Glycolysis

Graded Quiz Question #1

How does insulin help glucose enter an adipocyte?

A. Active transport through GLUT1
B. Active transport through GLUT4
C. Passive transport through GLUT1
D. Passive transport through GLUT4

Graded Quiz Question #2

Which enzyme has a Km for glucose near the physiological range:

A. Glucokinase
B. Hexokinase
C. Phosphofructokinase
D. GLUT4

Graded Quiz Question #3

Which of the following is a target for glucagon dependent regulation in the liver?

A. GLUT2
B. PFK1
C. PFK2
D. Hexokinase

Graded Quiz Question #4

Why is fructose more lipogenic than glucose

A. It is a disaccharide and therefore has more energy content
B. It promotes insulin secretion more potently than glucose
C. Its catabolism skips several metabolic control points
D. Fructose is primarily metabolized in the adipose tissue

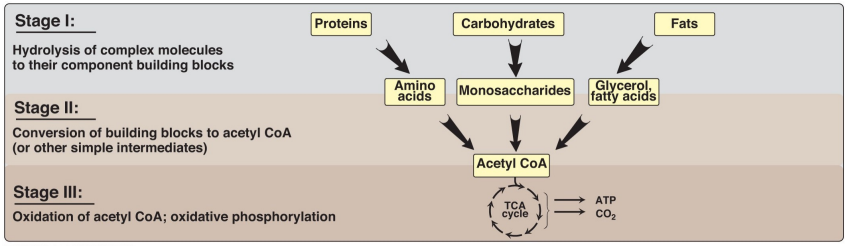
Graded Quiz Question #5

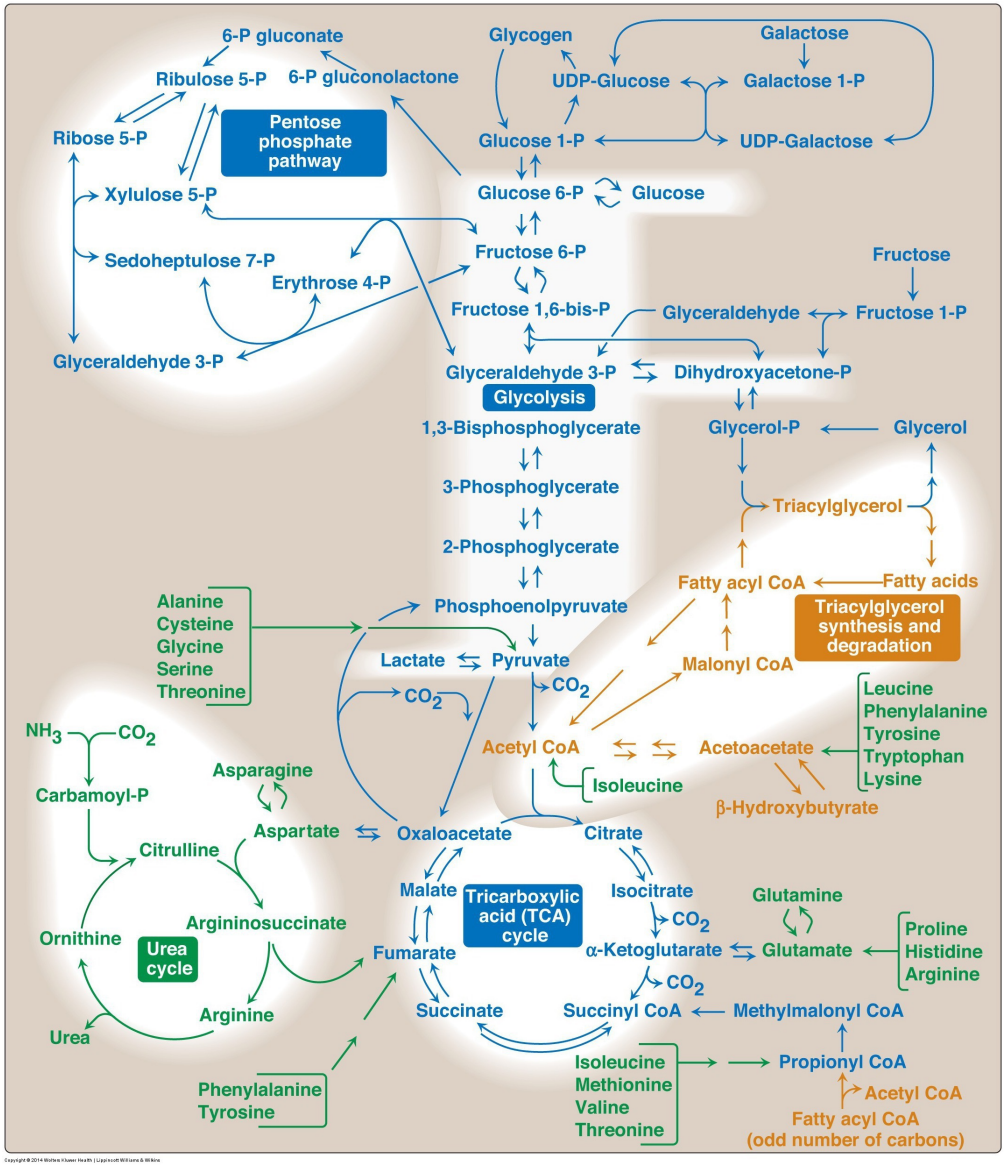
- What statement is **not** true of GALT?
  A. It can be treated by limiting galactose in the diet
  B. It can be treated by ingestion of lactase
  C. Children can be given soy-based formula
  D. Leads to an accumulation of galactose-1-phosphate

CHO Metabolism Overview

Part 2: Carbohydrate Metabolism

- September 19th: Lecture 4: Carbohydrate Structure, Digestion, Absorption, and Transport
- September 21st: Lecture 5: Glycolysis
- September 26th: Lecture 6: TCA Cycle and Oxidative Phosphorylation
- September 28th: Lecture 7: Glycogen Metabolism
- October 3rd: Lecture 8: Gluconeogenesis and the Pentose Phosphate Shunt
- October 5th: In Class Review Session: Overview and Carbohydrate Metabolism
  - Carbohydrate Metabolism Discussions
- October 10th: No Class, School of Public Health Symposium
- October 12th: Midterm Exam #1



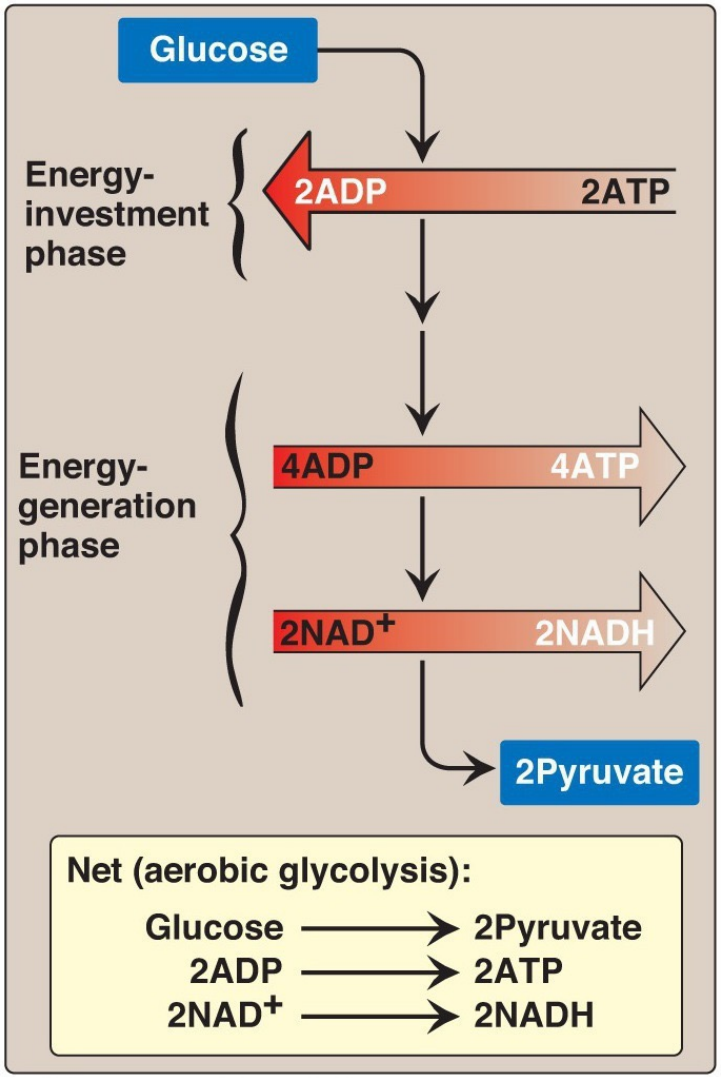


Glycolysis Learning Objectives

- Describe the relative roles of glycolysis, gluconeogenesis, the TCA cycle as central nodes of nutrient metabolism.
- Explain the catalytic differences and tissue distributions of glucokinase vs hexokinase and why this is important.
- Understand how ATP is produced from glycolysis, and the efficiency of aerobic vs non-aerobic glycolysis
- Understand the key points of regulation of glycolysis and how these regulatory points are controlled, notably how glucokinase/hexokinase, PFK1 and PK are regulated including what signals are important in what tissues.
- Describe the potential fates of pyruvate, and what dictates the next steps in its metabolism
- Explain how non-glucose carbohydrates such as galactose and fructose enter glycolysis, and how their point of entry affects how they are regulated.

