Carbohydrate Metabolism

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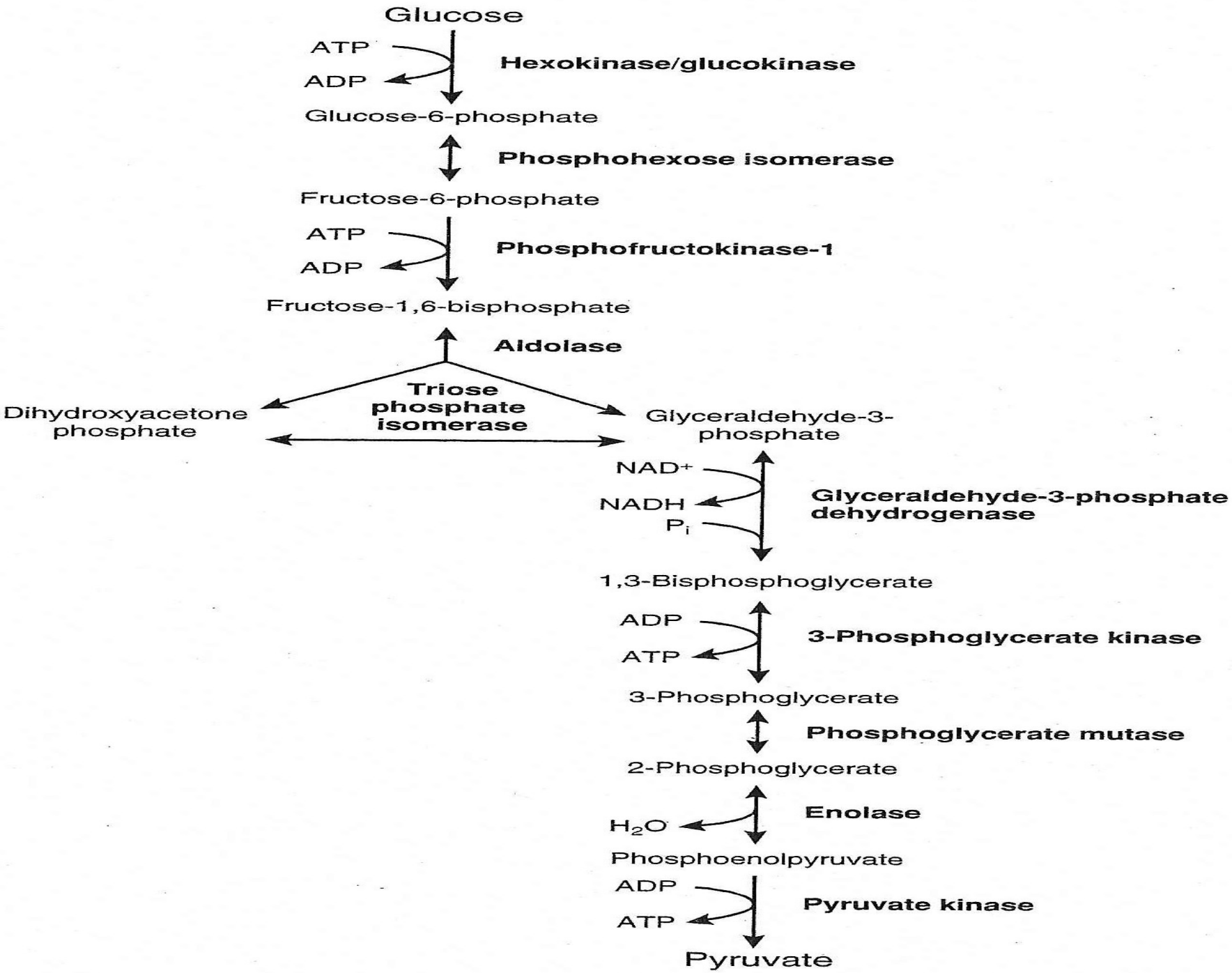
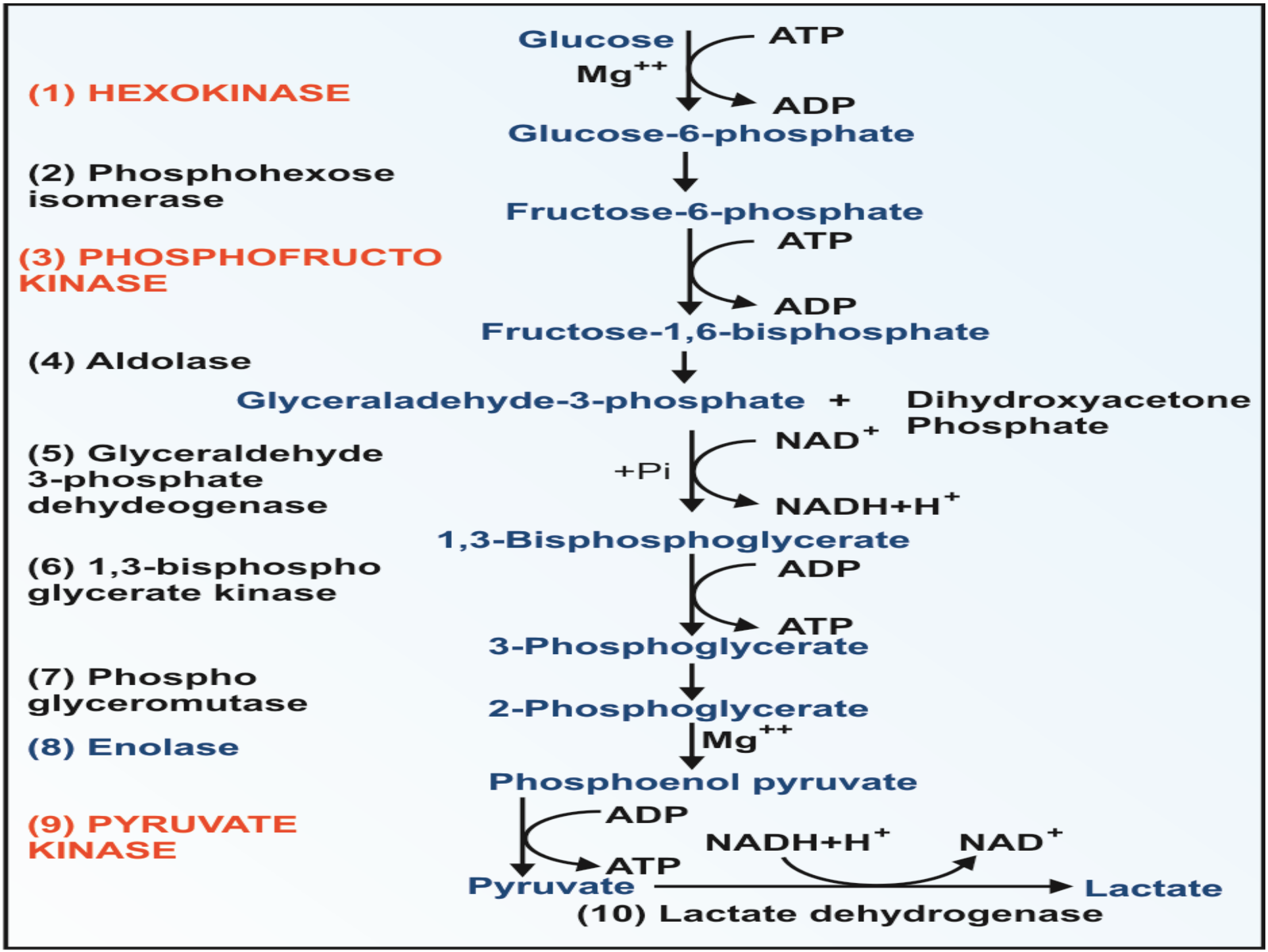
Surat

- Glycolysis
- Gluconeogenesis
- Glycogenesis
- Glycogenolysis

Glycolysis


Glucose
ATP
ADP
Hexokinase/glucokinase
Glucose-6-phosphate
Phosphohexose isomerase
Fructose-6-phosphate
ATP
ADP
Phosphofructokinase-1
Fructose-1,6-bisphosphate
Aldolase
Triose phosphate isomerase
Dihydroxyacetone phosphate
Glyceraldehyde-3-phosphate
NAD+
NADH
Pi
Glyceraldehyde-3-phosphate dehydrogenase
1,3-Bisphosphoglycerate
ADP
ATP
3-Phosphoglycerate kinase
3-Phosphoglycerate
Phosphoglycerate mutase
2-Phosphoglycerate
H2O
Enolase
Phosphoenolpyruvate
ADP
ATP
Pyruvate kinase
Pyruvate


Glucose
ATP
Mg++
(1) HEXOKINASE
ADP
Glucose-6-phosphate
(2) Phosphohexose isomerase
Fructose-6-phosphate
ATP
(3) PHOSPHOFRUCTO KINASE
ADP
Fructose-1,6-bisphosphate
(4) Aldolase
Glyceraladehyde-3-phosphate
+
Dihydroxyacetone Phosphate
NAD+
(5) Glyceraldehyde 3-phosphate dehydeogenase
+Pi
NADH+H+
1,3-Bisphosphoglycerate
ADP
(6) 1,3-bisphospho glycerate kinase
ATP
3-Phosphoglycerate
(7) Phospho glyceromutase
2-Phosphoglycerate
(8) Enolase
Mg++
Phosphoenol pyruvate
ADP
NADH+H+
NAD+
(9) PYRUVATE KINASE
ATP
Pyruvate
Lactate
(10) Lactate dehydrogenase

Glycolysis: General Functions

- Oxidation of glucose
- Products:
  - Pyruvate
  - ATP
  - NADH
- Generate intermediates for other pathways
  - HMP pathway
  - Glycogen synthesis
  - Pyruvate dehydrogenase
    - Fatty acid synthesis
    - Krebs' Cycle
  - TG synthesis

Specific tissue functions

- RBC's
  - Rely exclusively for energy
- Skeletal muscle
  - Source of energy during exercise
- Adipose tissue & Liver
  - Source of glycerol-P for TG synthesis
  - Source of acetyl-CoA for FA synthesis

Regulation of Cellular Glucose Uptake

- Brain & RBC:
  - GLUT-1 has high affinity (low Km)for glucose and are always saturated.
  - Insures that brain and RBC always have glucose.
- Liver:
  - GLUT-2 has low affinity (hi Km) and high capacity.
  - Uses glucose when fed at rate proportional to glucose concentration
- Muscle & Adipose:
  - GLUT-4 is sensitive to insulin

Glucose Utilization

- Hexokinase:
  - High affinity for glucose
  - muscle and other tissues
- Glucokinase:
  - Low affinity for glucose
  - liver

Properties of Glucokinase and Hexokinase

Table 11-1

	Glucokinase	*Hexokinase*
Kinetic parameters		
K_m	High (10 mM)	Low (<100 μM)
V_{max}	High	Low
Tissue distribution	Liver Pancreatic beta cells	Most tissues
Regulation		
Short-term	Activity responds to changes in glucose concentration	Inhibited by glucose-6-phosphate
Long-term	Synthesis induced by insulin	Constitutive

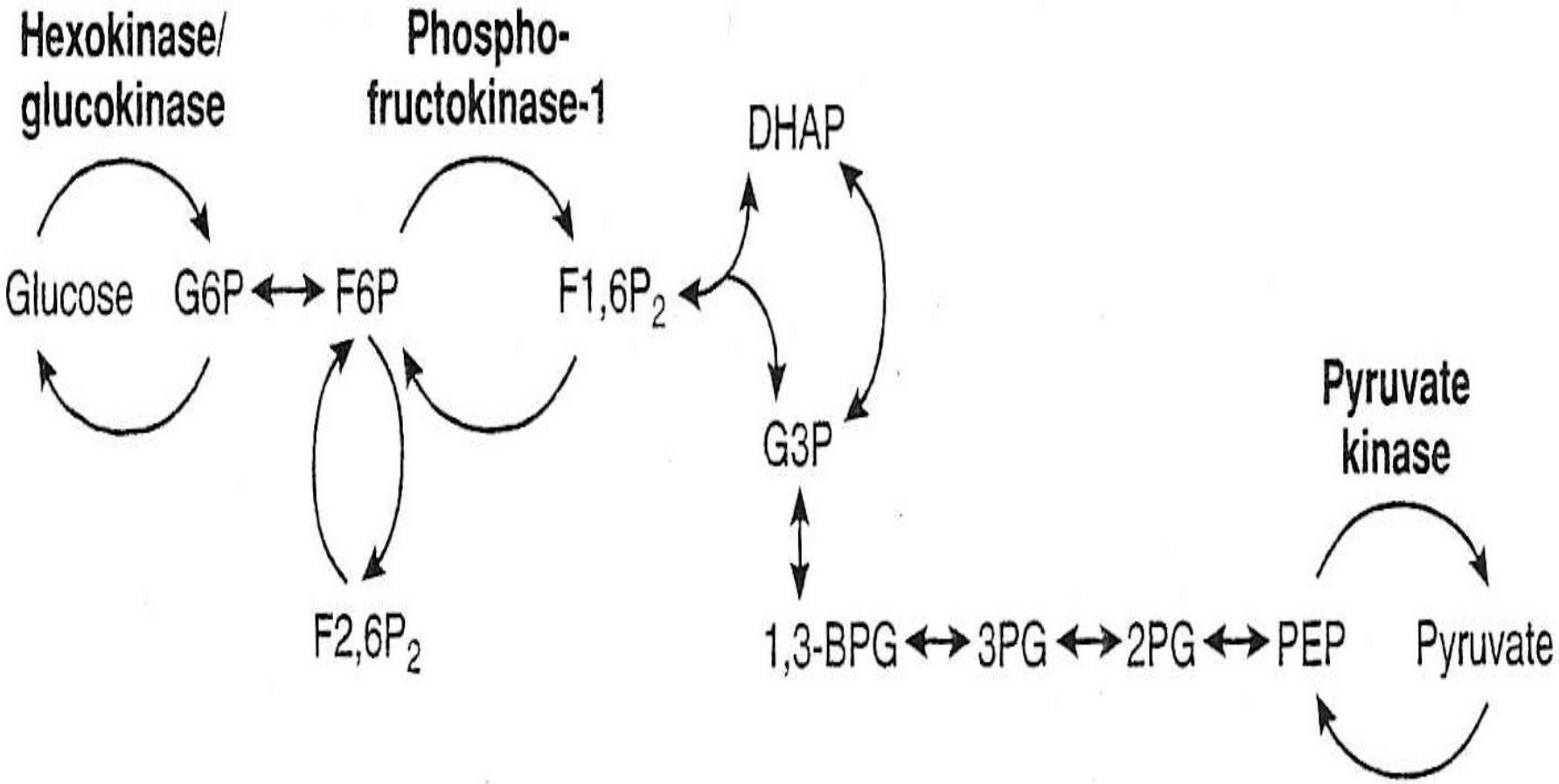
Regulation of Cellular Glucose Utilization in the Liver

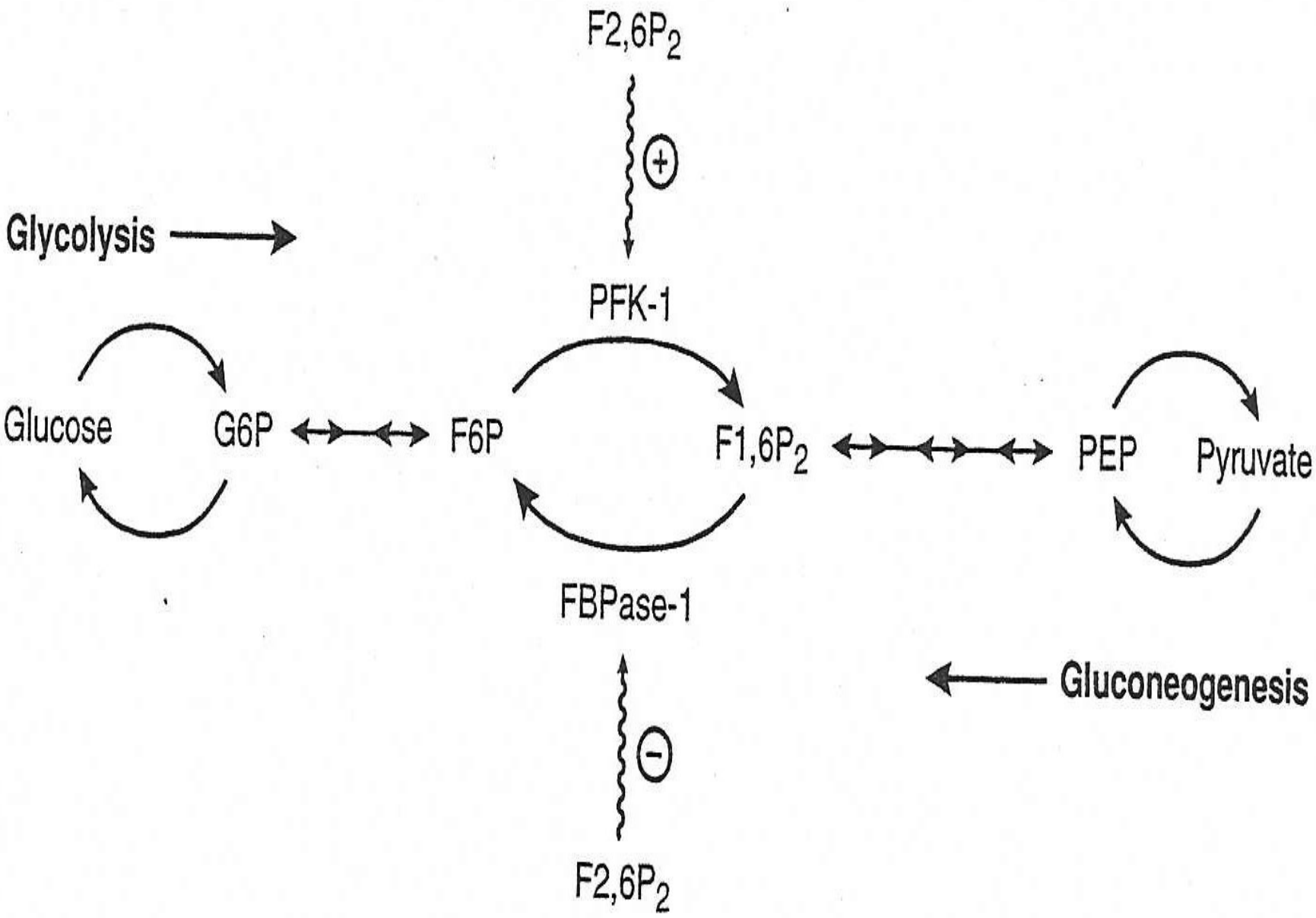
- **Feeding**
  - Blood glucose concentration high
  - Glucokinase induced by insulin
  - GLUT-2 taking up glucose
  - Glucose use for Glycogen synthesis by liver
- **Post-absorptive state**
  - Blood & cell glucose low
  - Glucokinase not phophorylating glucose
  - GLUT-2 not taking up glucose
  - Liver not utilizing glucose
- Starvation

