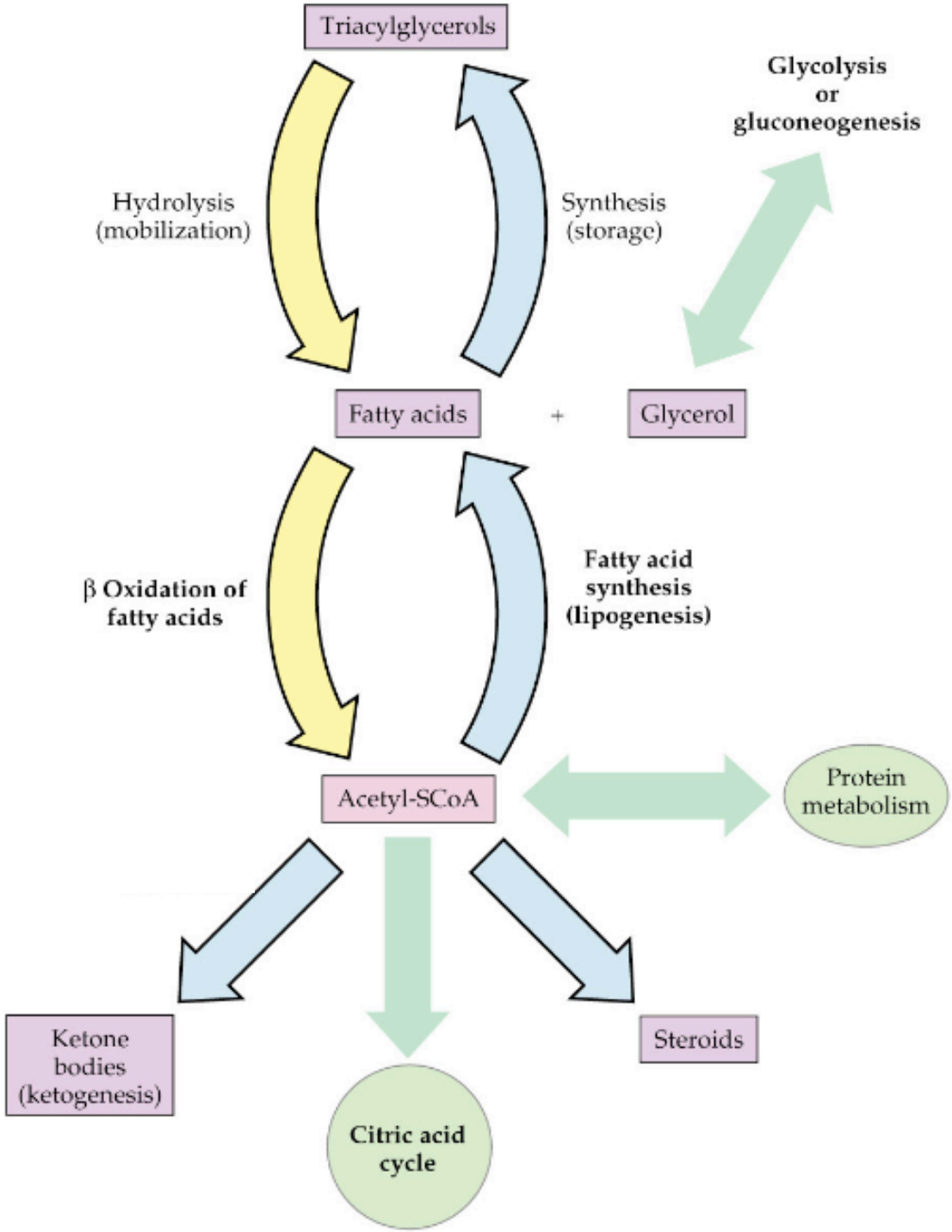

Triacylglycerols
Glycolysis
or
gluconeogenesis
Hydrolysis
(mobilization)
Synthesis
(storage)
Fatty acids
+
Glycerol
β Oxidation of
fatty acids
Fatty acid
synthesis
(lipogenesis)
Acetyl-SCoA
Protein
metabolism
Ketone
bodies
(ketogenesis)
Citric acid
cycle
Steroids

Biosynthesis of Fatty Acids

Fatty acid biosynthesis takes place in the cytosol rather than the mitochondria and requires a different activation mechanism and different enzymes and coenzymes than fatty acid degradation in the mitochondria.

Fatty acid biosynthesis takes place when there is an abundance of ATP, NADPH, and acetyl-*S*-CoA.

Acetyl-*S*-CoA is made in large amounts in the mitochondria from carbohydrates after a high carbohydrate meal.

