Insulin

- 1st molecule shown to have hormone effects
- 1st protein to be sequenced
- 1st protein to be crystallized
- 1st protein to be chemically synthesized
- 1st hormone to be made clinically available by recombinant DNA technology

- Insulin is an anabolic hormone – leads to:
  - Increased glycogenesis
  - Increased lipogenesis
  - Increased protein synthesis

- Insulin is the single hormone which opposes the effects of: glucagon, epinephrine, norepinephrine, and others.

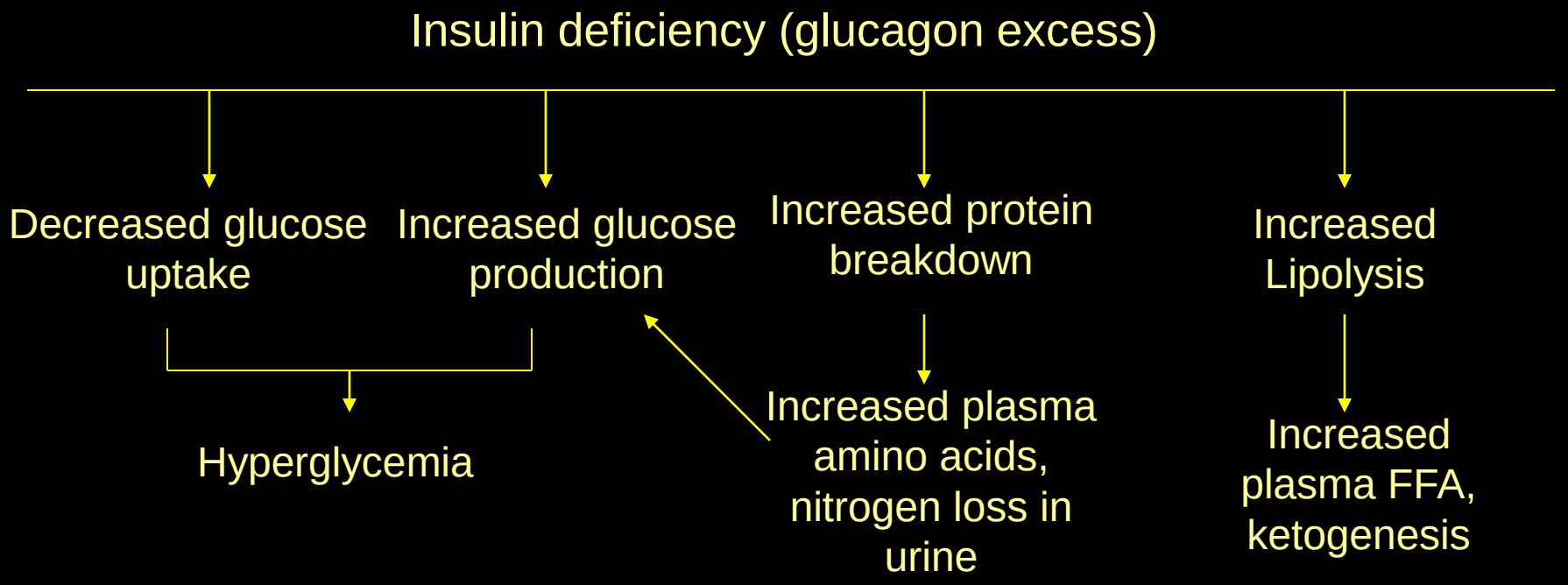


Table 51–3. Enzymes whose degree of phosphorylation and activity are altered by insulin.[1]

Enzyme	Change in Activity	Possible Mechanism
cAMP metabolism		
Phosphodiesterase (low K_m)	Increase	Phosphorylation
Protein kinase (cAMP-dependent)	Decrease	Association of R and C subunits
Glycogen metabolism		
Glycogen synthase	Increase	Dephosphorylation
Phosphorylase kinase	Decrease	Dephosphorylation
Phosphorylase	Decrease	Dephosphorylation
Glycolysis and gluconeogenesis		
Pyruvate dehydrogenase	Increase	Dephosphorylation
Pyruvate kinase	Increase	Dephosphorylation
6-Phosphofructo-2-kinase	Increase	Dephosphorylation
Fructose-2,6-bisphosphatase	Decrease	Dephosphorylation
Lipid metabolism		
Acetyl-CoA carboxylase	Increase	Dephosphorylation
HMG-CoA reductase	Increase	Dephosphorylation
Triacylglycerol lipase	Decrease	Dephosphorylation
Signaling molecules		
p42/44MAP kinase	Increase	Dephosphorylation
p90RSK	Increase	Dephosphorylation
GSK3	Decrease	Dephosphorylation
p70 S6 kinase	Increase	Dephosphorylation
Phosphoprotein phosphatase 1G	Increase	Dephosphorylation

[1]Modified and reproduced, with permission, from Denton RM et al: A partial view of the mechanism of insulin action. Diabetologia 1981;21:347.

Also: ↑glucose transporters

↑PFK, PK, PFK2/FBPase mRNA

Insulin Deficiency – Diabetes Mellitus

Biochemistry –

The cells (the body) starve for glucose under conditions of severe HYPERGLYCEMIA!!!

Body Fuels are broken down constantly to increase lipolysis, increase glycogenolysis increase protein degradation.