Regulation of Cellular Glucose Utilization in the Muscle

- Exercising Muscle (fed or starved)
  - Low G6P (being used in glycolysis)
  - No inhibition of HK
  - High glycolysis from glycogen or blood glucose

Regulation of Glycolysis



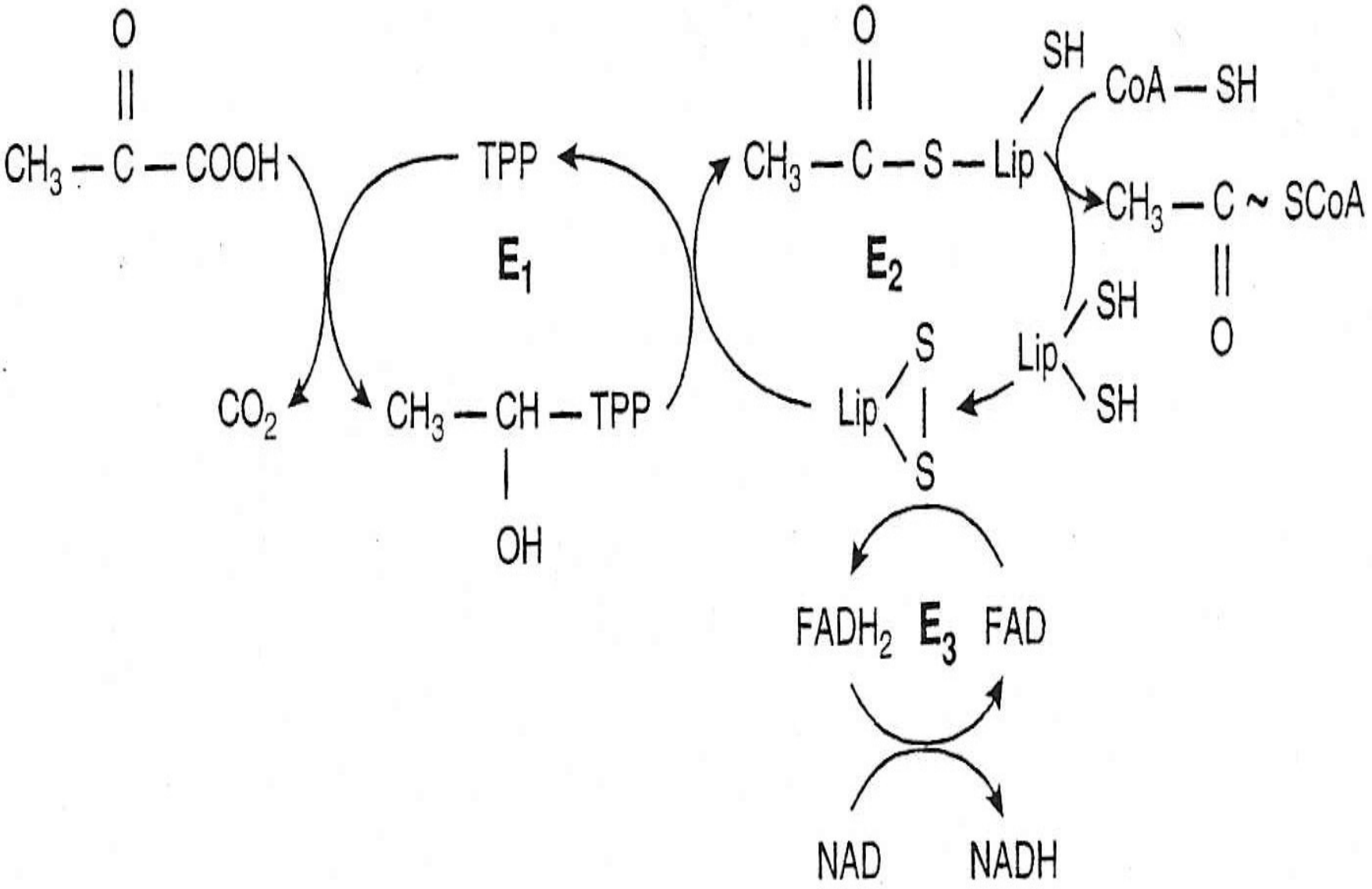

F2,6P2
+
Glycolysis
PFK-1
Glucose
G6P
F6P
F1,6P2
PEP
Pyruvate
FBPase-1
Gluconeogenesis
−
F2,6P2

The PDH Complex

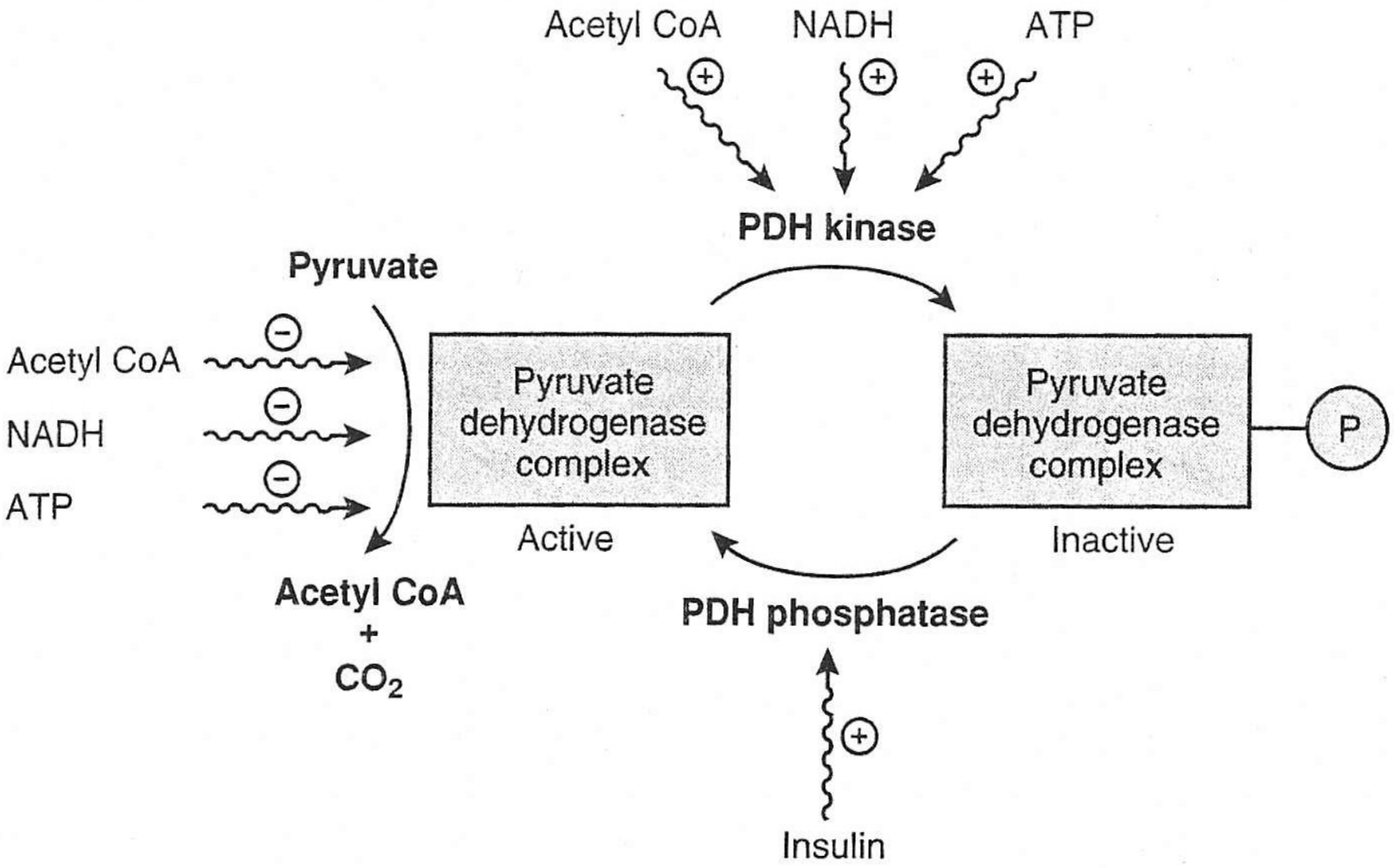
- Multi-enzyme complex
  - Three enzymes
  - 5 co-enzymes
  - Allows for efficient direct transfer of product from one enzyme to the next

Enzymes	*Cofactors*	*Role in Overall Reaction of PDH Complex*
E_1 (pyruvate dehydrogenase)	Thiamine pyrophosphate	Decarboxylation
E_2 (dihydrolipoyl transacetylase)	Lipoic acid	Oxidation
	CoA-SH	Acyl transfer
E_3 (dihydrolipoyl dehydrogenase)	FAD	Regeneration of lipoic acid
	NAD+	
PDH kinase		Phosphorylation and inactivation of E_1
PDH phosphatase		Dephosphorylation and activation of E_1

The PDH Reaction



Regulation of PDH



Pyruvate Kinase Deficiency

- RBC dependent on glycolysis for energy
  - Sodium/potassium ion pumps require ATP
  - Abnormal RBC shape a result of inadequate ion pumping
  - Excessive RBC destruction in spleen
    - Hemolysis
    - Jaundice (elevated bilirubin, fecal urobilinogens)
    - Increased reticulocyte count

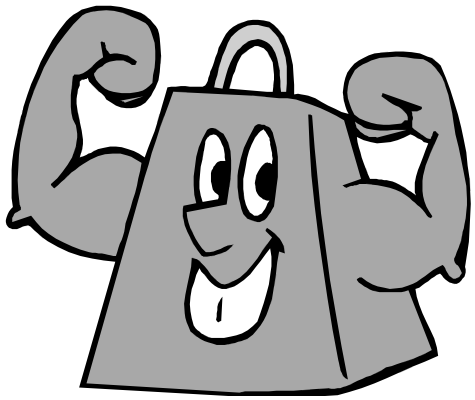
Gluconeogenesis

The Meaning of It All…

- Gluconeogenesis means
  - To make new glucose
  - Make glucose from non-carbohydrate precursors
  - Create new glucose from the products of its breakdown

Plain Glucose Please

- Some tissues use glucose exclusively for energy:
  - Brain, RBCs
- Other tissues use it according to metabolic demand:
  - Remember Respiratory quotient?
  - Muscle

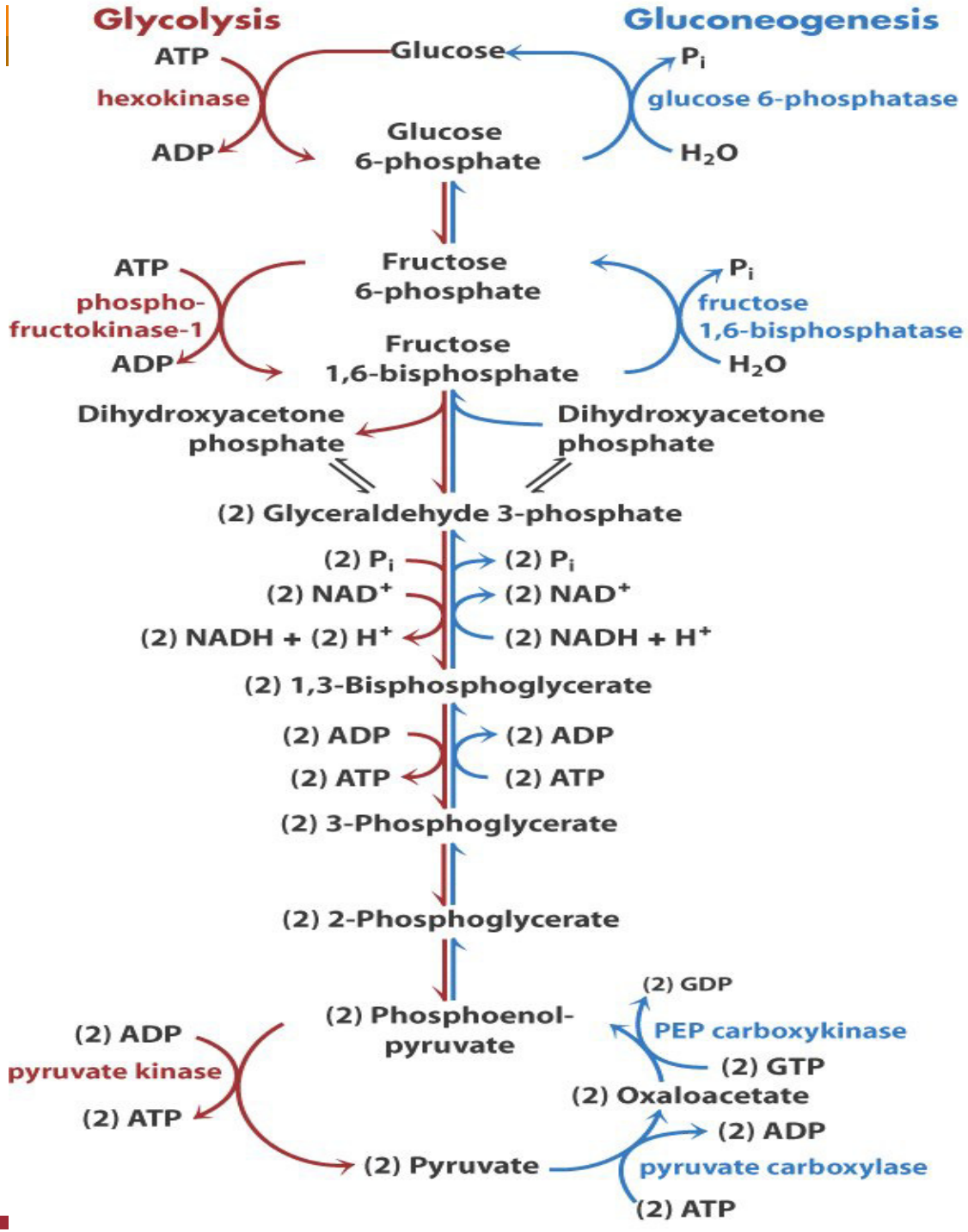


What are the sources of precursors for gluconeogenesis?

- ✓ *Pyruvate* - major precursor
- ✓ *Lactate* –from muscle, forms pyruvate
- ✓ some *amino acid* carbon skeletons- from diet or breakdown of muscle protein during starvation- most important is alanine
- ✓ *TCA cycle intermediates*
- ✓ *propionate* from breakdown of fatty acids and amino acids.
- ✓ *glycerol* from certain lipids.

