

ANSC/NUTR 618
Lipids & Lipid Metabolism
Fatty Acid Synthesis

I. Overall concepts

A. Definitions

1. ***De novo* synthesis** = synthesis from non-fatty acid precursors

a. Carbohydrate precursors (glucose and lactate)

1) *De novo* fatty acid synthesis uses glucose absorbed from the diet rather than glucose synthesized by the liver.

2) *De novo* fatty acid synthesis uses lactate derived primarily from glucose metabolism in muscle and red blood cells.

b. Amino acid precursors (e.g., alanine, branched-chain amino acids)

1) *De novo* fatty acid synthesis from amino acids is especially important during times of excess protein intake.

2) Use of amino acids for fatty acid synthesis may result in nitrogen overload (e.g., the Atkins diet).

c. Short-chain organic acids (e.g., acetate, butyrate, and propionate)

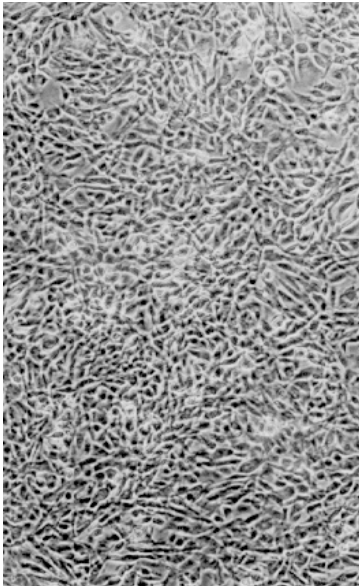
1) The rumen of ruminants is a major site of short-chain fatty acid synthesis.

2) Only small amounts of acetate circulate in non-ruminants.

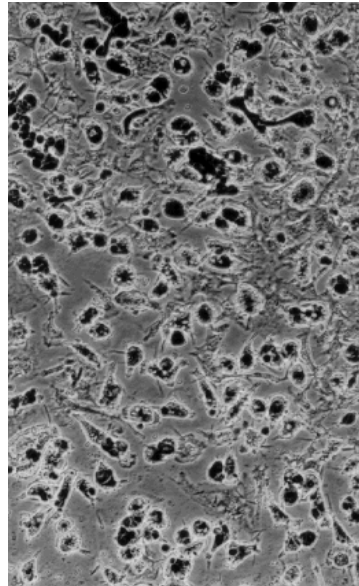
2. ***Lipogenesis*** = fatty acid *or* triacylglycerol synthesis

a. From preformed fatty acids (from diet or *de novo* fatty acid synthesis)

b. Requires source of carbon (from glucose or lactate) for glycerol backbone



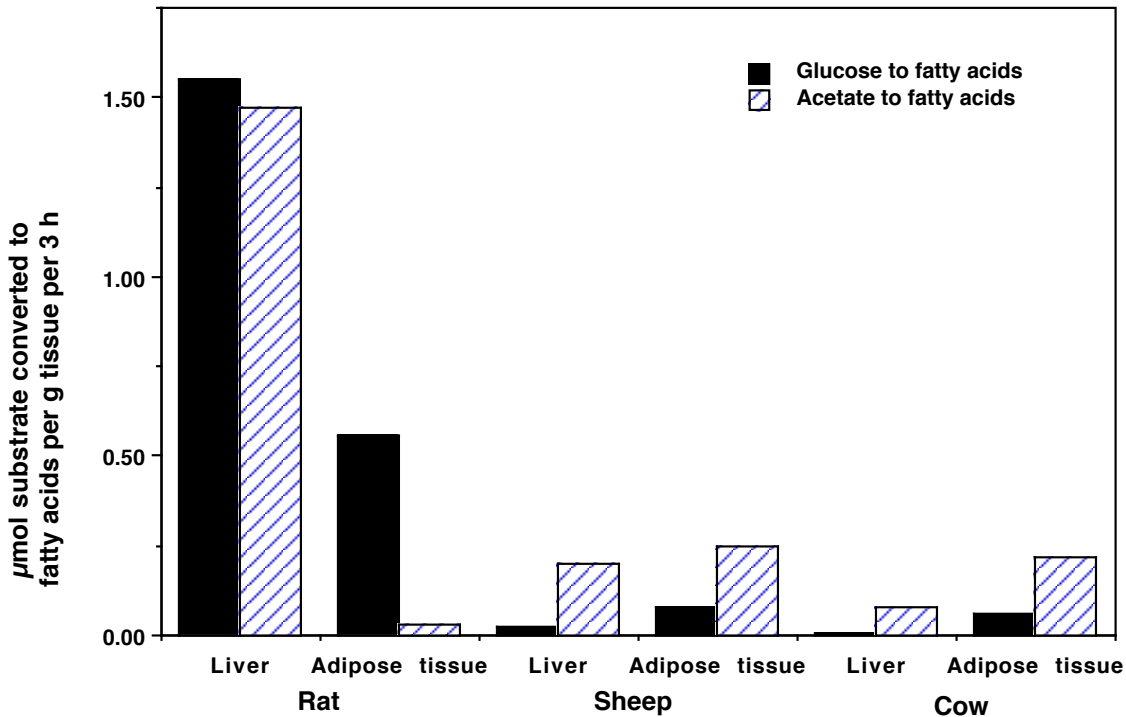
3T3-L1 Preadipocytes at confluence. No lipid filling has yet occurred.



