyl-CoA carboxylase activity.

It increases the transport of glucose into the cell (eg, in adipose tissue), increasing the availability of both pyruvate for fatty acid synthesis and glycerol 3-phosphate for esterification of the newly formed fatty acids, and also converts the inactive form of pyruvate dehydrogenase to the active form in adipose tissue but not in liver.

# Insulin Also Regulates Lipogenesis by Other Mechanisms

Insulin also—by its ability to depress the level of intracellular cAMP—**inhibits lipolysis in adipose** tissue and thereby reduces the concentration of plasma free fatty acids and therefore long-chain acyl-CoA, an inhibitor of lipogenesis.