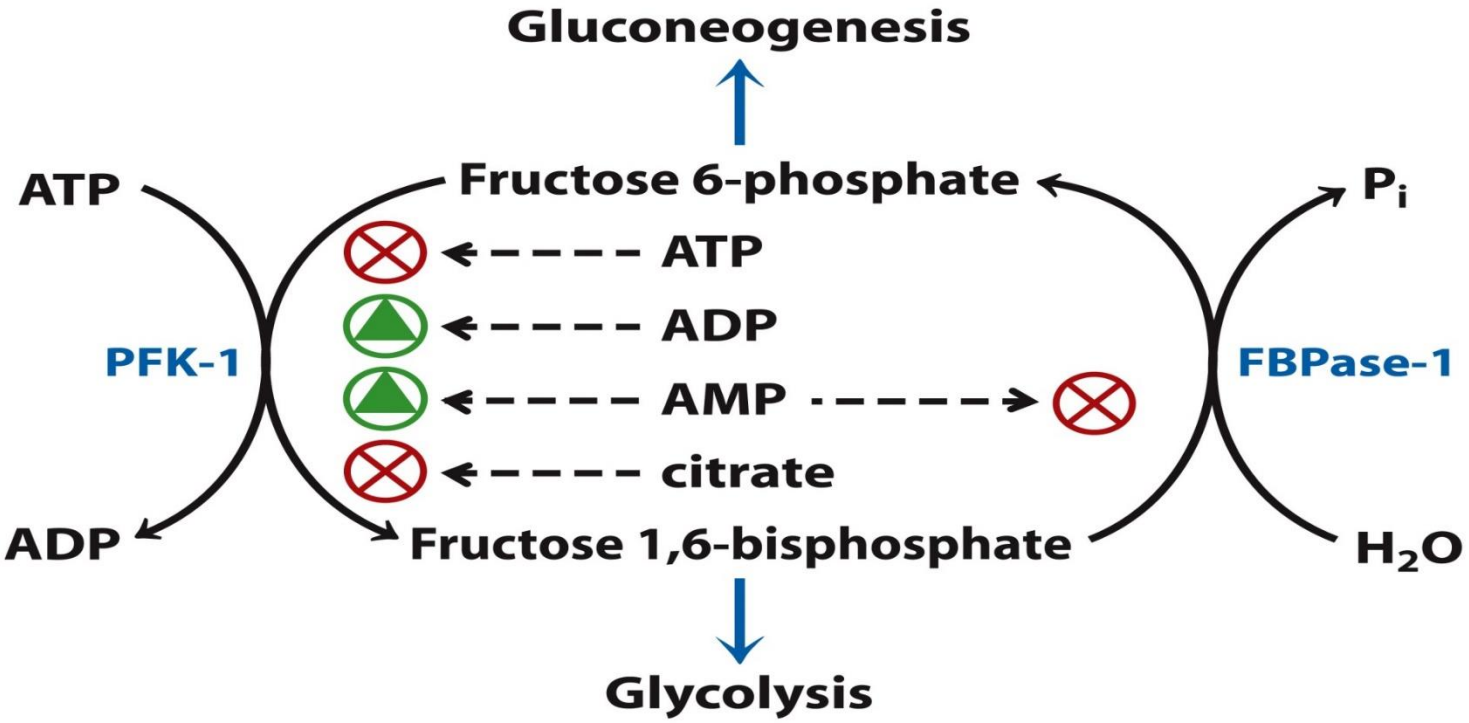
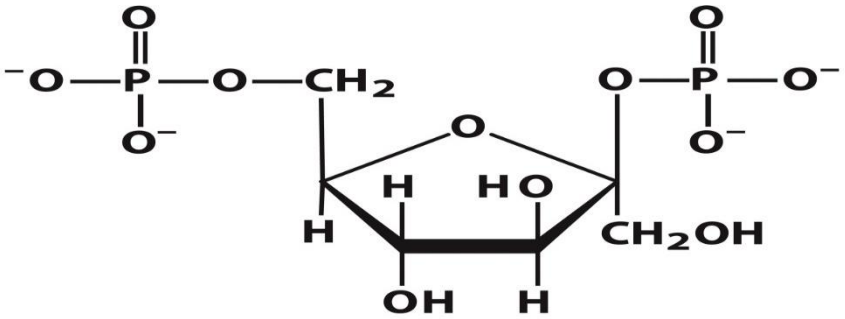
Regulation of Phosphofructokinase 1 and Fructose 1,6-Bisphosphatase

- Go glycolysis if AMP is high and ATP is low
- Go gluconeogenesis if AMP is low



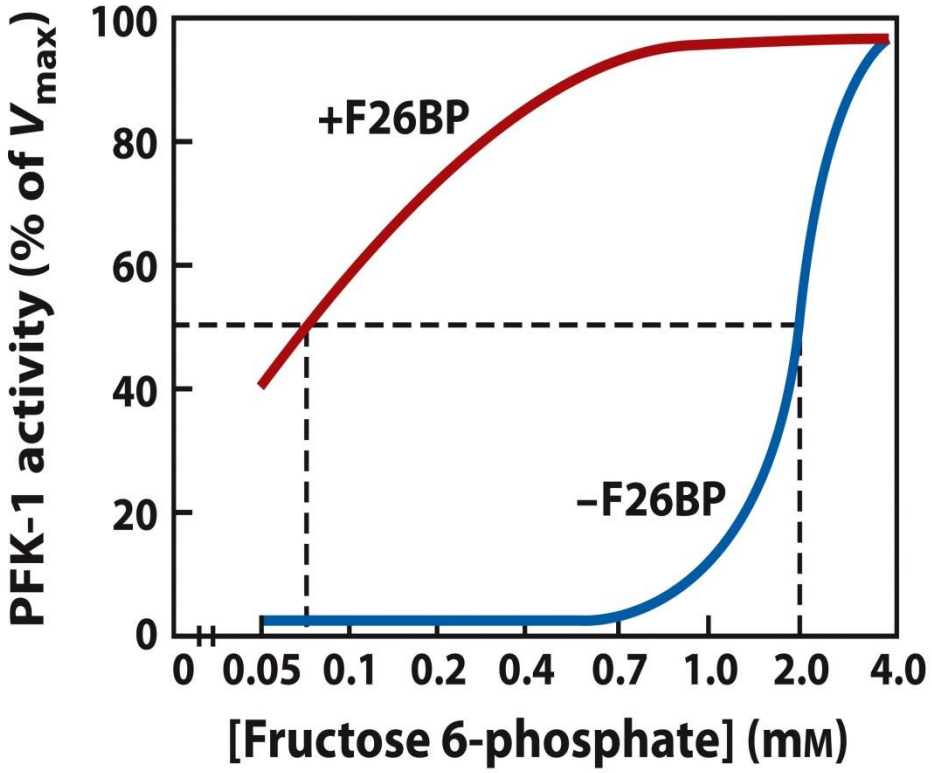
Fructose 2,6-Bisphosphate

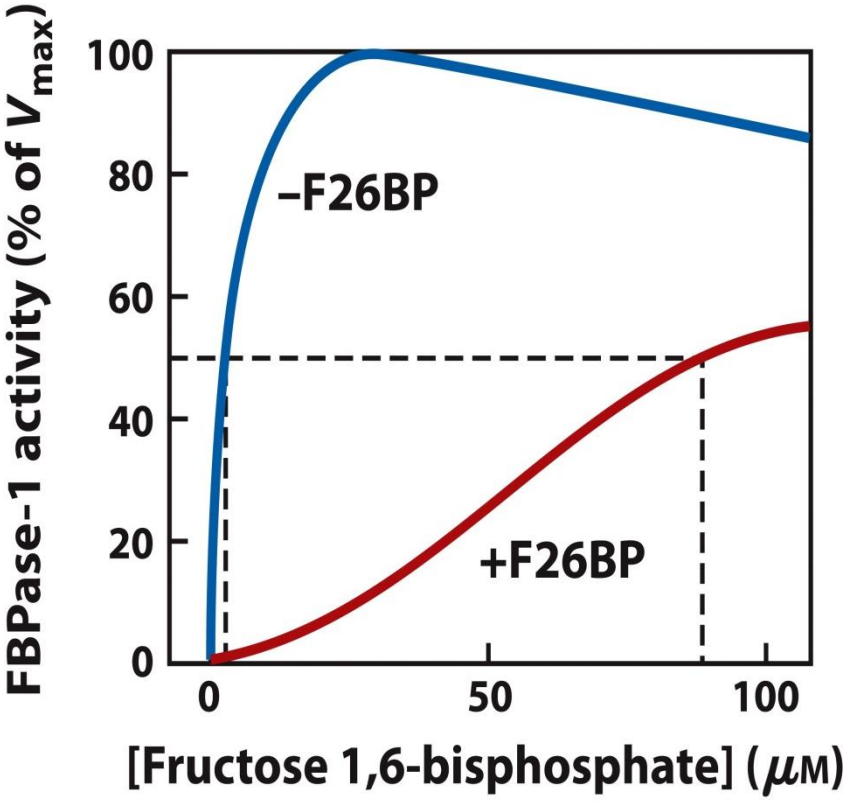
- NOT a glycolytic intermediate, only a regulator
- Produced specifically to regulate glycolysis and gluconeogenesis
  - activates phosphofructokinase (glycolysis)
  - inhibits fructose 1,6-bisphosphatase (gluconeogenesis)