Glycolysis

- Main pathway of monosaccharide degradation
- Main tissue sites
  - Liver, muscle
- Occurs in <u>cytoplasm</u> of the cell
- Glucose conversion to **<u>two</u>** 3-<u>carbon products</u>: pyruvate



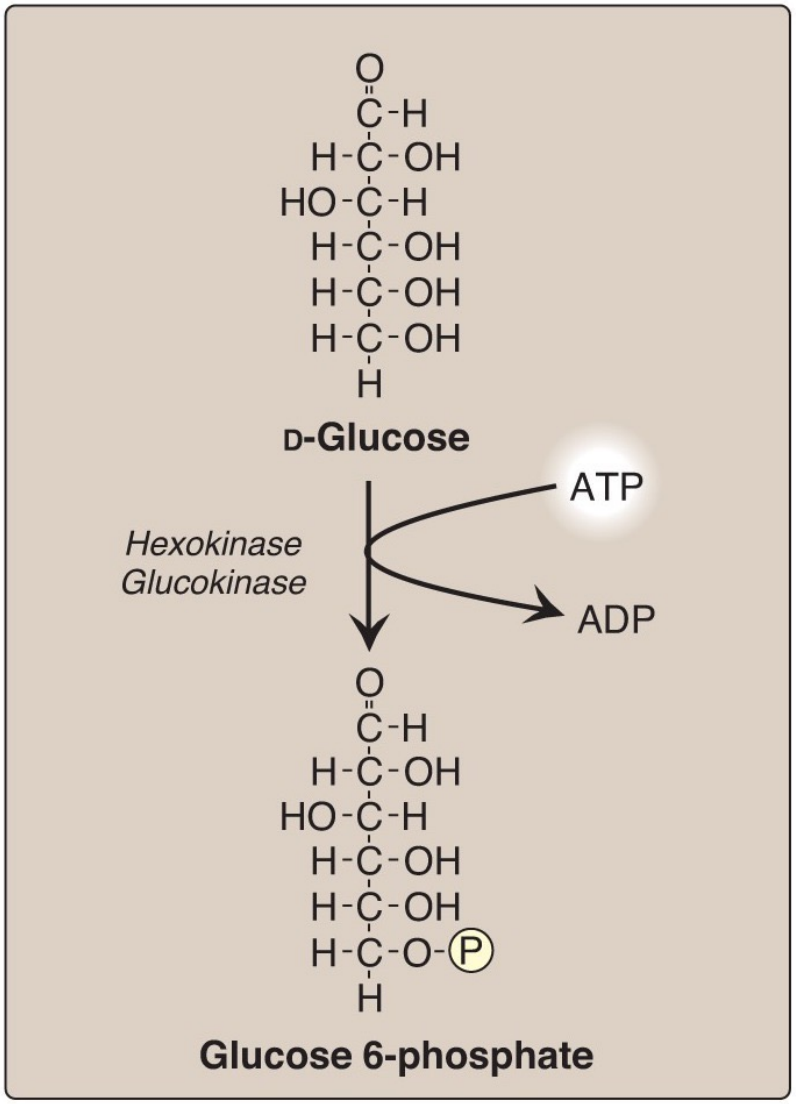
Staring with the End

- End product: two pyruvates
  - Aerobic Conditions
    - Becomes Acetyl-CoA
      - In presence of CHO but need energy -> TCA Cycle
      - In presence of CHO but don't need energy -> Lipids
      - In absence of CHO (relevant for lipid oxidation)
        - » Ketone Bodies (if OAA absent)
        - » Gluconeogenesis (if OAA present)
  - Anaerobic conditions
    - Becomes lactate
    - Lactate goes to liver for reconversion back to glucose

What is Glycolysis Accomplishing?

- Think about muscle, liver and fat.
- When would we want to activate or inactivate glycolysis in these tissues. Is it always the same?

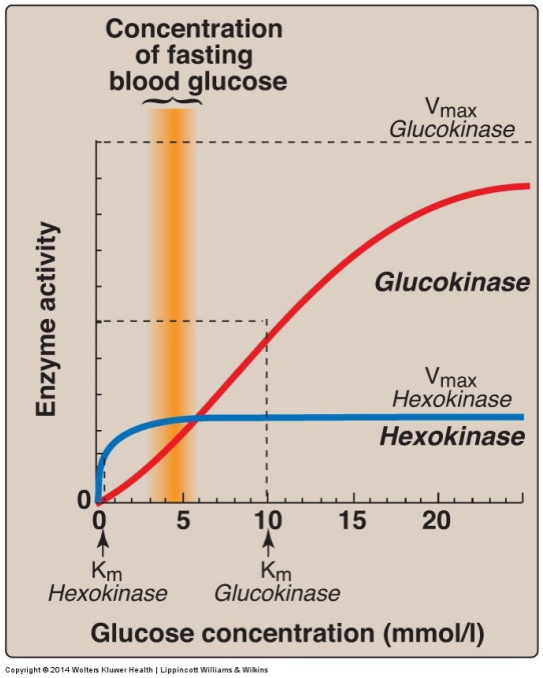
Generating Glucose-6-Phosphate



- Traps glucose in the cell
- Consumes ATP
- Reversible by Glucose-6-Phosphatase (in liver)

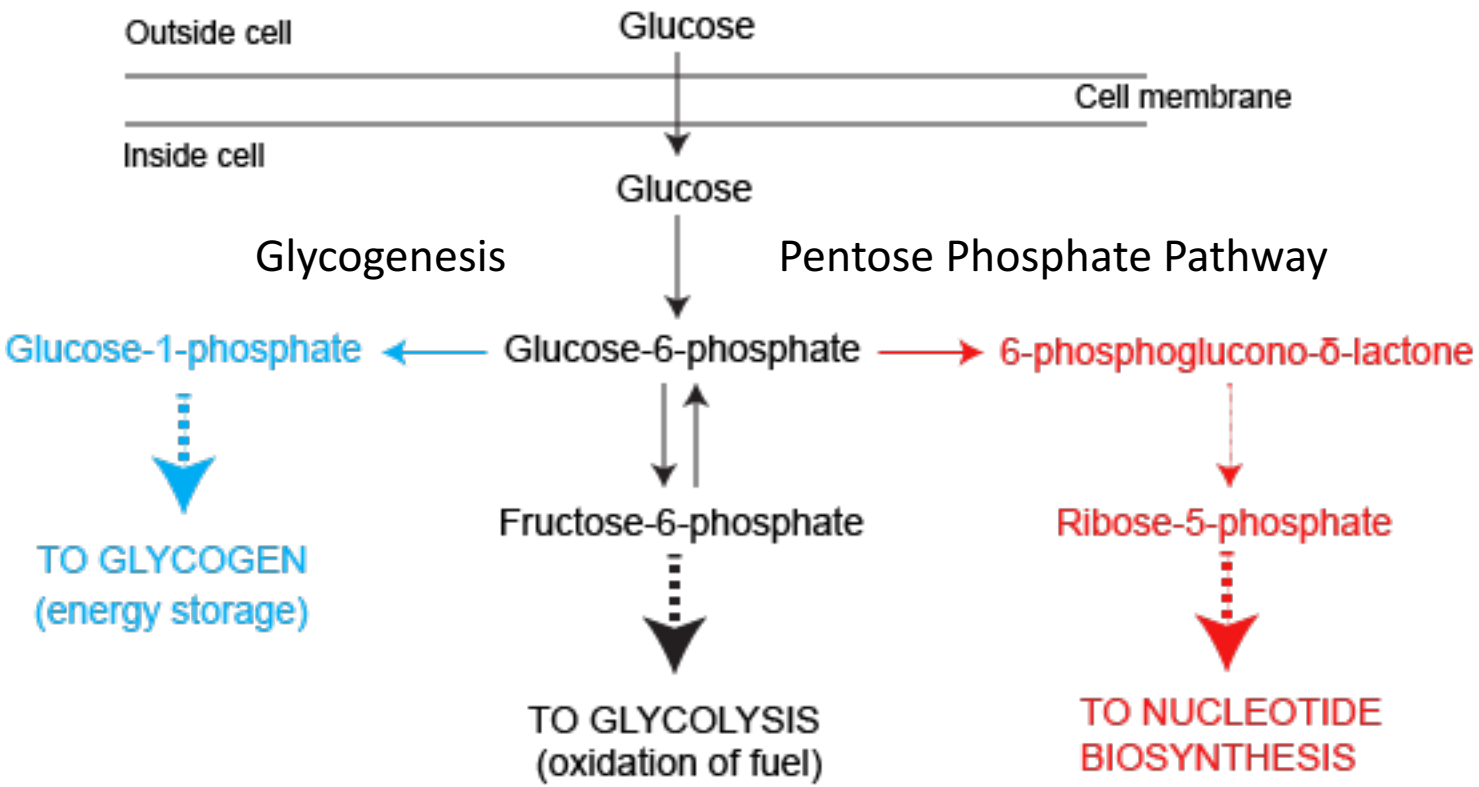
Glucokinase vs Hexokinase

Enzyme	Tissue	Regulation	Kinetics
Glucokinase	Liver/Pancreas		Co-operative/ Fast
Hexokinase	Fat/Muscle	-G6P	High Affinity

