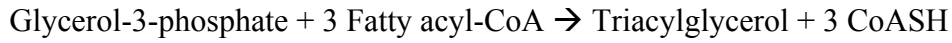


**ANSC/NUTR 618**  
**LIPIDS & LIPID METABOLISM**  
**Triacylglycerol and Fatty Acid Metabolism**

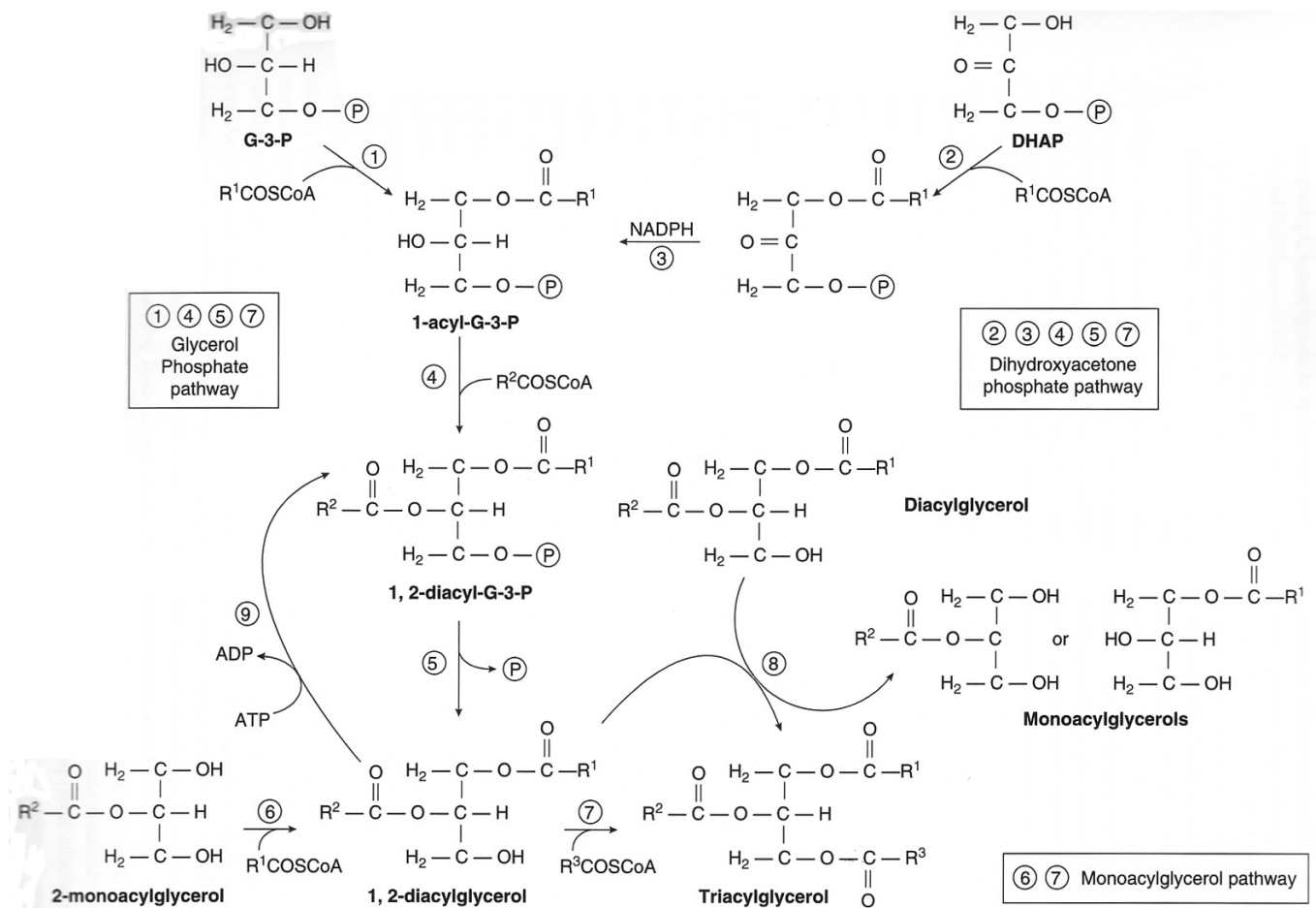
**II. Triacylglycerol synthesis**

A. Overall pathway



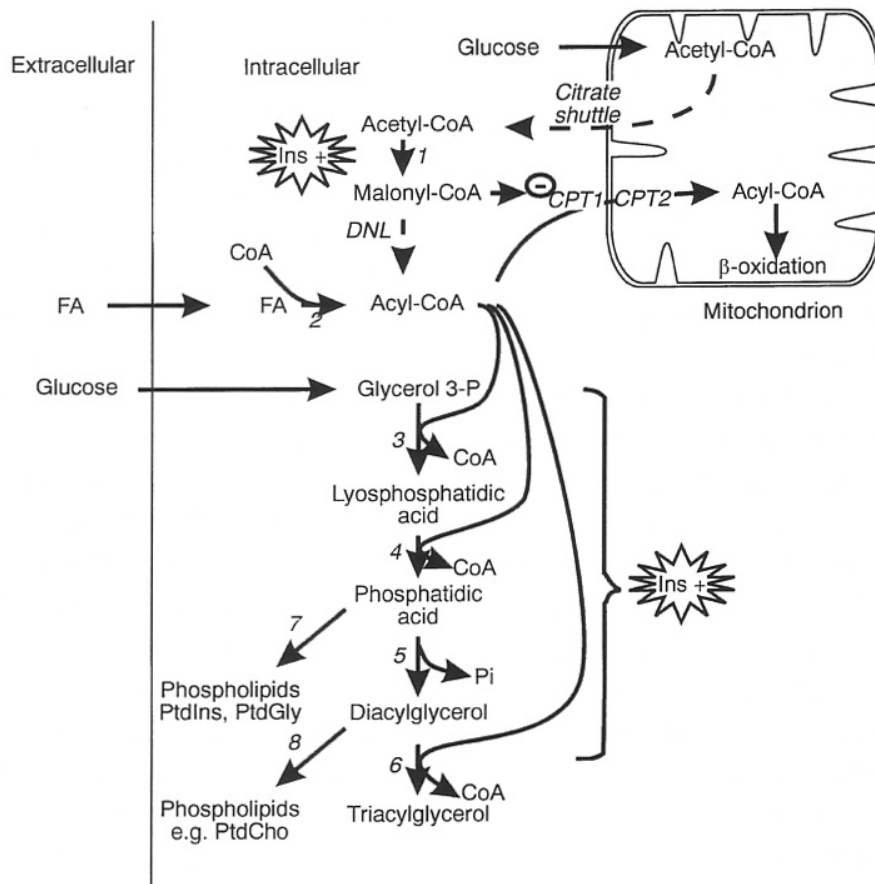
B. Enzymes

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  $\alpha$ -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  $\Delta^9$  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  $\rightarrow$  2,3-DAG + fatty acid  $\rightarrow$  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.