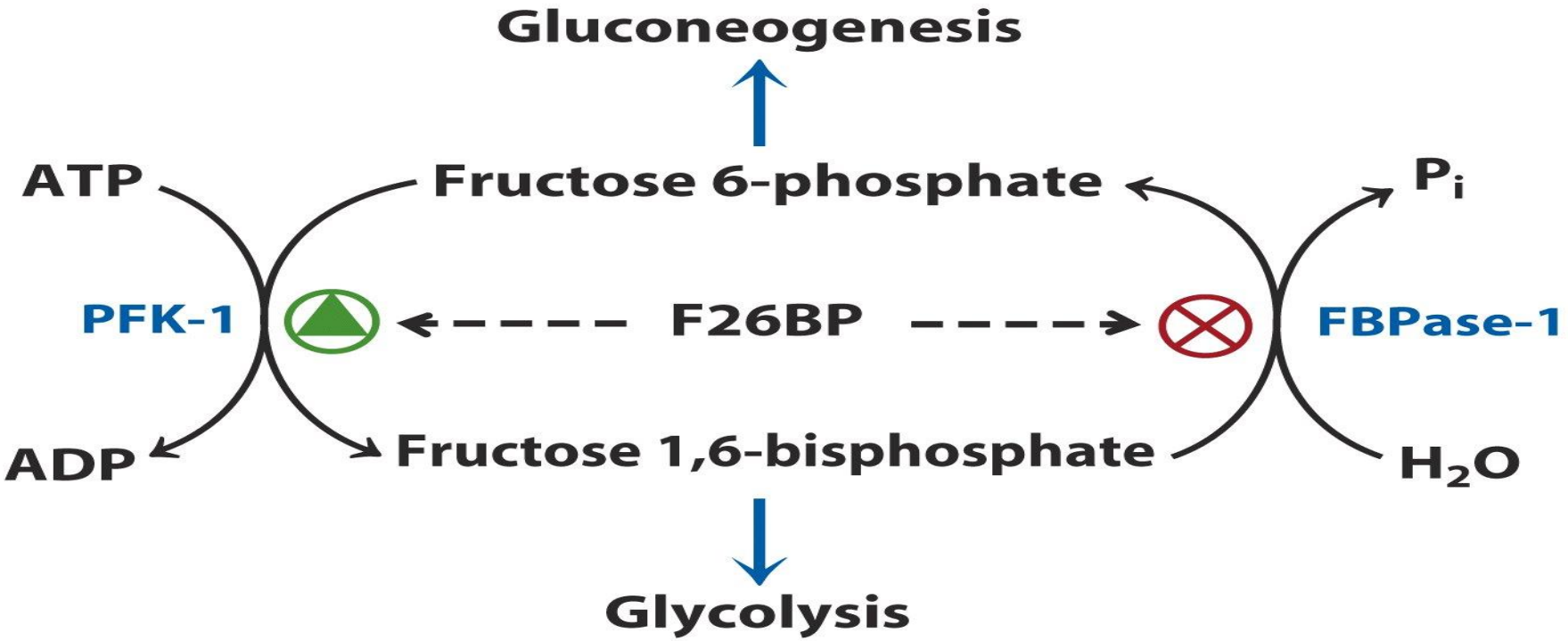


Fructose 2,6-bisphosphate

Glycolysis and gluconeogenesis are differentially regulated by F-2,6-bP



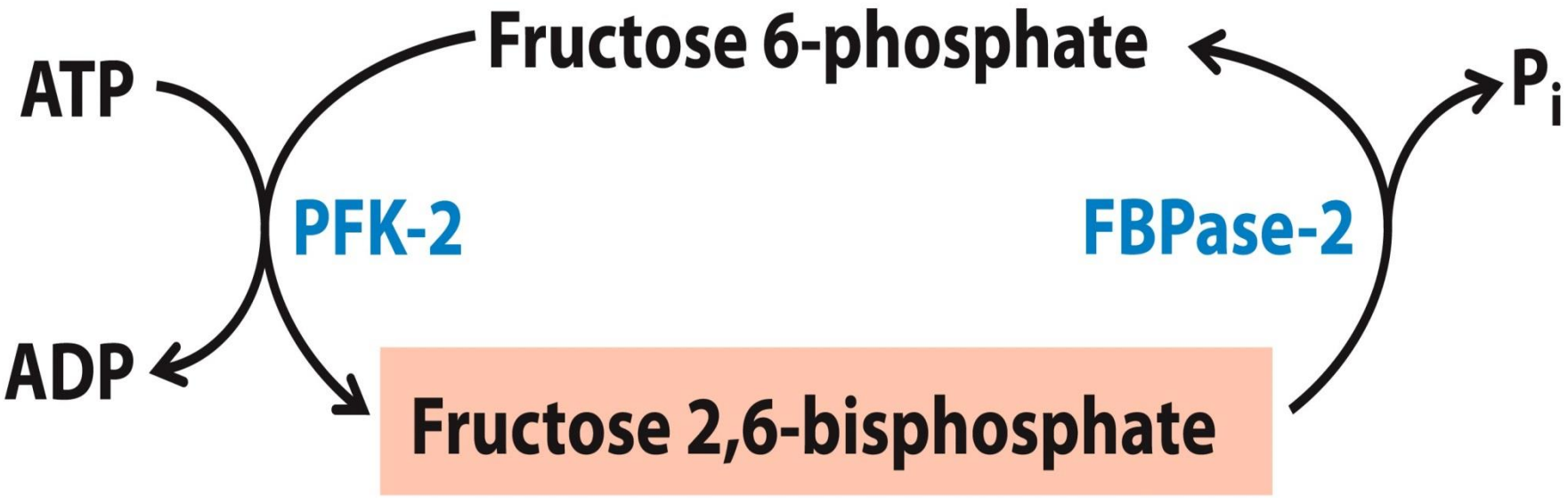




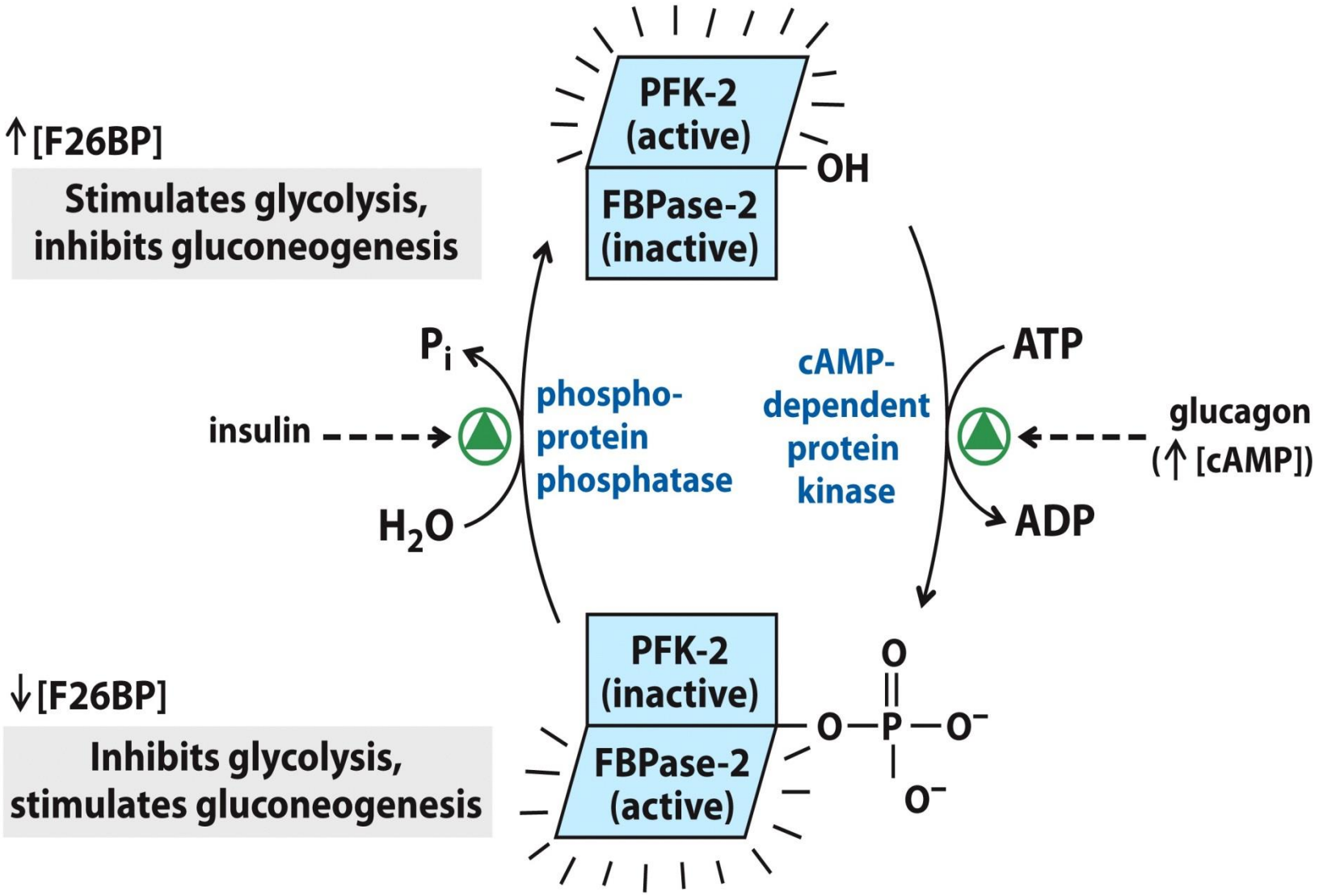
The apparent energetic disadvantage of the futile cycle is outweighted by advantage of allowing this type of control of pathway direction;

→ Differential regulation of glycolysis and gluconeogenesis by F,2,6-BP

F-2,6-bP is produced from fructose-6-phosphate