3T3-L1 Adipocytes after 6 days of differentiation. Dark spots are lipid droplets.

B. Tissue sites of *de novo* fatty acid biosynthesis

1. **Liver.** In birds, fish, humans, and rodents (approx. 50% of fatty acid biosynthesis).
2. **Adipose tissue.** All livestock species synthesize fatty acids in adipose tissue; rodents synthesize about 50% of their fatty acids in adipose tissue.
3. **Other tissues.** Brain (and other nervous tissues) and lungs.



Rates of conversion of glucose and acetate to fatty acids in liver and adipose tissue of rat, sheep, and cows. Liver and subcutaneous adipose tissue was incubated *in vitro* with ^{14}C -labeled glucose or acetate, lipids were extracted, and radioactivity was counted on a liquid scintillation spectrometer.

II. Substrates for fatty acid biosynthesis

A. **Glucose.** All species can utilize glucose to some extent.

1. **Nonruminants** (rats, pigs, fish, humans)
 - a. Glucose is a major nutrient absorbed from the small intestine.
 - b. Glucose also is essential for fatty acid synthesis from acetate to provide G3P and NADPH (via the pentose cycle).
2. **Ruminants** (sheep, goats, cattle)
 - a. Very little free glucose is absorbed from the small intestine.
 - b. Glucose is incorporated into fatty acids at about 1/10th the rate seen for acetate or lactate.