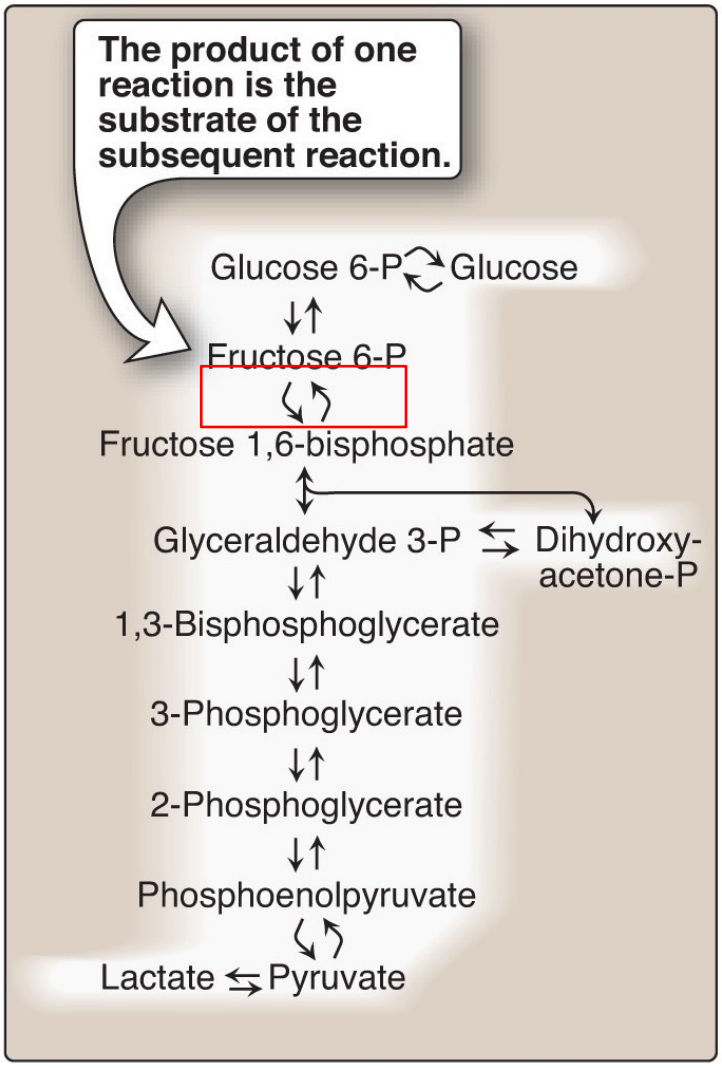


What is the advantage of these different kinetics in these tissues?

Fates of Glucose-6-Phosphate



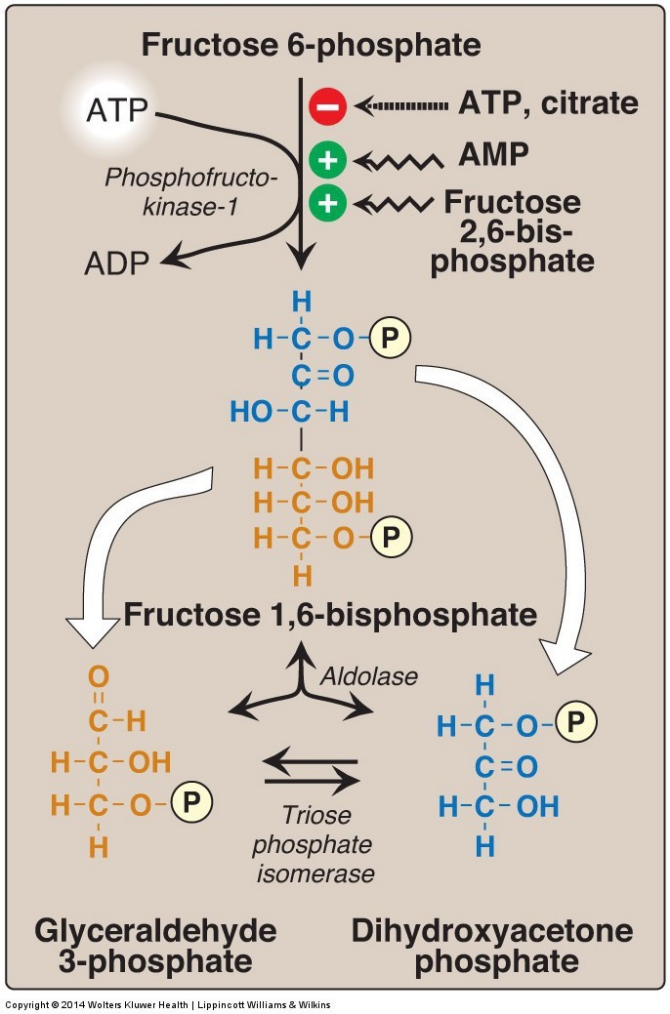
The Next Regulated Step is PFK1



Taurui's Disease

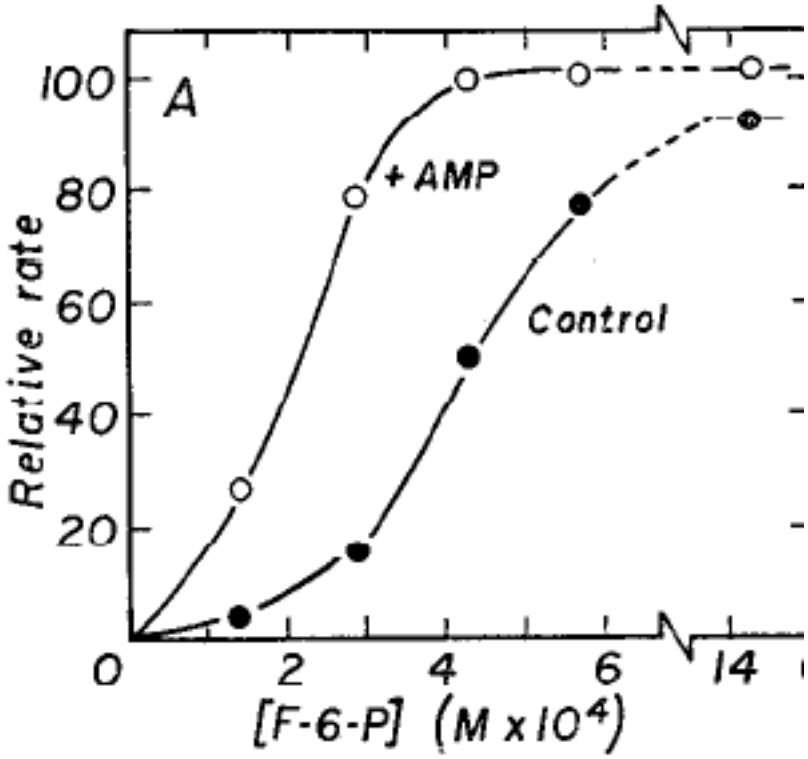
- Heritible loss of the PFK1 isoform in Muscle (*PFKM*)
- Symptoms include
  - Muscle weakness
  - Increased glycogen in muscle
  - Myopathy
- Possible treatments?