Acetyl-*S*-CoA in the mitochondria is exported to the cytosol by the following mechanism:

Oxaloacetate + acetyl-*S*-CoA → Citrate

Citrate (mitochondria) → Citrate (cytosol)

Citrate + ATP + CoA-SH → acetyl-*S*-CoA + oxaloacetate + ADP + P_i

Oxaloacetate + NADH → L-malate + NAD^+

L-malate + $NADP^+$ → Pyruvate + CO_2 + NADPH

Pyruvate (cytosol) → Pyruvate (mitochondria)

Pyruvate + CO_2 + ATP → Oxaloacetate + ADP + P_i

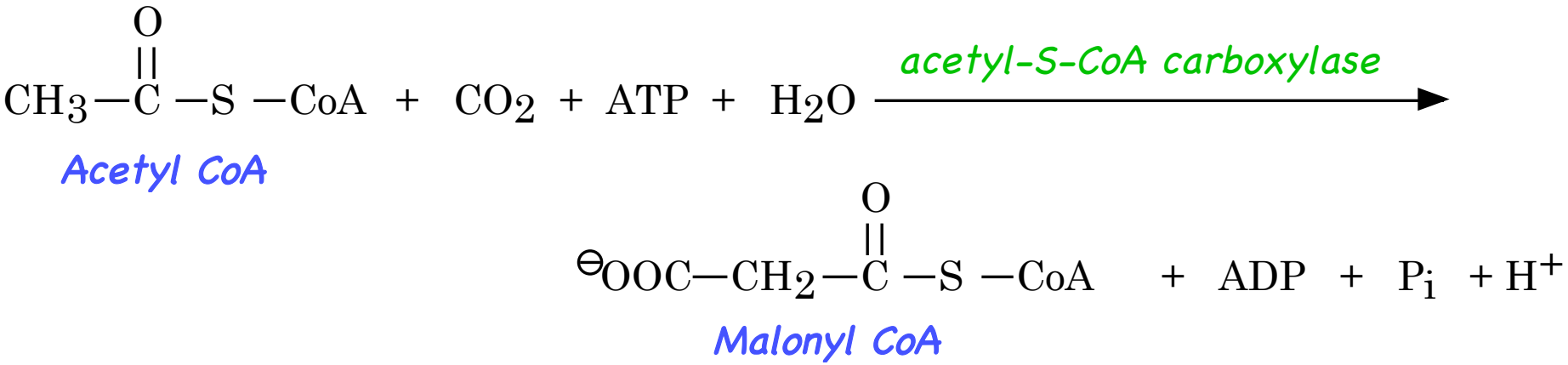
The overall reaction is:

Acetyl-*S*-CoA (mitochondria) + **2 ATP** + **NADH + $NADP^+$**

Acetyl-*S*-CoA (cytosol) + **2 ADP + 2 P_i** + **NAD^+ + NADPH**

Acetyl-S-CoA Carboxylase

The rate-limiting step in fatty acid biosynthesis is the synthesis of malonyl-*S*-CoA .

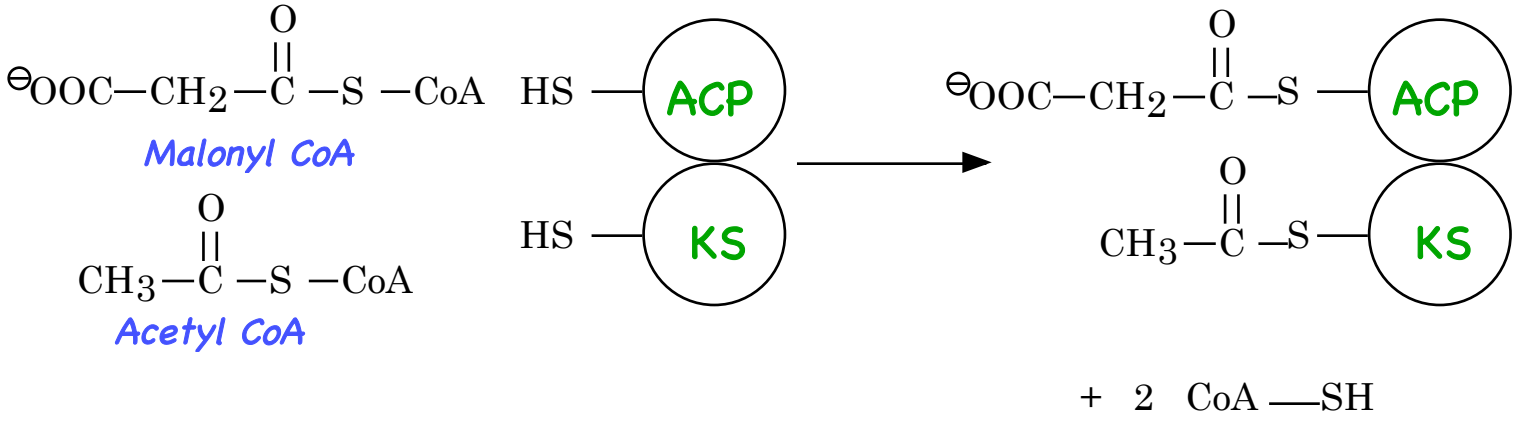


Note: *Acetyl-S-CoA carboxylase* is activated by citrate, the carrier molecule for acetyl-*S*-CoA across the mitochondrial membrane. **Biotin** is a necessary cofactor in this reaction.