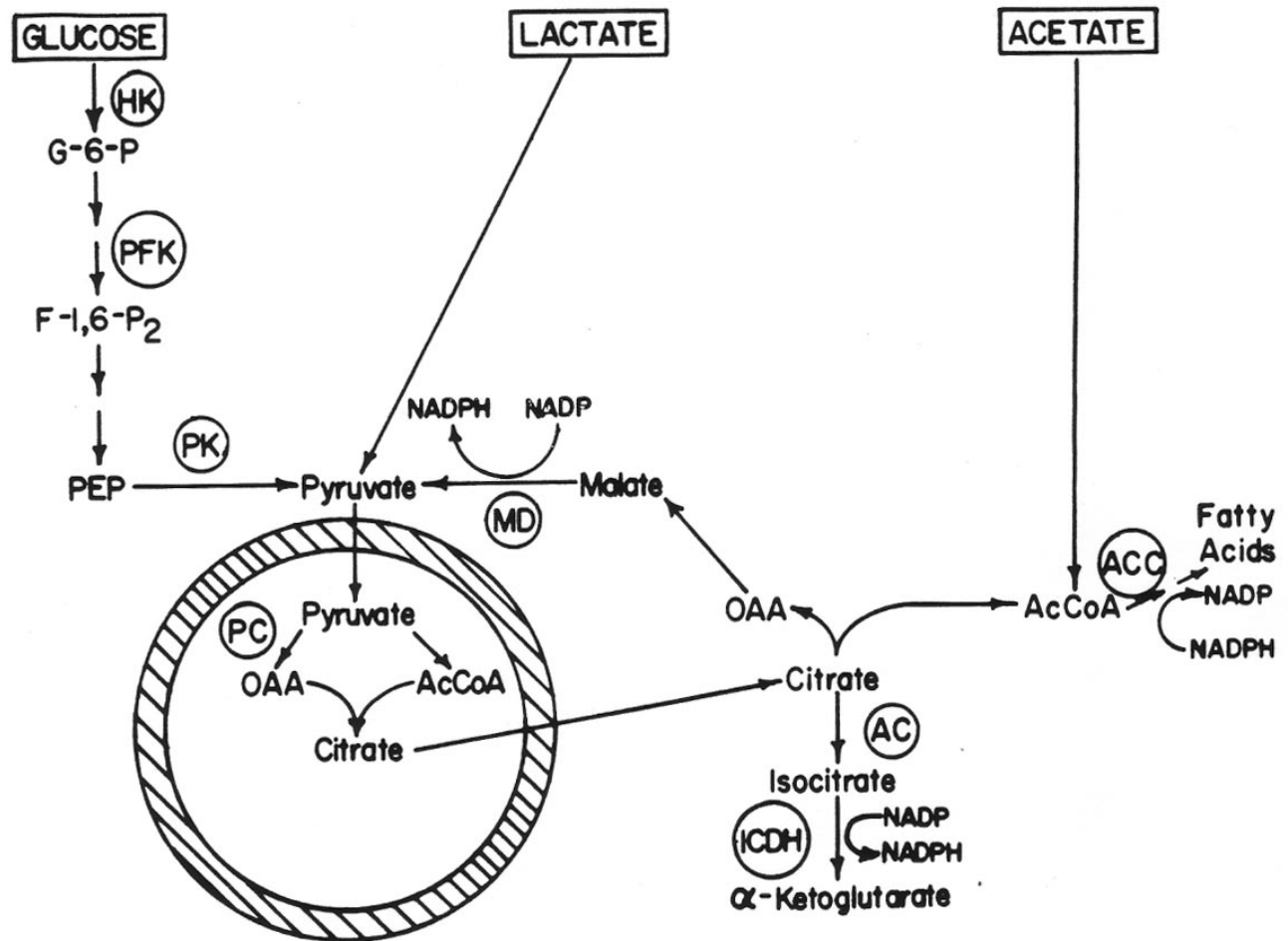
B. **Acetate.** All species can utilize acetate to some extent.

1. **Nonruminants.** In the presence of glucose, acetate is incorporated into fatty acids at high rates. Virtually no fatty acid synthesis occurs from acetate in the absence of glucose.
2. **Ruminants.** Ruminants have evolved to effectively utilize acetate.

C. **Lactate.** All species utilize lactate very effectively.

III. Pathways of fatty acid biosynthesis

Fatty acid biosynthesis occurs in the cytoplasm.



A. **Glucose.** Most of the carbon from glucose enters fatty acid synthesis via glycolysis.

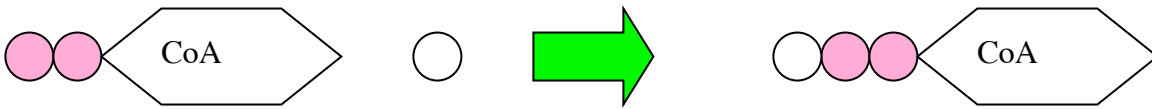
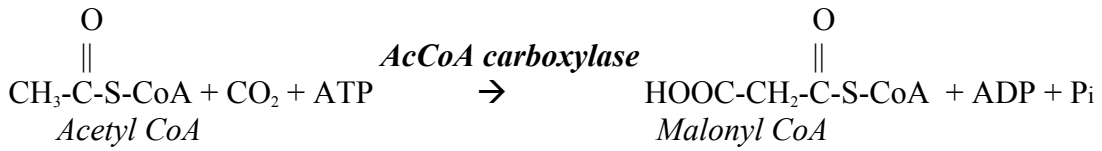
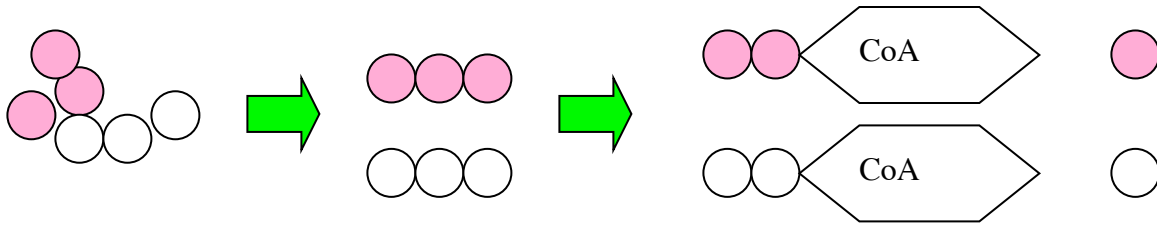
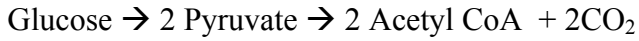
1. Carbon must enter the mitochondria and be converted to both OAA and AcCoA, which form citrate.
2. The citrate exits the mitochondria and is hydrolyzed by citrate lyase (or citrate cleavage enzyme).
3. The AcCoA is utilized for fatty acid synthesis (*palmitate*).
4. The OAA is reduced to malate, when then is oxidatively decarboxylated back to pyruvate generating NADPH. This cycle can produce about 1/2 the NADPH required for fatty acid biosynthesis.