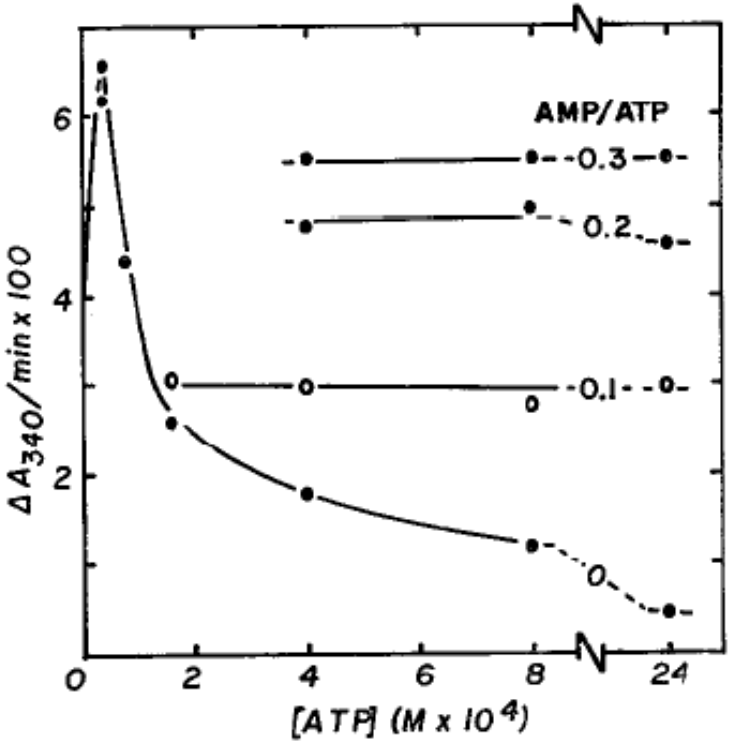
Regulation of PFK1



- Priority of regulators
  1. F26bP
  2. AMP
  3. ATP
  4. Citrate

Allosteric Regulation of PFK1

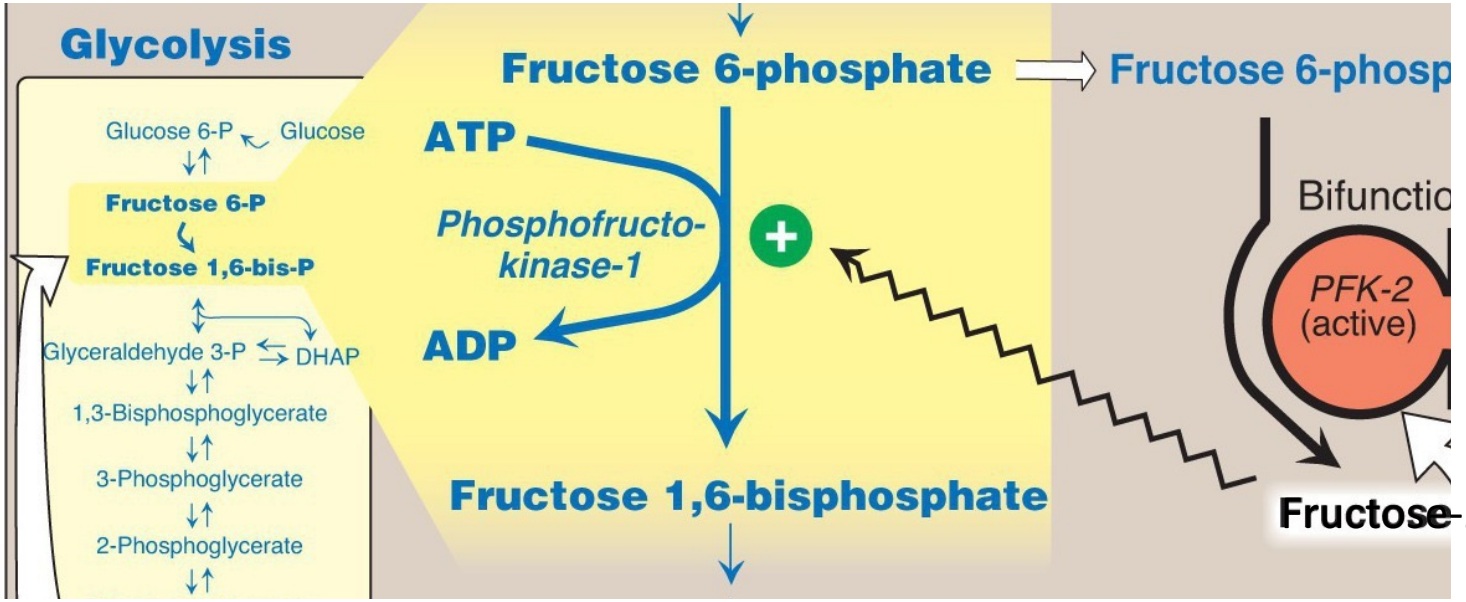




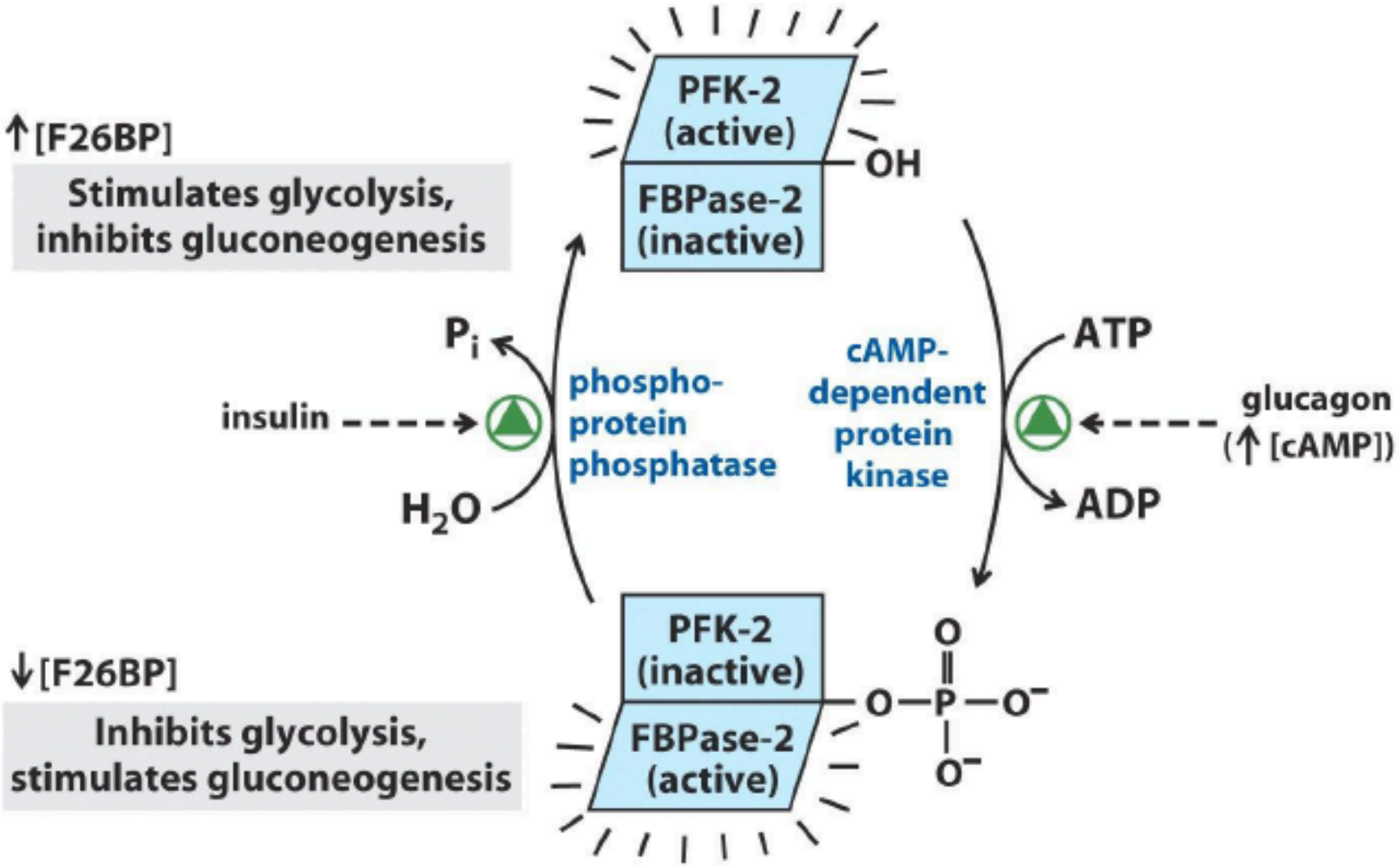
F6P is held constant here

Mansour TE. Studies on Heart Phosphofructokinase : Studies on Heart Phosphofructokinase : Inhibition , and Activation. *J. Biol. Chem.* 1963;238(7):2285–2292.

Regulating the Regulator



Regulating the Regulator of the Regulator



What is the point of all this?