I’m Back…

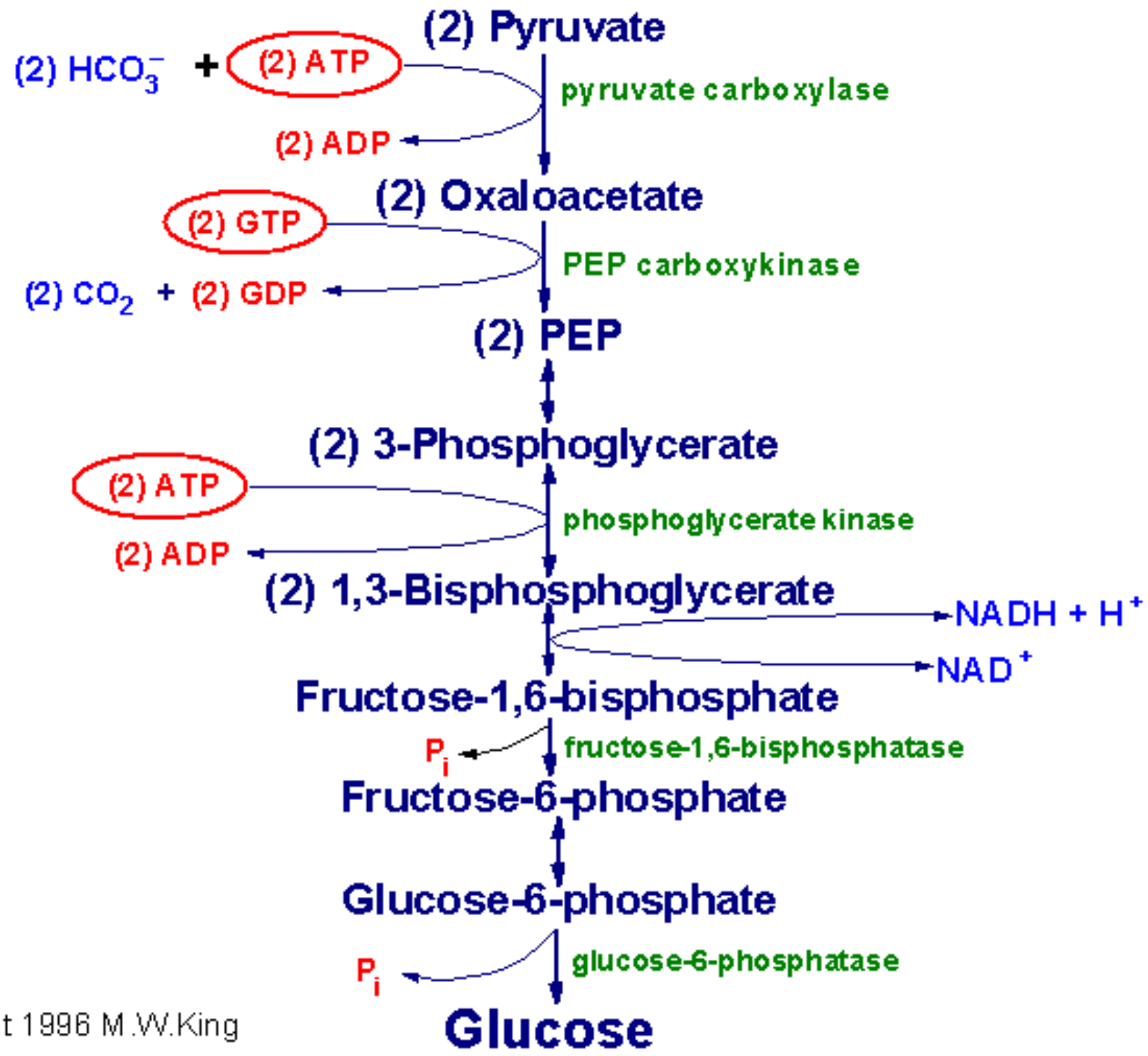
- Glycolysis
- Key Enzymes:
  - Hexokinase
  - PFK
  - Pyruvate Kinase
- These enzymes catalyze the irreversible reactions of Glycolysis that must be overcome in Gluconeogenesis.


Glycolysis
Gluconeogenesis
ATP
hexokinase
ADP
Glucose
Glucose 6-phosphate
P_i
glucose 6-phosphatase
H_2O
ATP
phospho-fructokinase-1
ADP
Fructose 6-phosphate
Fructose 1,6-bisphosphate
P_i
fructose 1,6-bisphosphatase
H_2O
Dihydroxyacetone phosphate
Dihydroxyacetone phosphate
(2) Glyceraldehyde 3-phosphate
(2) P_i
(2) NAD^+
(2) NADH + (2) H^+
(2) P_i
(2) NAD^+
(2) NADH + H^+
(2) 1,3-Bisphosphoglycerate
(2) ADP
(2) ATP
(2) ADP
(2) ATP
(2) 3-Phosphoglycerate
(2) 2-Phosphoglycerate
(2) Phosphoenol-pyruvate
(2) ADP
pyruvate kinase
(2) ATP
(2) Pyruvate
(2) GDP
PEP carboxykinase
(2) GTP
(2) Oxaloacetate
(2) ADP
pyruvate carboxylase
(2) ATP

Glycolysis		GNG
Hexokinase	Undone by	Glucose-6-Phosphatase
PFK	Undone by	Fru-1,6-BisPhosphatase
Pyruvate Kinase	Undone by	Pyruvate Carboxylase AND PEP Carboxykinase

Gluconeogenesis

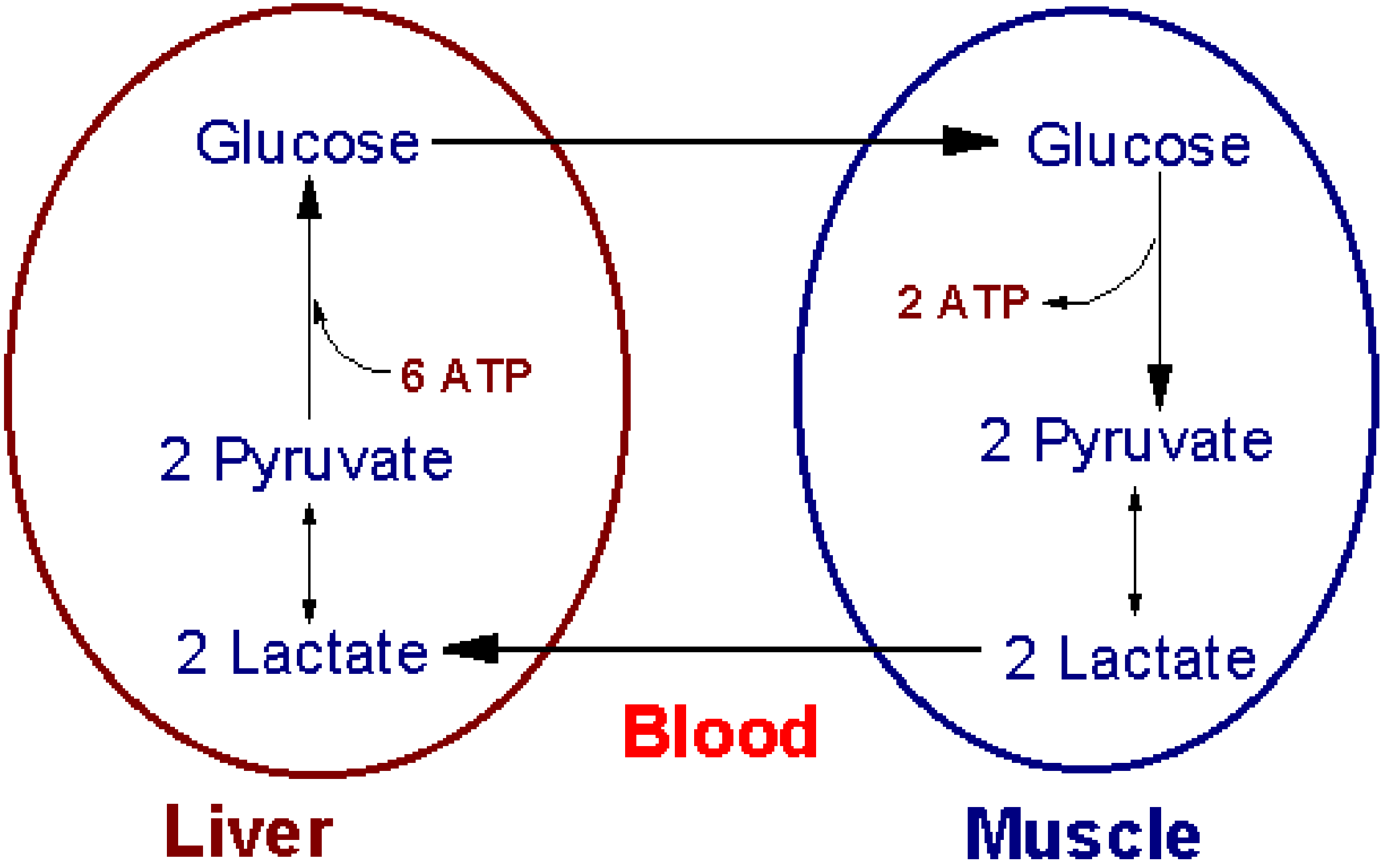
- The Basics
  - Location:
    - Cytosol
  - Purpose:
    - Make Glucose
  - Key Enzymes:
    - Pyruvate Carboxylase
    - PEP Carboxykinase
    - Fructose 1,6 Bisphosphatase
    - Glucose 6 Phosphatase



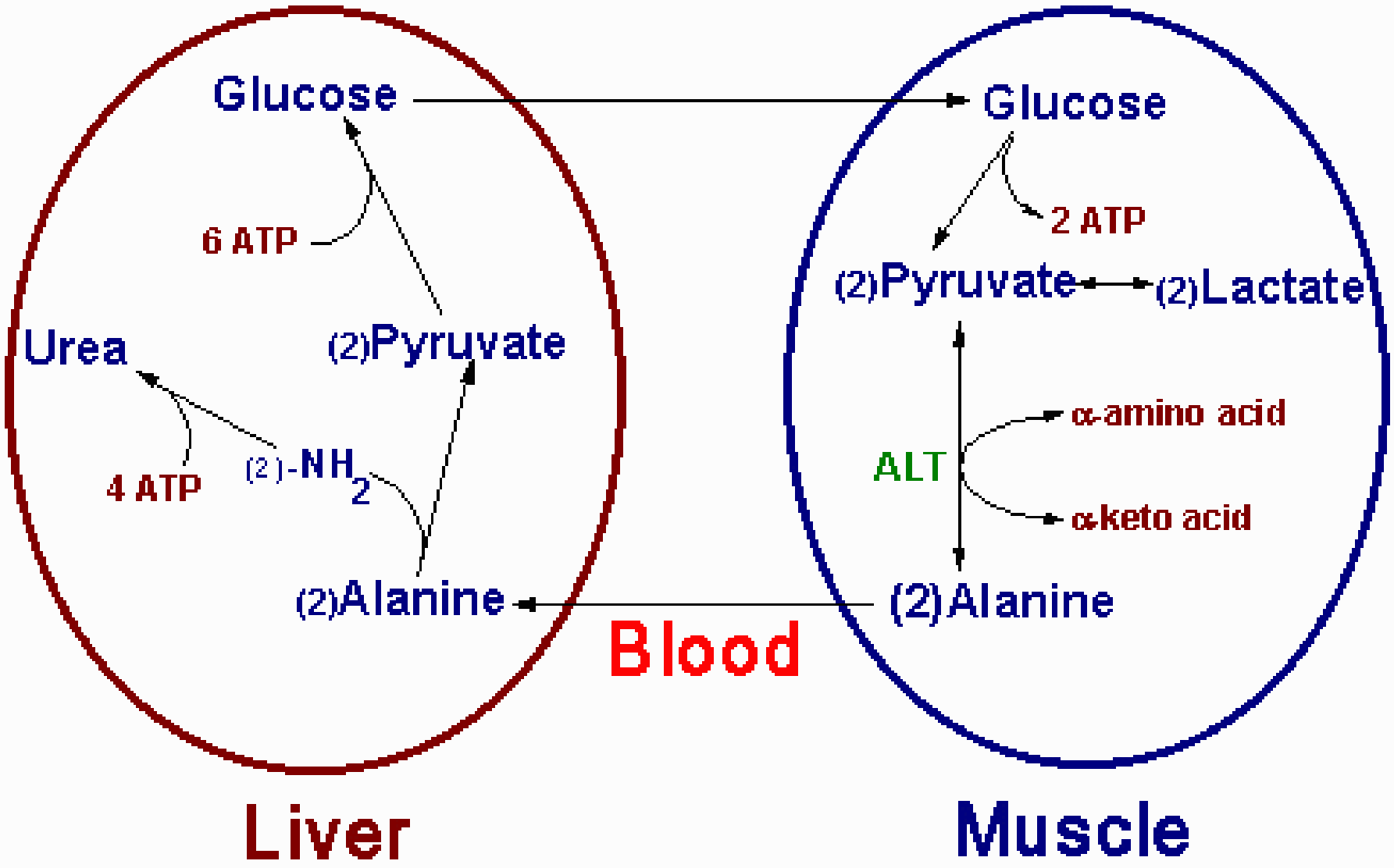
The Cori Cycle

- The Gluconeogenic cycle that uses Lactate to move Pyruvate from the cell to the liver.