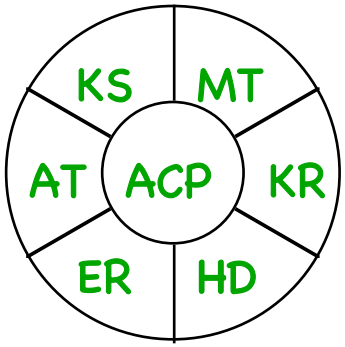
Fatty Acid Synthesis in Two Carbon Pieces

In animal cells, different catalytic domains of a single multifunctional polypeptide chain utilize one molecule of acetyl-*S*-CoA, seven molecules of malonyl-*S*-CoA, and 14 molecules of NADPH to synthesize a C-16 saturated fatty acid

The synthesis is initiated by a molecule of acetyl-*S*-CoA reacting with a thiol group on the **condensing enzyme** (**CE**) (*β-ketoacyl ACP synthase*) and a malonyl-*S*-CoA reacting with a protein carrier called **acyl carrier protein** (**ACP**)



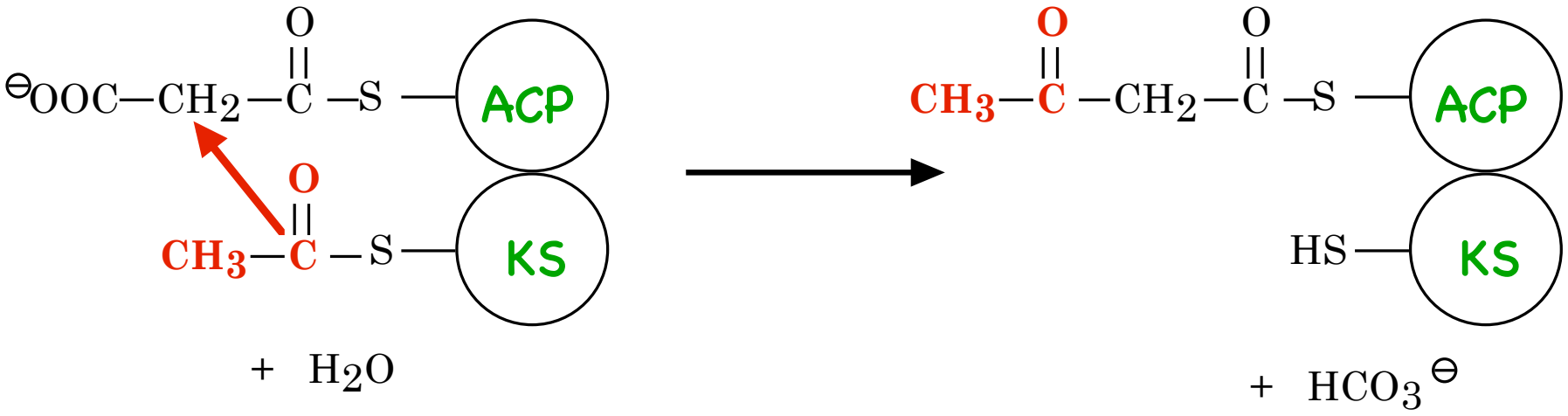
ACP and KS are parts of a multienzyme complex which includes:



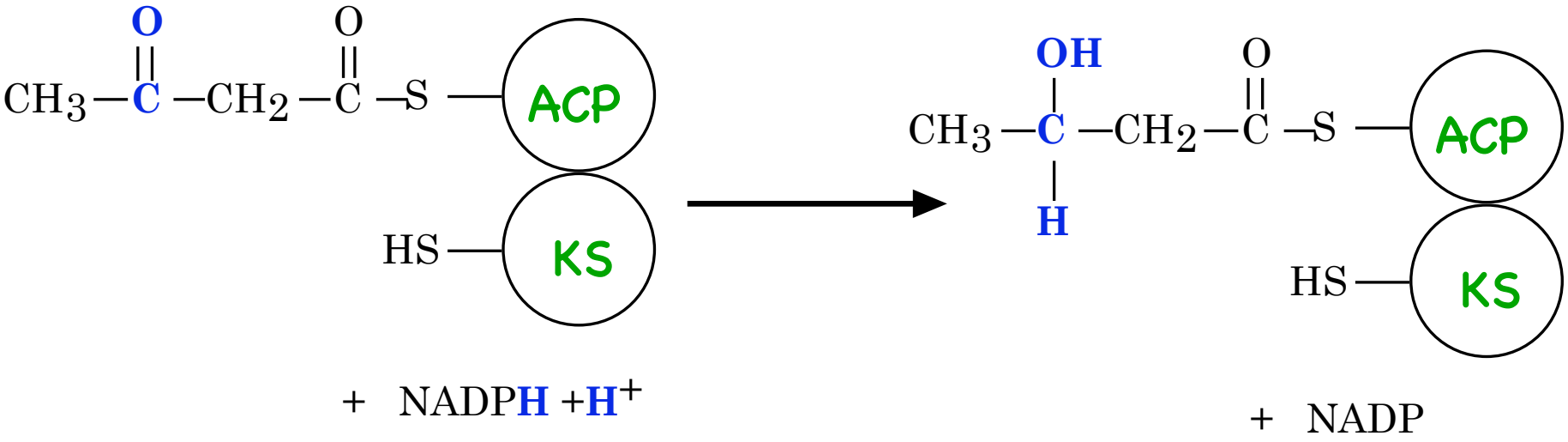
Acyl carrier protein
β-Ketoacyl ACP synthase
Acetyl-CoA-ACP transacetylase
Enoyl-ACP reductase
β-Hydroxyacyl-ACP dehydratase
β-Ketoacyl ACP reductase
Malonyl-CoA ACP transferase

Subsequent reactions at different sites within the complex lead to the extension of the growing fatty acid chain by two carbon atoms:

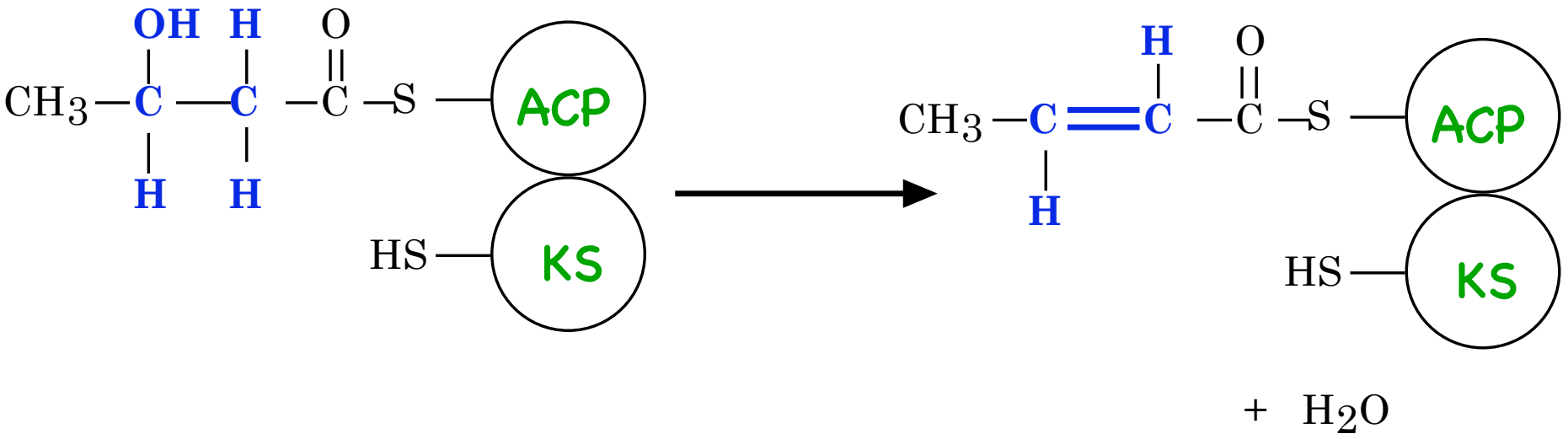
Chain Elongation



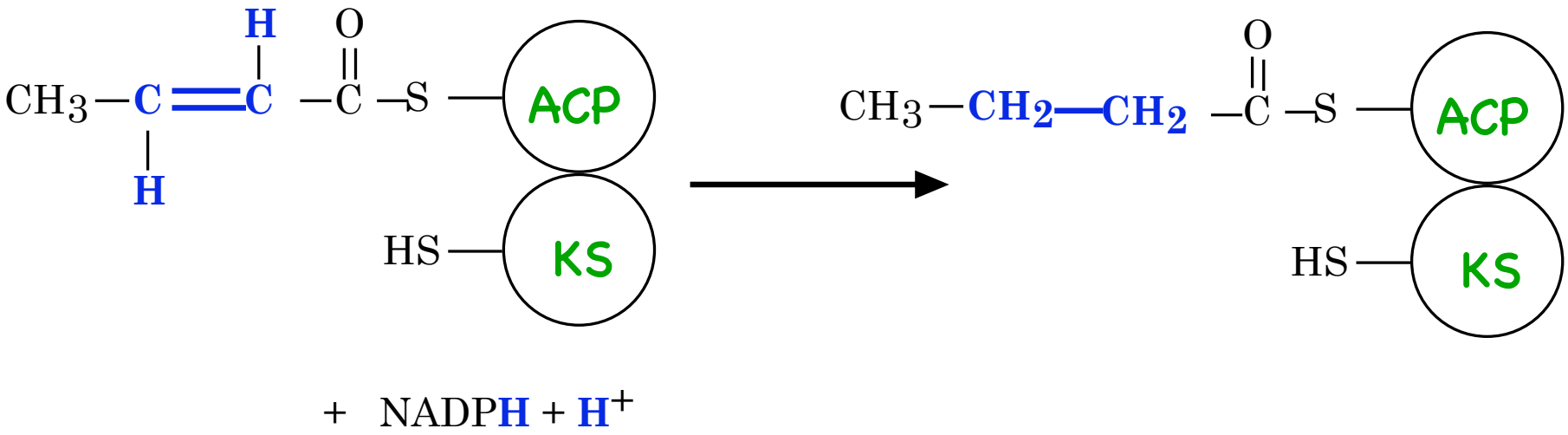
Reduction



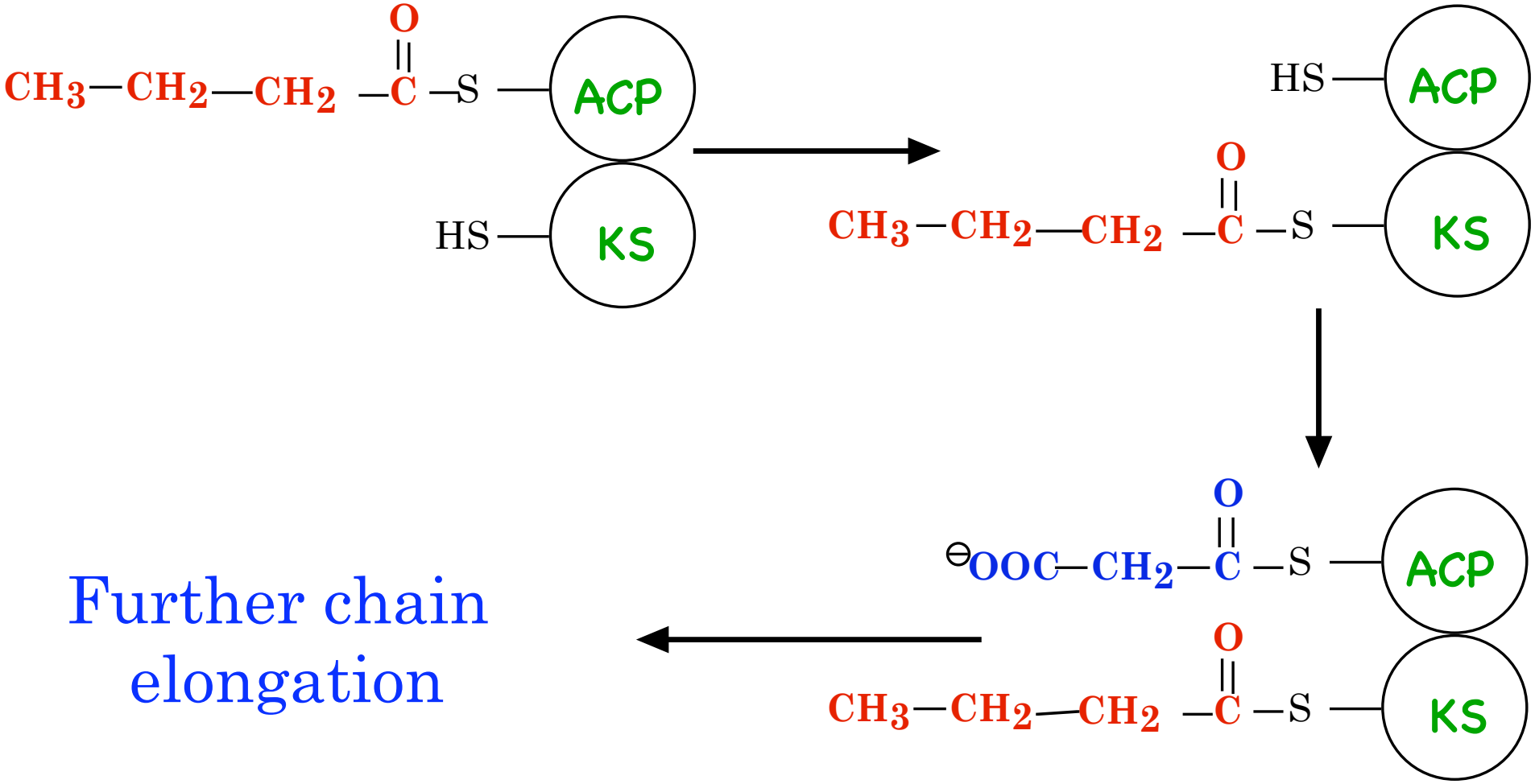
Dehydration



Reduction



At this point, the four-carbon fatty acid is transferred to the condensing enzyme, and another molecule of malonyl-*S*-CoA is loaded into the ACP site.



The synthetic process now repeats, forming a C6 saturated fatty acid. When the fatty acid reaches a specific length, a *thioesterase* releases a free fatty acid molecule.

The overall stoichiometry for a C-16 fatty acid is:

$$8\ \text{Acetyl-S-CoA} + 7\ \text{ATP}^{4-} + 14\ \text{NADPH} + 7\ \text{H}^{+}$$

$$\rightarrow \text{palmitoyl-S-CoA} + 14\ \text{NADP}^{+} + 7\ \text{CoA-SH} + 7\ \text{ADP}^{3-} + 7\ \text{P}_i^{2-}$$

Hormonal Regulation of Fatty Acid Biosynthesis

1) **Glucagon** initiates a sequence of reactions that phosphorylate and inactivate *acetyl-S-CoA carboxylase* and shuts down fatty acid biosynthesis.

2) **Insulin** activates the phosphodiesterase that hydrolyzes cyclic AMP to noncyclic AMP, ending the glucagon initiated cascade, and allowing fatty acids to be synthesized and stored.

Biosynthesis of Triacyglycerols

The precursors of triacylglycerols are fatty acyl-*S*-CoA and glycerol-3-phosphate. The steps in the synthesis are:

2 Fatty acyl-*S*-CoA + glycerol-3-PO_4 → diacylglycerol-3-PO_4 + 2 CoA-SH

Diacylglycerol-3-PO_4 + H_2O → Diacylglycerol + P_i

Diacylglycerol + Fatty acyl-*S*-CoA → Triacylglycerol

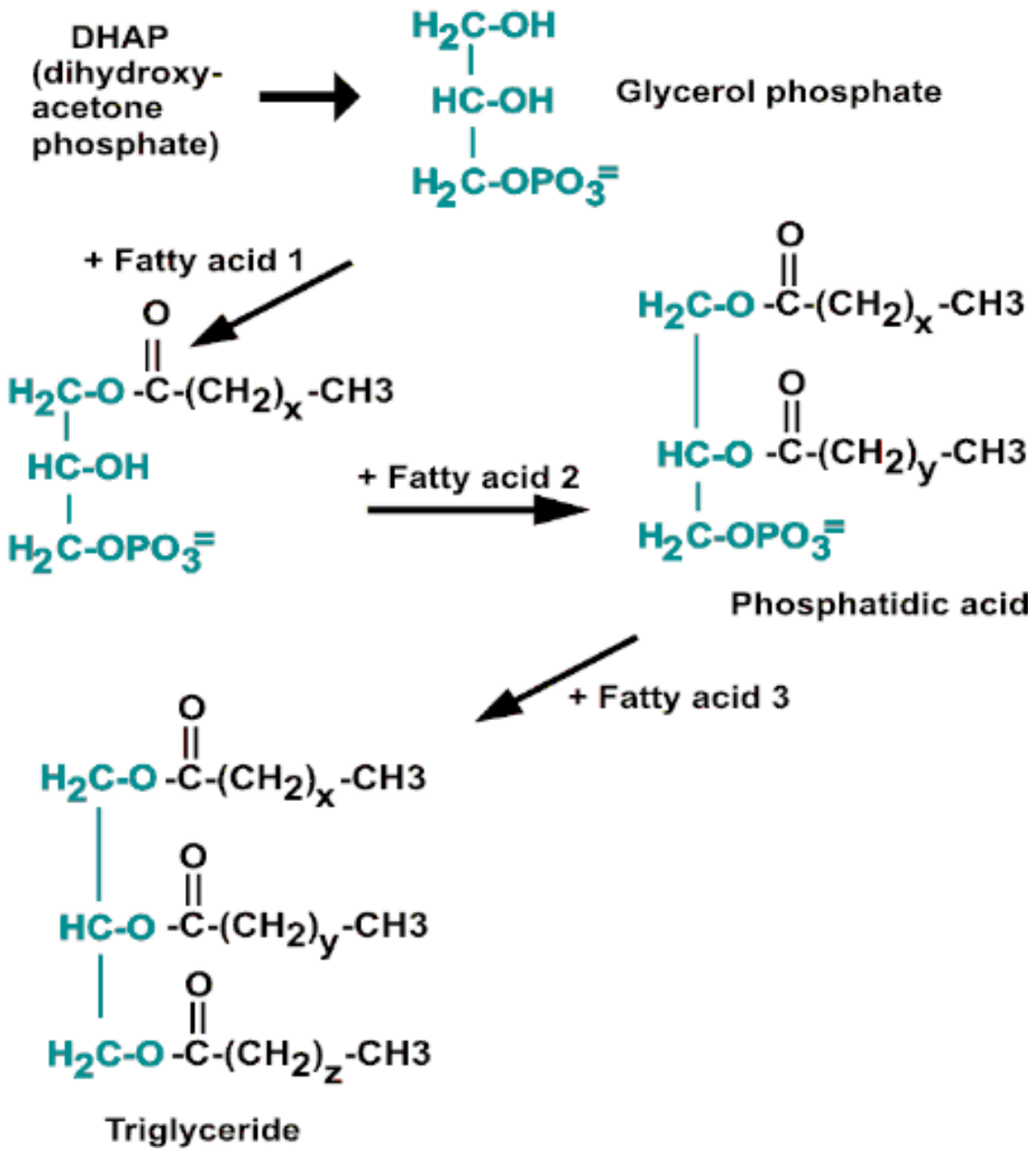
The intermediate, diacylglycerol-3-PO_4, is called phosphatidic acid or phosphatidate, and is a key intermediate in membrane-lipid biosynthesis.

Seven moles of ATP are required for the biosynthesis of a triacylglycerol from glycerol and three fatty acids:

1 ATP to form glycerol-3-PO_4 from glycerol

6 ATP to form 3 fatty acyl-*S*-CoA from 3 fatty acids and 3 CoA-SH.

Triglyceride (fat) biosynthesis



Biosynthesis of Membrane Lipids

The biosynthesis of membrane lipids begins with diacylglycerol.

The lipid is completed by the addition of the remainder of the polar head group to the existing phosphate group.

Phosphatidyl ethanolamine synthesis requires three steps:

Ethanolamine + ATP → Phosphoethanolamine + ADP

Phosphoethanolamine + CTP → CDP-ethanolamine + PPi

Diacylglycerol + CDP-ethanolamine →
Phosphatidylethanolamine + CMP

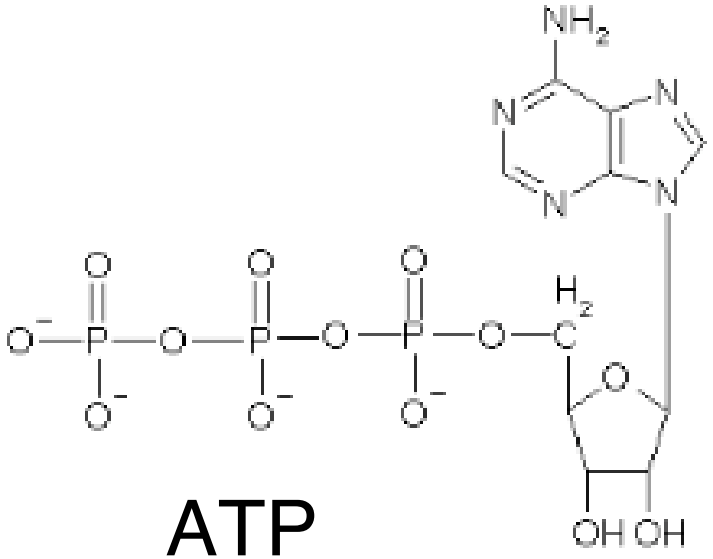
The last step is analogous to the addition of glucose to glycogen from UDP-glucose.

(Other CDP-derivatives react with diacylglycerol to produce other membrane phospholipids such as: phosphatidylcholine, phosphatidylserine, phosphatidylinositol, and cardiolipin.