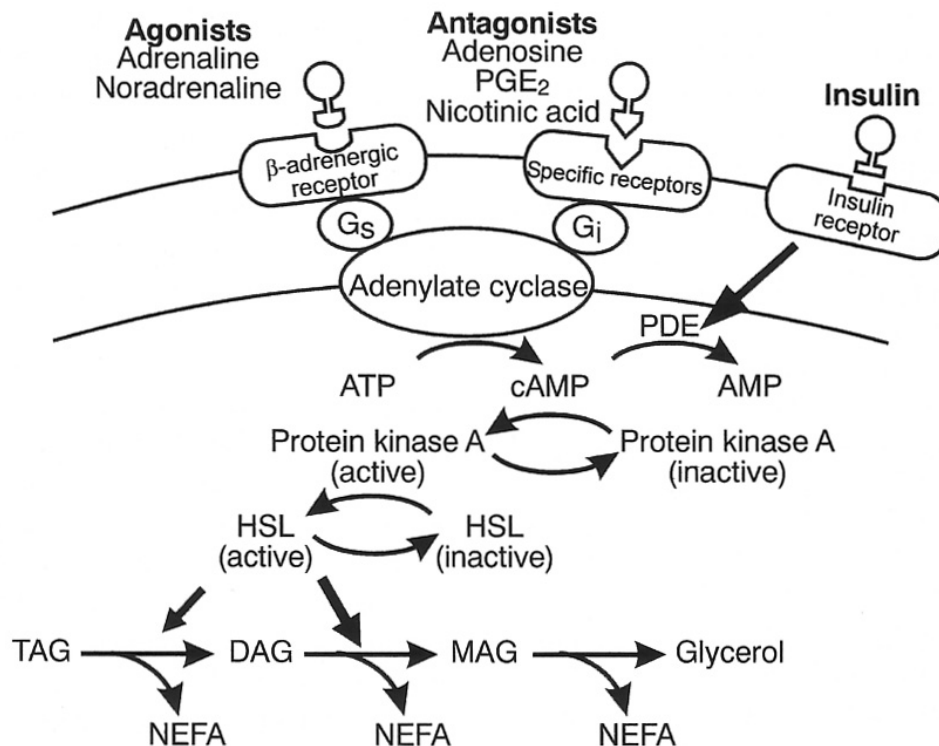
b. **Perilipin** (a protein that coats lipid droplets) can be phosphorylated by cAMP-dependent protein kinase A, which causes HSL to migrate to the surface of the lipid droplet, where it initiates hydrolysis of TAG. **\*\*Now known to be more important than phosphorylation of HSL.**

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 phosphatases, 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)

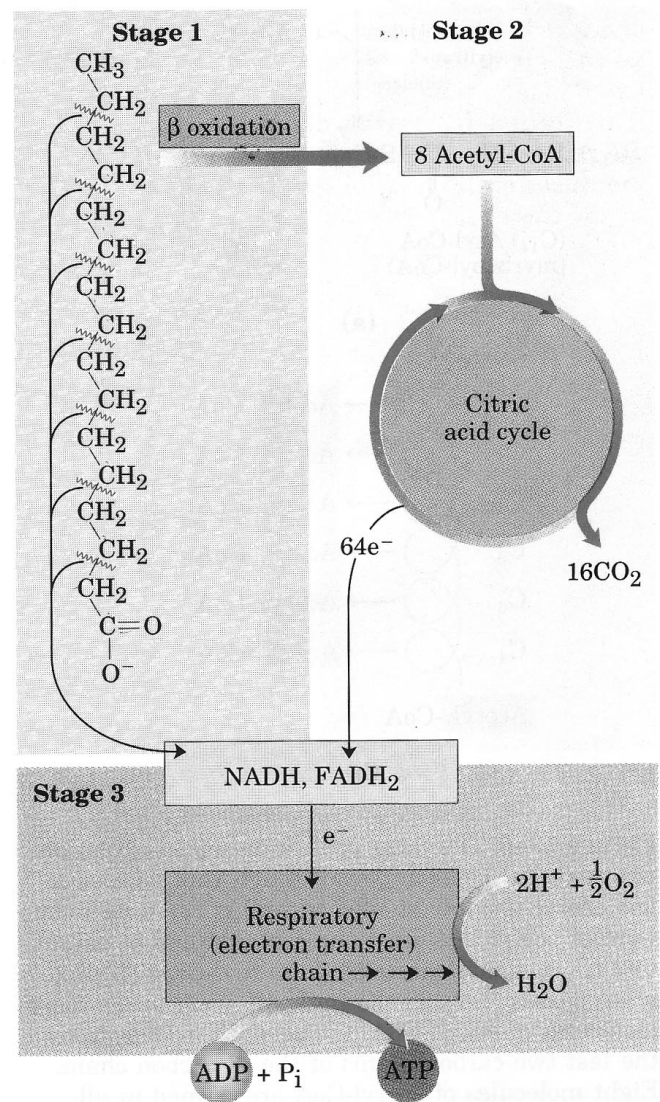
III.  $\beta$ -Oxidation of fatty acids (revisited)

## A. In muscle:

- a. Oxidation yields acetyl-CoA, NADH, and FADH<sub>2</sub>.
- b. Acetyl-CoA is further oxidized by the TCA cycle for more NADH and FADH<sub>2</sub>.
- c. Reduced coenzymes are used to produce ATP.

