ANSC/NUTR 618
LIPIDS & LIPID METABOLISM
Triacylglycerol and Fatty Acid Metabolism

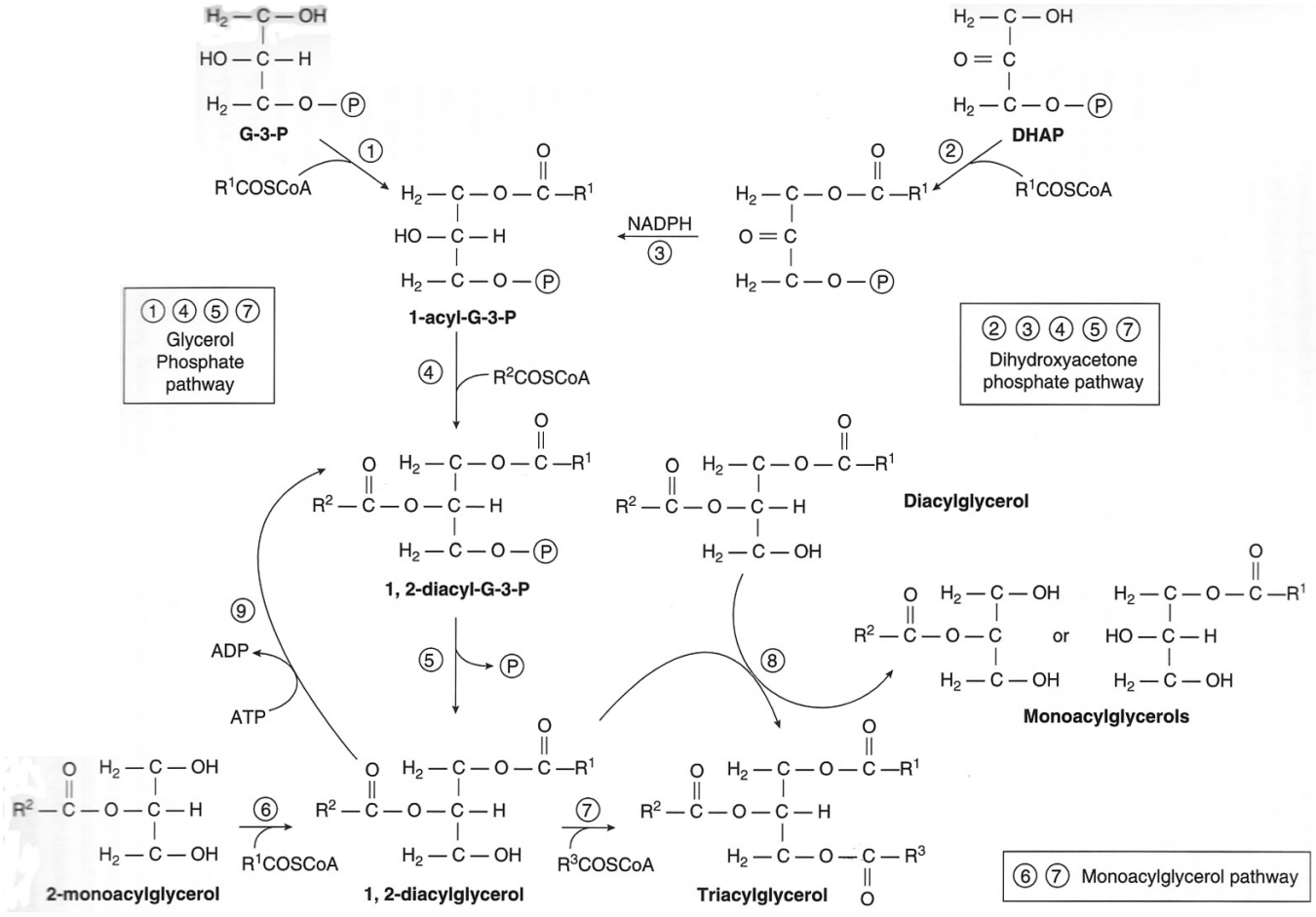
II. Triacylglycerol synthesis

A. Overall pathway

Glycerol-3-phosphate + 3 Fatty acyl-CoA → Triacylglycerol + 3 CoASH

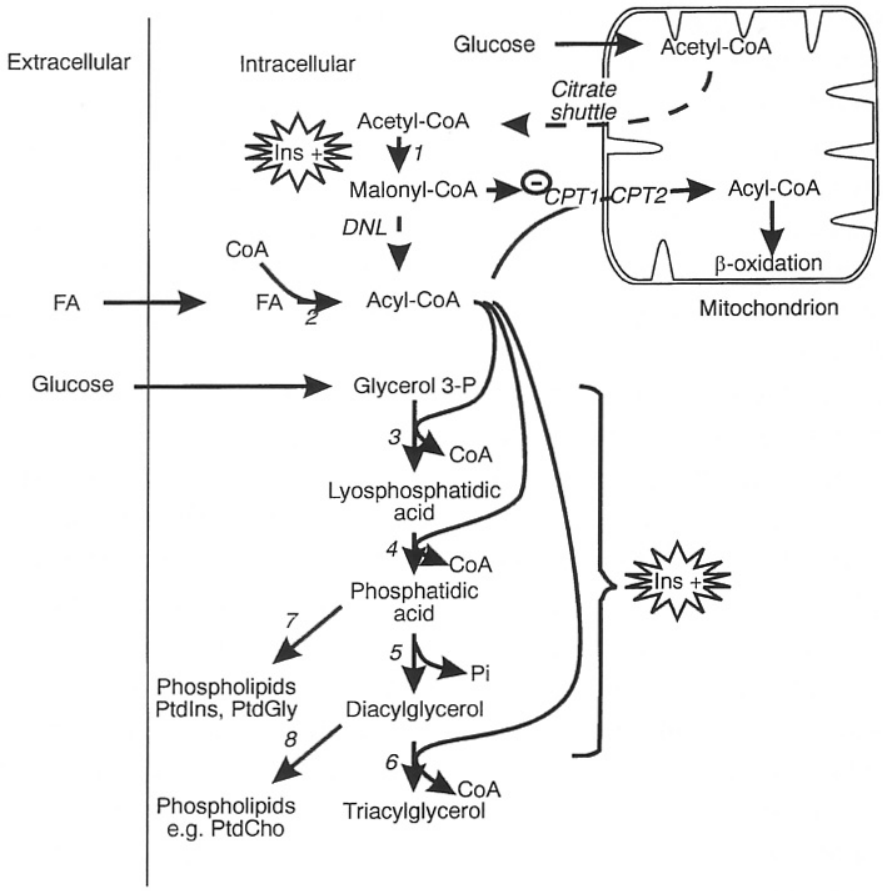
B. Enzymes

1. Acyl-CoA synthase
2. Glycerol-phosphate acyltransferase (GPAT) (#1 below)
3. Lysophosphatidate acyltransferase (LPAT) (#4 below)
4. Phosphatidate phosphorylase (PPH) (#5 below)
5. Diacylglycerol acyltransferase (DGAT) (#7 below)



C. Substrates

1. Glycerol-3-phosphate (G-3-P or α-GP)
   a. Glucose (via reduction of DHAP derived from glycolysis)
   b. Glycerol (liver, small intestine, kidney cortex); requires glycerokinase activity.
2. Fatty acyl-coenzyme A
   a. Fatty acids derived from circulation
      1) VLDL (from the liver) and chylomicrons (dietary fats) via lipoprotein lipase
         (a) Essential fatty acids (18:2n-6 and 18:3(n-3))
         (b) Nonessential fatty acids from liver
      2) Nonesterified fatty acids released from adipose tissue
   b. Fatty acids derived from endogenous synthesis in adipose tissue
      1) 16:0 via fatty acid synthase
      2) 18:0 via fatty acid elongase
      3) 18:1 via Δ^9 desaturase



II. Triacylglycerol hydrolysis (lipolysis)

A. Hormone sensitive lipase (HSL), encoded by *LIPE* gene

1. Intracellular, in cytosol
2. Translocates to lipid droplet when activated.
3. Reaction: TAG → 2,3-DAG + fatty acid → 2-MAG + FA

(There is also a monoacylglycerol lipase.)