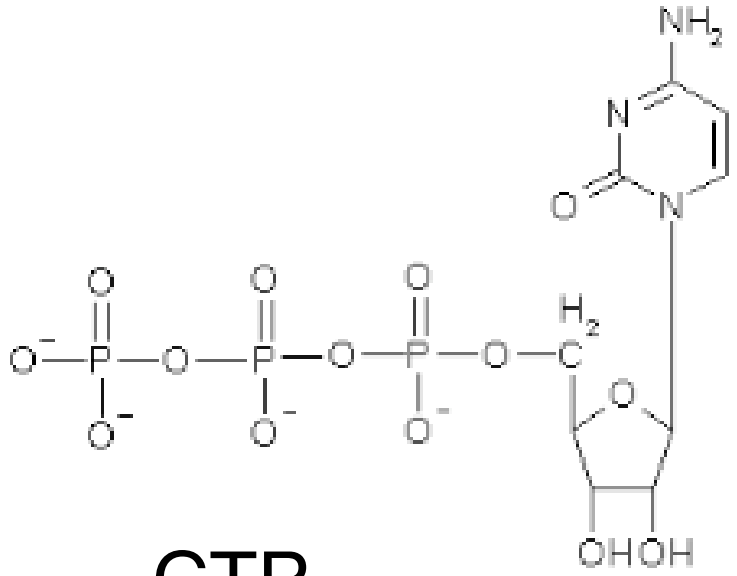
Membrane lipids are turned over rapidly in the cell, however, the rates of synthesis and degradation are usually closely balanced. Imbalances in these two rates are the causes of many early-childhood diseases.)

Lysosomal Diseases Due to Faulty Degradation of Membrane Lipids

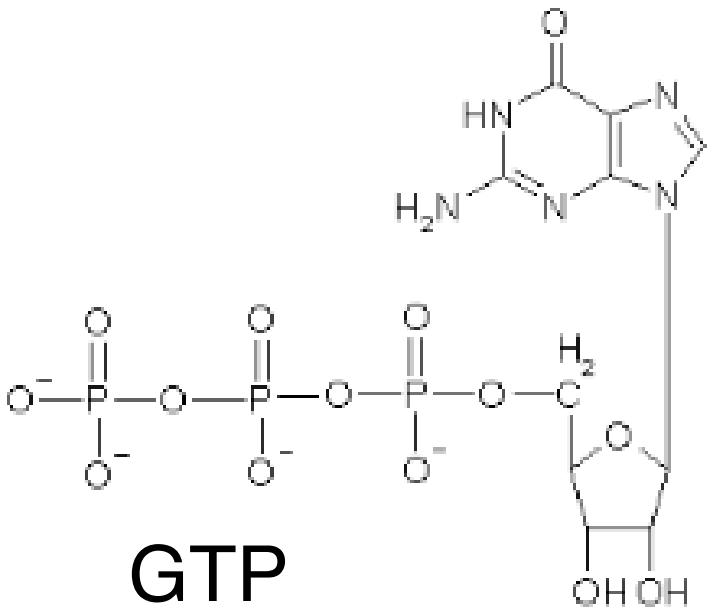
Disease	Defective enzyme
Gaucher's disease	glucocerebrosidase
Tay-Sachs disease	*N*-acetylhexosaminidase
Fabry's disease	trihexosylceramide galactosyl hydrolase
Hurler's syndrome	α-L-iduronidase
Krabbe's disease	galactosylceramide β-galactosylhydrolase
Niemann-Pick disease	sphingomyelinase



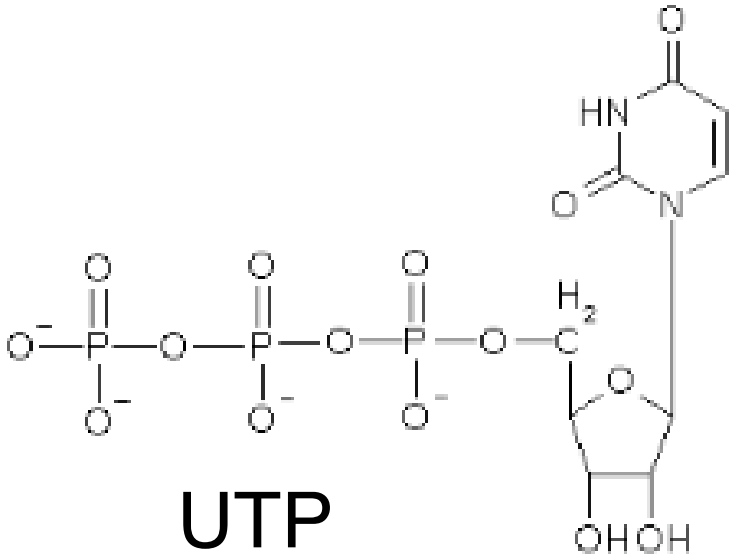
ATP



CTP



GTP



UTP