Regulation of F-2,6-bP Levels

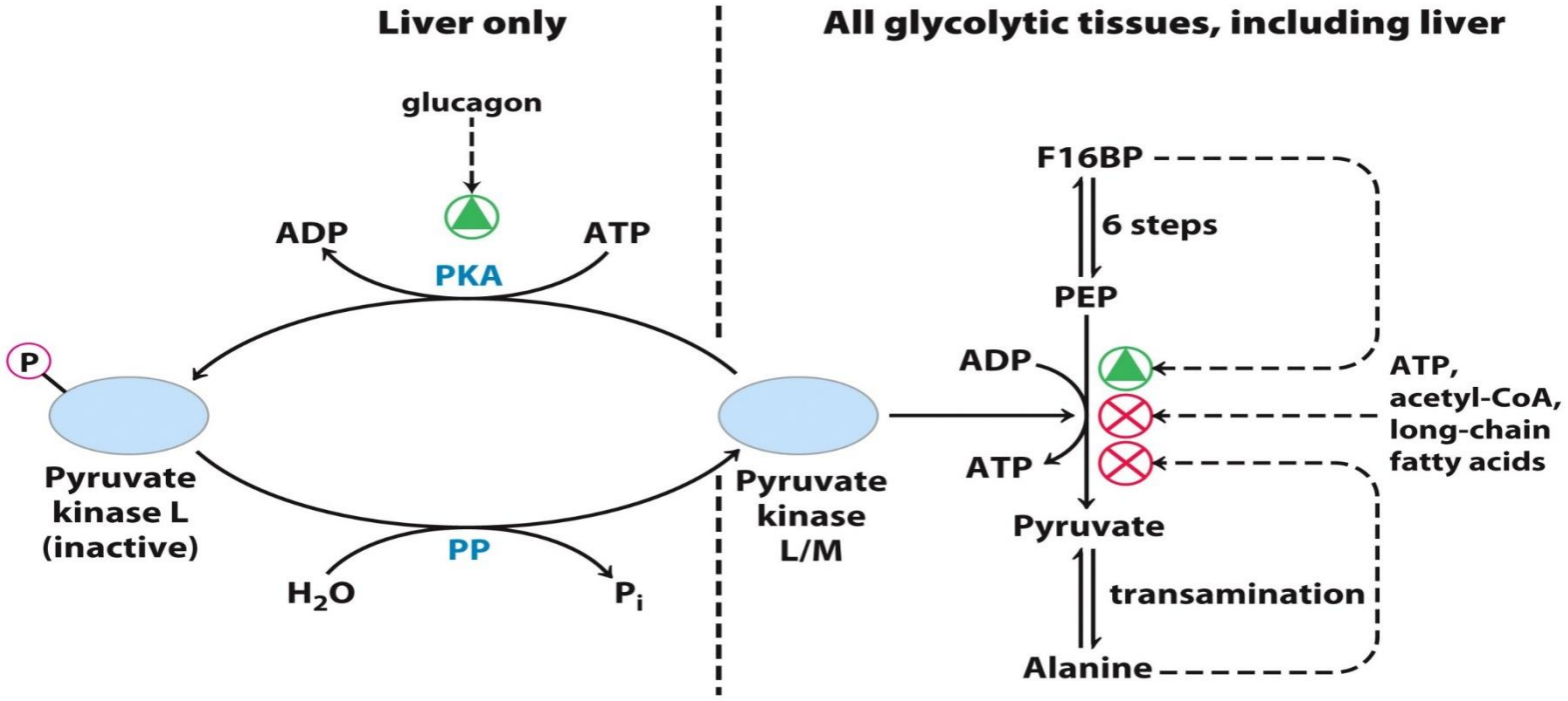


Regulation of Pyruvate Kinase

- Allosterically activated by fructose-1,6-bisphosphate
  - High flow through glycolysis
- Allosterically inhibited by signs of abundant energy supply (all tissues)
  - ATP
  - Acetyl-CoA and long-chain fatty acids
  - Alanine (enough amino acids)
- Inactivated by phosphorylation in response to signs of glucose depletion (glucagon) (liver only)
  - Glucose from liver is exported to brain and other vital organs