Ketone bodies are formed → metabolic acidosis

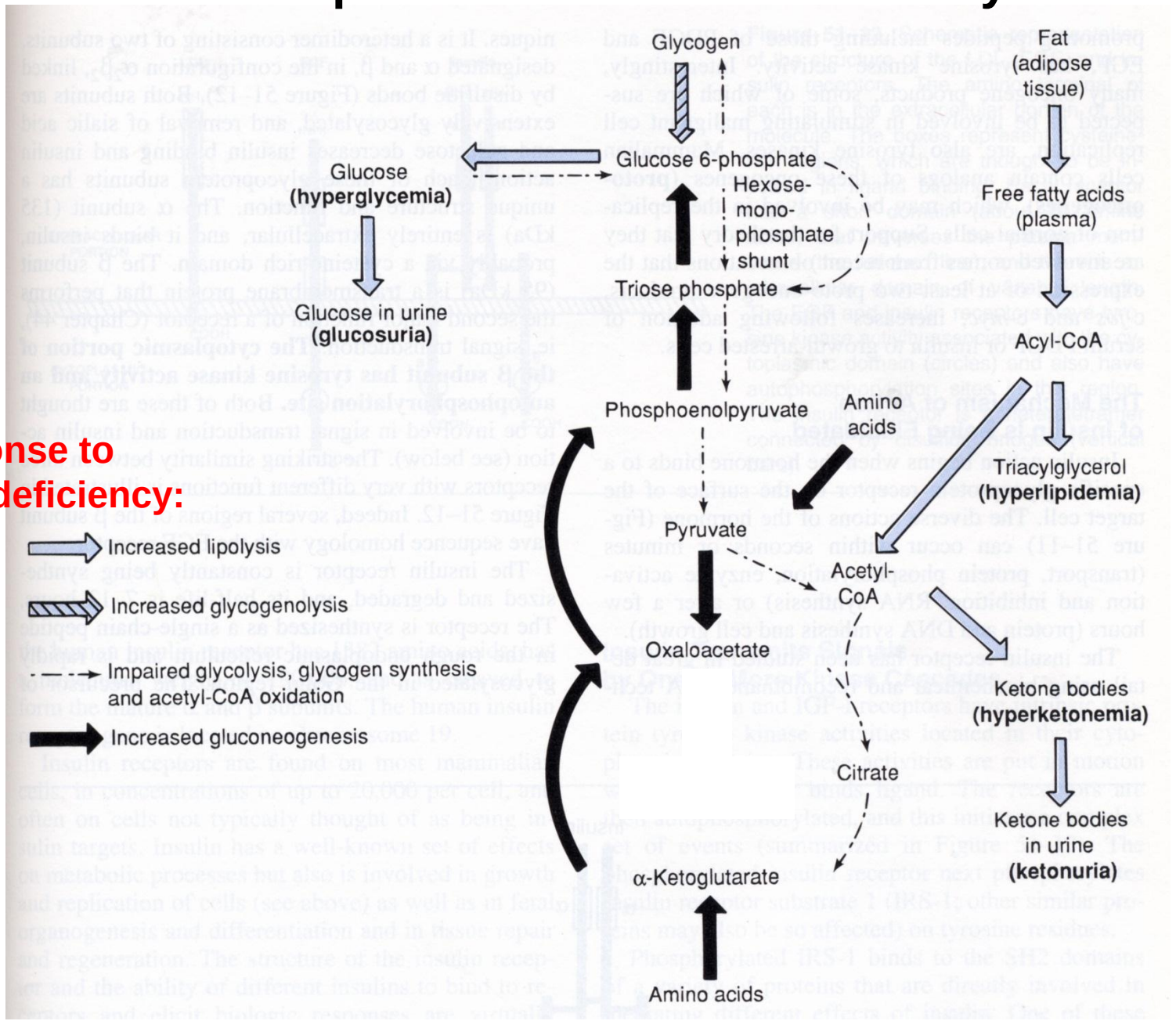
Causes and Types of Diabetes

- I Insulin Dependent – juvenile onset ~ 10%
  - defect in insulin production
  - autoimmune disease against pancreas

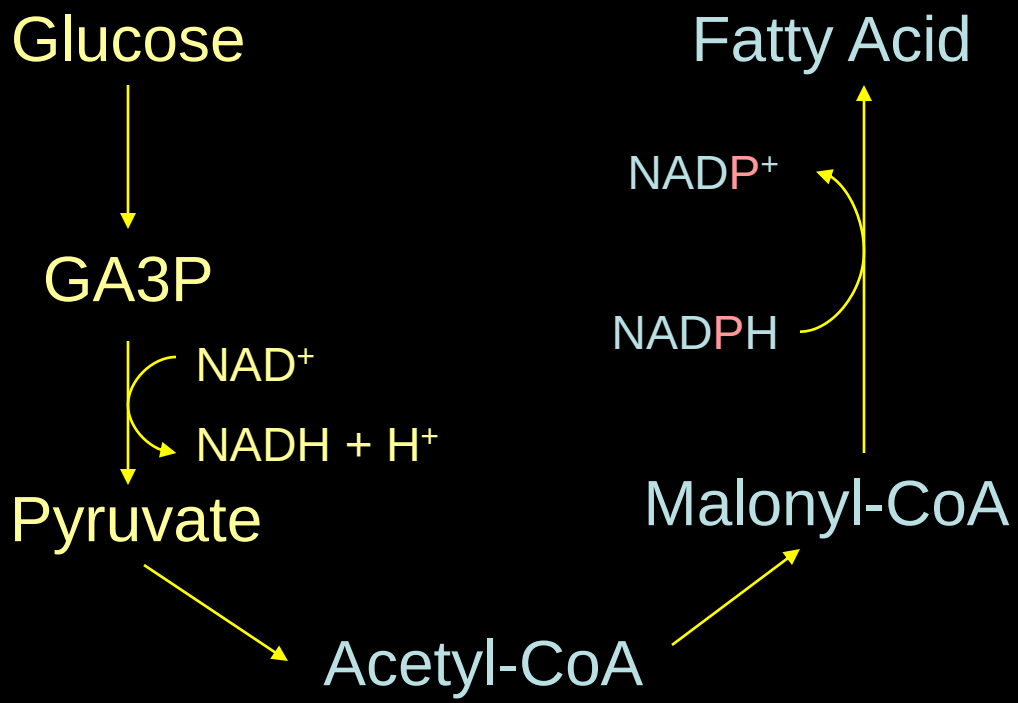
- II Non-Insulin Dependent – adult onset ~ 90%
  - defect in insulin receptor?
  - can be autoimmune disease
  - often associated with obesity
  - can be controlled be diet, exercise

Metabolic Responses to Insulin Deficiency

In response to insulin deficiency:



Fatty Acid Synthesis



Intracellular: $NADH / NAD^+ \sim 1/1000$

$NADPH / NADP^+ \sim 100/1$

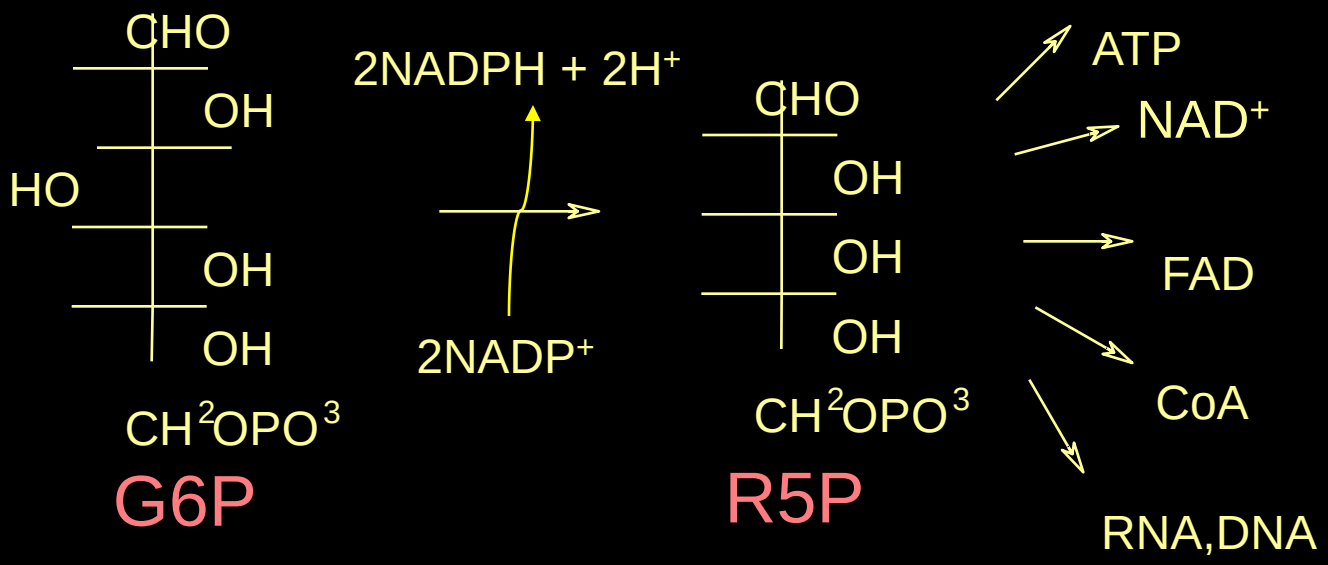
Pentose Phosphate Pathway

2 Functions:

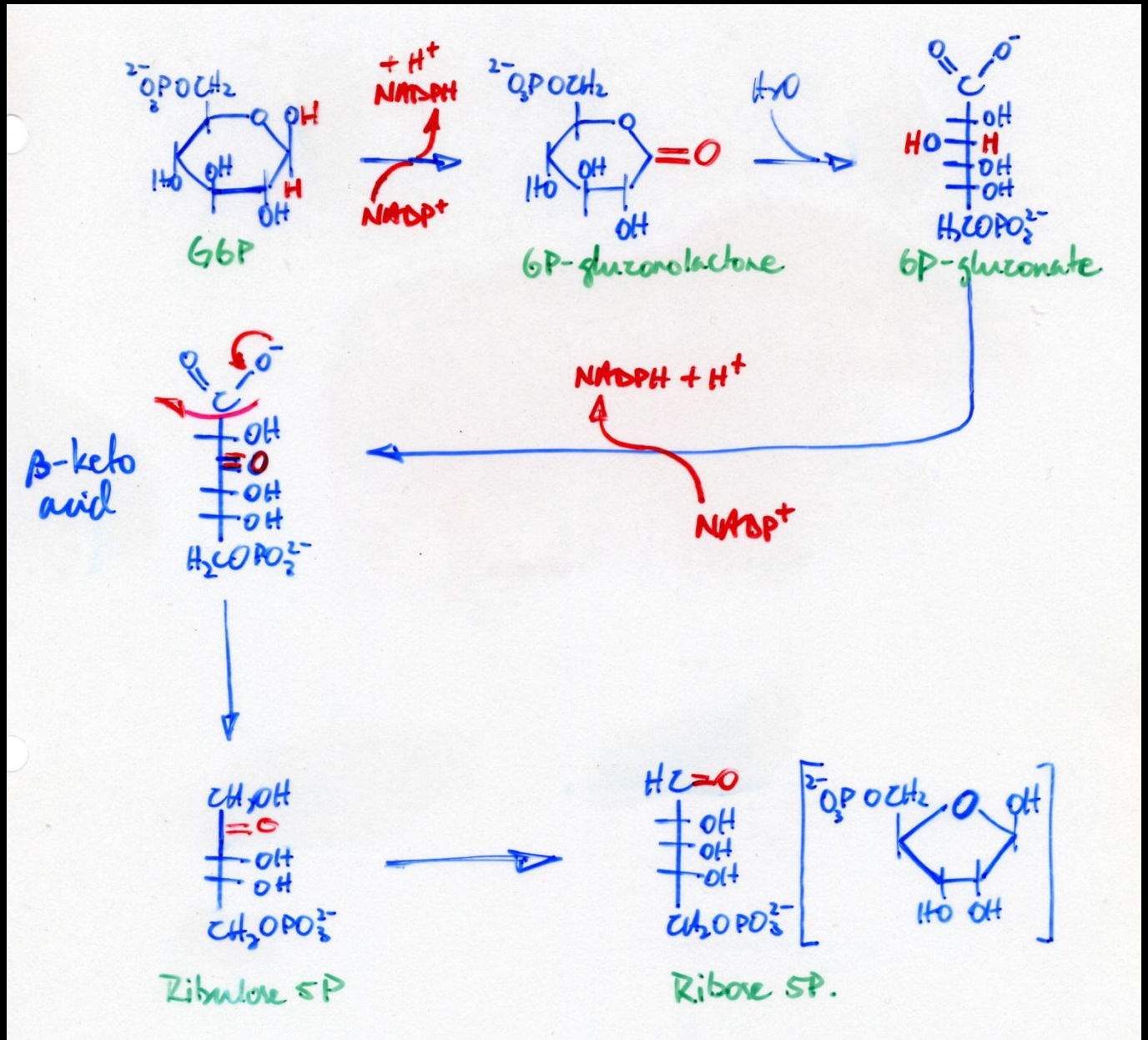
1) generate NADPH

2) generate ribose-5-phosphate

Substrate is Glucose-6-P:

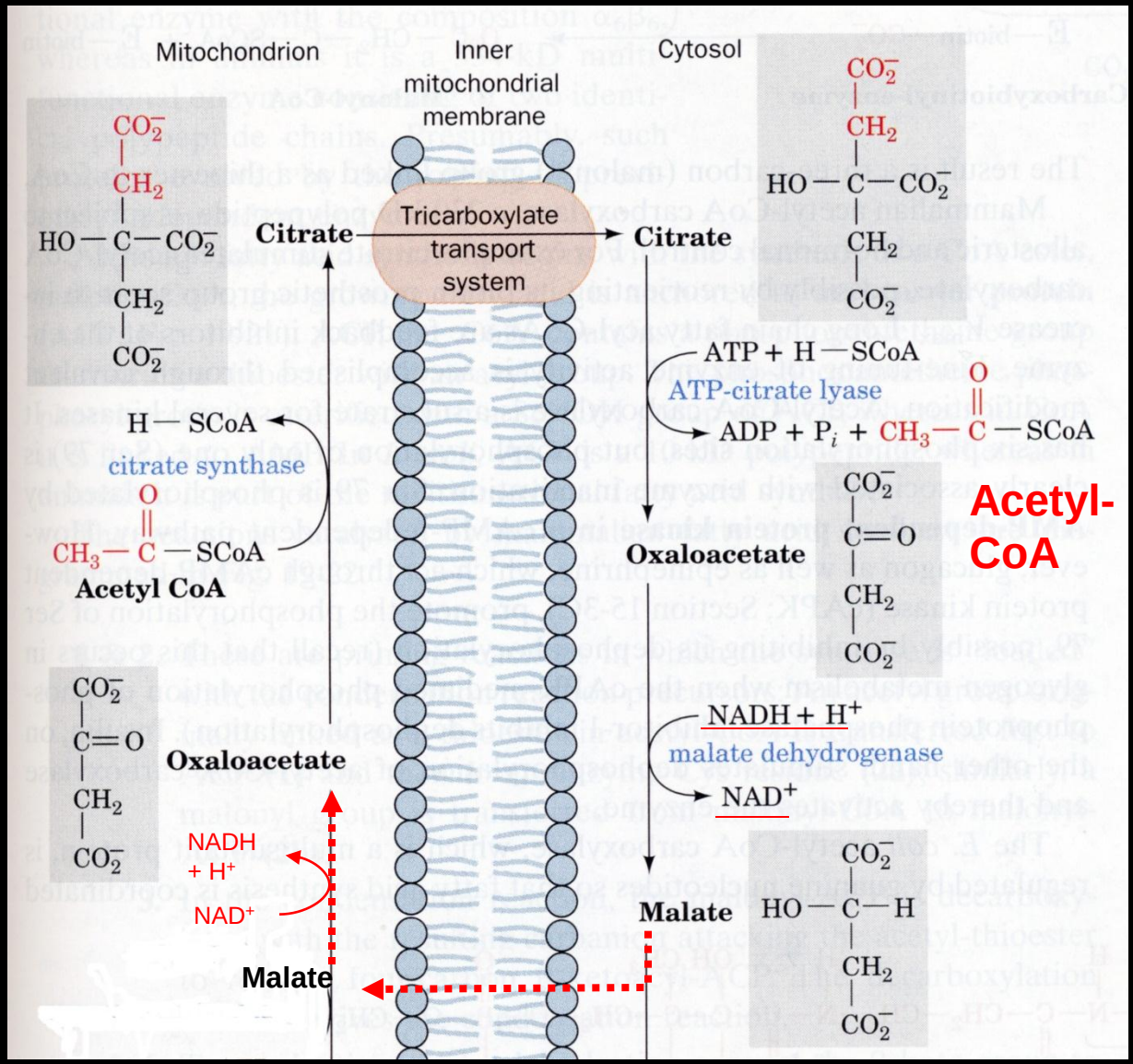


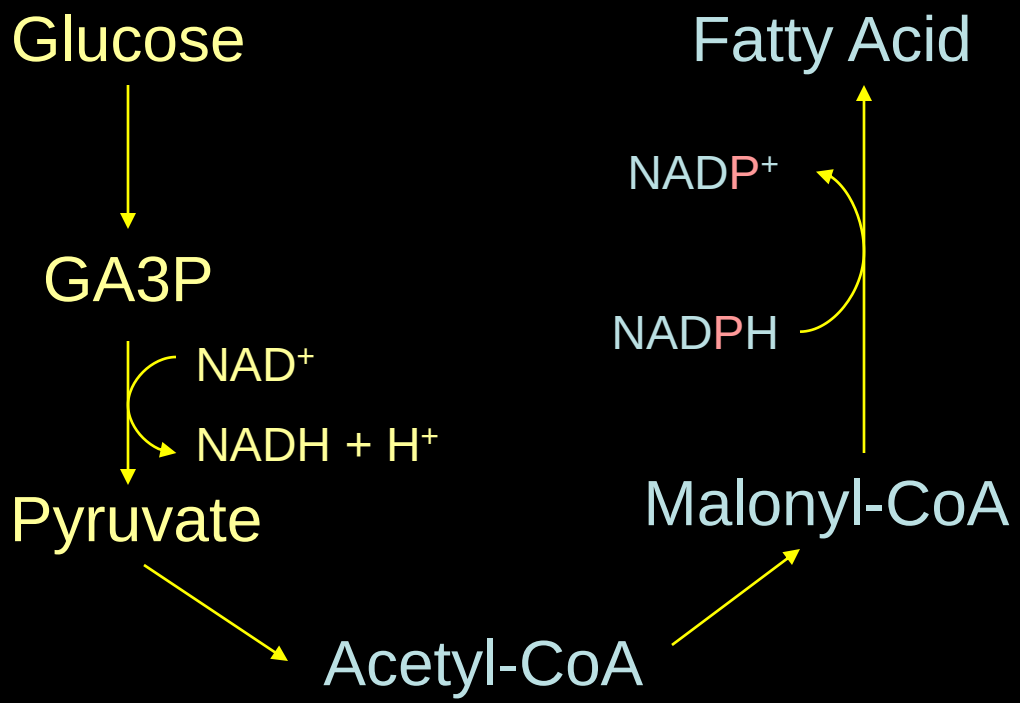
Pentose Phosphate Pathway



- Fatty acid synthesis occurs in the cytosol
- Acetyl CoA is the substrate, and therefore acetyl CoA must be transported out from the mitochondria.
- FA synthesis requires NADPH – which comes from the pentose phosphate pathway.