B. **Acetate.** Acetate is converted to AcCoA in the cytoplasm.

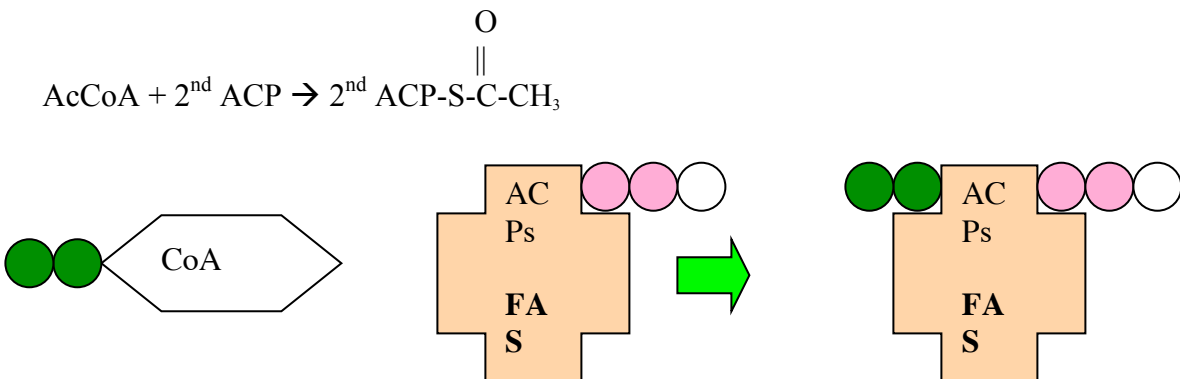
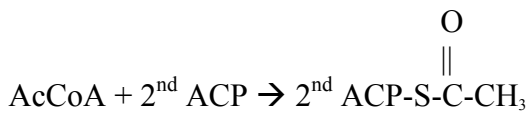
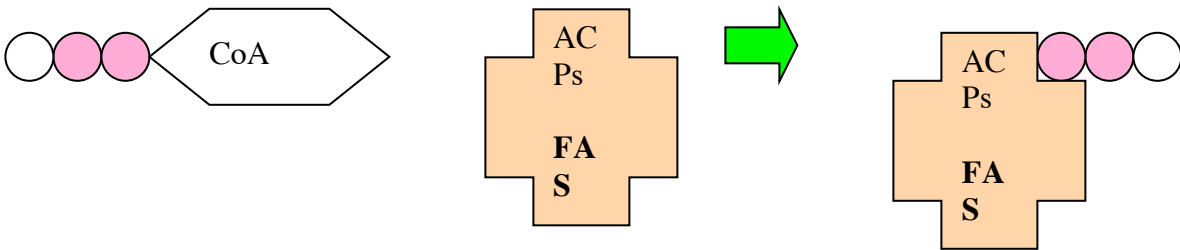
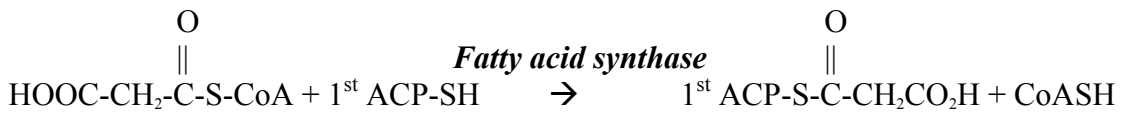
C. **Lactate.** Follows the same pathway as glucose; enters the pathway at pyruvate.