4. Complete hydrolysis yields 3 fatty acids + free glycerol.

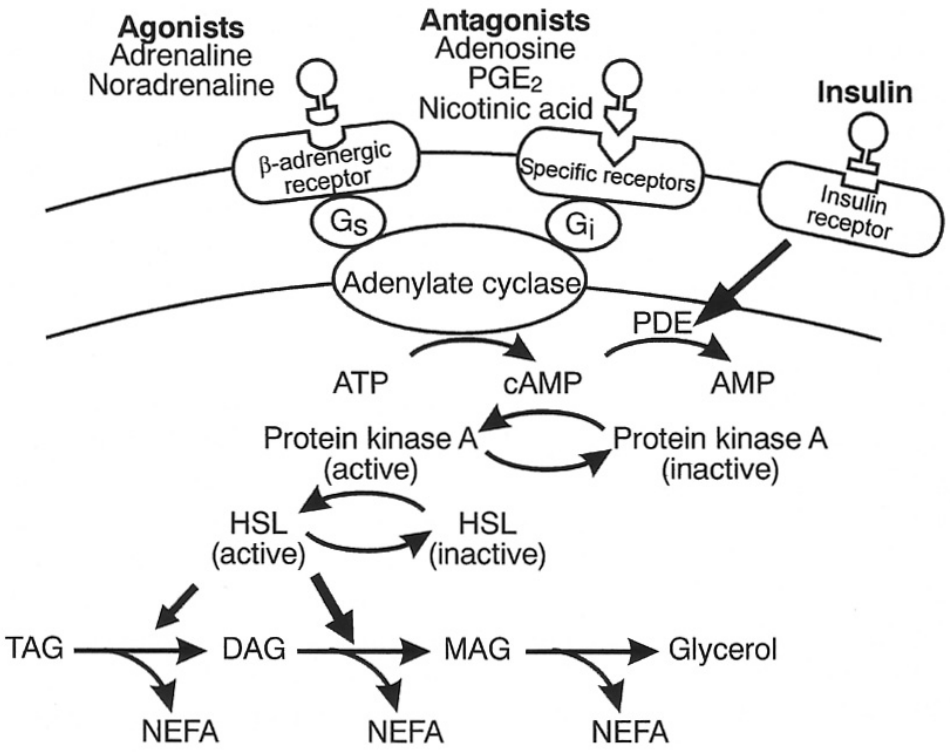
B. Regulation of HSL

1. Activation

a. HSL can be **phosphorylated** by cAMP-dependent protein kinase A.

b. **Perilipin** (a protein that coats lipid droplets) can be phosphorylated by cAMP-dependent protein kinase A, which causes HSL to migrate to the surface of the lipid droplet, where it initiates hydrolysis of TAG. ****Now known to be more important than phosphorylation of HSL.**

2. Activated by epinephrine (adrenalin; in adipose tissue and muscle) and glucagon (liver).
3. **Insulin**
   a. Causes conversion of cAMP to AMP, so activation of protein kinase ceases.
   b. Activates protein phosphates, so activated HSL becomes inactivated.



C. Fate of products of lipolysis

1. Glycerol → liver for synthesis of glucose or G-3-P (via glycerol kinase).
2. Fatty acids
   a. Oxidation within adipose tissue (minor)
   b. Release to other tissues and oxidation (major)

III. ß-Oxidation of fatty acids (revisited)

A. In muscle:

a. Oxidation yields acetyl-CoA, NADH, and $FADH_2$.

b. Acetyl-CoA is further oxidized by the TCA cycle for more NADH and $FADH_2$.

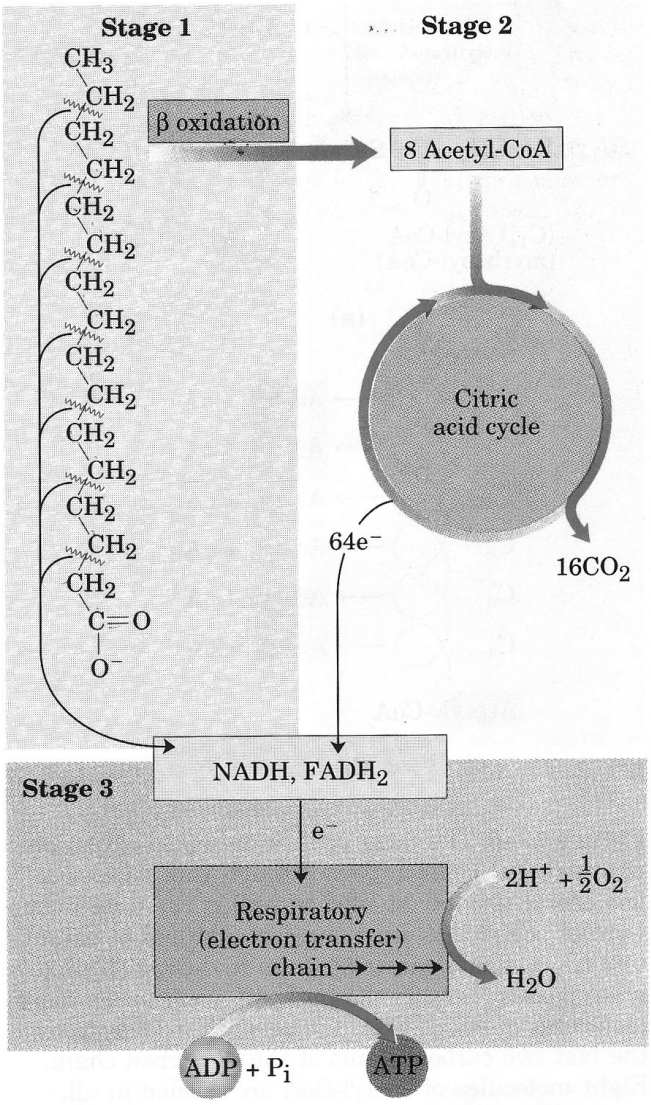
c. Reduced coenzymes are used to produce ATP.