- Buildup of TCA cycle intermediates can slow glycolysis (**Citrate**)
- That can be over-ridden by energy needs (**ATP/AMP**)
- BUT glucose flux can over-ride energy needs (**F26bP**)
- AND hormones can over-ride glucose flux (**PFK2 inhibition, reducing F26bp**)

How does glucagon/adrenaline inhibit PFK-2 activity in liver not muscle

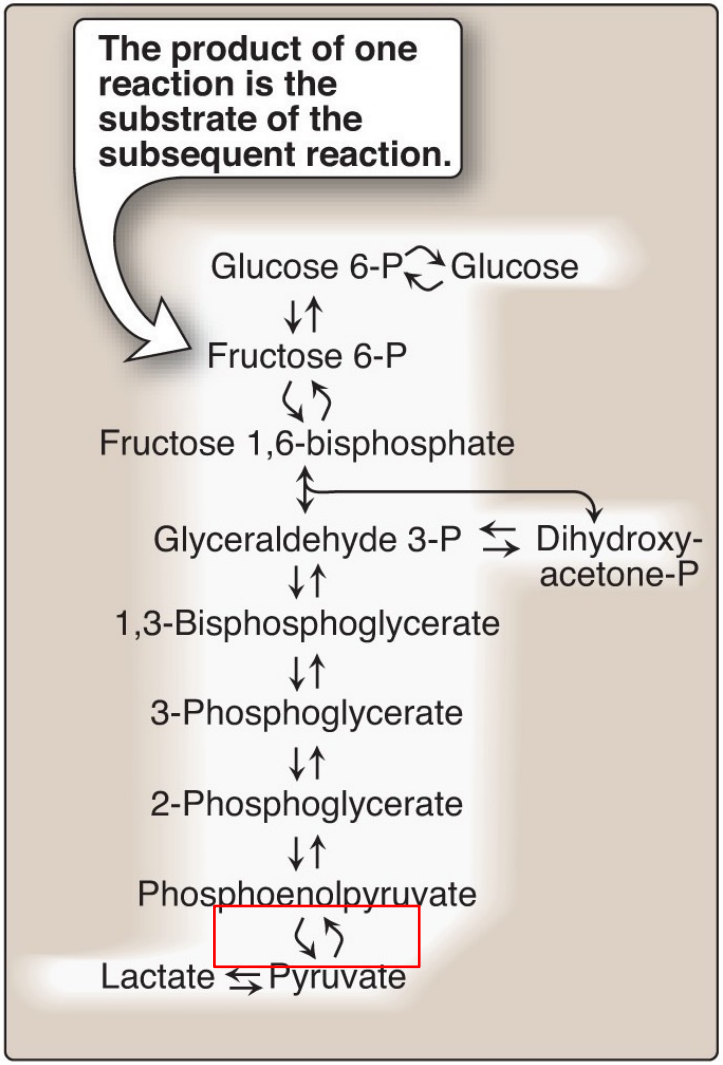
A. Muscle doesn't have PFK-2 activity
B. Glucagon/Adrenaline do not activate PKA in muscle
C. Muscle PFK-2 can't be phosphorylated by PKA
D. There are no Glucagon/Adrenline receptors in muscle

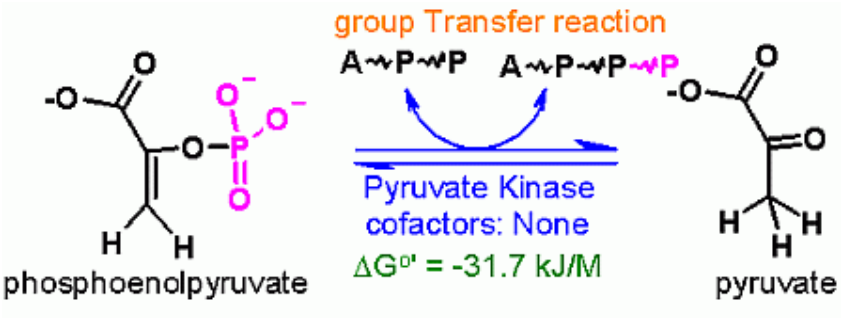
Tissue Specificity in PFK2 Regulation

- Glucagon/Adrenaline can phosphorylate and inhibit Liver PFK2 but **not** Muscle PFK2

Pourquoi?