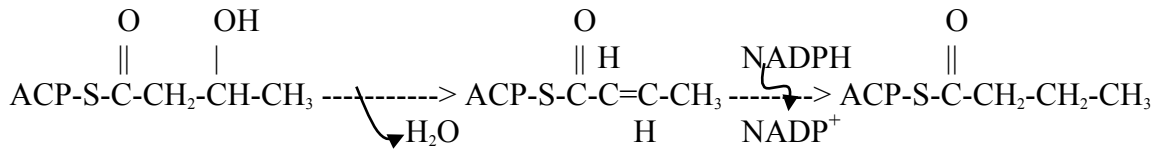
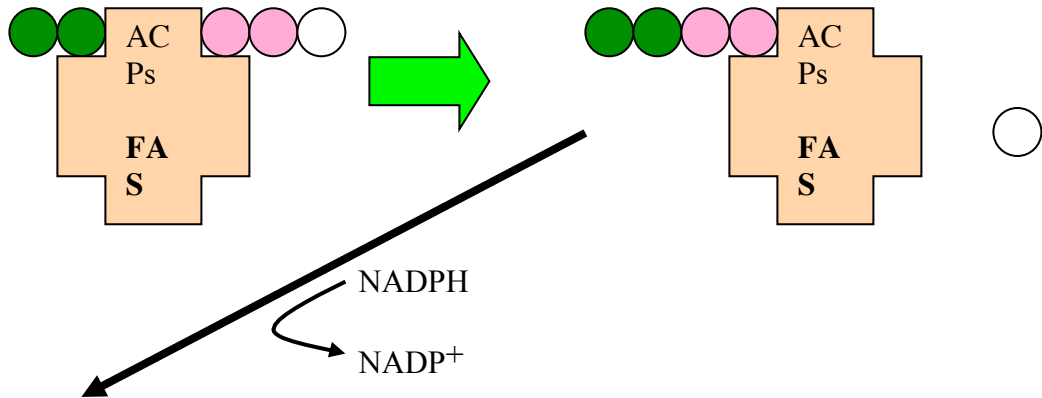
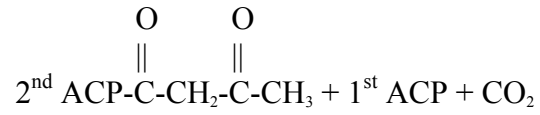
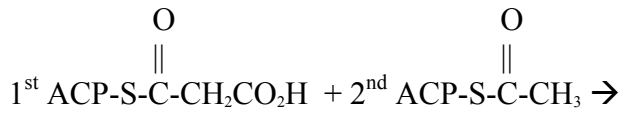
D. The assembly of fatty acids