The Tricarboxylate Transporter



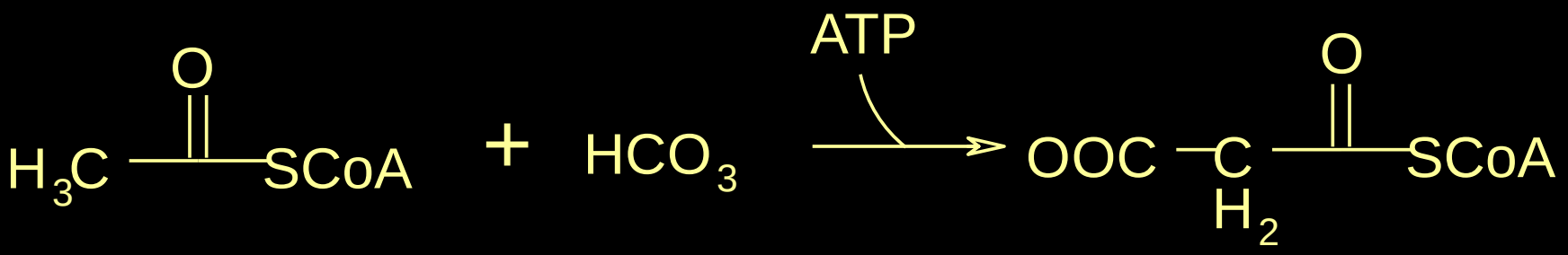


Intracellular: $NADH / NAD^+ \sim 1/1000$

$NADPH / NADP^+ \sim 100/1$

NADH is maintained low, while NADPH is maintained high to drive glycolysis and fatty acid synthesis at the same time.

Activation of Acetyl-CoA



Acetyl-CoA

Malonyl-CoA

- See mechanism of pyruvate carboxylase

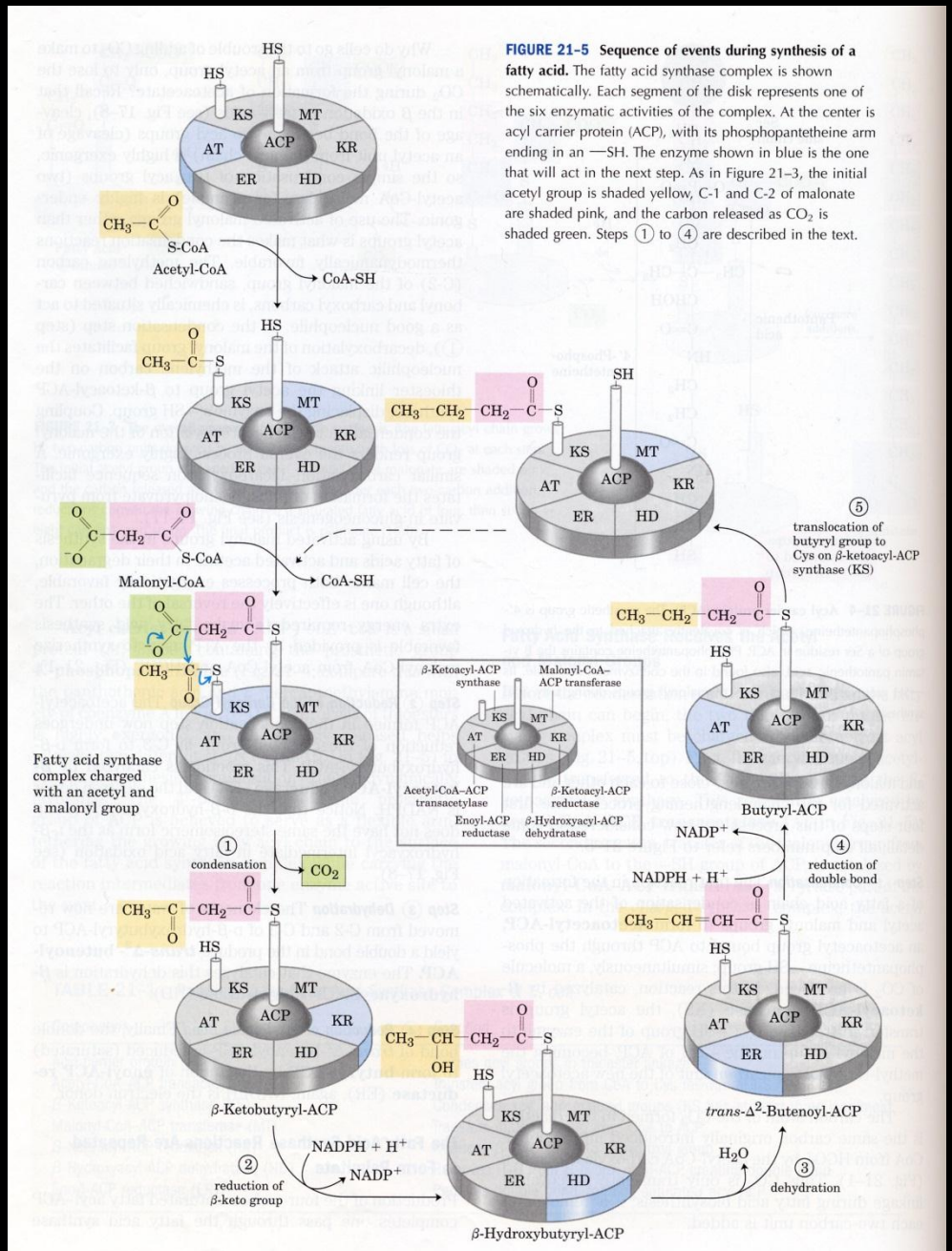
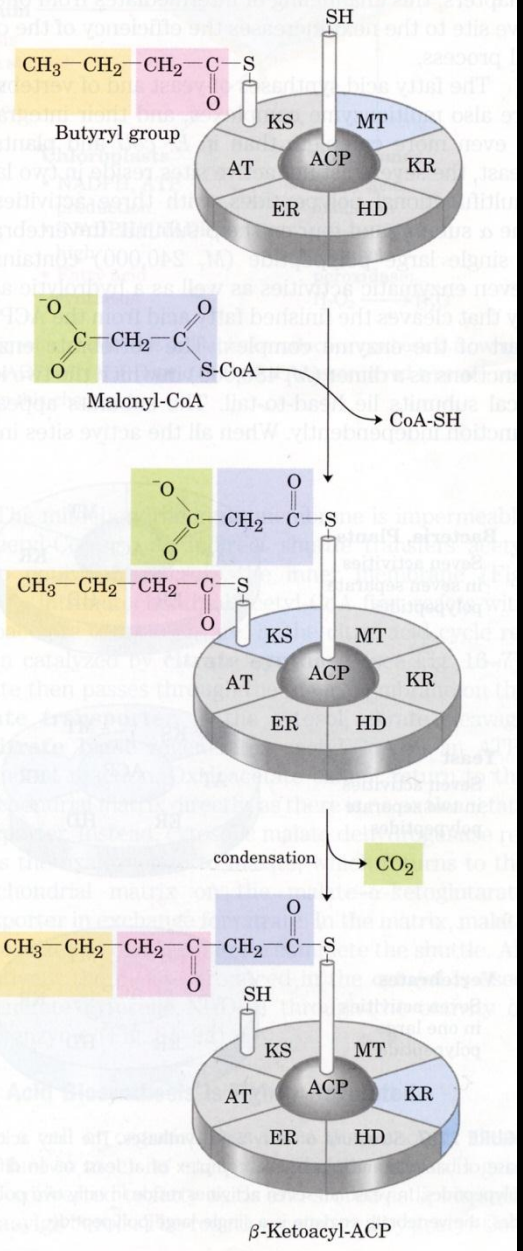
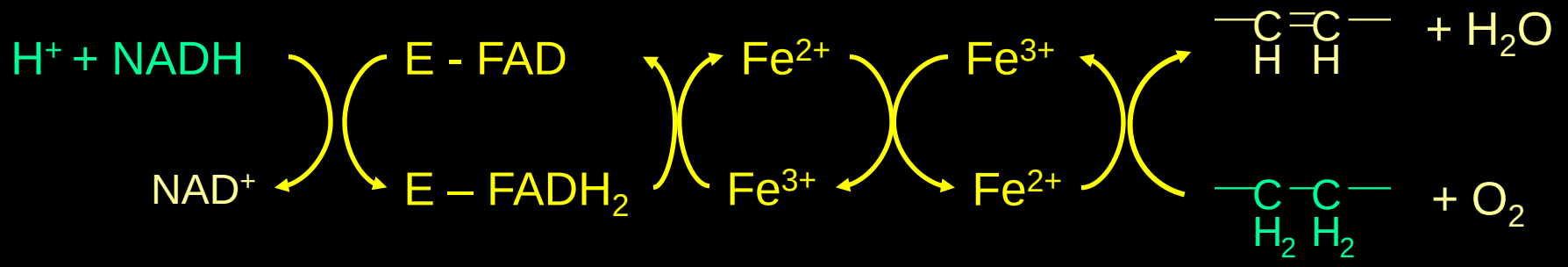