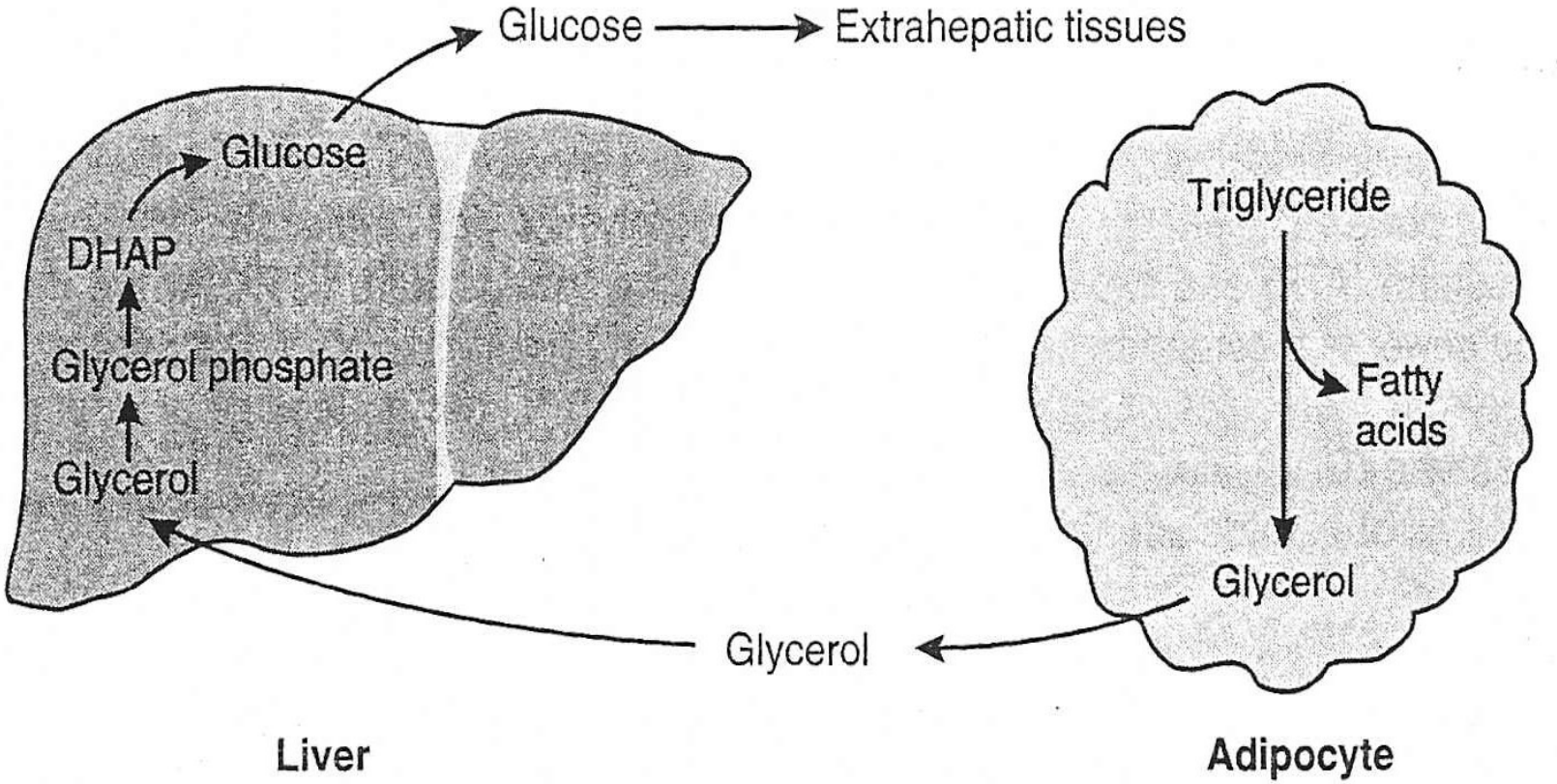
The Cori Cycle

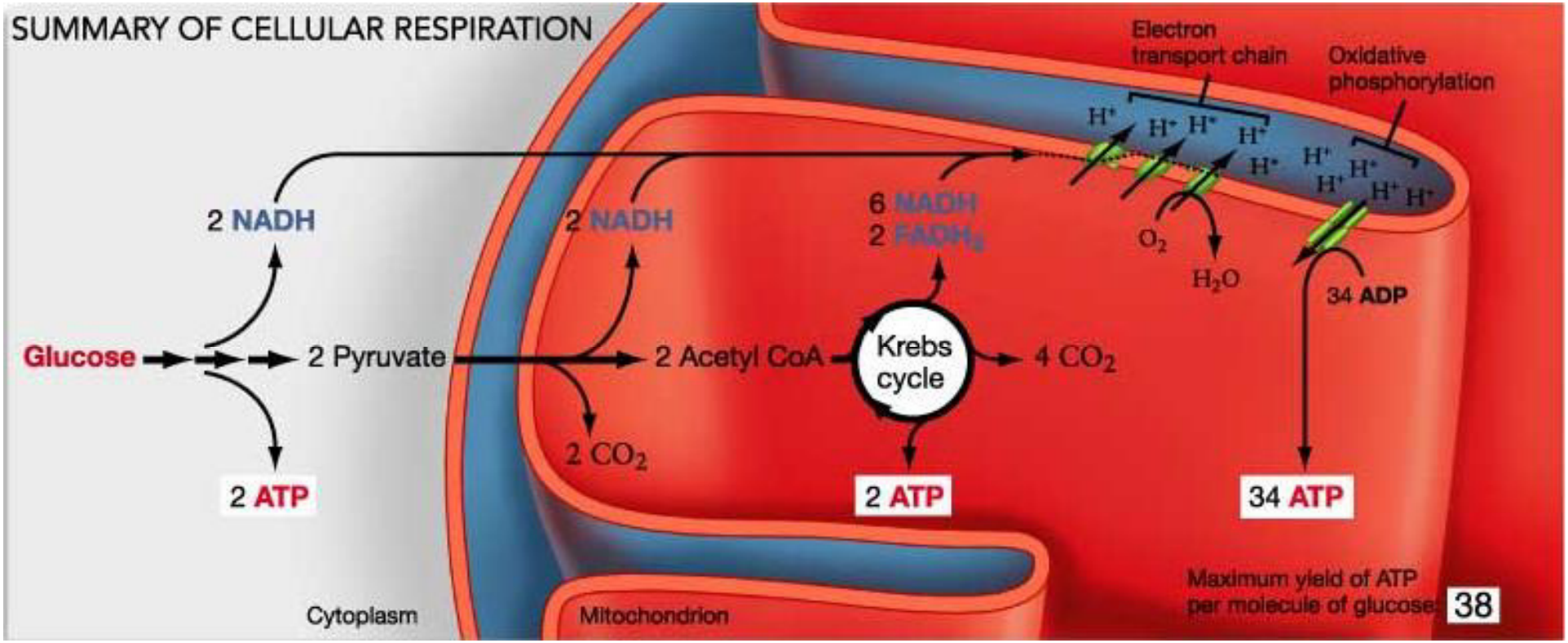


Glucose/Alanine Cycle



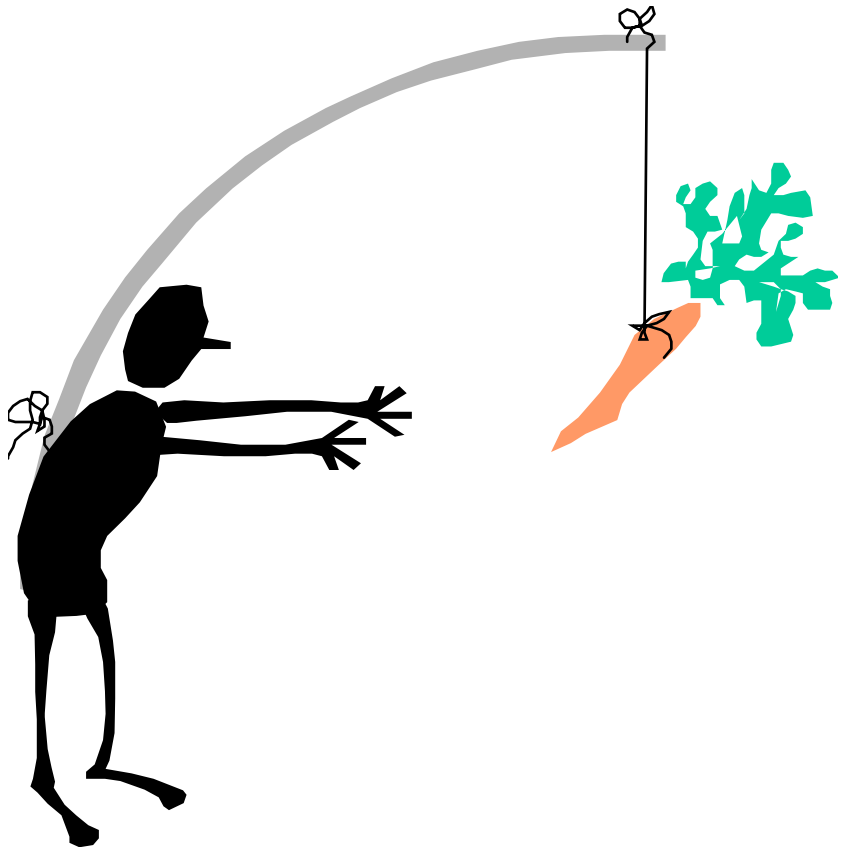
- Glycerol
  - derived from adipocyte lipolysis
  - hepatic glycerol kinase




SUMMARY OF CELLULAR RESPIRATION
Electron transport chain
Oxidative phosphorylation
2 NADH
2 NADH
6 NADH
2 FADH2
Glucose
2 Pyruvate
2 Acetyl CoA
Krebs cycle
4 CO2
2 CO2
2 ATP
2 ATP
34 ATP
34 ADP
O2
H2O
Cytoplasm
Mitochondrion
Maximum yield of ATP per molecule of glucose:
38

Regulation

- Stimulation
  - Low blood Glucose
  - Glucagon
  - ATP
  - Citrate
  - Acetyl Co A
  - Pyruvate
  - Lactate
  - Alanine
  - OAA



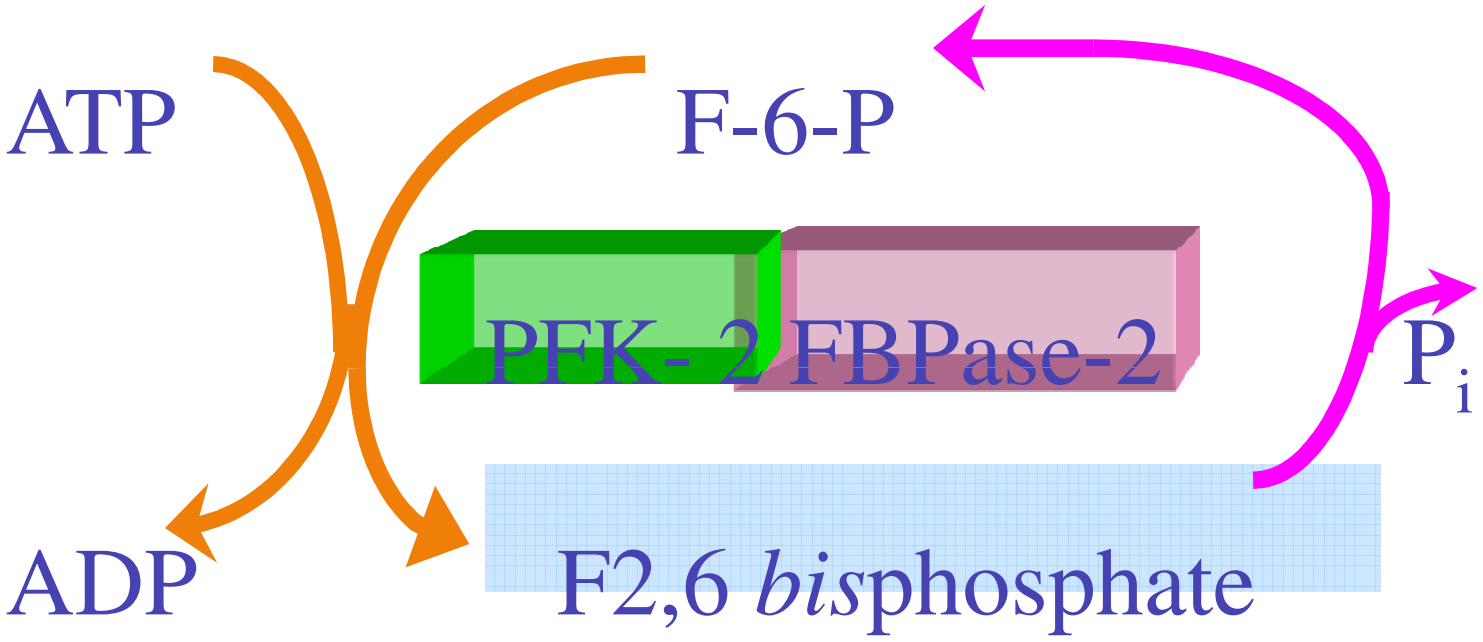
Regulation

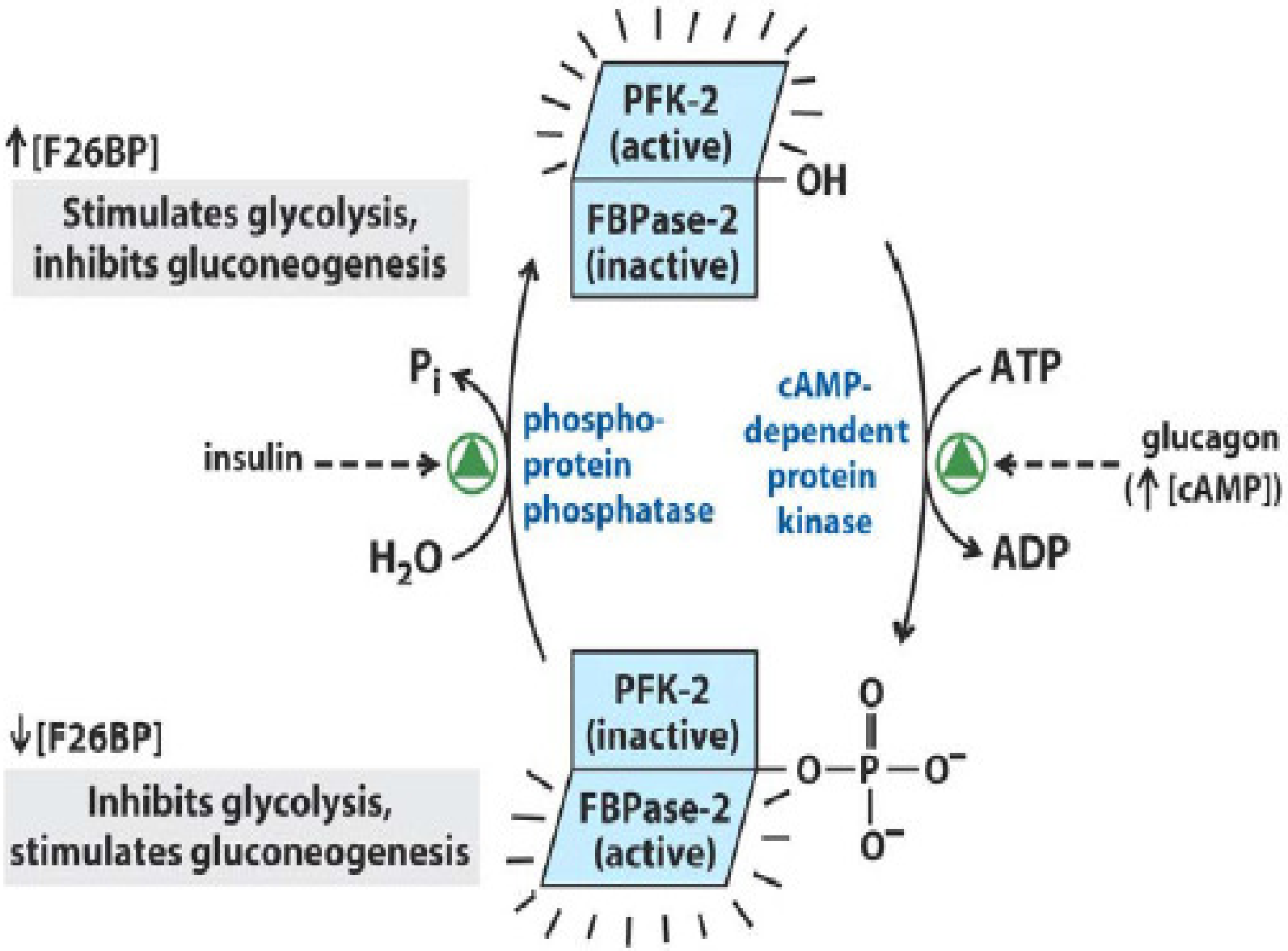
- Inhibition
  - High blood Glucose
  - Insulin
  - Low Energy Charge
  - Fructose - 2,6 - BisPhosphate

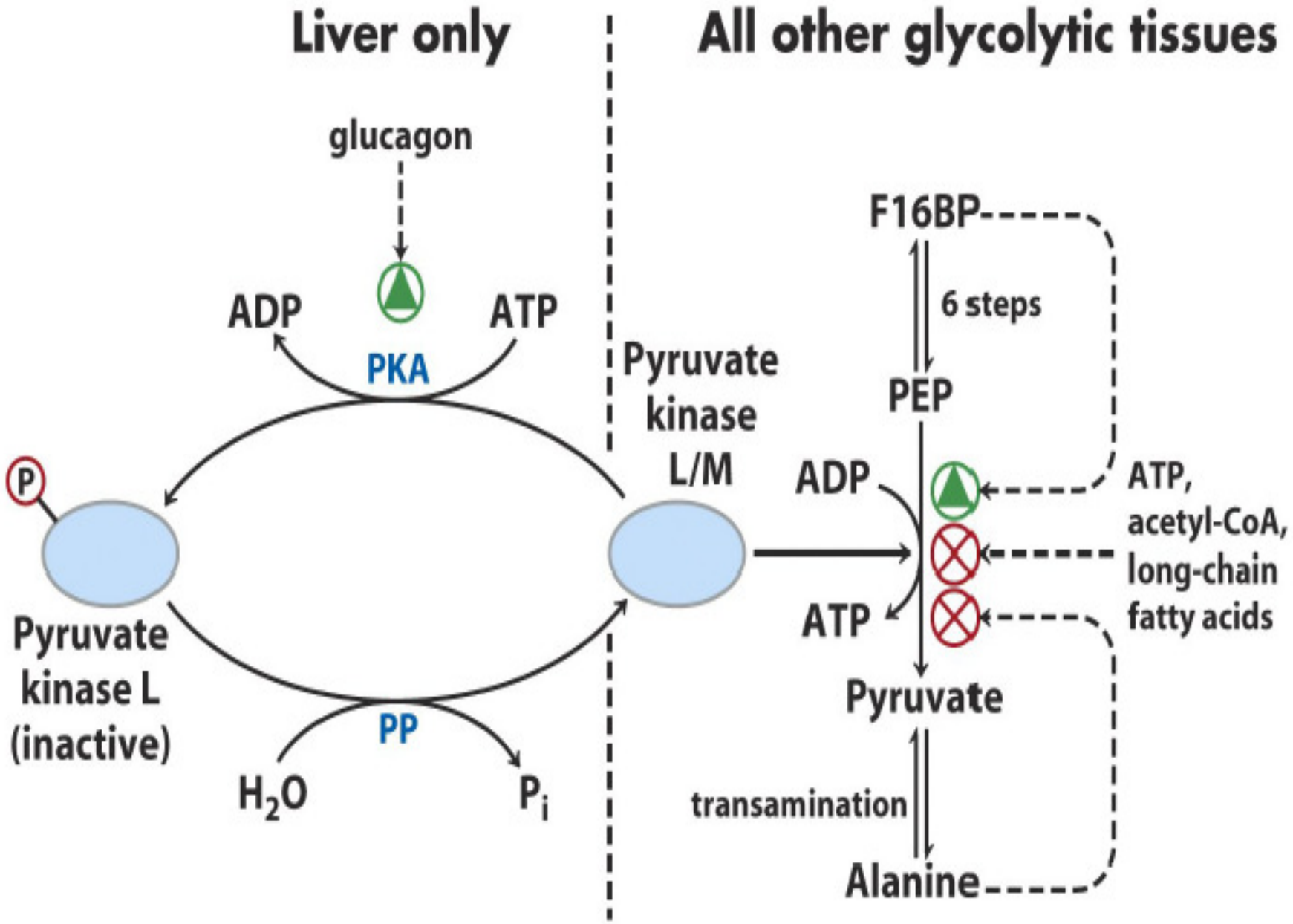
Regulation of Gluconeogenesis and Glycolysis

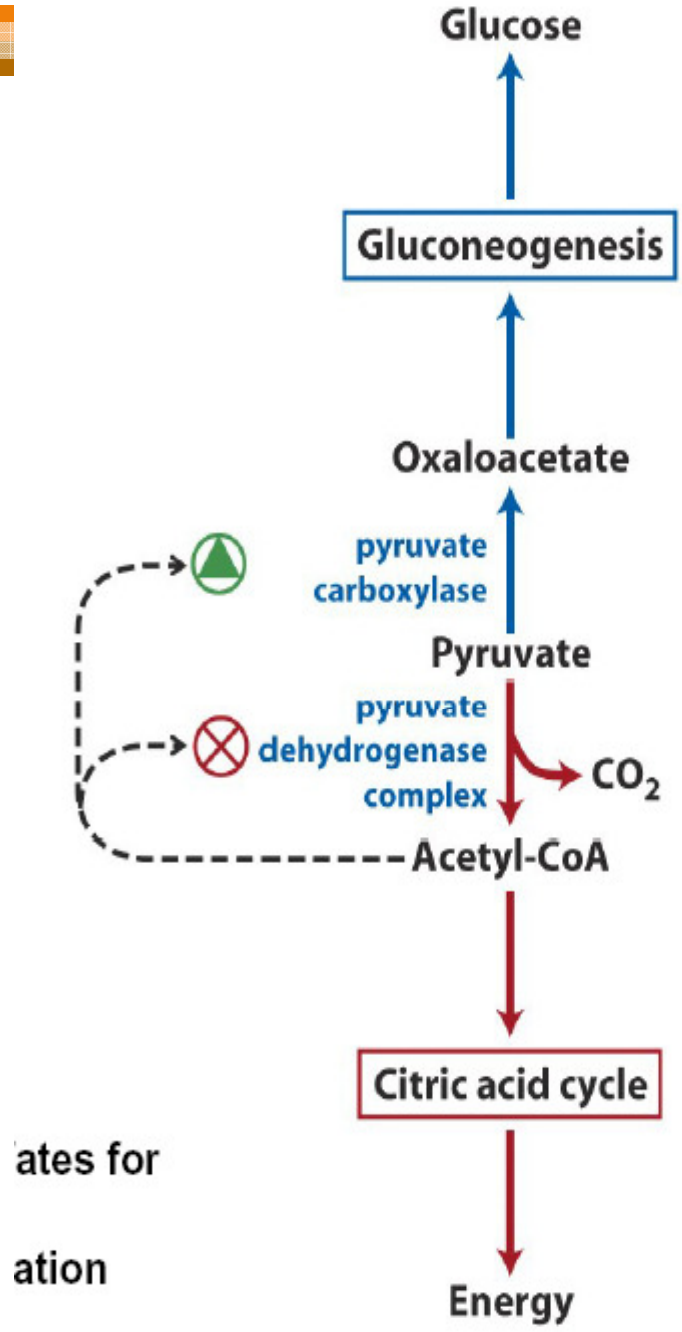
- **Allosteric Effects**
- Pyruvate kinase vs Pyruvate carboxylase
  - PK - Inhibited by ATP and alanine
  - PC - Activated by acetyl CoA
  - Fasting results in gluconeogenesis
- PFK-1 vs FBPase-1
  - FBPase-1 inhibited by AMP & $F2,6P_2$
  - PFK-1 activated by AMP and & $F2,6P_2$
  - Feeding results in glycolysis