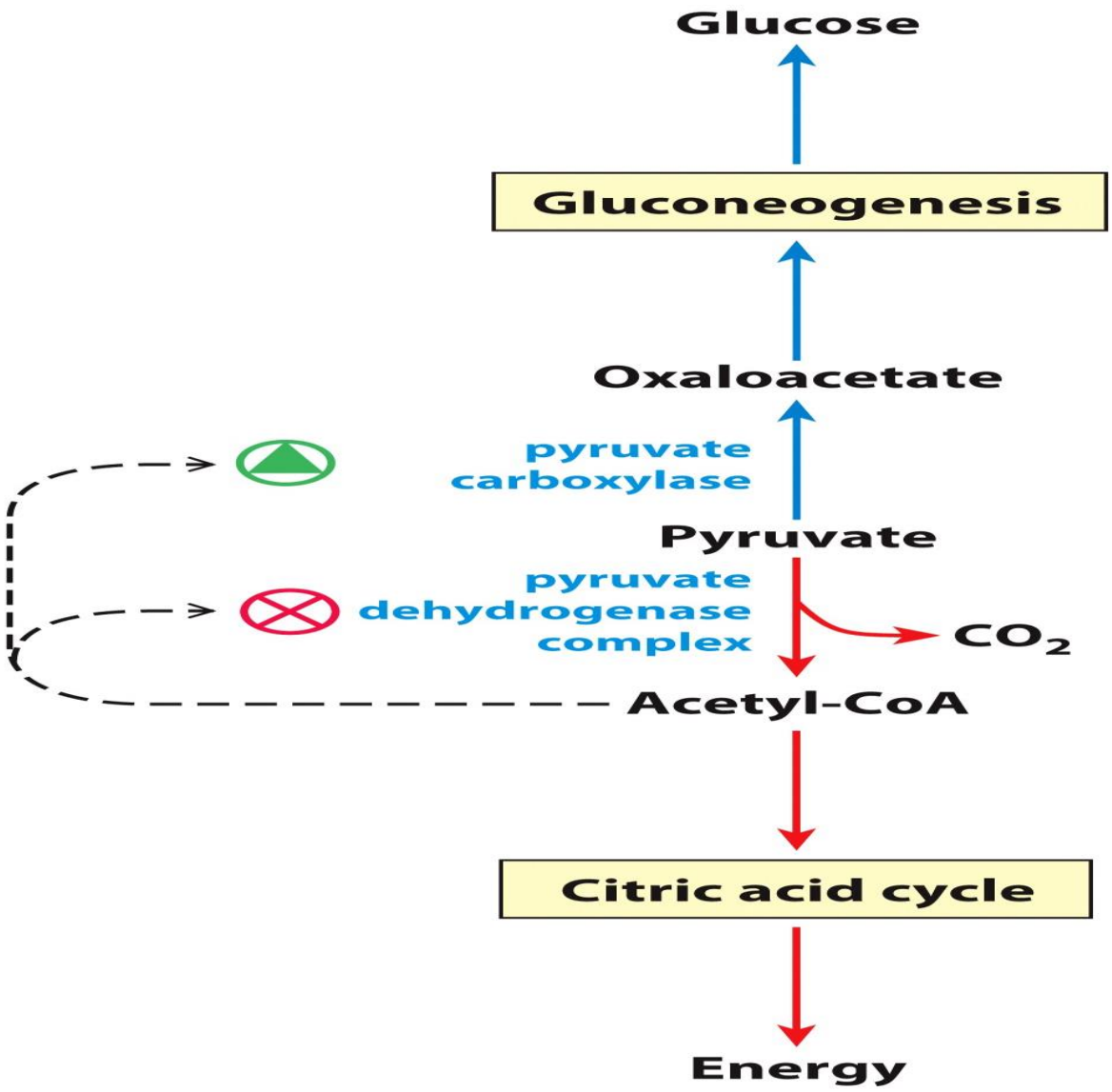
Regulation of Pyruvate Kinase

when blood glucose is low
; instead, the liver exports glucose.

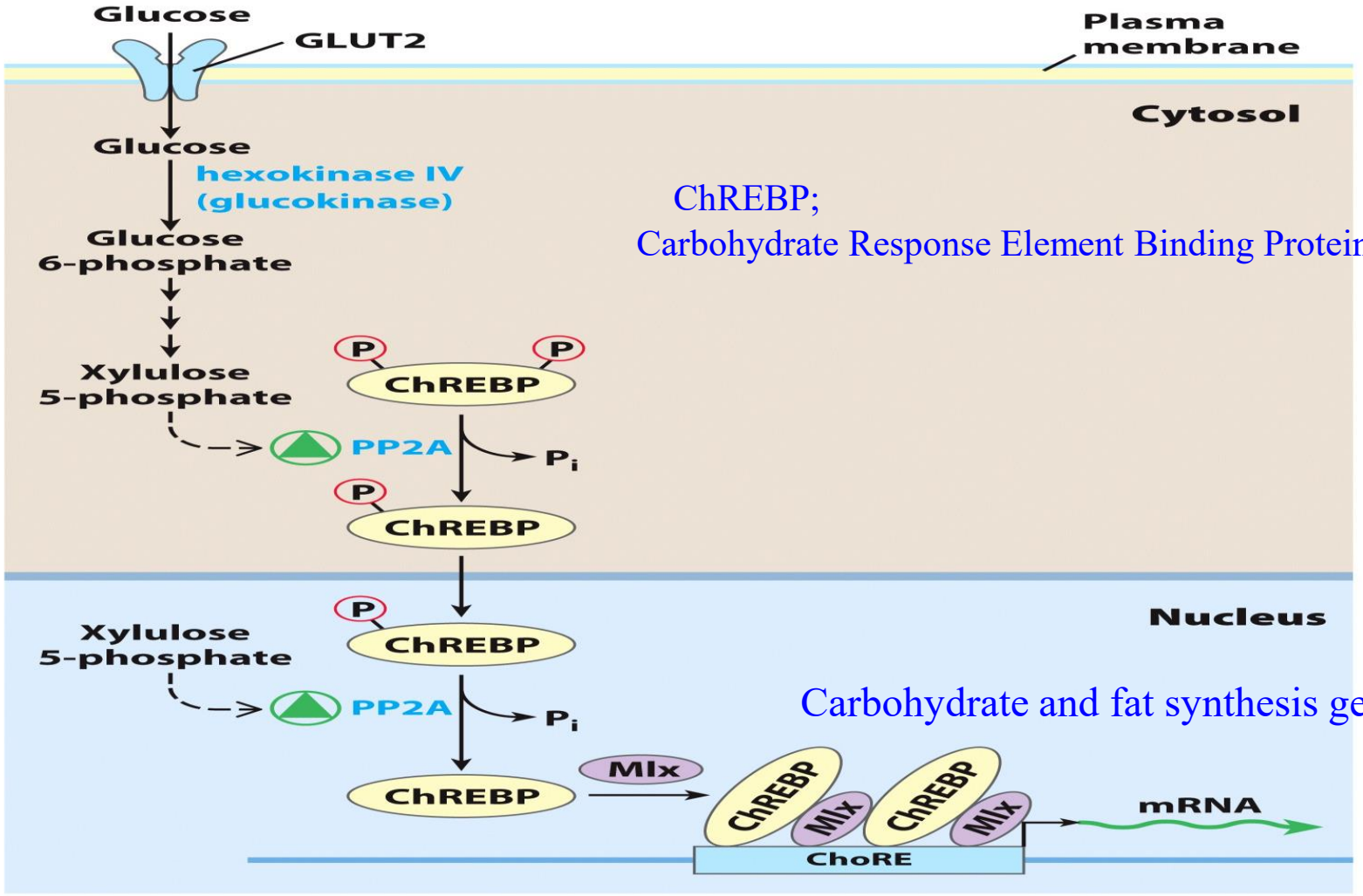


This mechanism prevents the liver from consuming glucose by glycolysis when blood glucose is low; instead, the liver exports glucose. The muscle isozyme (M form) is not affected by this phosphorylation mechanism.