## B. In liver:

- a. Oxidation yields acetyl-CoA, NADH, and FADH<sub>2</sub>.
- 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.  $\text{AcCoA} + \text{AcCoA}$

→  $\text{AcAcCoA}$

2.  $\text{AcAcCoA} +$

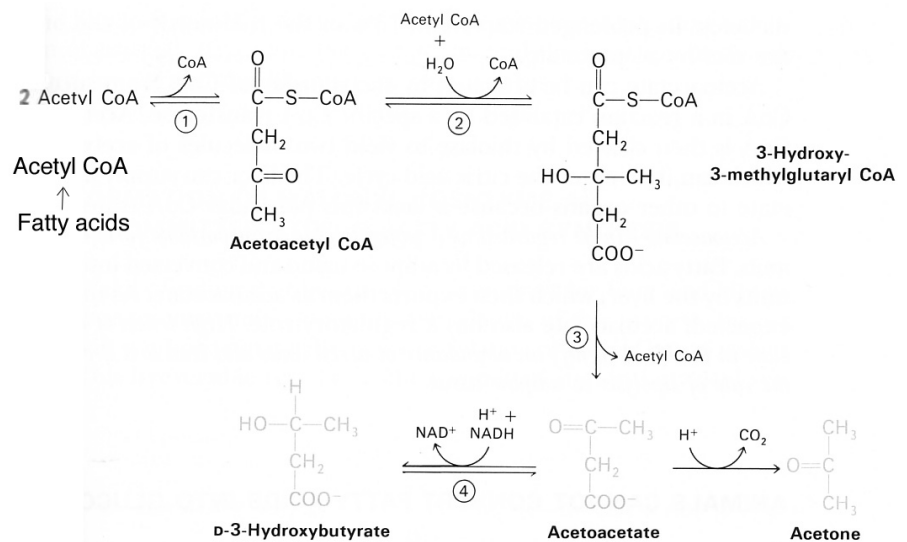
$\text{AcCoA} \rightarrow \text{HMGC CoA}$

+ CoASH

3.  $\text{HMGC CoA} \rightarrow$

Acetoacetate +

$\text{AcCoA}$



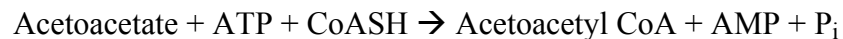
C. Further metabolism of acetoacetate

1. Acetoacetate → Acetone +  $\text{CO}_2$

2. Acetoacetate → D-β-Hydroxybutyrate (D-3-hydroxybutyrate)

D. Metabolism of ketone bodies in liver

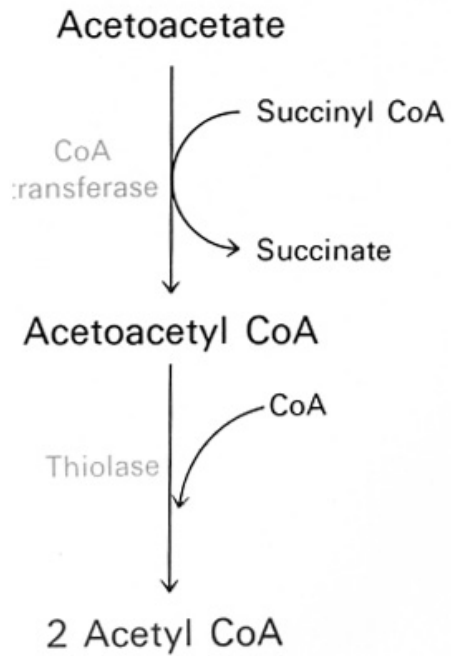
1. Acetoacetate is activated to acetoacetyl CoA in liver *microsomes*.



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.  $\text{Acetoacetate} + \text{SuccCoA} + \text{GTP} \rightarrow \text{Acetoacetyl CoA} + \text{Succinate} + \text{GDP}$
  - 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.