PHOSPHOFRUCTOKINASE-2/ FRUCTOSE *BIS*PHOSPHATASE-2




↑[F26BP]
Stimulates glycolysis, inhibits gluconeogenesis
PFK-2 (active)
FBPase-2 (inactive)
OH
P_i
insulin
H_2O
phospho-protein phosphatase
cAMP-dependent protein kinase
ATP
ADP
glucagon (↑[cAMP])
↓[F26BP]
Inhibits glycolysis, stimulates gluconeogenesis
PFK-2 (inactive)
FBPase-2 (active)
O
O—P—O⁻
O⁻


Liver only
All other glycolytic tissues
glucagon
ADP
ATP
PKA
P
Pyruvate kinase L (inactive)
PP
H_2O
P_i
Pyruvate kinase L/M
F16BP
6 steps
PEP
ADP
ATP
ATP, acetyl-CoA, long-chain fatty acids
Pyruvate
transamination
Alanine



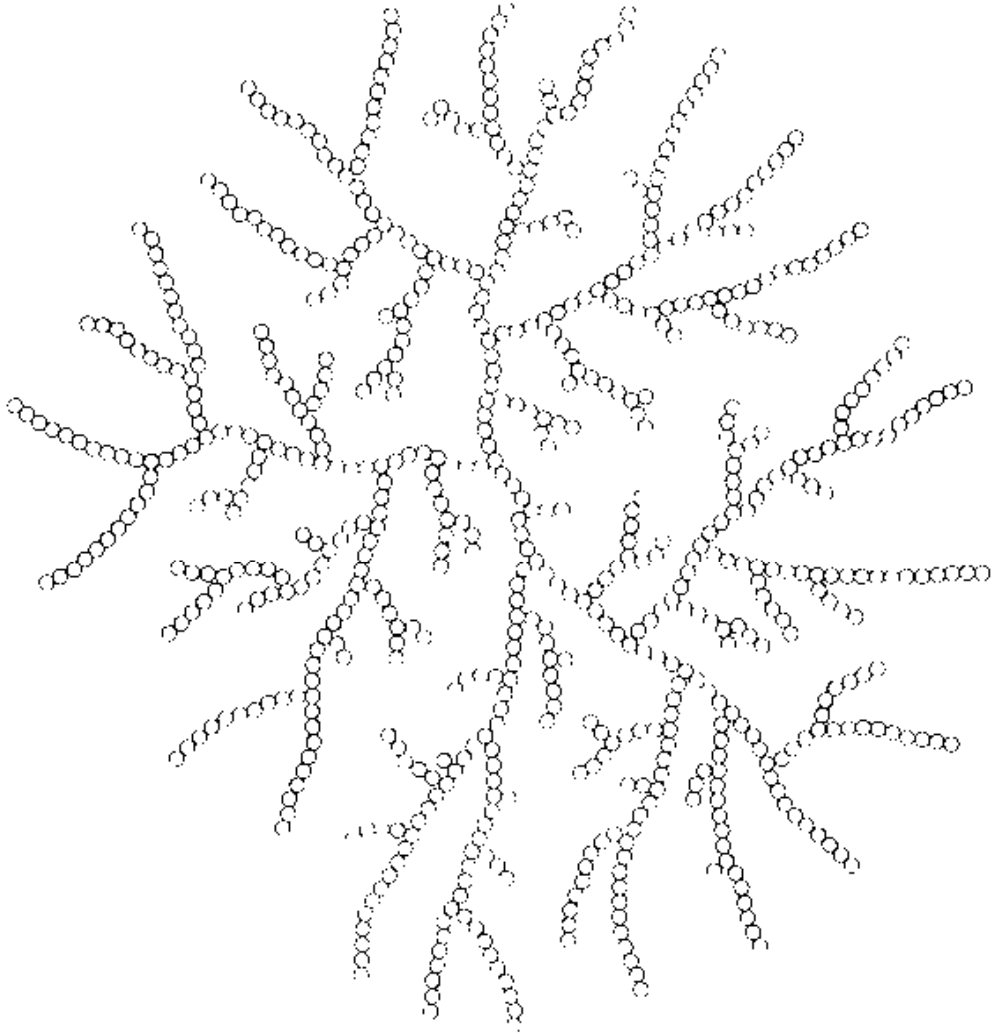
ates for

ation

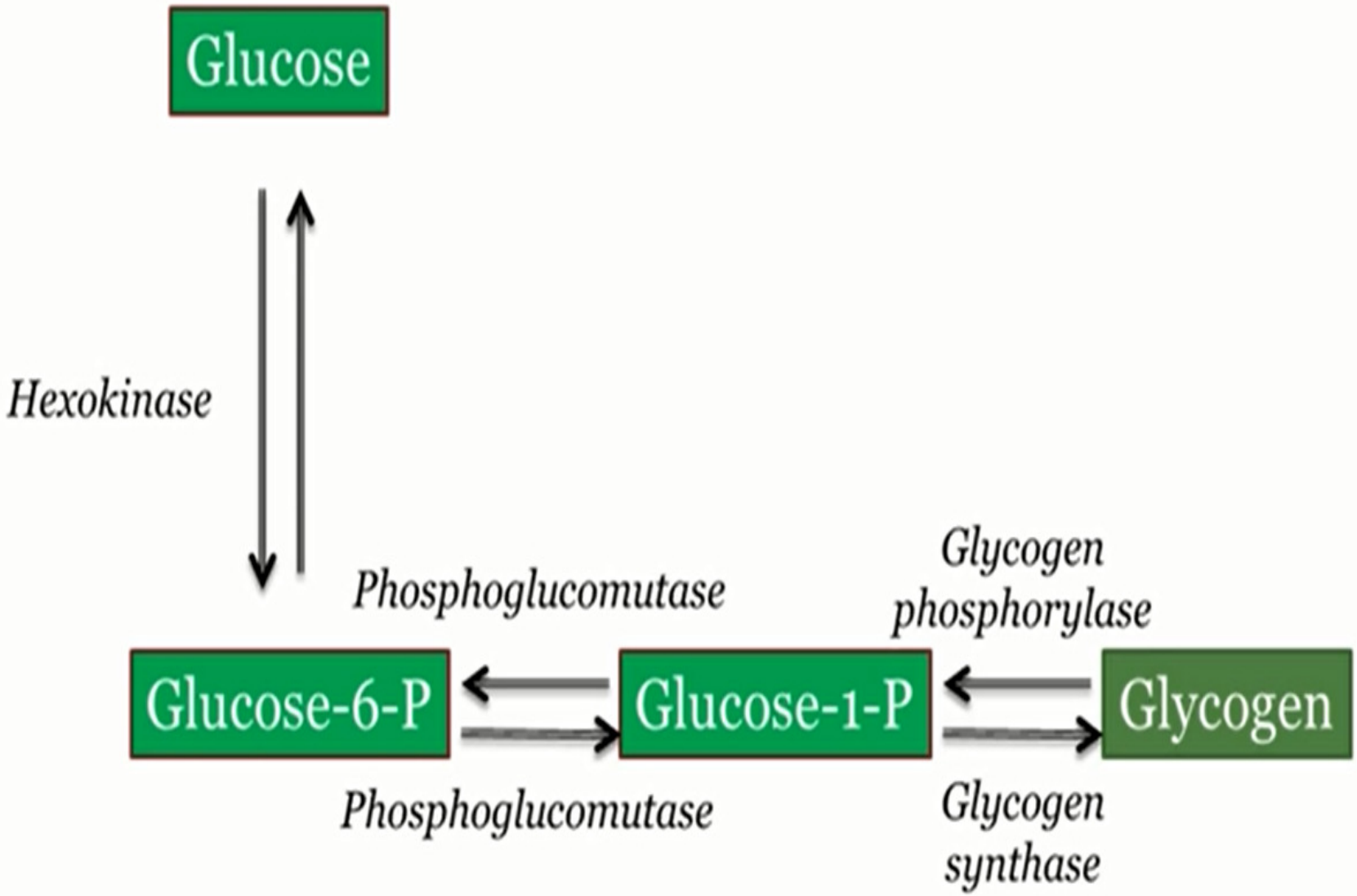
GLYCOGEN METABOLISM

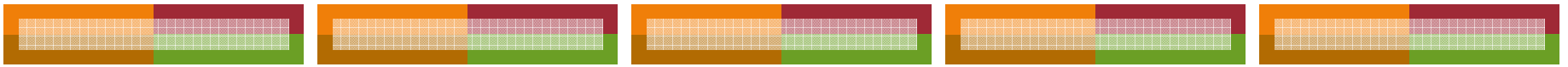
Highly
branched polymer

Glycosidic links
α 1→4.
α 1→6.



- Glucose stored as glycogen mostly in the liver and skeletal muscle.
- Glucose can be rapidly delivered to the blood stream when needed = **Glycogenolysis**
- Enough glucose and energy triggers = **Glycogenesis**


Glucose
Hexokinase
Phosphoglucomutase
Glycogen phosphorylase
Glucose-6-P
Glucose-1-P
Glycogen
Phosphoglucomutase
Glycogen synthase



STEP - 1 Conversion of glucose-6-phosphate to glucose-1-phosphate

Enzyme = ***phosphoglucomutase***

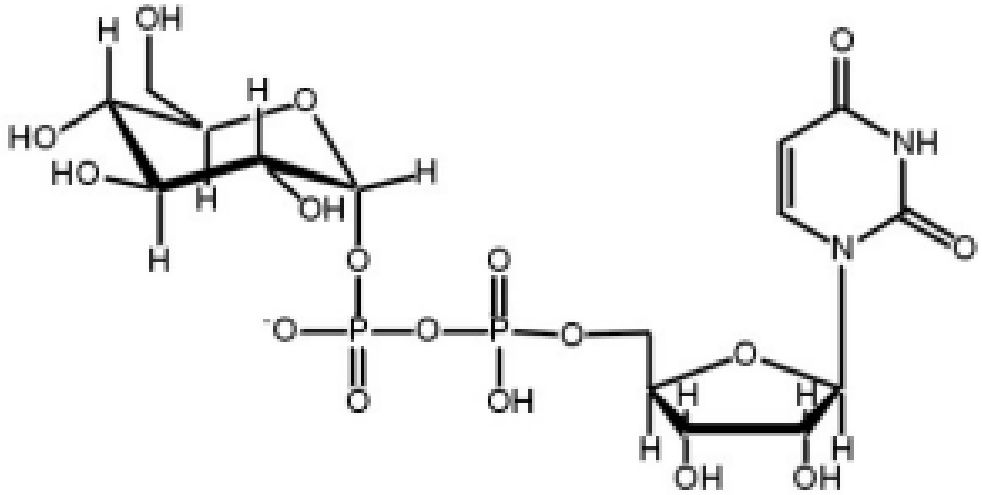
α-D-glucose-6-phosphate ⟷ α-D- glucose-1-phosphate

STEP 2- Synthesis of Uridine Diphosphoglucose

Enzyme = ***UDP-glucose pyrophosphorylase***

Reaction:

glucose-1-phosphate + UTP →



UDP-glucose

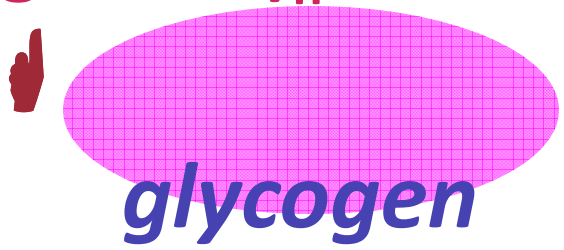
+ PP_i

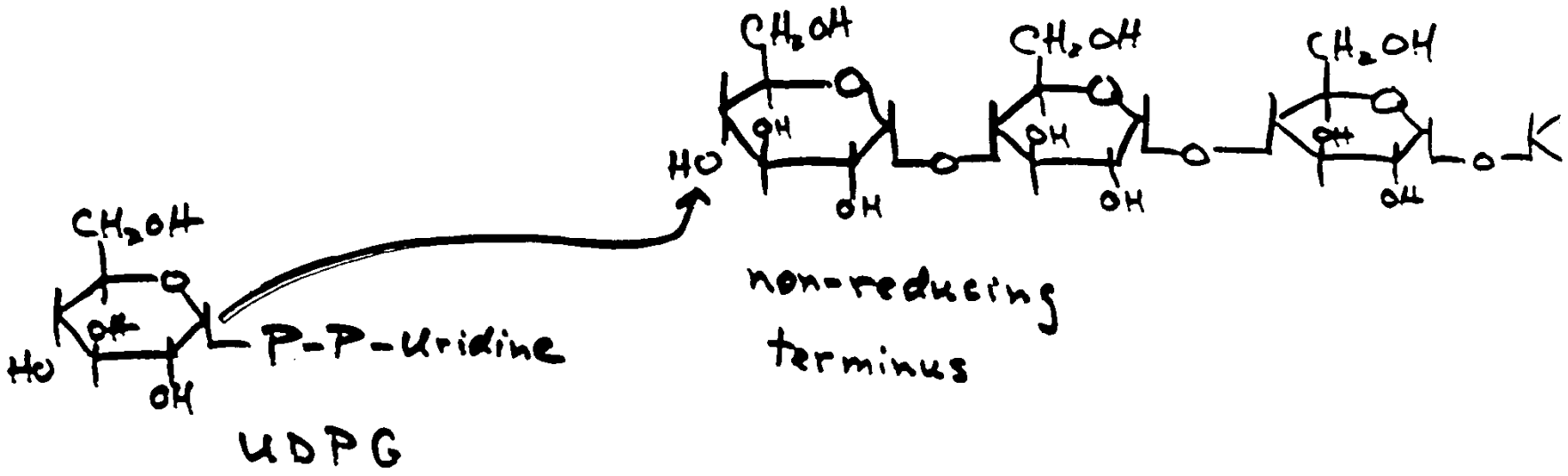
Then PP_i → $2\ P_i$

STEP – 3 Glycogen synthesis

Enzyme = ***glycogen synthase***

UDP-glucose + $(glucose)_n$ → UDP + $(glucose)_{n+1}$





- Glucose always added to *nonreducing* end. The glycosidic bond formed is ***α (1 → 4)***.
- Glycogen synthase is inhibited by phosphorylation, regulated by glucagon

STEP – 4 Branching

Enzyme = ***branching enzyme***

- introduces branching by ***transferring*** a teminal fragment of ***6-7 residues*** from a growing chain to a ***6-position*** farther back in a chain.
- makes a branch with an ***α (1→6)*** link creating *two* ends to add glucose.
- branching accelerates the rate of glucose release during degradation.