Two Alternative Fates for Pyruvate



ChREBP activates transcription in response to glucose



ChREBP;
Carbohydrate Response Element Binding Protein

Carbohydrate and fat synthesis gene

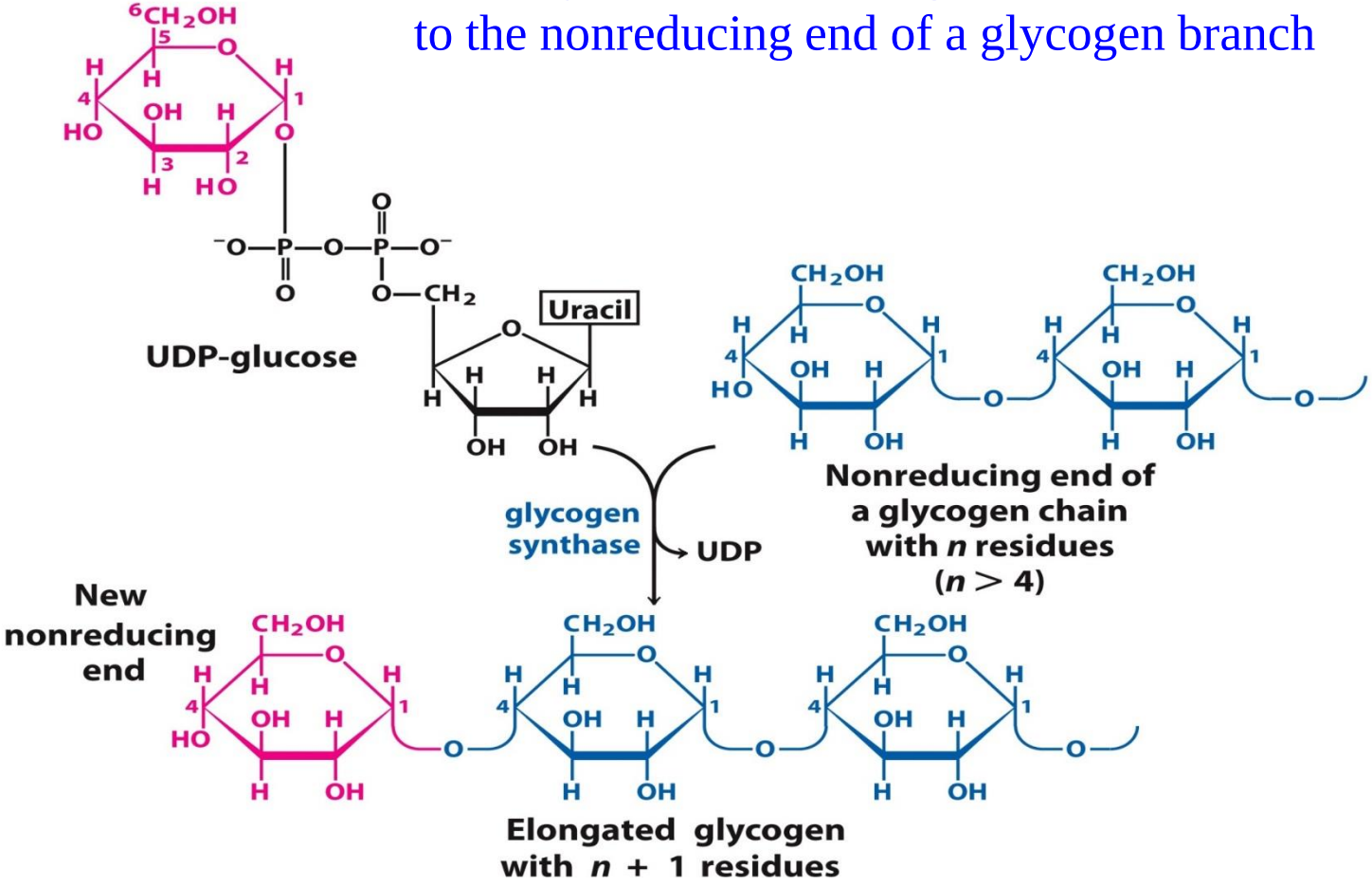
ChoRE: carbohydrate response element

Dealing with Branch Points in Glycogen

- Glycogen phosphorylase works on non-reducing ends until it reaches four residues from an ($\alpha 1 \rightarrow 6$) branch point
- Debranching enzyme transfers a block of three residues to the non-reducing end of the chain
- Debranching enzyme cleaves the single remaining ($\alpha 1 \rightarrow 6$)–linked glucose

Glycogen is synthesized by glycogen synthase

The enzyme transfers the glucose residue of UDPglucose to the nonreducing end of a glycogen branch



Von Gierke disease- A glycogen-storage disease

Massive accumulation of glycogen in liver and kidney

; hepato-nephromegalia glycogenia (간장-신비대성 당생성증)

= von Gierke disease

= Type Ia glycogen storage disease

Result from genetic defect of glucose-6-phosphatase → no glycogen breakdown

; elevation of serum TG, excess adipose tissue in cheek, short stature,

delay of puberty, curvature of lumbar spine

; accumulation of G6P → increased glycolysis, TCA cycle

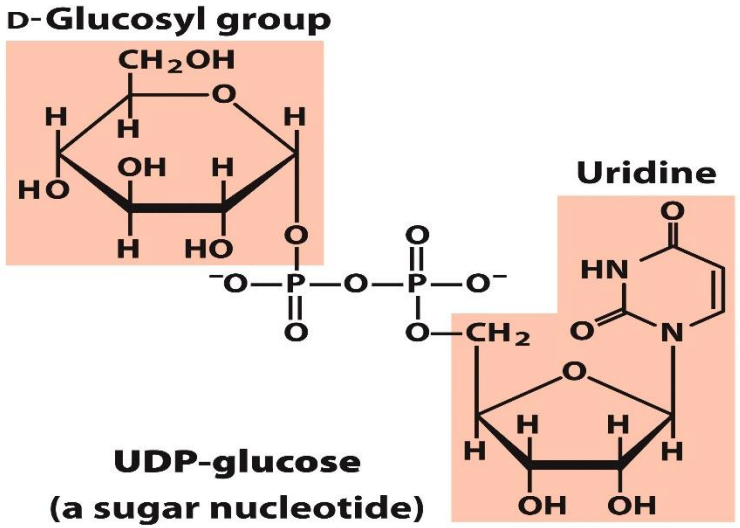
→ hypoglycemia, lactic acid increase (lactic acidosis), excess NADH

; Administration:

oral administration of large amount of glucose in its various form

(uncooked cornstarch→ slowly release of glucose)

UDP-glucose is the substrate for glycogen synthase



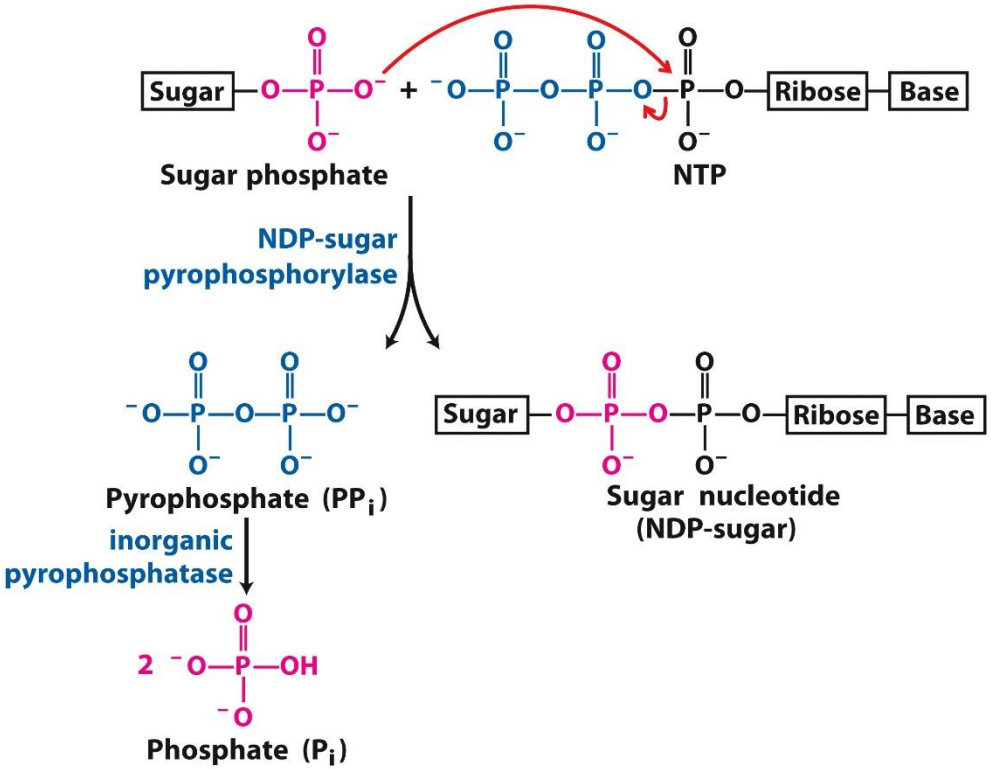
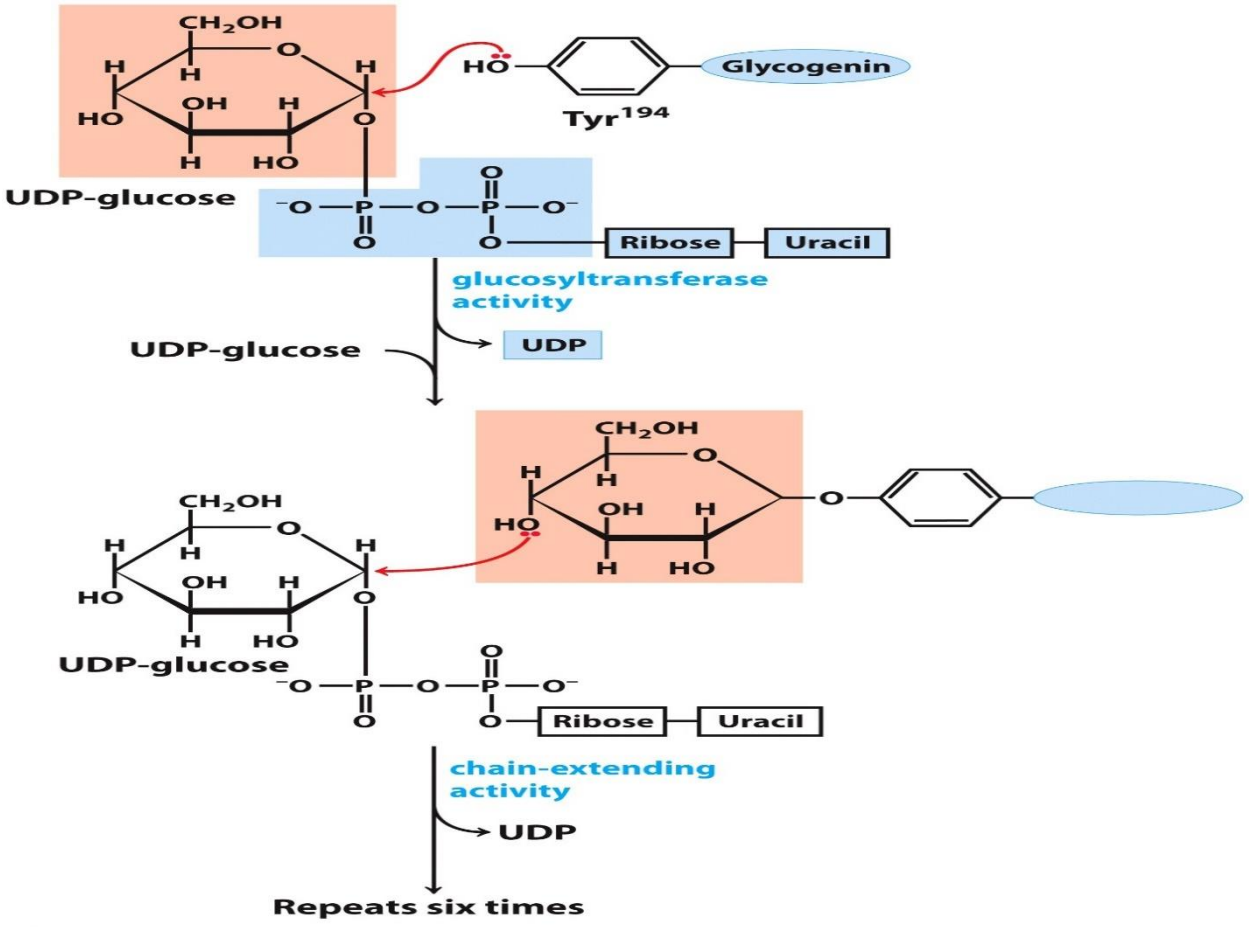