The third regulated step in glycolysis is Pyruvate Kinase





Substrate mediated ADP phosphorylation

How is Pyruvate Kinase Regulated

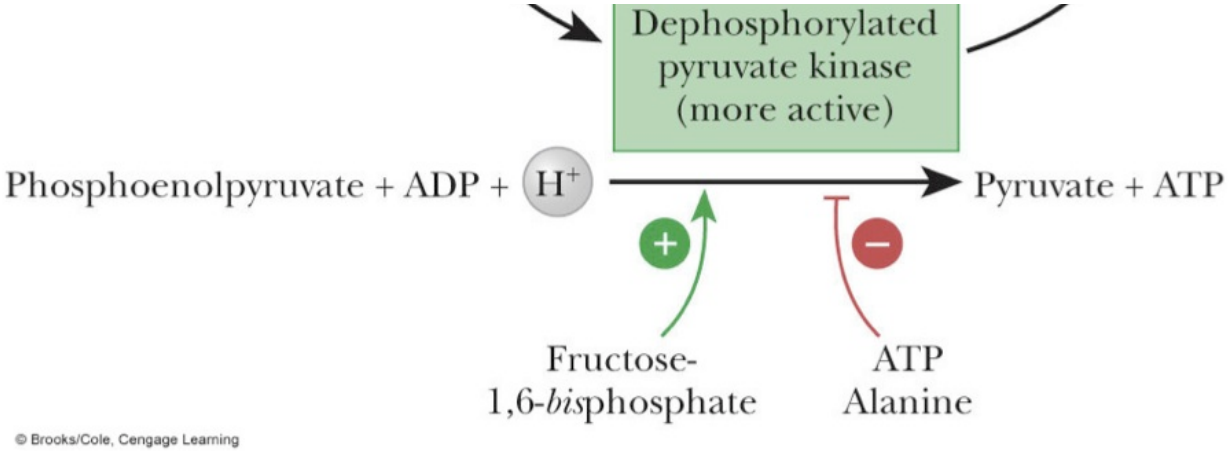


Fig. 18-13, p. 535

Post-Translational Regulation of Pyruvate Kinase

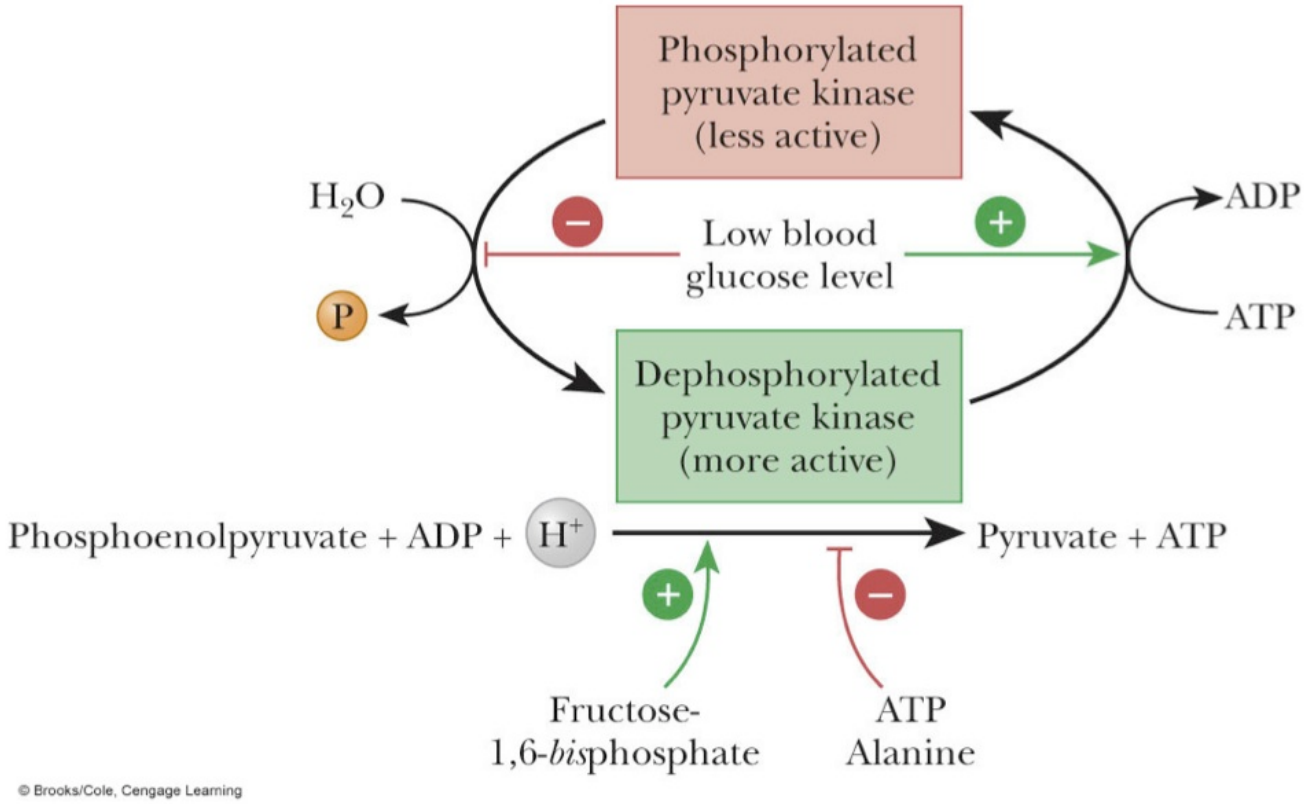


Fig. 18-13, p. 535

Alanine inhibition only in liver

What would PFK2 deficiency do to Pyruvate Kinase Activity

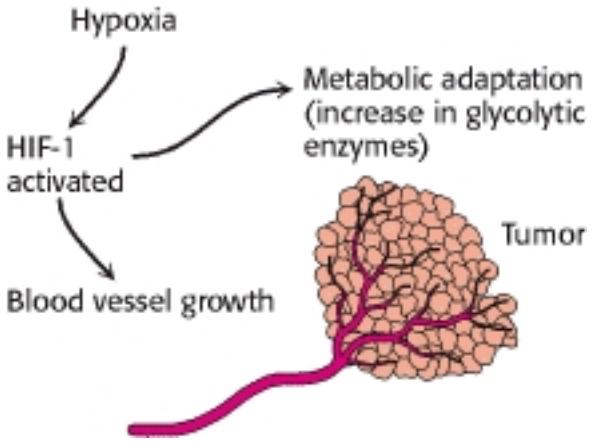
A. Increase it because of less Fructose-1,6-bisphosphate
B. Decrease it because of less Fructose-1,6-bisphosphate
C. Increase it because of less Fructose-2,6-bisphosphate
D. Decrease it because of less Fructose-2,6-bisphosphate

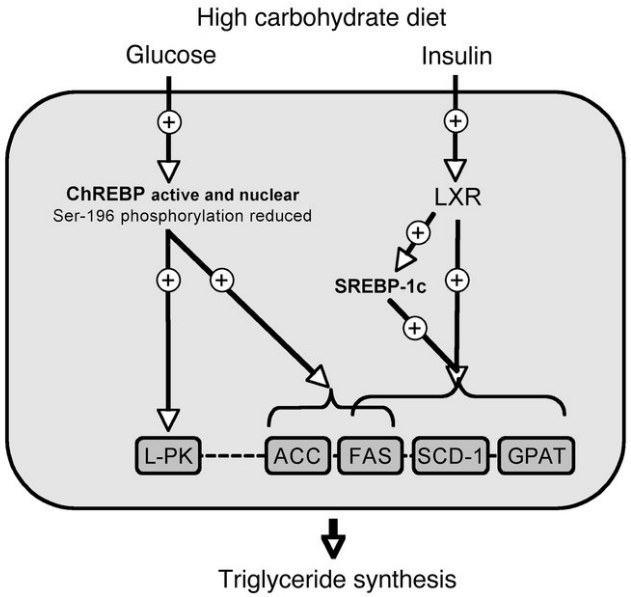
Tissue Specific Regulation of Glycolysis Summary

Component	Liver	Muscle
Glucokinase/Hexokinase	Not inhibited by G6P	Inhibited by G6P
Phosphofructokinase	Inhibition of PFK-2 (regulates via F26bP)	PFK-2 not inhibited by phosphorylation
Pyruvate Kinase	Inhibition of PK by alanine and by phosphorylation	PK not inhibited by alanine or phosphorylation

Transcriptional Regulation of GK/HK, PFK1 and PK Promotes Glycolysis

- Hypoxia (HIF)
- Carbohydrate sensing (ChREBP – L-PK)
- Chronic glucagon (CREB - GK)





Glycolysis Net ATP

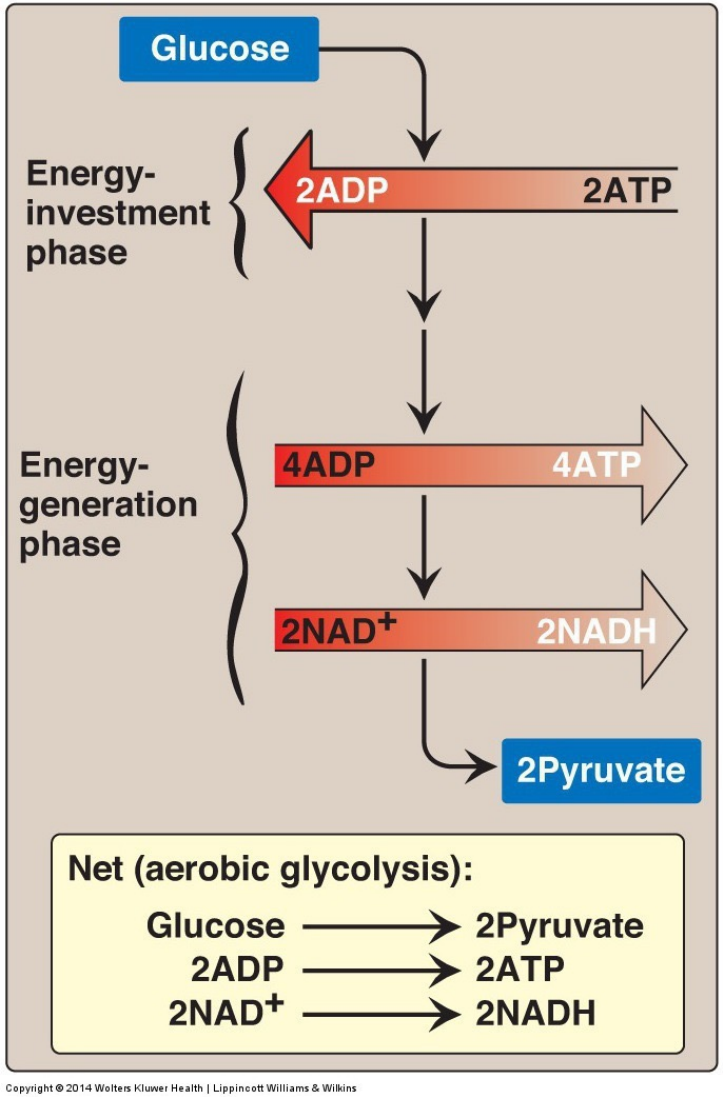
- Note: NADH is energy equivalent to 3 ATP (from the ETC)