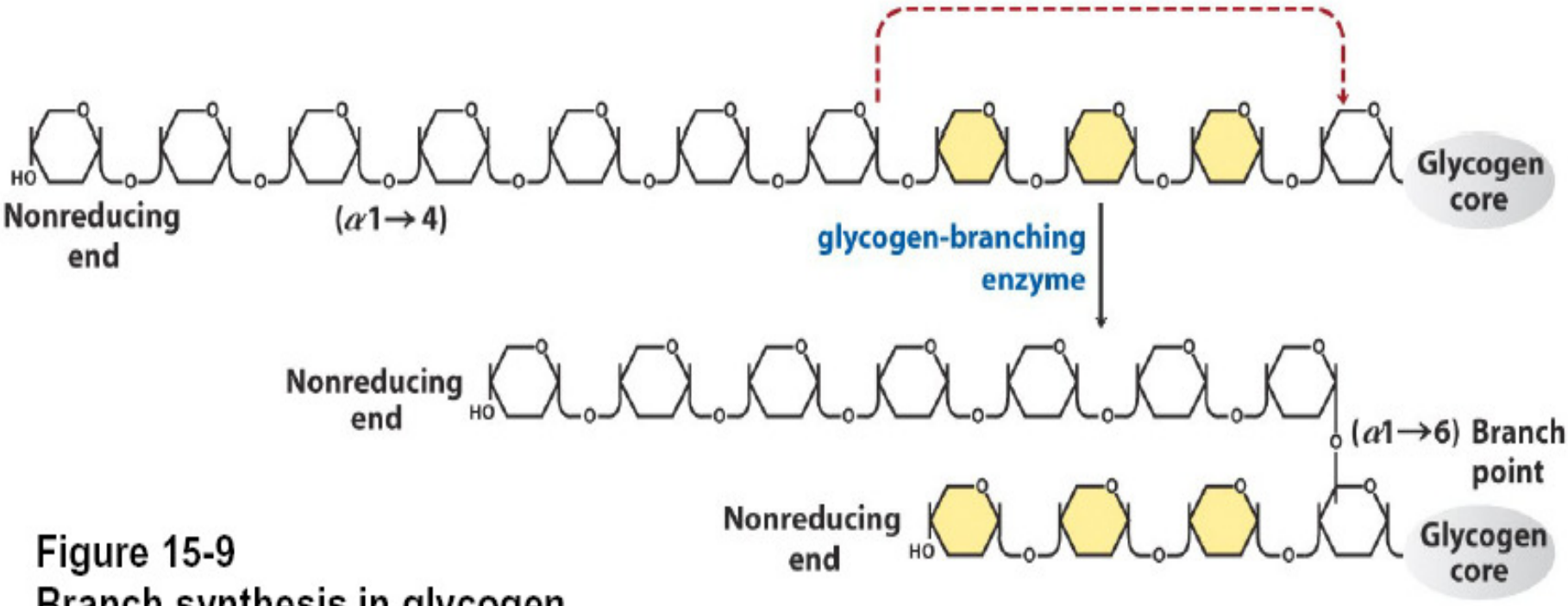
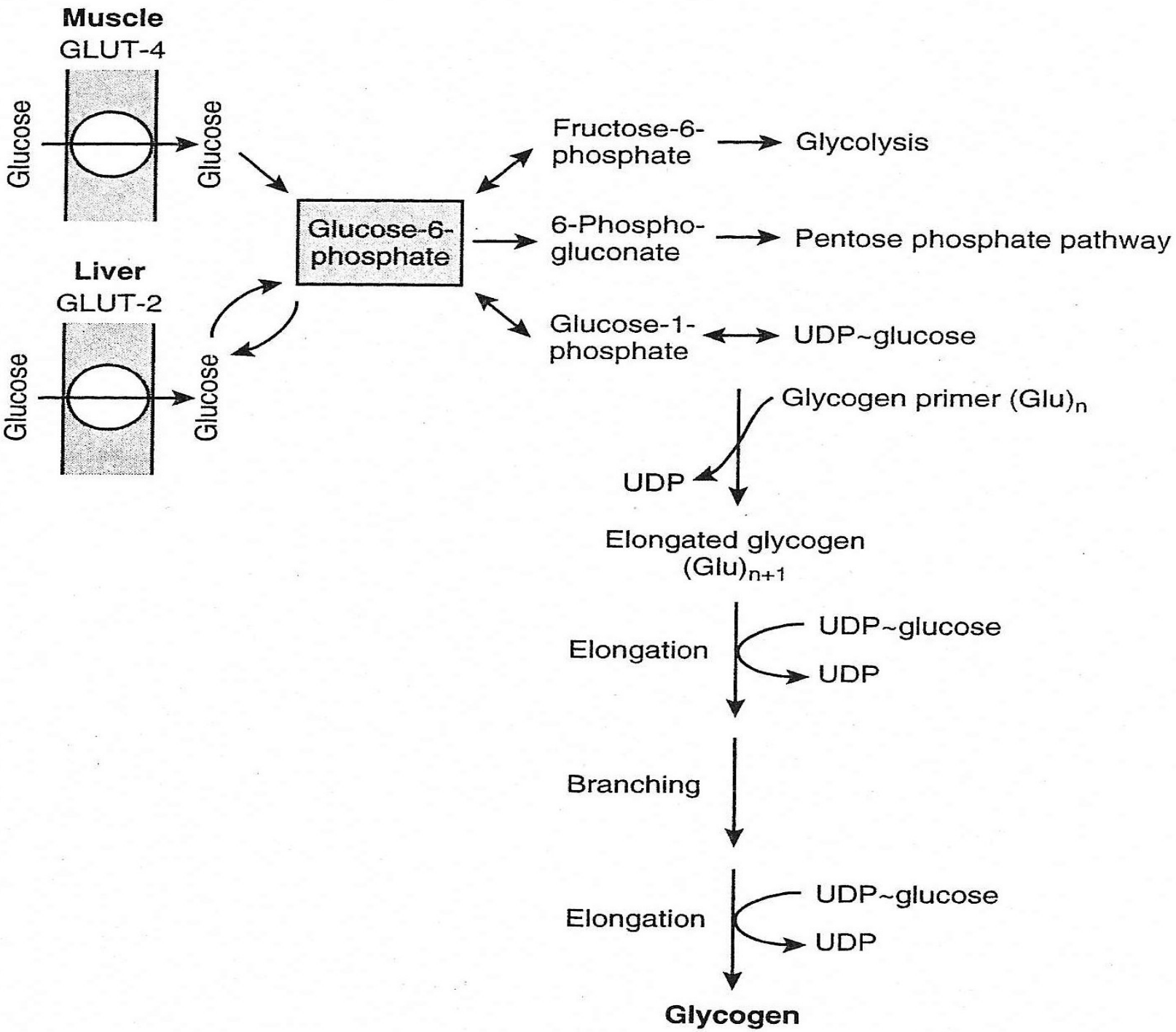
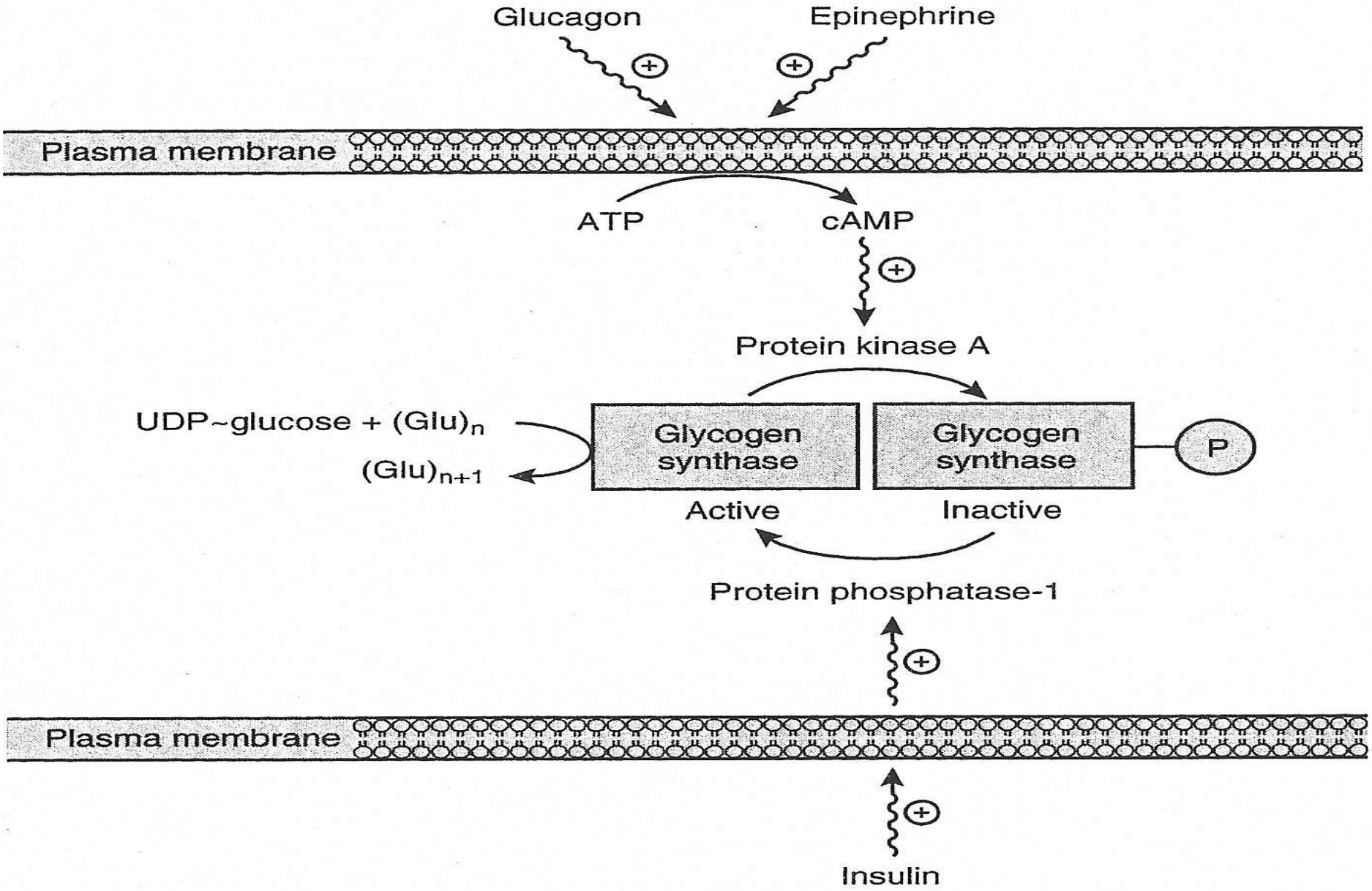


Figure 15-9
Branch synthesis in glycogen


Muscle
GLUT-4
Glucose
Glucose
Liver
GLUT-2
Glucose
Glucose
Glucose-6-phosphate
Fructose-6-phosphate
Glycolysis
6-Phospho-gluconate
Pentose phosphate pathway
Glucose-1-phosphate
UDP~glucose
Glycogen primer $(Glu)_n$
UDP
Elongated glycogen $(Glu)_{n+1}$
Elongation
UDP~glucose
UDP
Branching
Elongation
UDP~glucose
UDP
Glycogen

Regulation of Glycogenesis



Regulation of Glycogenesis

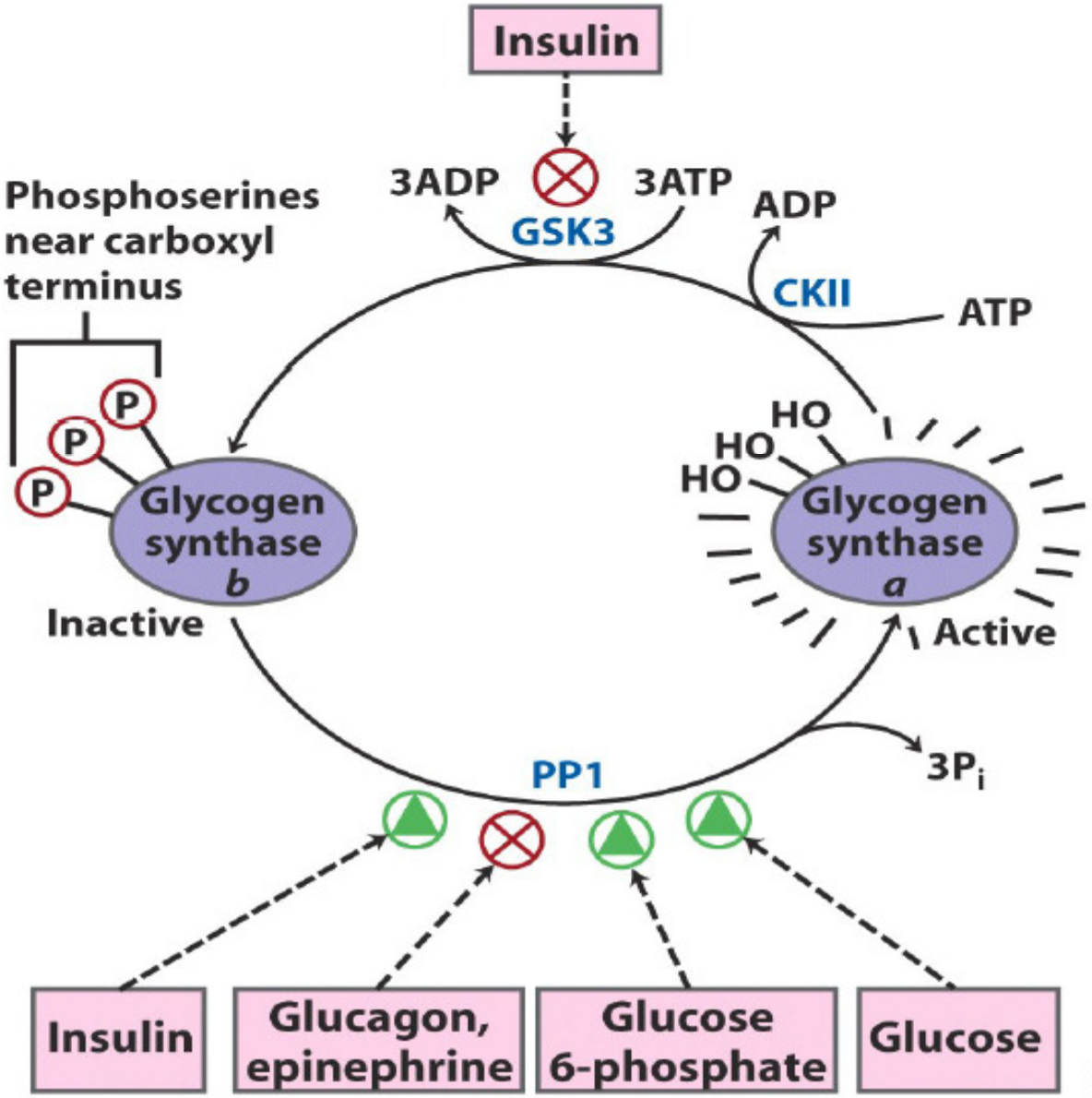
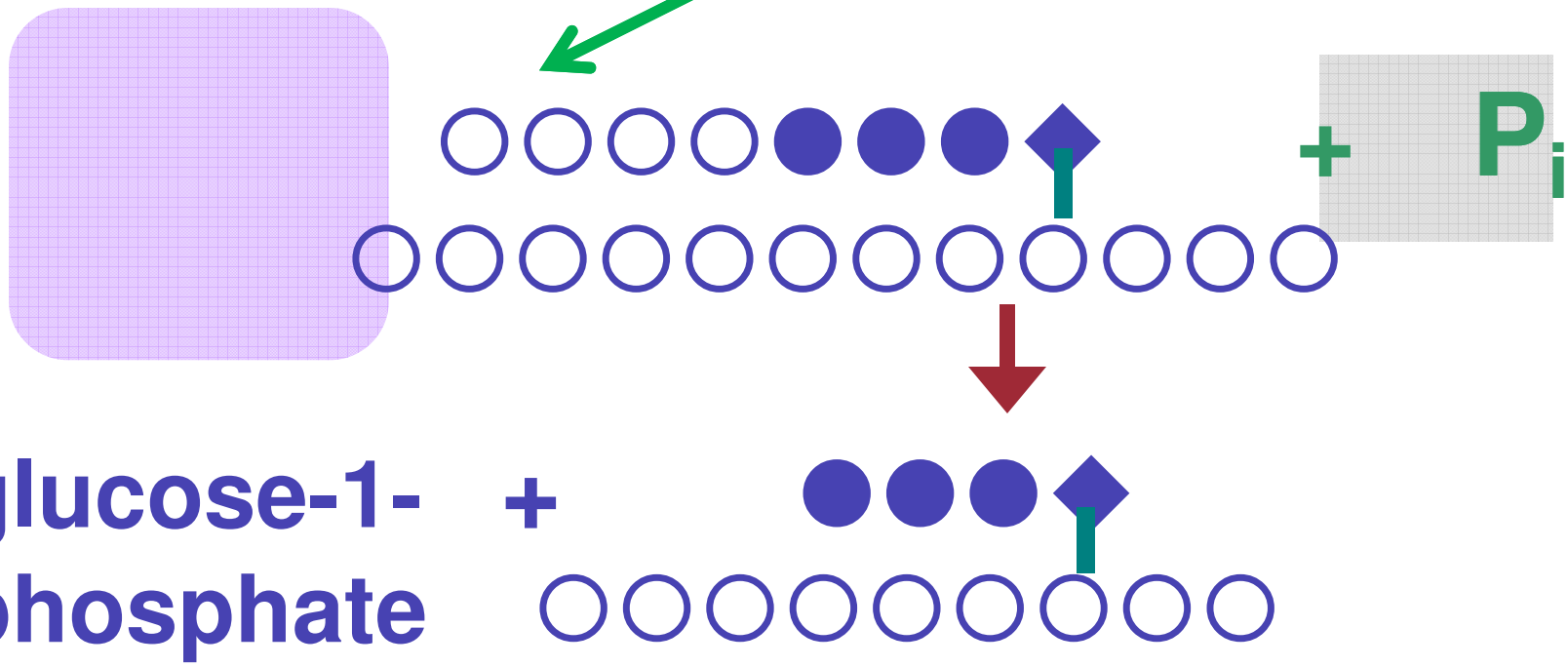


Figure 15-27
Effects of GSK3 on glycogen synthase activity

GLYCOGENOLYSIS

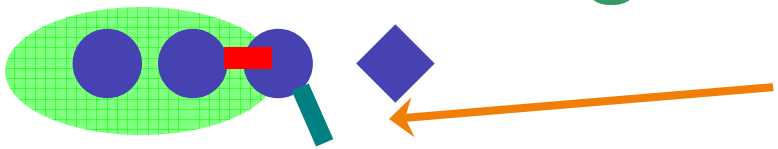
STEP - 1 Release of glucose-1-phosphate

Enzyme = ***glycogen phosphorylase***



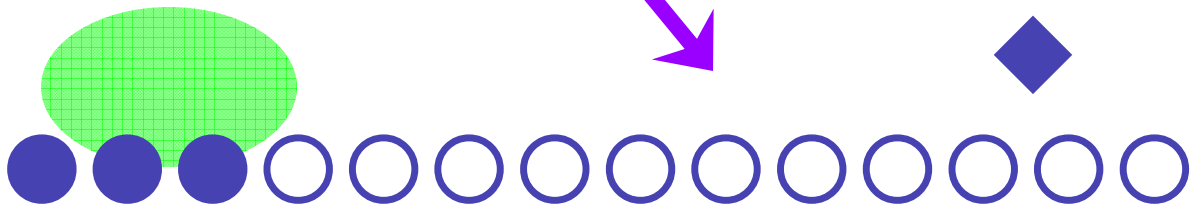
STEP - 2 Debranching - two parts

Enzyme = **debranching enzyme** (both)