Figure 15-31
Lehninger Principles of Biochemistry, Sixth Edition

Glycogenin starts a new glycogen chain

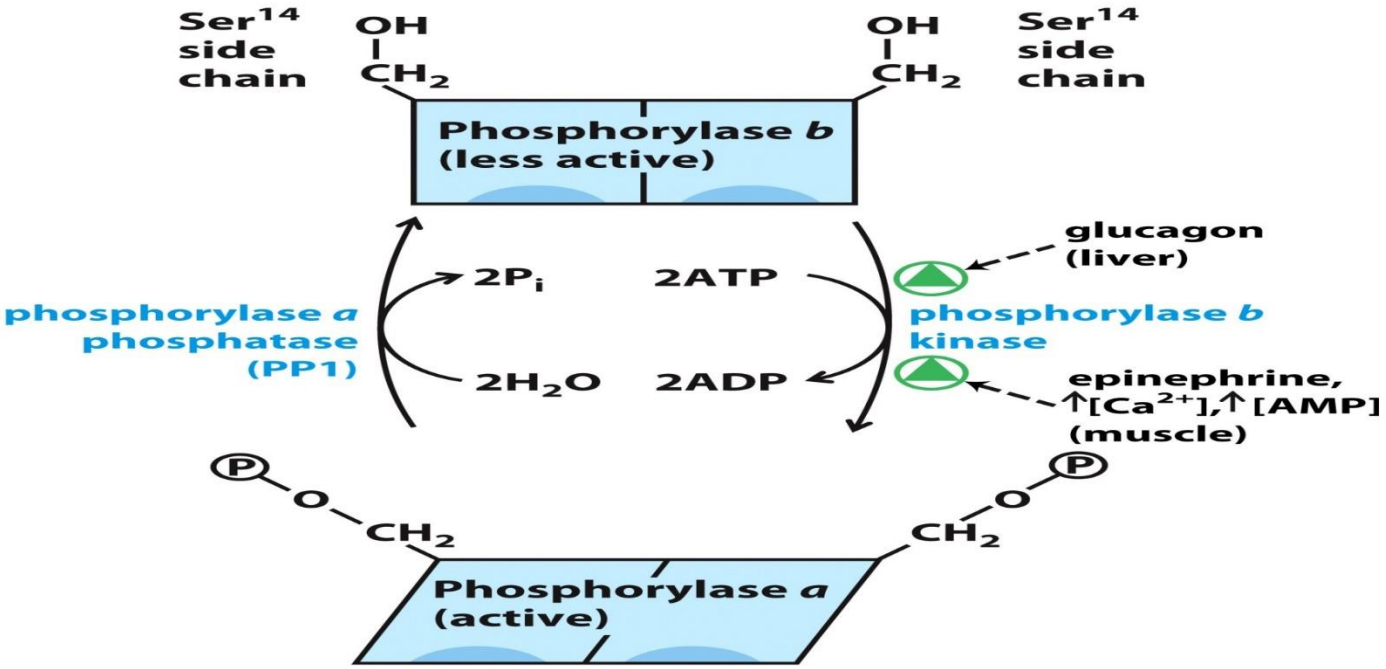


form a nascent glycogen molecule of eight glucose residues attached by (1→4) glycosidic linkages.

Control of Glycogen Breakdown

- Glucagon/Epinephrine signaling pathway
  - Starts phosphorylation cascade vis cAMP
  - activates glycogen phosphorylase

- Glycogen phosphorylase cleaves glucose residues off glycogen, generating glucose-1-phosphate