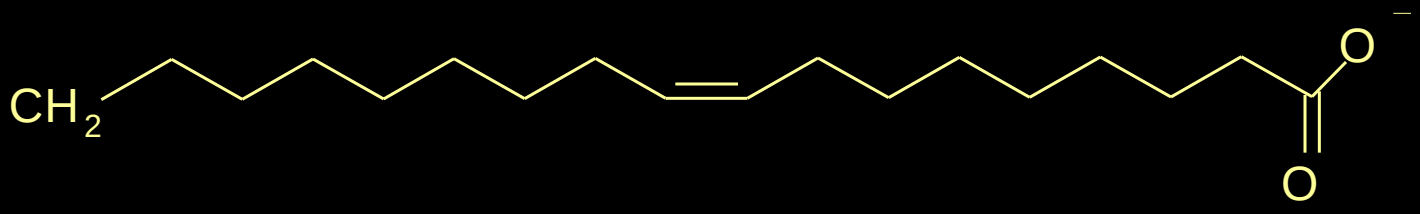
FIGURE 21–5 Sequence of events during synthesis of a fatty acid. The fatty acid synthase complex is shown schematically. Each segment of the disk represents one of the six enzymatic activities of the complex. At the center is acyl carrier protein (ACP), with its phosphopantetheine arm ending in an —SH. The enzyme shown in blue is the one that will act in the next step. As in Figure 21–3, the initial acetyl group is shaded yellow, C-1 and C-2 of malonate are shaded pink, and the carbon released as CO_2 is shaded green. Steps ① to ④ are described in the text.



Desaturation

- occurs on the membrane of the ER.
- involves oxidation carried out by a mini e- transport chain
- O_2 is the final e- acceptor
- Requires NADH!





Oleic acid [C18:1]

Mammals cannot introduce double bonds further out than C_9.

Hence, linoleic acid (18:2 cis Δ^9 ,Δ^{12}) and linolenic acid (18:3 cis Δ^9 ,Δ^{12} , Δ^{15}) cannot be made.

They must be obtained from the diet.