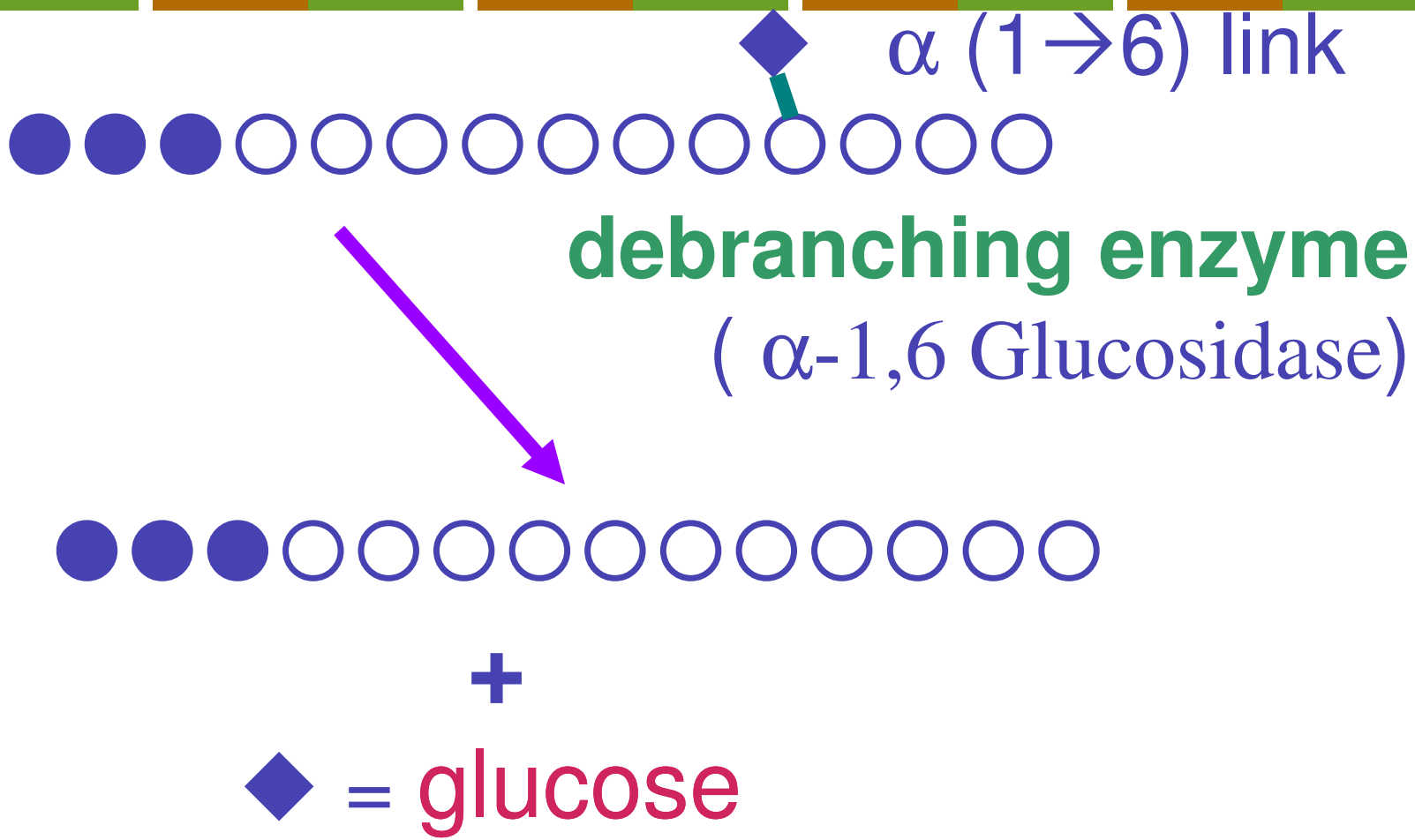


α (1→6) link

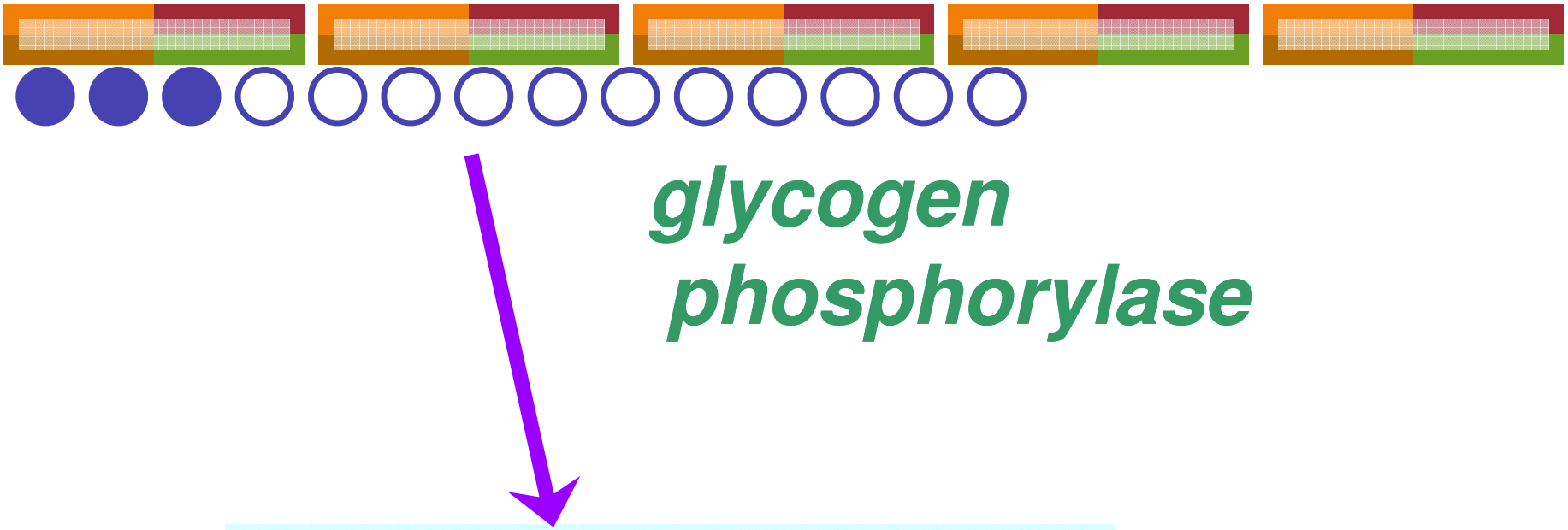
α-1,4 → α-1,4 Glucan Transferase



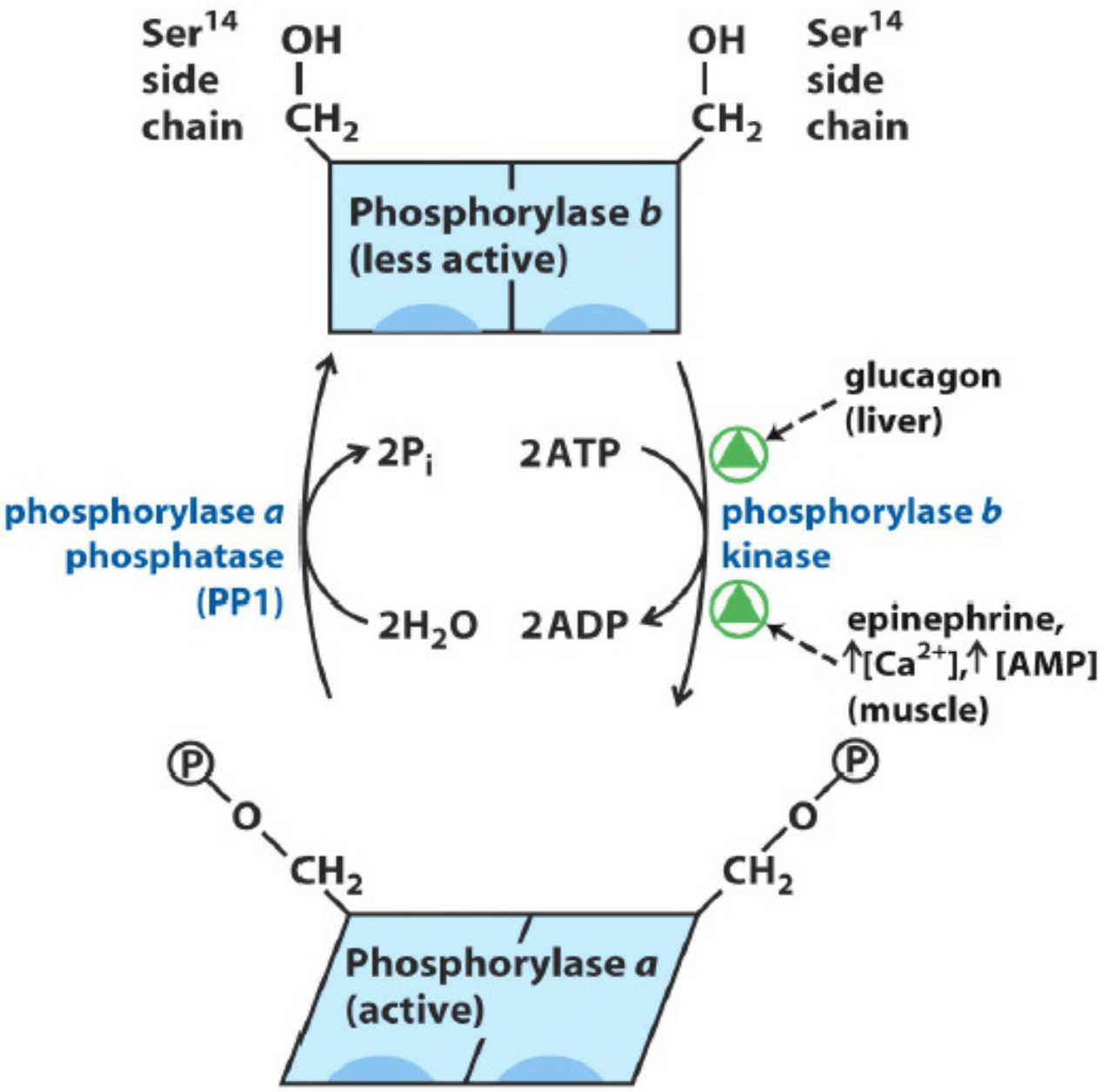
Transfers chain of three glucoses to ***any*** nonreducing end

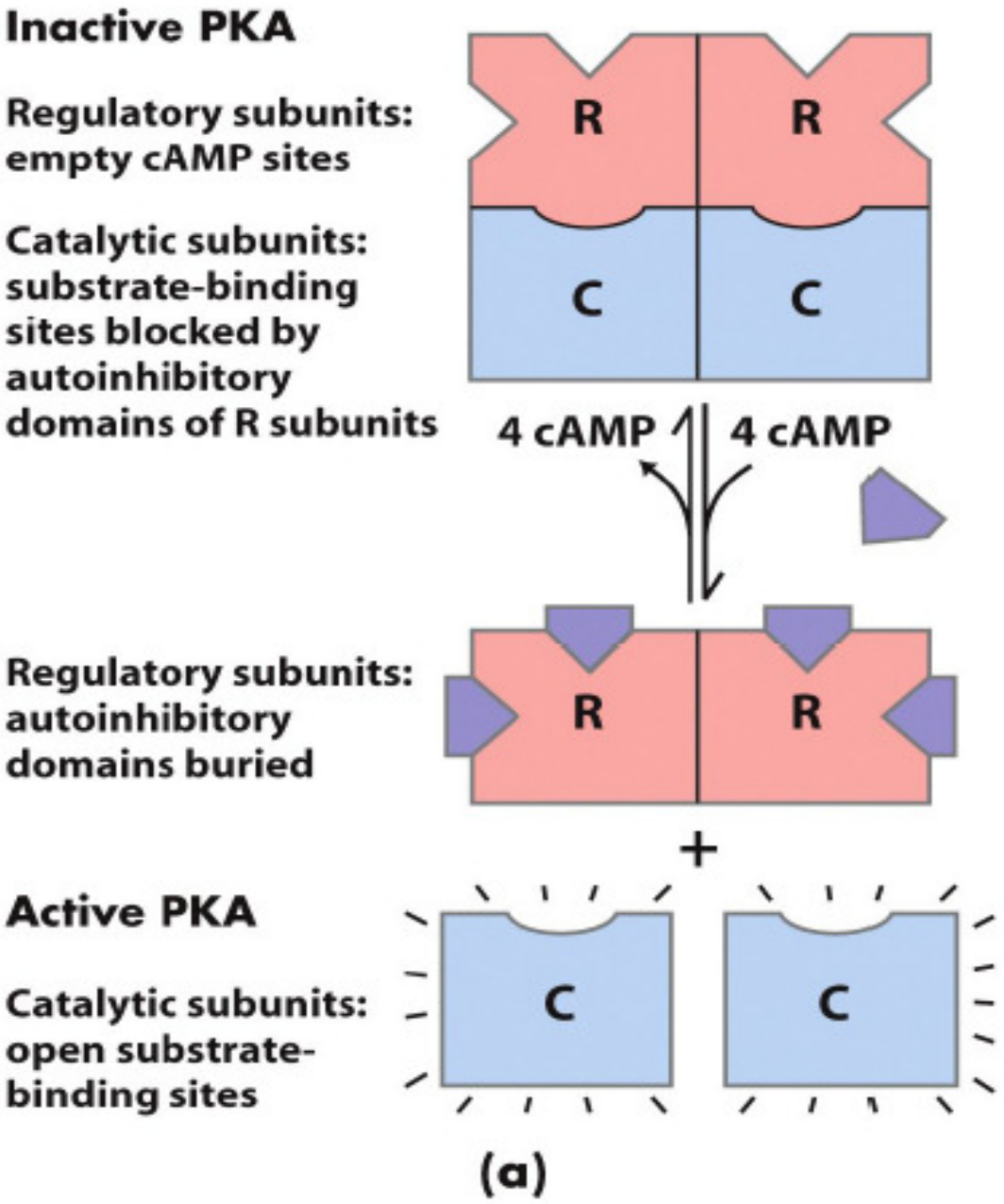


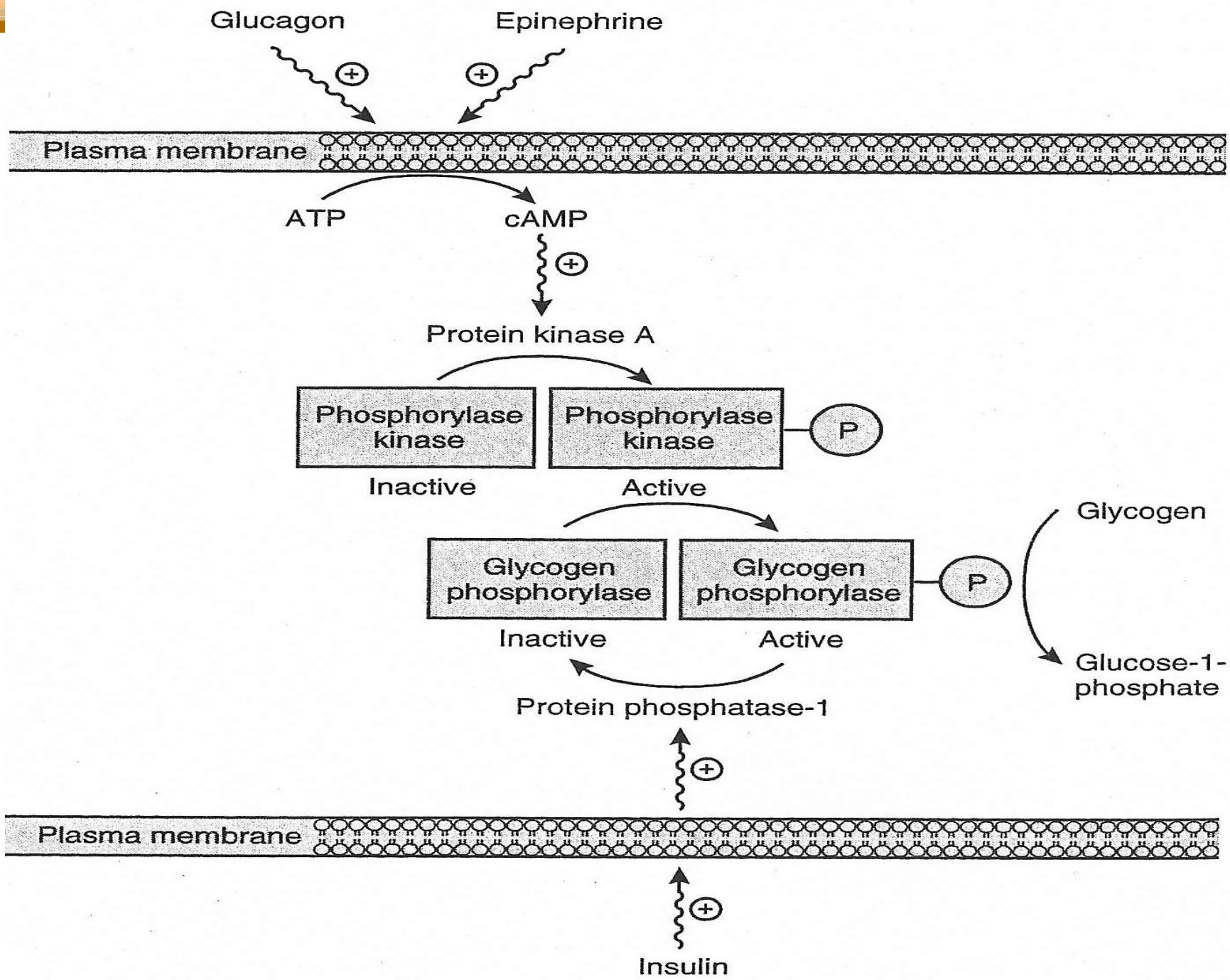
1,6 linkage cleaved



-- Phosphoglucomutase then yields glucose-6-phosphate, which can be dephosphorylated or enter glycolysis.