Epinephrine and glucagon stimulate breakdown of glycogen

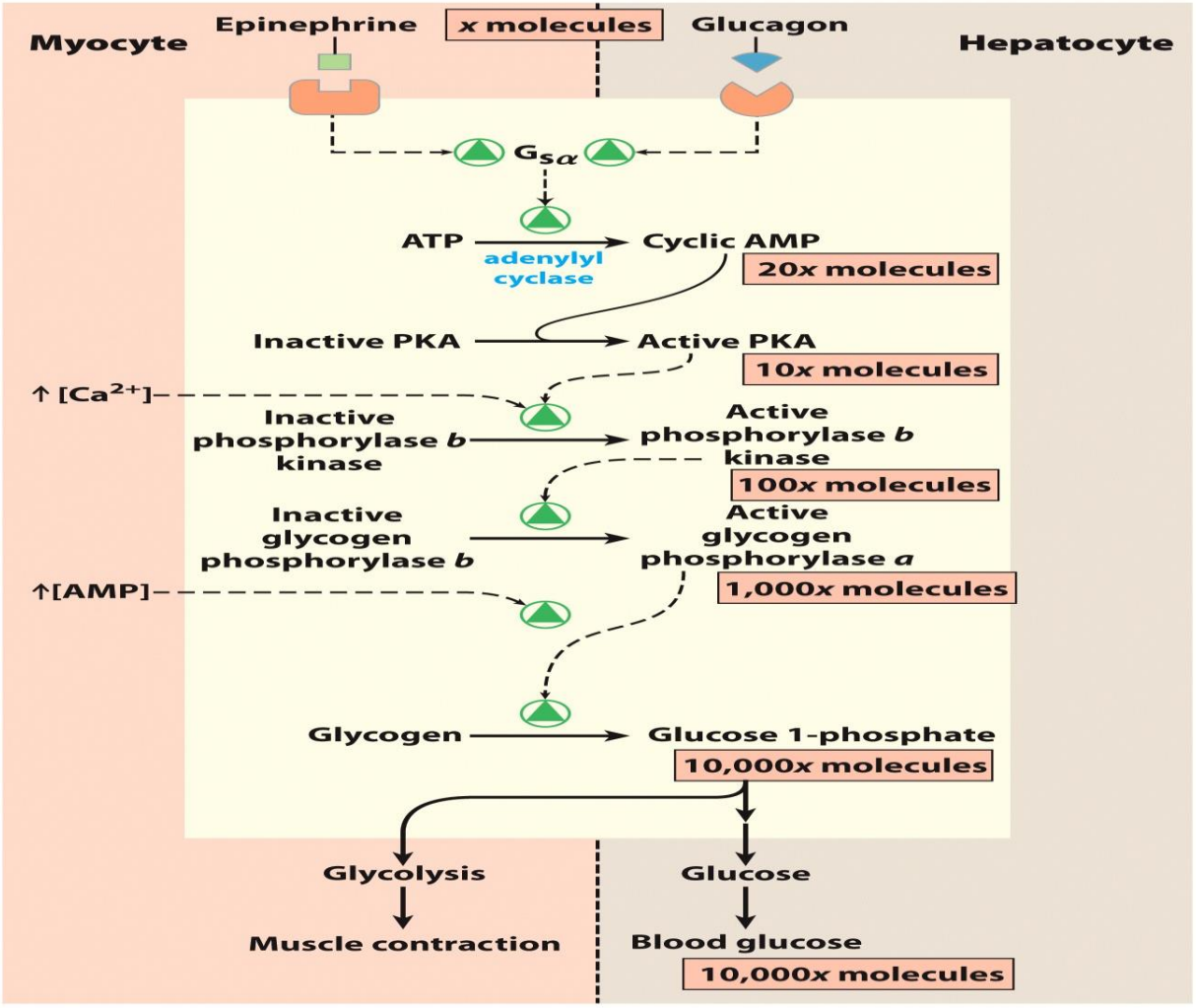


Figure 15-37
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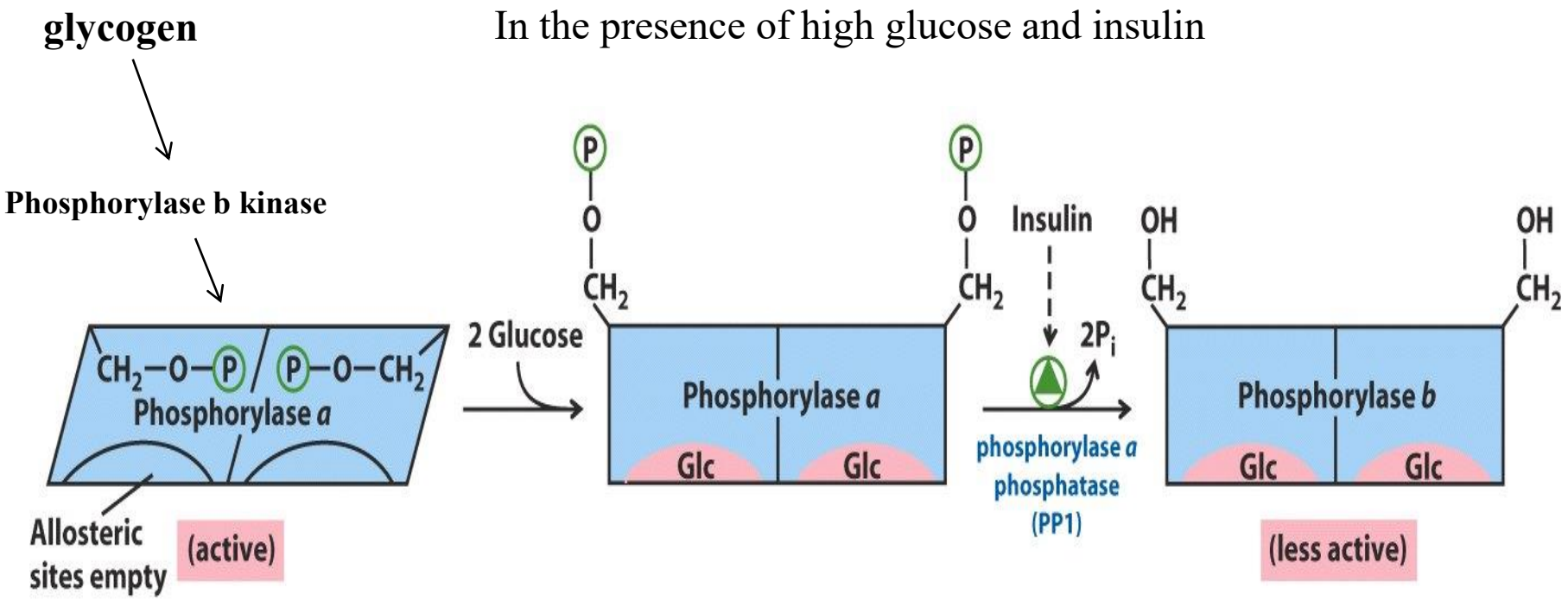
Glycogen phosphorylase of liver as glucose sensor



- Glu binding to glycogen phosphorylase a of liver → conformational change
→ exposure of p-ser to
→ conversion to phosphorylase b by dephosphorylation via phosphorylase a phosphatase (PP1)
→ Slowing glycogen breakdown in response to high blood glucose

- insulin → PP1 stimulation → slow glycogen breakdown

Control of Glycogen Synthesis

- Insulin-signaling pathway
  - increases glucose import into muscle
  - stimulates the activity of muscle hexokinase
  - activates glycogen synthase
- Increased hexokinase activity enables activation of glucose
- Glycogen synthase makes glycogen for energy storage