- Energy Consuming Reactions:
  - Reactions 1: 1 ATP
  - Reaction 3: 1 ATP

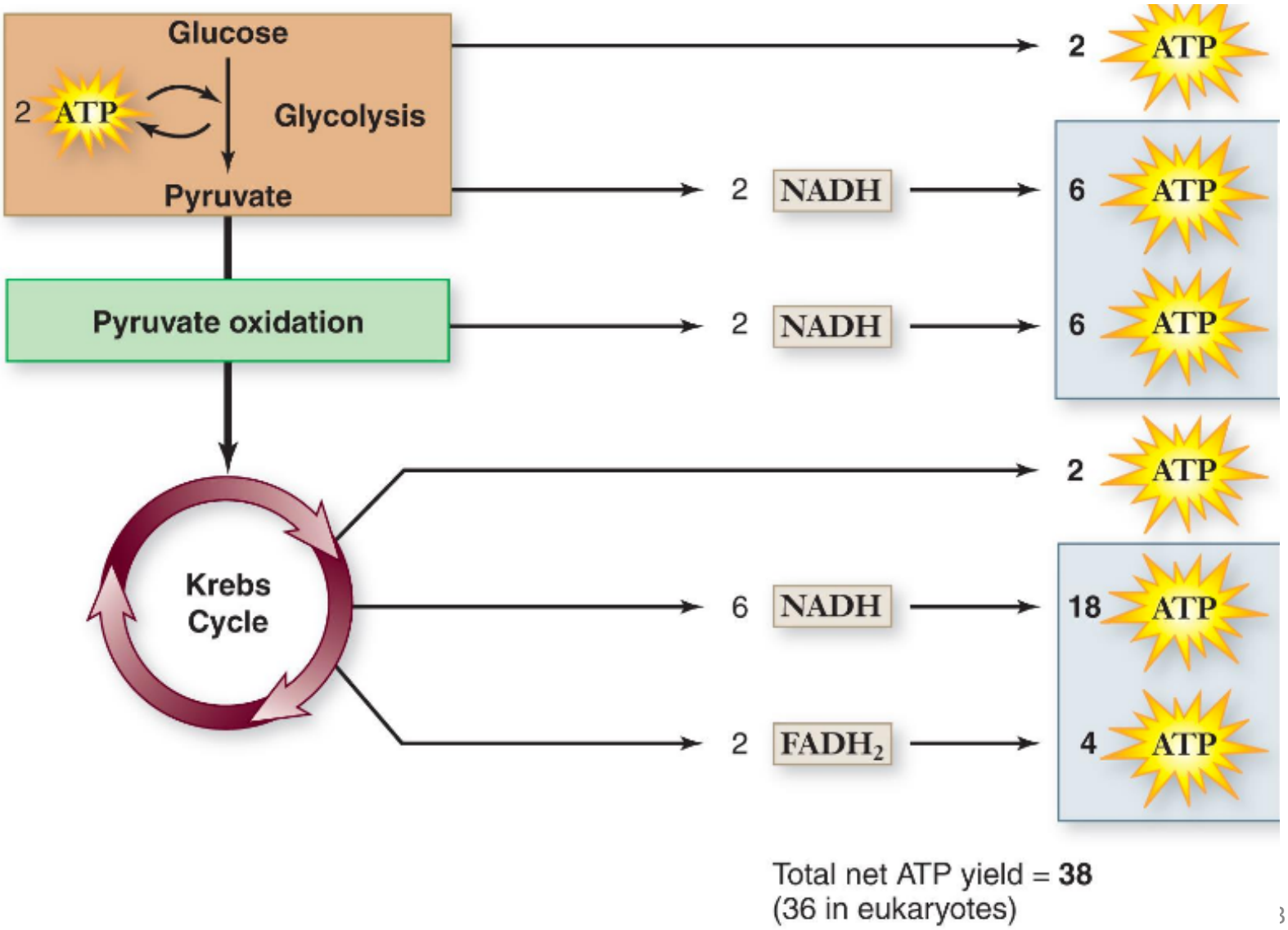
- Energy Generating Reactions:
  - Reaction 6: 1 NADH x 2 (3 ATP x 2 = 6 ATP)
  - Reaction 7: 1 ATP x 2 (2 ATP)
  - Reaction 10: 1 ATP x 2 (2 ATP)

Net Energy Gain:

4 ATP + 2 NADH minus 2 ATP = **8 ATP generated** from glycolytic breakdown of glucose

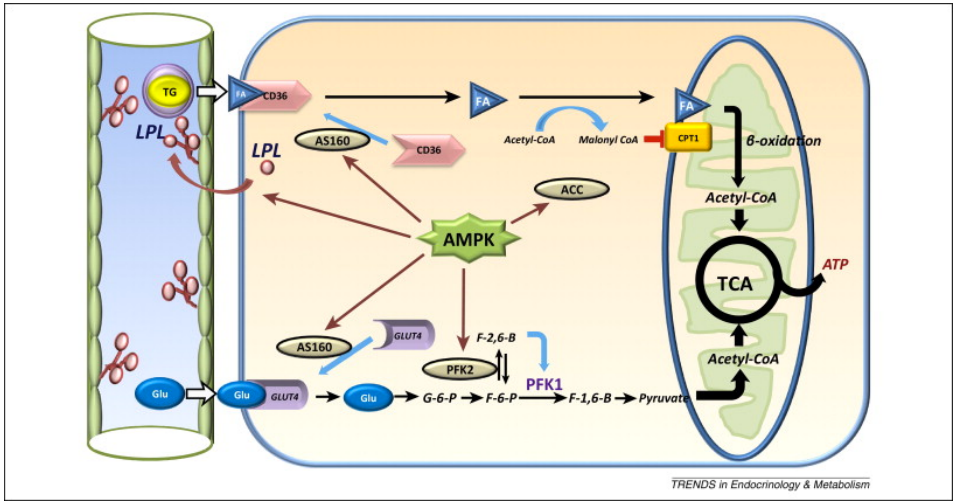


TCA Cycle Net ATP



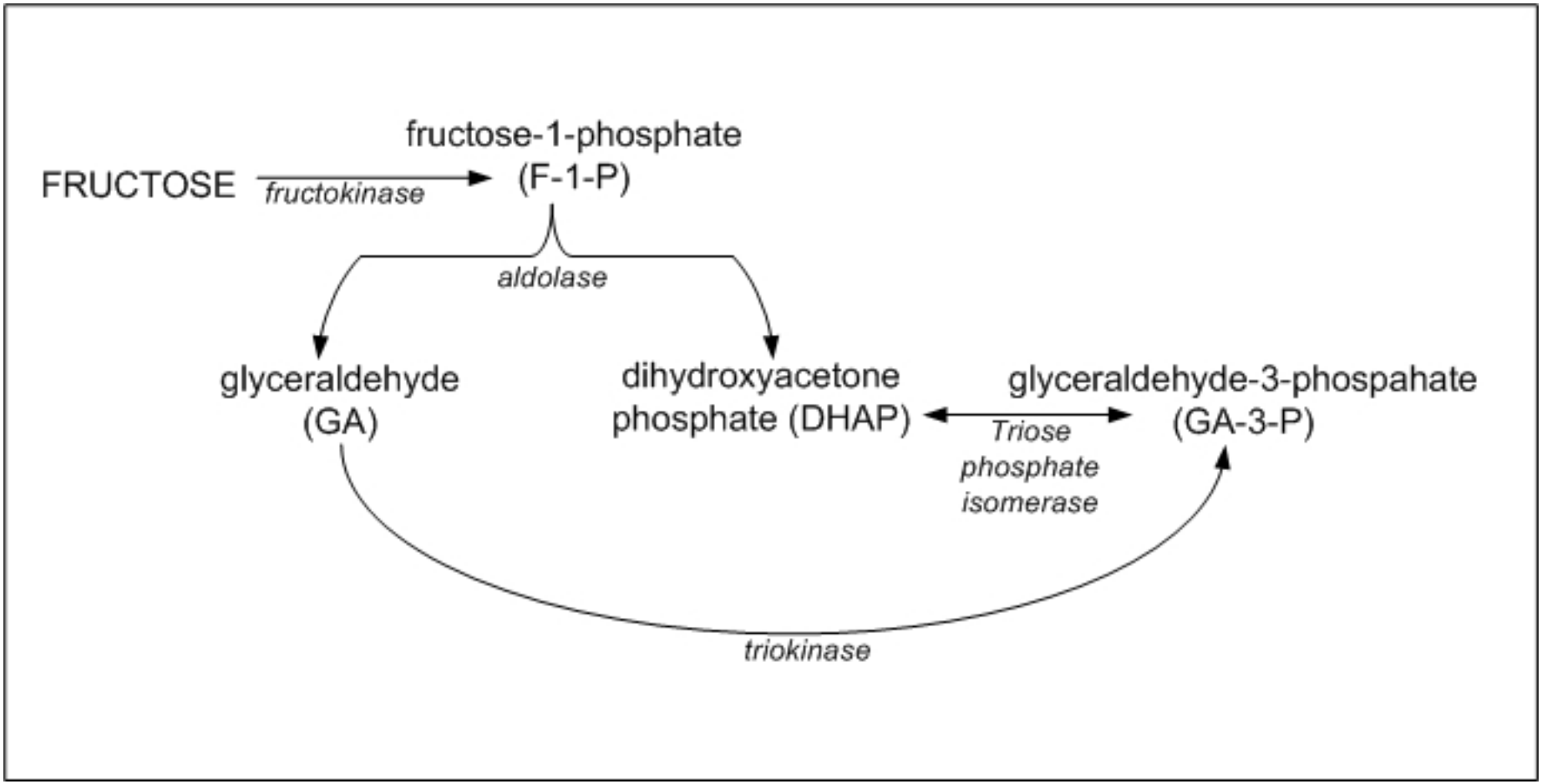
Energy Stress and Glycolysis

- We have discussed 2 ways in which elevated low energy can activate glycolysis, do you remember what they are?
- AMPK can regulate glycolysis, think of an example of how it could do this