Ser14 side chain
OH
CH2
OH
CH2
Ser14 side chain
Phosphorylase b (less active)
glucagon (liver)
2Pi
2ATP
phosphorylase a phosphatase (PP1)
phosphorylase b kinase
2H2O
2ADP
epinephrine, ↑[Ca2+],↑ [AMP] (muscle)
P
O
CH2
P
O
CH2
Phosphorylase a (active)


Inactive PKA
Regulatory subunits: empty cAMP sites
Catalytic subunits: substrate-binding sites blocked by autoinhibitory domains of R subunits
R
R
C
C
4 cAMP
4 cAMP
Regulatory subunits: autoinhibitory domains buried
R
R
+
Active PKA
Catalytic subunits: open substrate-binding sites
C
C
(a)


Glucagon
Epinephrine
Plasma membrane
ATP
cAMP
Protein kinase A
Phosphorylase kinase
Phosphorylase kinase
P
Inactive
Active
Glycogen
Glycogen phosphorylase
Glycogen phosphorylase
P
Inactive
Active
Glucose-1-phosphate
Protein phosphatase-1
Plasma membrane
Insulin

- Primary hormones =

-- ***epinephrine***

-- ***glucagon***

-- ***insulin***

- Primary enzyme targets in glycogen metabolism=

  Glycogen phosphorylase and

  Glycogen synthase.

The actions of the hormones are indirect.

Example- hormones and diet

Dinner at 9:00 pm -- steak, mashed potatoes, sherbert for dessert, wine

Sleep immediately, sleep late

During sleep: amino acids, CH_2O

→ high blood glucose levels

→ higher insulin

→ glycogenesis

Wake late for class  →adrenaline rush

→ run to class

glycogen → glucose → lactate

epinephrine (= adrenaline) →

glycogenolysis

======== *HORMONES* =========

Glucagon* - *low glucose levels

-- Acts primarily on **liver** cells.

-- Stimulates glycogen breakdown

-- Inhibits glycogenesis.

-- Blocks glycolysis

-- Stimulates gluconeogenesis.

Epinephrine - low glucose levels

-- Acts primarily on skeletal **muscle**.
-- Stimulates glycogen breakdown
-- Inhibits glycogenesis.

Glucagon and epinephrine both stimulate intracellular pathway via increasing levels of cAMP.

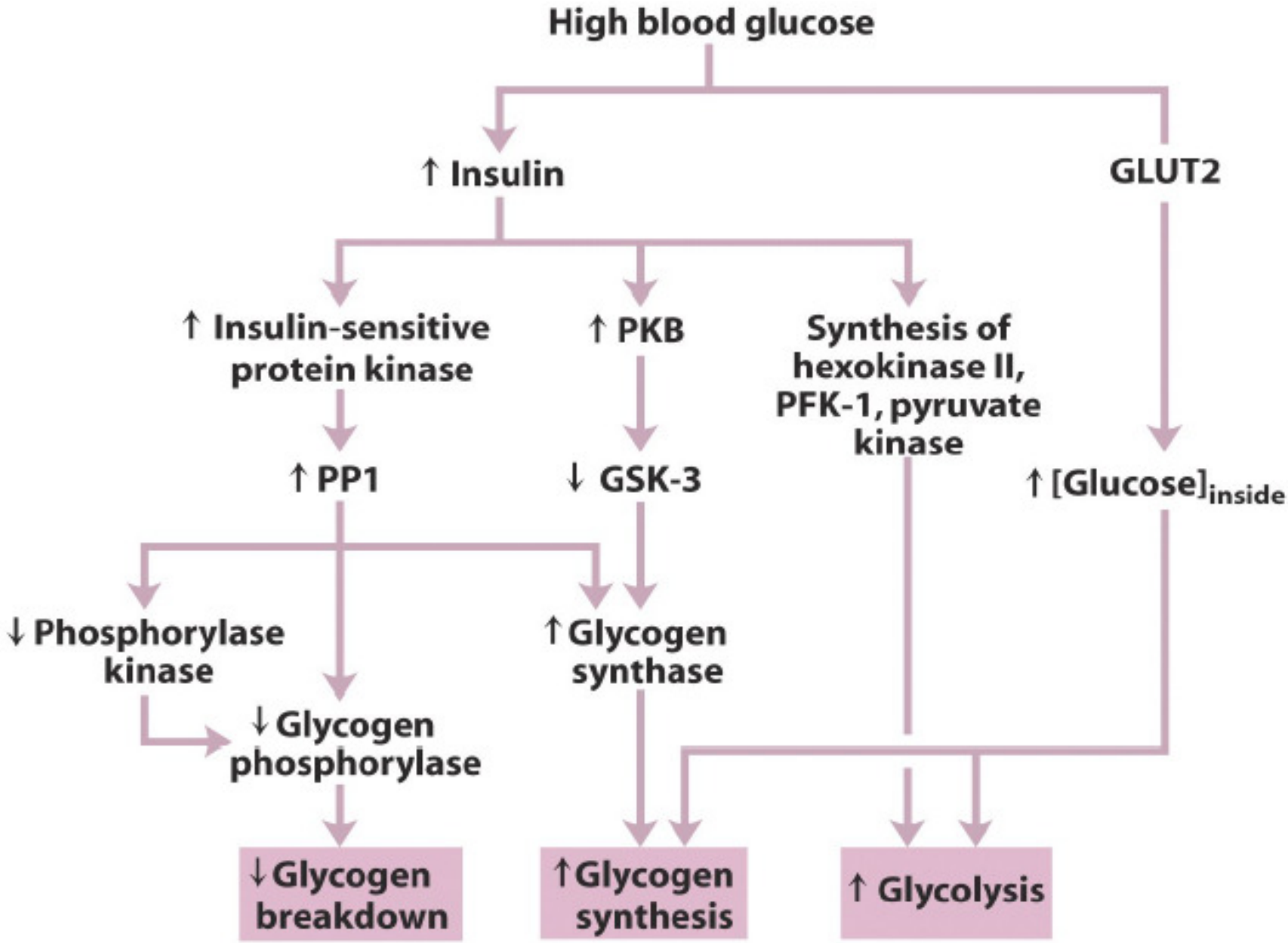
Insulin

-- ***High levels of glucose*** induce release of insulin from β-cells of islets of Langerhan in the pancreas.

-- Detected by receptors at surface of ***muscle*** cells.

-- Increases glycogenesis in muscle.

--


High blood glucose
↑ Insulin
GLUT2
↑ Insulin-sensitive protein kinase
↑ PKB
Synthesis of hexokinase II, PFK-1, pyruvate kinase
↑ PP1
↓ GSK-3
↑ [Glucose]inside
↓ Phosphorylase kinase
↑ Glycogen synthase
↓ Glycogen phosphorylase
↓ Glycogen breakdown
↑ Glycogen synthesis
↑ Glycolysis

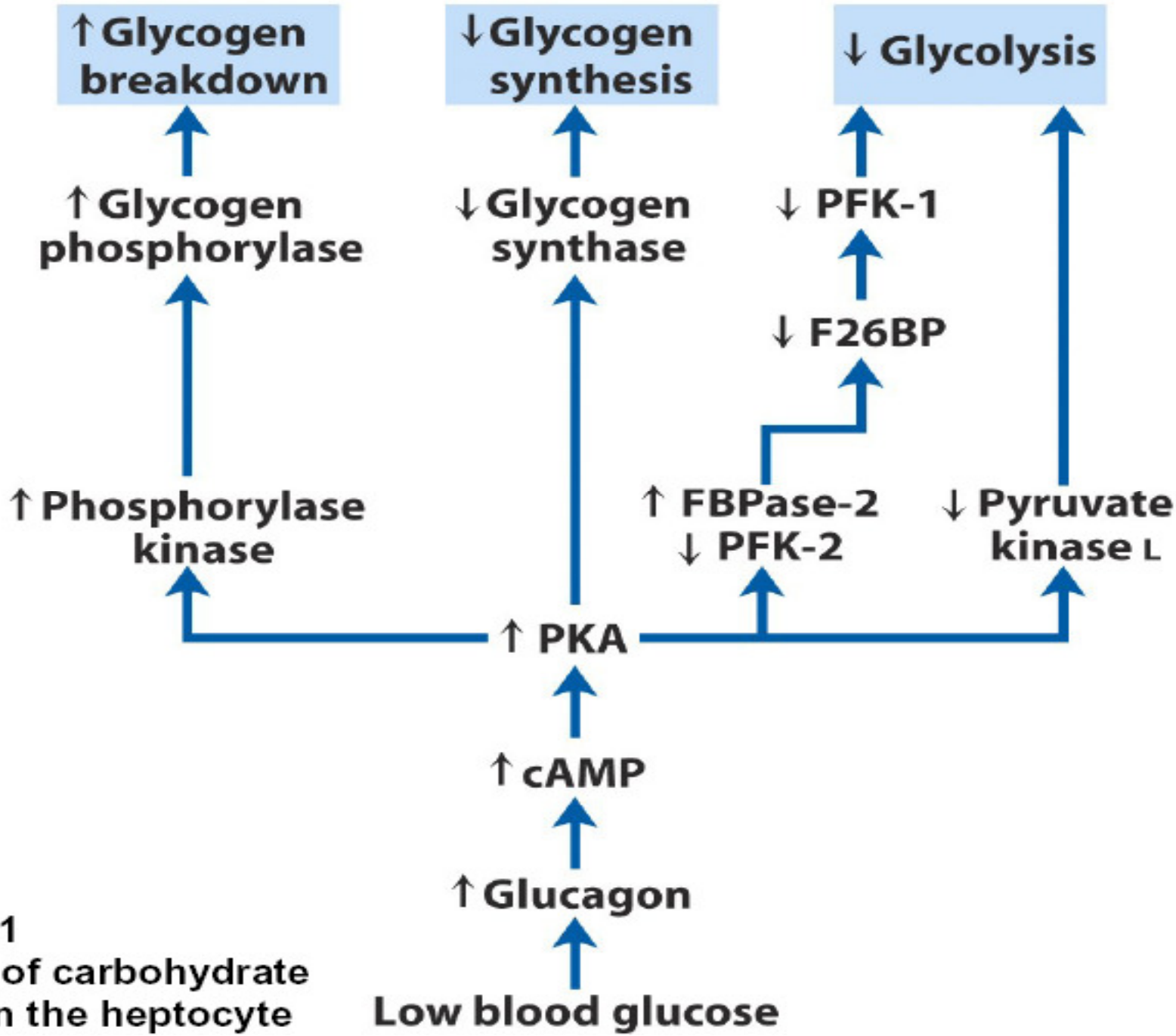


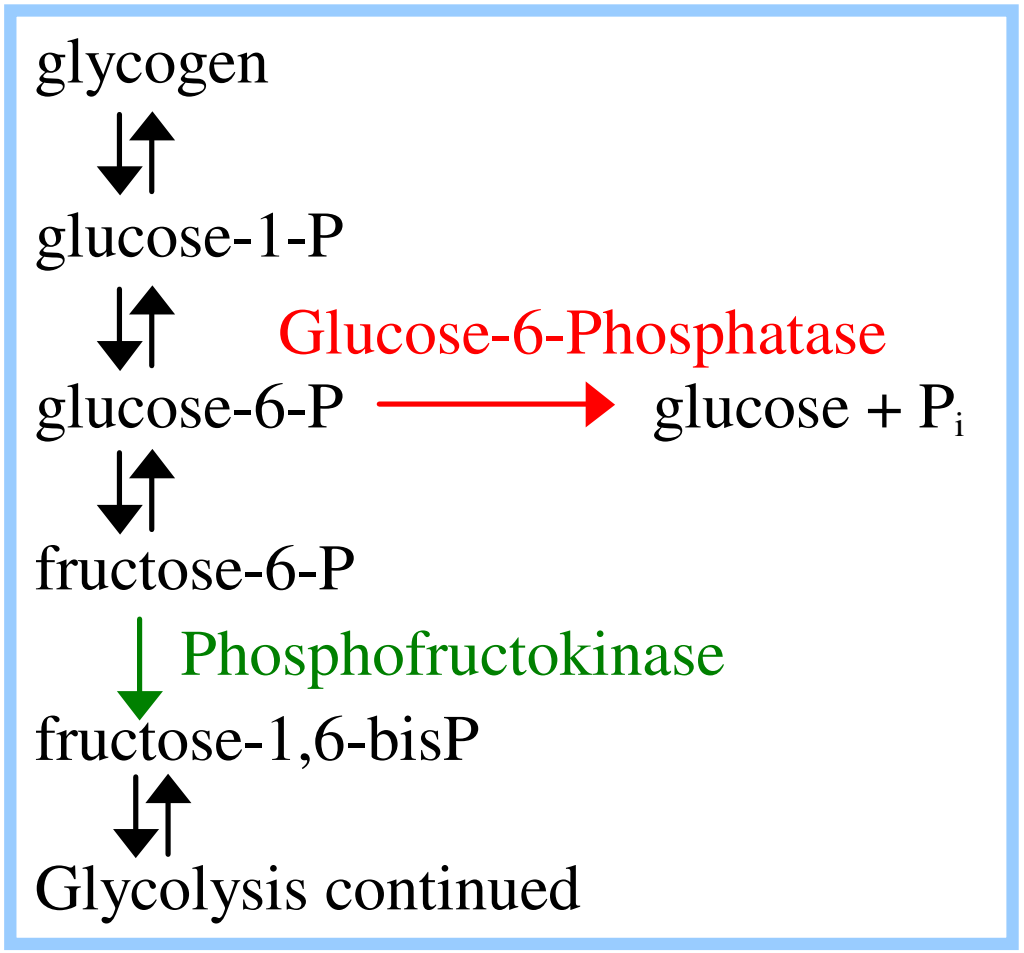
Figure 15-31
Regulation of carbohydrate synthesis in the heptocyte

Glycogen Storage Diseases:

-- A family of serious, although not necessarily fatal, diseases caused by mutations in the enzymes involving in glycogen storage and breakdown.

Glycogen Storage Diseases are genetic enzyme deficiencies associated with **excessive glycogen accumulation** within cells.

Some enzymes whose deficiency leads to glycogen accumulation are part of the inter-connected pathways shown here.



Glycogen Storage Disease	**Symptoms**, in addition to glycogen accumulation
Type I, liver deficiency of **Glucose-6-phosphatase** (von Gierke's disease)	**hypoglycemia** (low blood glucose) when fasting, liver enlargement.
Type IV, deficiency of **branching enzyme** in various organs, including liver (Andersen's disease)	**liver dysfunction** and early death.
Type V, muscle deficiency of **Glycogen Phosphorylase** (McArdle's disease)	**muscle cramps** with exercise.
Type VII, muscle deficiency of **Phosphofructokinase**.	**inability to exercise**.

Von Gierke's disease

- Deficiency of glucose 6 phosphatase enzyme
  - Hypoglycemia
  - Retard growth
  - Lactic acidosis
  - Ketosis
  - Hyperlipidemia
  - Hyperuricemia
  - Cirrhosis

Types of Glycogen Storage Disease

Some forms of GSDs are life-threatening while others cause little in the way of illness. These *genetic diseases* are caused by mutations in the enzymes involved in glycogen storage and breakdown.

Type	Enzyme Deficiency	Name	Tissue	Characteristics
I	glucose-6-phosphatase	Von Gierke's disease	liver, kidney	Enlarged liver, liver loaded with glycogen, severe hypoglycemia, ketosis, hyperlipemia
II	α-glucosidase(lysosome)		liver, heart, muscle	fatal; glycogen accumulates in lysosomes
III	debranching enzyme	Pompe's disease	liver, muscle	short-chained glycogen, some hypoglycemia
IV	branching enzyme	Cori's disease	liver	fatal; long unbranched glycogen
V	phosphorylase	Andersen's disease McArdle's disease	muscle	severe cramps upon exercise; little glycogen in muscle
VI	phosphorylase	Hers' disease	liver	similar to I, but milder
VII	phosphofructokinase	Tarui's disease	muscle	similar to V; high G6P activates glycogen synthase; more glycogen accumulates in muscle; some erythrocyte involvement
VIII	phosphorylase kinase		liver	similar to I but milder
IX	glycogen synthase		liver	less glycogen in liver