Glycogen synthase is controlled by phosphorylation

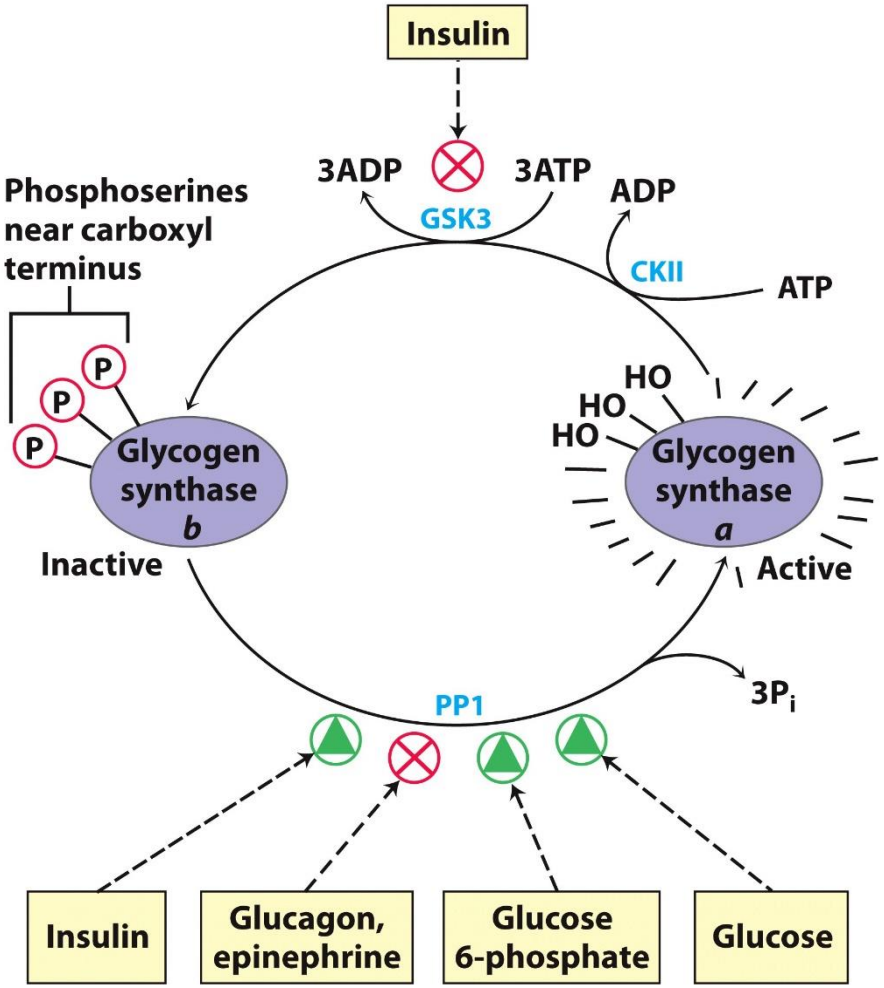


Figure 15-39
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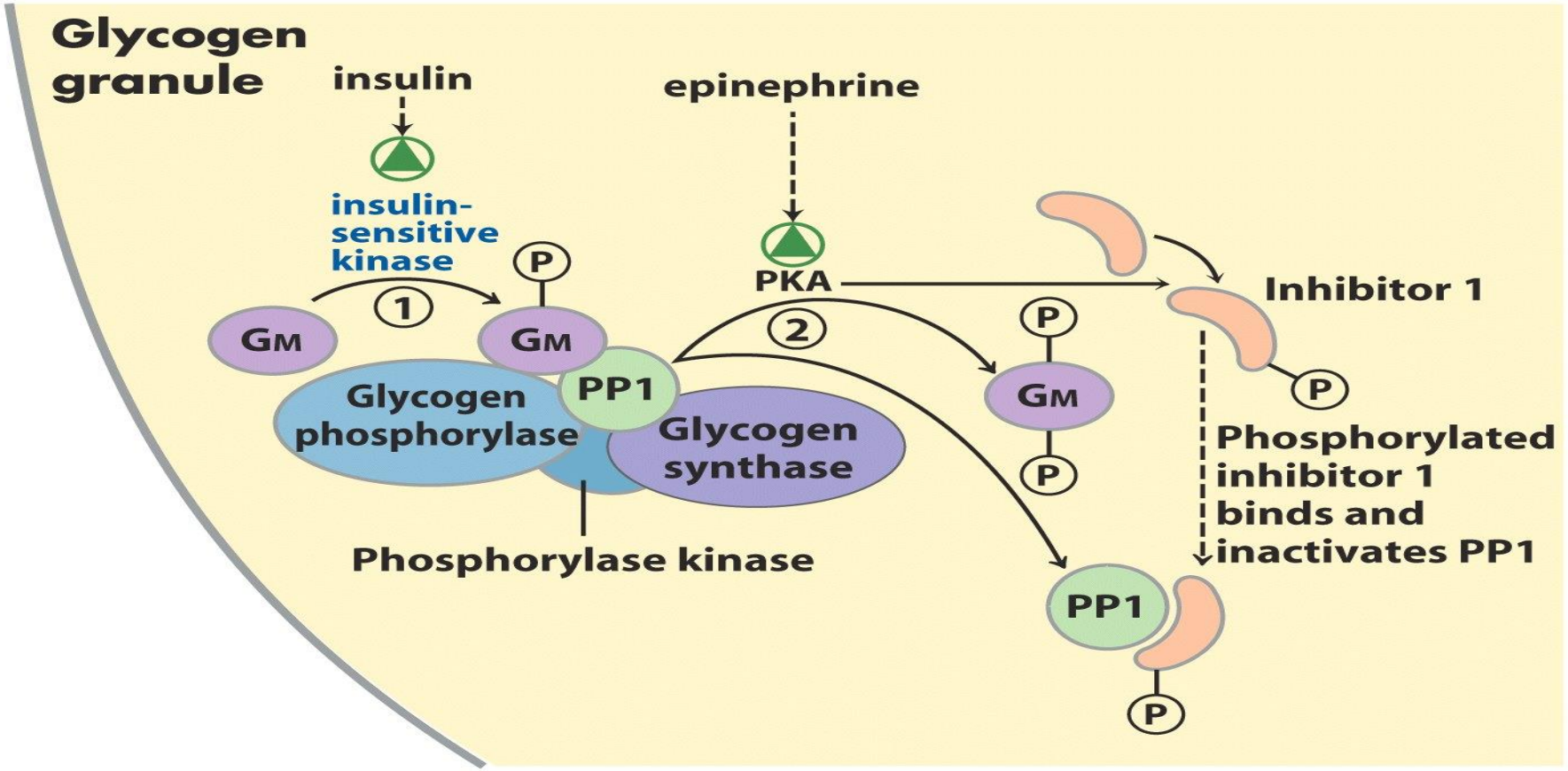
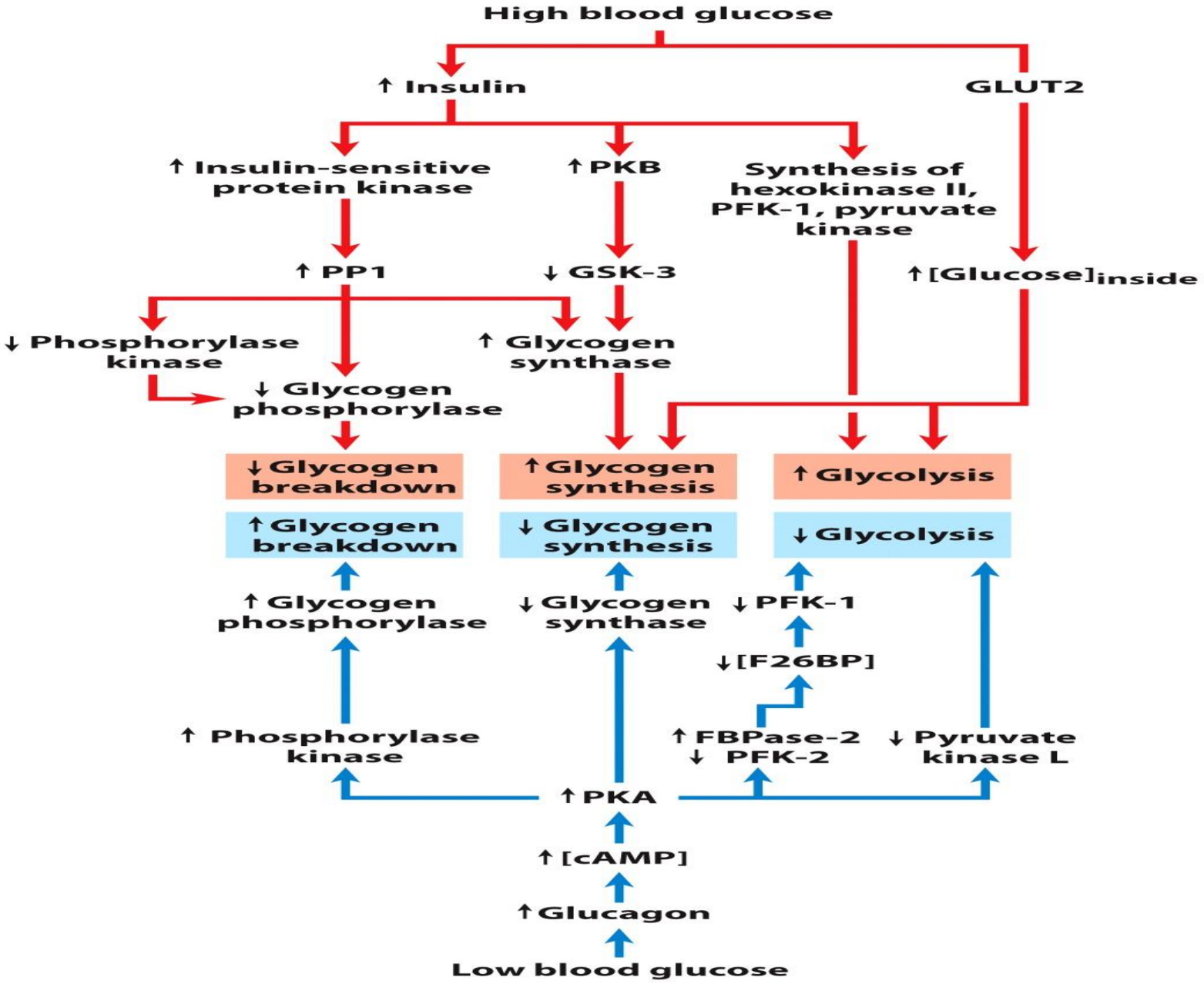
Glycogen-targeting protein G_M



- Insulin: P of G_M site 1 → PP1 activation → dephosphorylation of the three enzymes → → inhibition of glycogen breakdown, stimulation of glycogen synthesis

-epinephrine; P of GM site 2 → dissociation of PP1 from glycogen particle
PKA → phosphorylation of protein inhibitor 1 → inactivation of PP1

Control of Carbohydrate Metabolism in the Liver



Control of Carbohydrate Metabolism in the Liver vs. the Muscle