FRUCTOSE AND GALACTOSE

Liver Fructose Metabolism



Skips the regulatory steps of Glucokinase and PFK2

Fructose Consumption and Metabolic Health

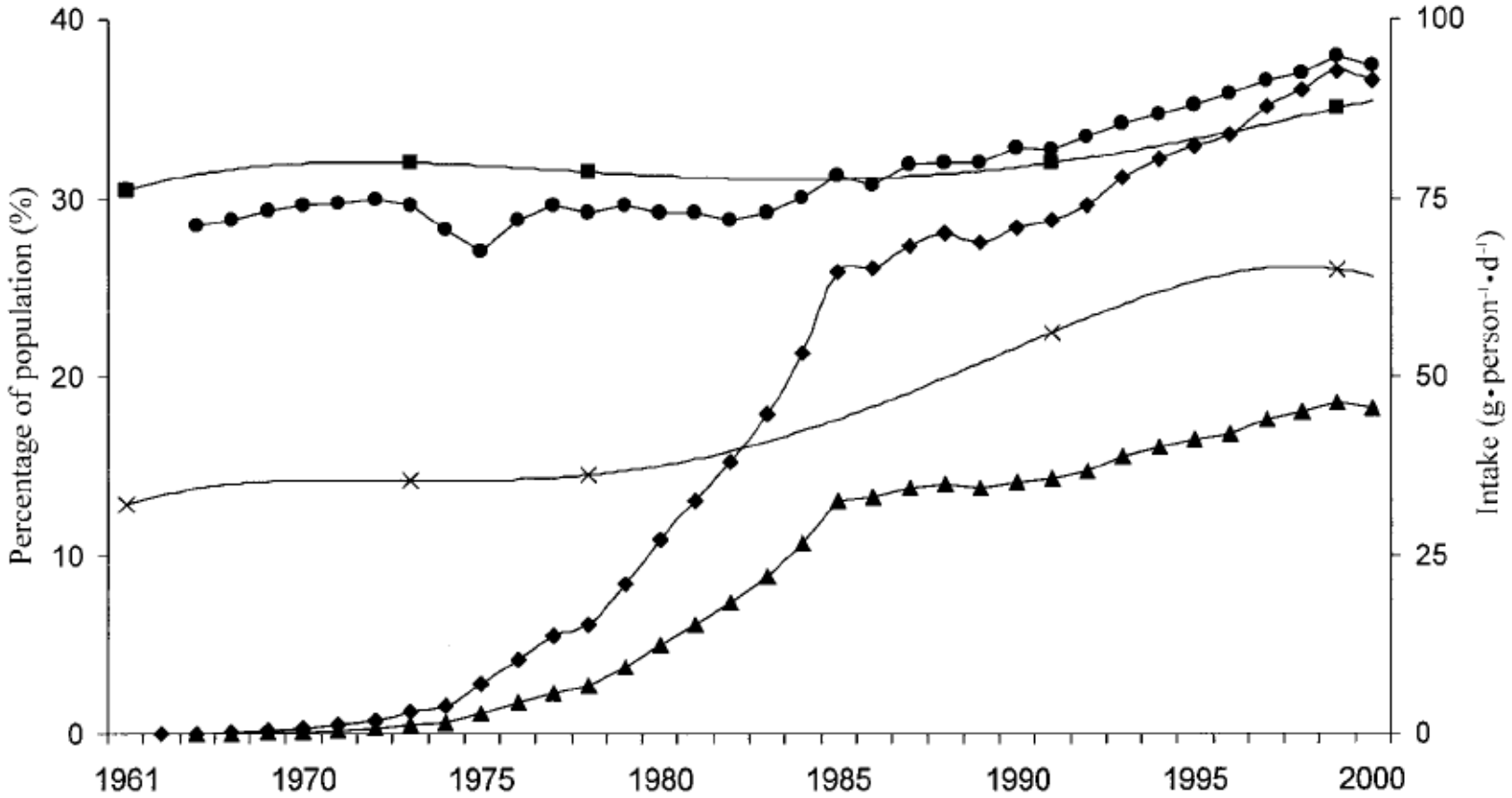


FIGURE 1. Estimated intakes of total fructose (●), free fructose (▲), and high-fructose corn syrup (HFCS, ♦) in relation to trends in the prevalence of overweight (■) and obesity (x) in the United States. Data from references 7 and 35.

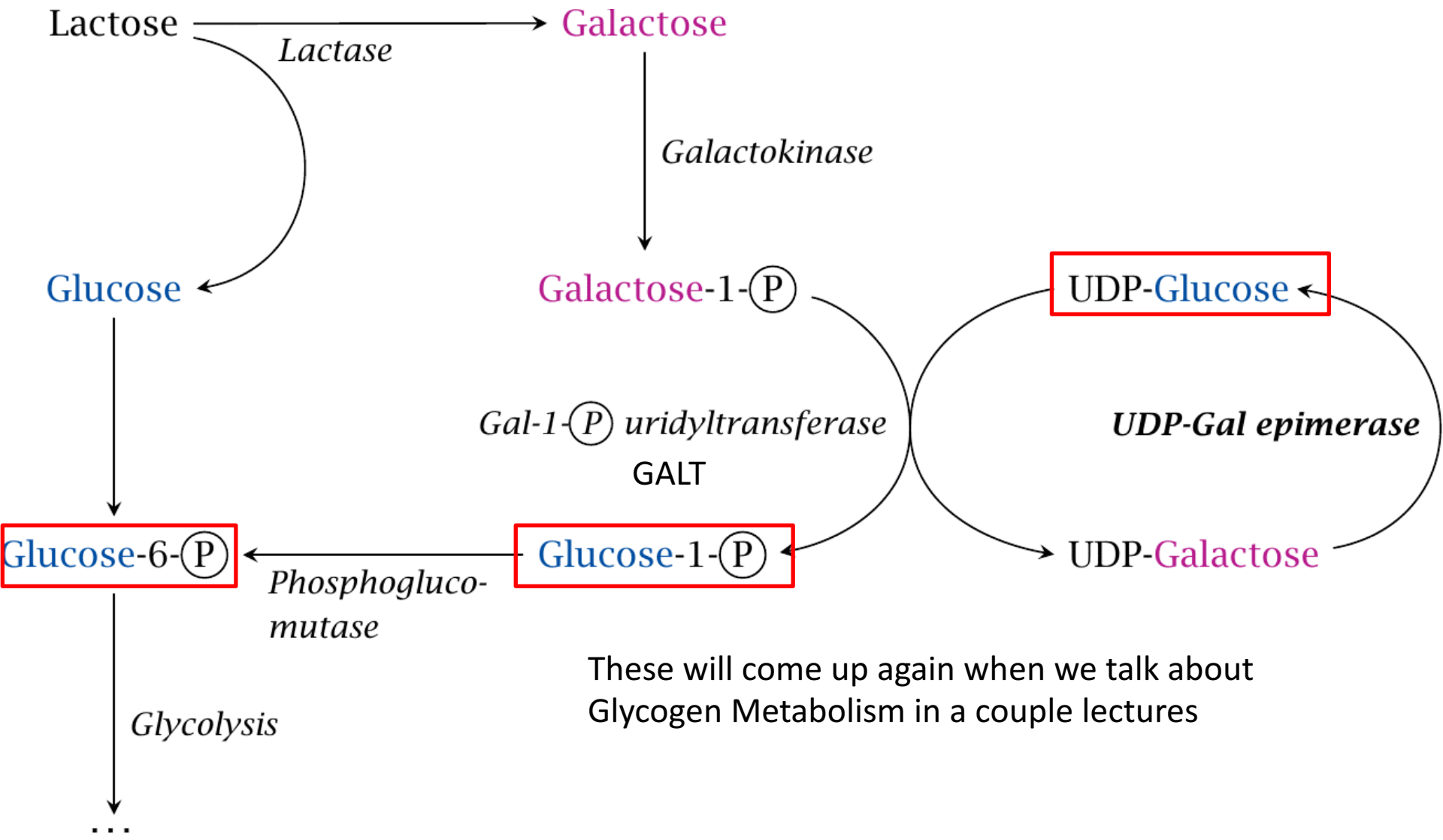
Inherited Disorders of Fructose Metabolism

- Fructokinase mutations
  - Fructose not trapped in the cell
  - Elevated fructose in the blood
  - Generally not pathological
- Aldolase B mutations
  - Buildup of Fructose-1-phosphate
  - Impaired gluconeogenesis and glycogenolysis
  - High risk of hypoglycemia
- What if fructokinase made Fructose-6-phosphate (it dosent)? How would that affect glycolysis?

Fructolysis Summary

- Fructose glycolysis in liver begins with FK
  - Bypasses two important regulatory step in glycolysis
    - Reaction 1 (glucokinase/hexokinase)
    - Reaction 3 (phosphofructokinase)
  - Pyruvate products may be shifted to pathways involved in fatty acid or cholesterol synthesis
- Outside the liver hexokinase can phosphorylate Fructose to make F6P, but this is very inefficient

Galactolysis



These will come up again when we talk about Glycogen Metabolism in a couple lectures

Galactolysis Summary

- Galactose kinase phosphorylates galactose to galactose 1-phosphate
- Galactose 1-P is coverted to Glucose 1-phosphate
  - G1P has different fates dependent on energy needs:
    1. Glycogenesis
    2. Glycolysis

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