Control of FA Synthesis

Acetyl-CoA

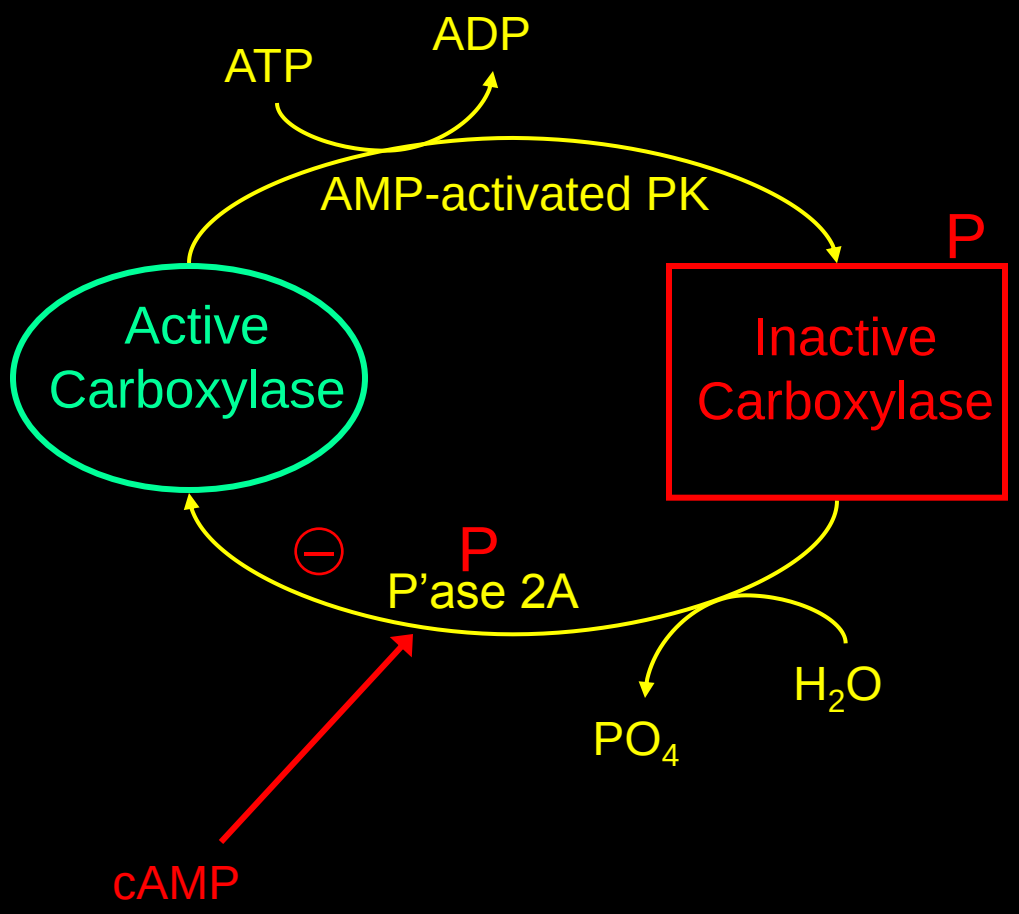
Acetyl CoA carboxylase

- Citrate ⊕
- Palmitoyl CoA ⊖
- AMP ⊖
- Glucagon ⊖
- Epinephrine ⊖
- Insulin ⊕
- cAMP ⊖

Malonyl CoA

Fatty Acids

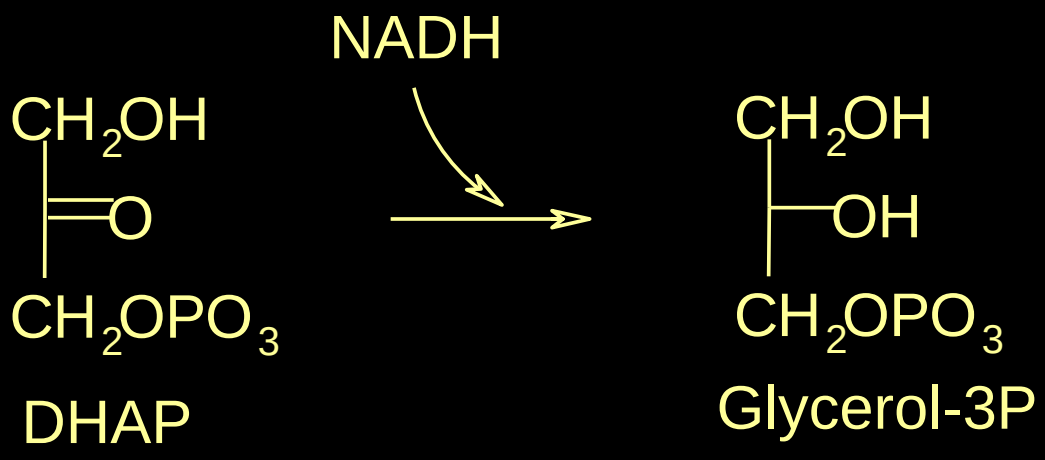
Acetyl CoA Carboxylase



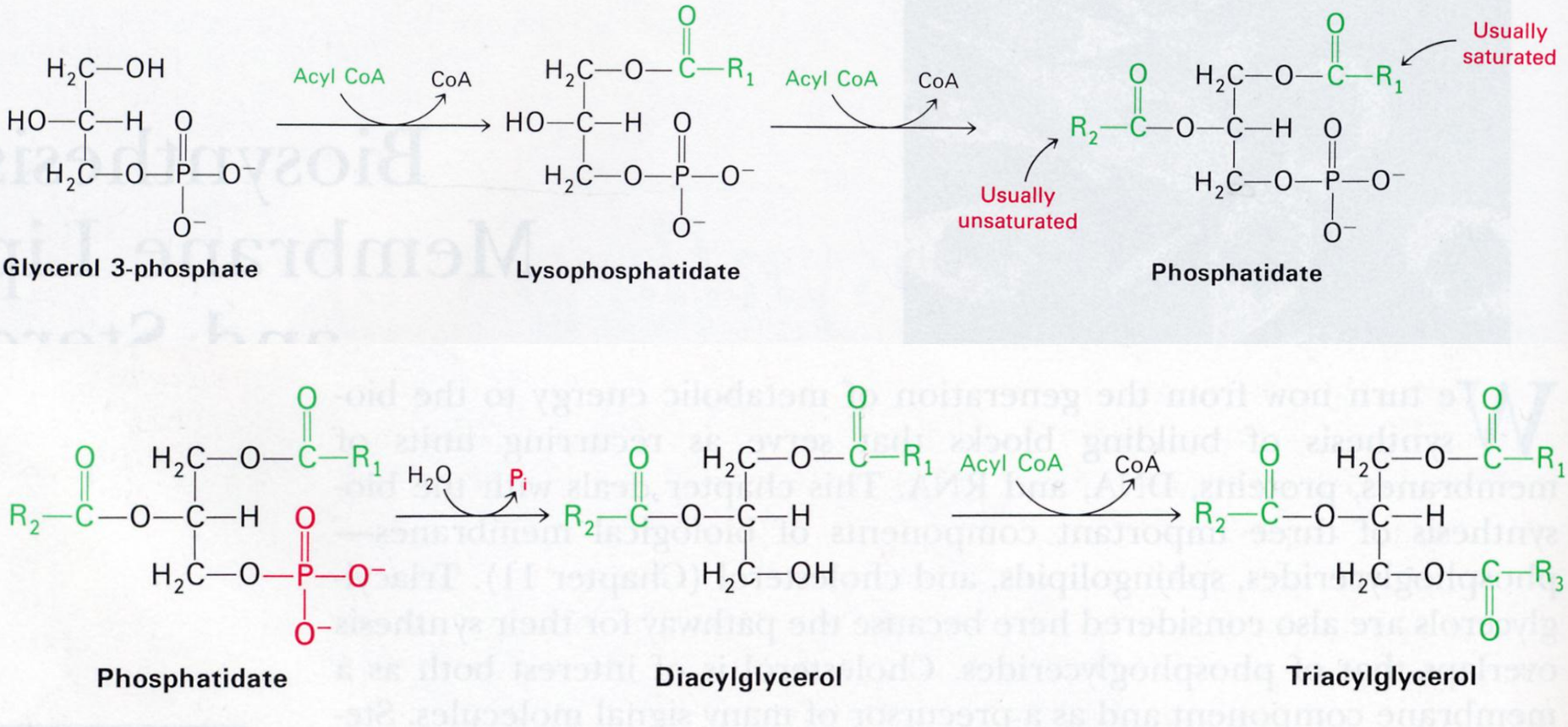
Synthesis of Palmitate Requires:

- 8 Acetyl-CoA
- 7 ATP
- 14 NADPH

Synthesis of Triacylglycerol

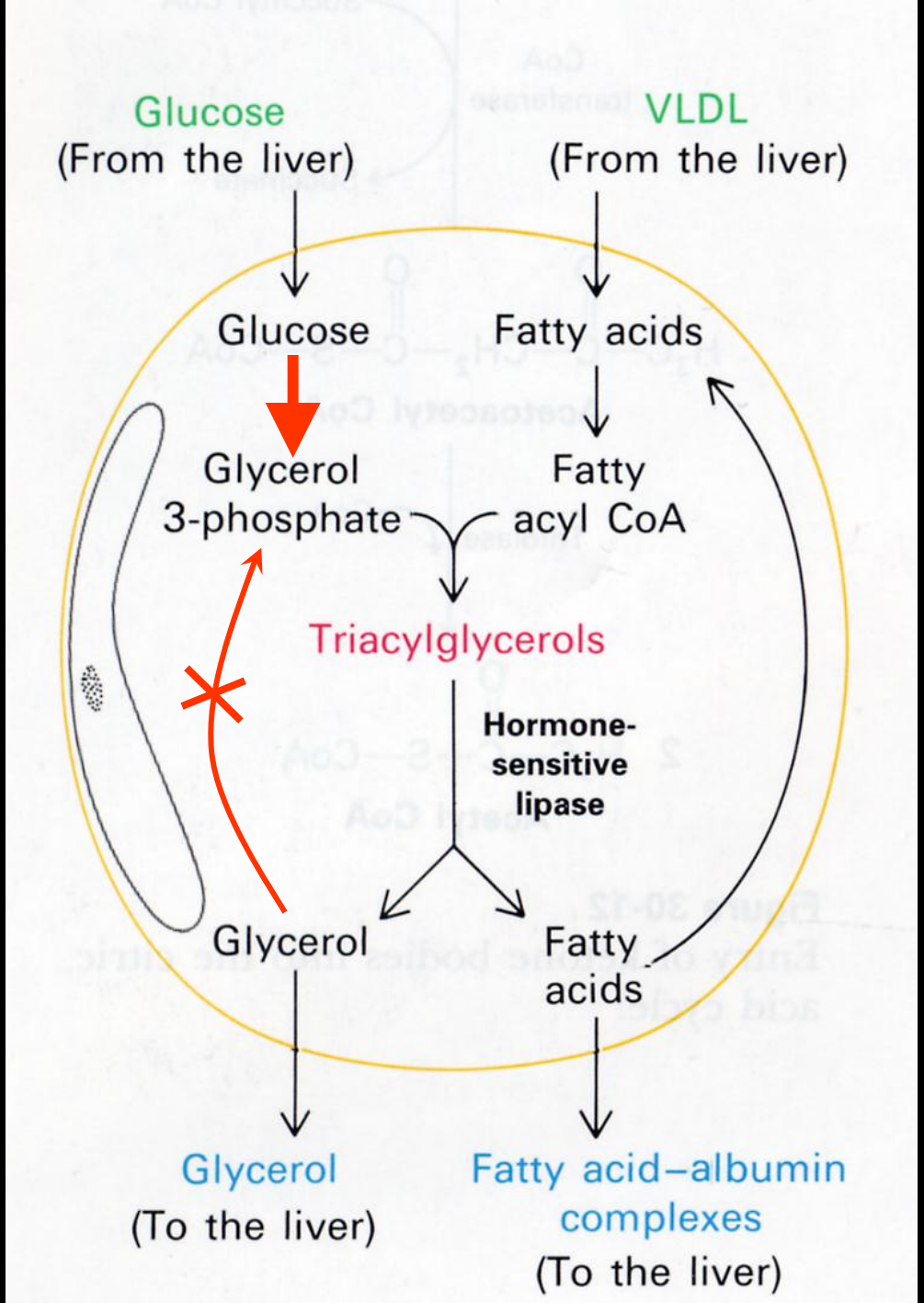


In adipose tissue, glucose is required to generate DHAP, the direct precursor of glycerol-3P



FA synthesis occurs primarily in **LIVER**, some in adipose tissue, some in skeletal muscle.

TAG is made in **LIVER** & adipose tissue. Main function of adipose tissue is **TAG STORAGE.**



In adipose tissue, G3P must be made from glucose.

G3P cannot be made from glycerol.

Thus, glucose is required in adipose tissue for synthesis of TAG.