B. In liver:

Oxidation yields acetyl-CoA, NADH, and $FADH_2$.

b. Acetyl-CoA is used to synthesize **ketone bodies.**

c. Ketone bodies travel to non-hepatic tissues for oxidation/energy.



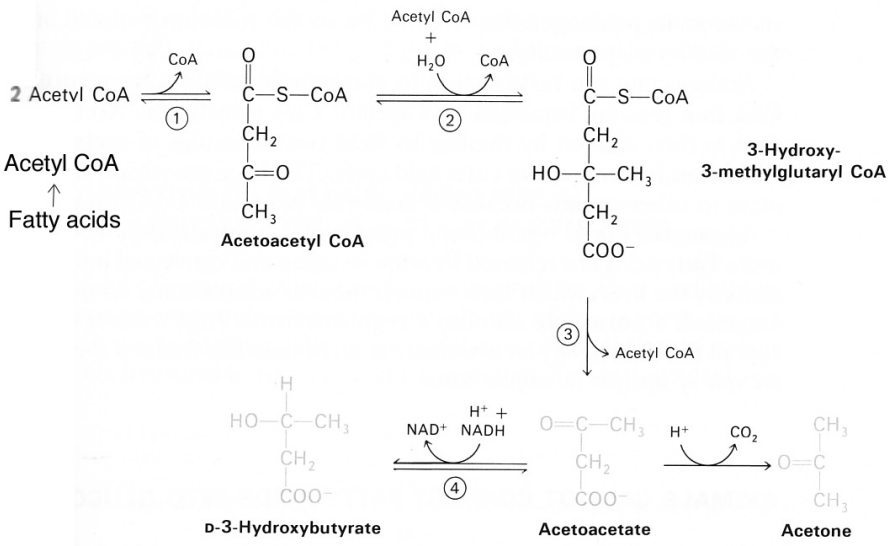
IV. Ketone body synthesis and metabolism

A. Oversupply of fatty acids in the liver → Ketone body formation

1. Liver mitochondria do not have enough oxaloacetate (OAA) to oxidize all of the acetyl-CoA produced from fatty acid oxidation.
2. Acetyl-CoA are used to produce ketone bodies in the mitochondria.

B. Pathway

1. AcCoA + AcCoA → AcAcCoA
2. AcAcCoA + AcCoA → HMGCoA + CoASH
3. HMGCoA→ Acetoacetate + AcCoA



C. Further metabolism of acetoacetate

1. Acetoacetate → Acetone + CO_2
2. Acetoacetate → D-ß-Hydroxybutyrate (D-3-hydroxbutryate)

D. Metabolism of ketone bodies in liver

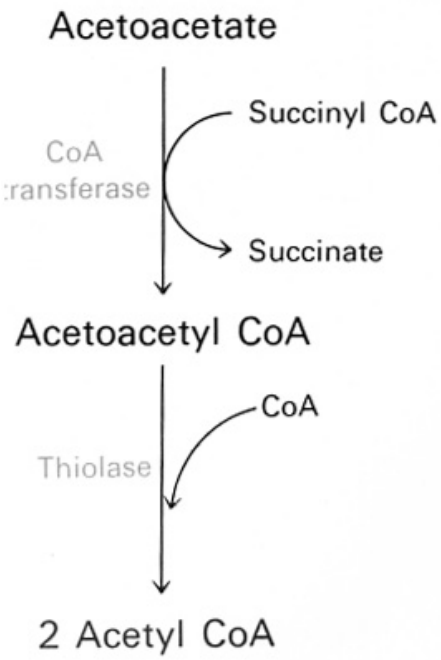
1. Acetoacetate is activated to acetoacetyl CoA in liver *microsomes.*

$$\text{Acetoacetate} + \text{ATP} + \text{CoASH} \rightarrow \text{Acetoacetyl CoA} + \text{AMP} + P_i$$

2. Used for cholesterol biosynthesis.

E. Metabolism of ketone bodies in heart, skeletal muscle, kidney, and brain (after adaptation to starvation)

1. Activated in mitochondria.
   a. Acetoacetate + SuccCoA + GTP → Acetoacetyl CoA + Succinate + GDP
   b. AcAcCoA synthetase reaction (***minor***)
2. Ketone bodies are preferred to fatty acids:
   a. Non-detergent, soluble.
   b. Activating enzymes are in *mitochondria.*
   c. Can be metabolized extensively by CNS tissues (fatty acids cannot).



F. Glucogenic and ketogenic amino acids

1. Amino acids that (in part) can be metabolized to pyruvate or a TCA cycle intermediate are glucogenic.
2. Amino acids that (in part) can be metabolized to acetyl CoA or acetoacetyl CoA are ketogenic.