1. *Acetyl CoA carboxylase and fatty acid synthase*



2. *Fatty acid synthase*

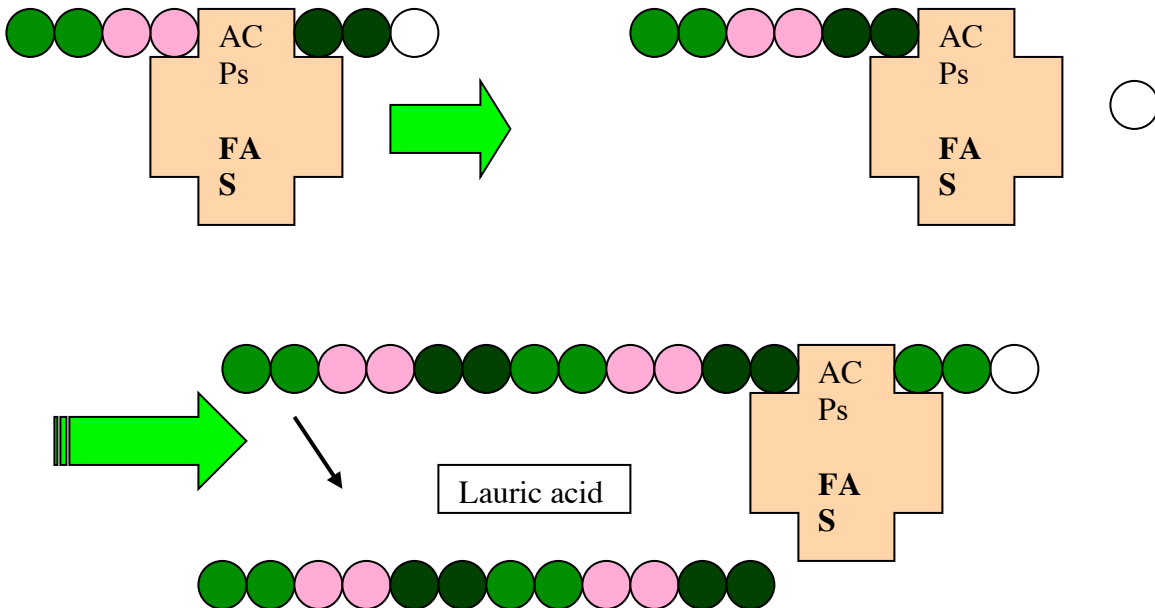




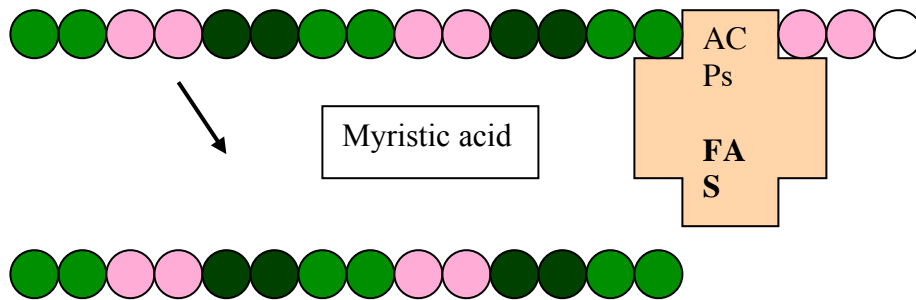
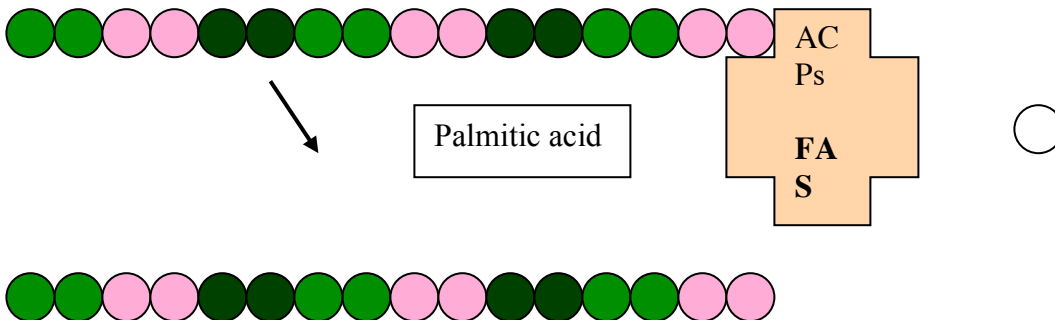
+ MalCoA, etc. → **Palmitic acid (plus some lauric and myristic acids)**

B. Elongation of fatty acids by fatty acid synthase

1. Lauric acid



2. Myristic acid

3. Palmitic acid (*final product of fatty acid synthase*)

IV. Supporting pathways for fatty acid biosynthesis

A. *Production of G3P.*

1. *Nonruminants.* G3P is provided by the metabolism of glucose (DHAP \rightarrow G3P).

2. *Ruminants.* Glucose also is the primary source of G3P. However, to conserve glucose, ruminants very effectively convert lactate to G3P.

B. *Production of NADPH.*

1. *Nonruminants.* Pentose cycle: 60% of the NADPH; malic enzyme: 40%.

2. *Ruminants.* Pentose cycle: 40-50% of the NADPH; malic enzyme: 10-20%; NADP-ICDH: 30-40%

V. What limits glucose use for fatty acid synthesis?

A. *Old theory:* Low activities of CCE and ME.

B. *New theory:*

1. Competition between glycolysis and the pentose cycle.

2. Glycolysis is blocked at **6-PFK**. Any glucose carbon that gets beyond PFK is drawn off to lactate and G3P.