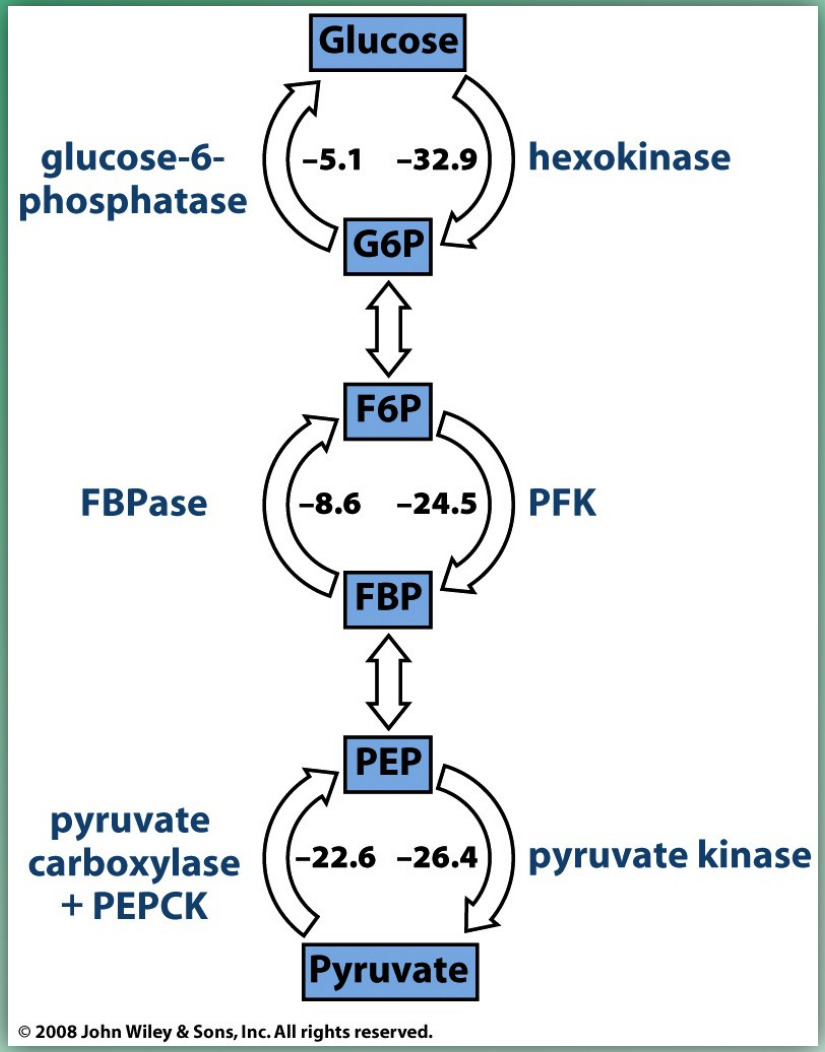
CHEM 539

Molecular Metabolism: Pathways and Regulation

PPT Set 6: Liver Gluconeogenesis (Part B)

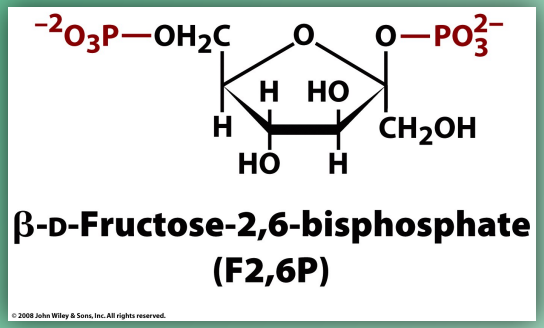
Regulators of gluconeogenic enzyme activity

Enzyme	Allosteric Inhibitors	Allosteric Activators	Enzyme Phosphorylation	Protein Synthesis
PFK	ATP, citrate	AMP, F2,6P		
FBPase	AMP, F2,6P			
Pyruvate kinase	Alanine	F1,6P	Inactivates	
Pyruvate carboxylase		Acetyl-CoA		
PEPCK				Stimulated by glucagon, thyroid hormone, and glucocorticoids, and inhibited by insulin
PFK-2	Citrate	AMP, F6P, P_i	Inactivates	
FBPase-2	F6P	Glycerol-3-P	Activates	



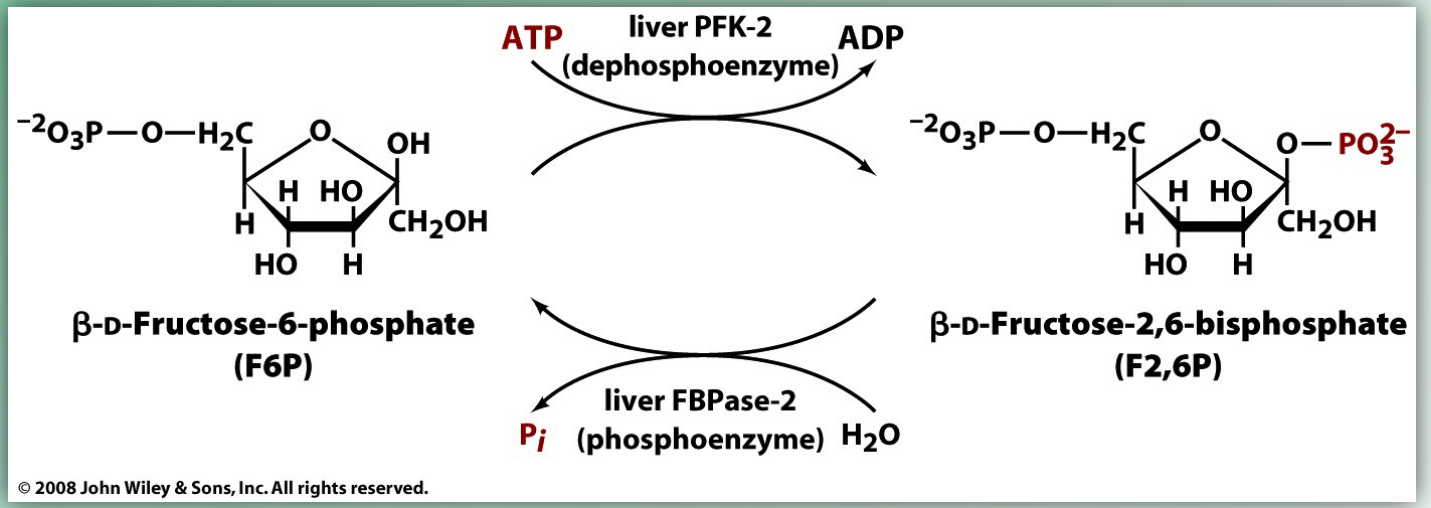
Substrate cycles in glucose metabolism

Glycolysis and gluconeogenesis are regulated independently (the ΔG values shown are for the corresponding reactions in liver; in kJ/mol). All six reactions are exergonic.



F2,6BP activates PFK-1 and inhibits FBPase-1.

The formation and degradation of F2,6BP in liver

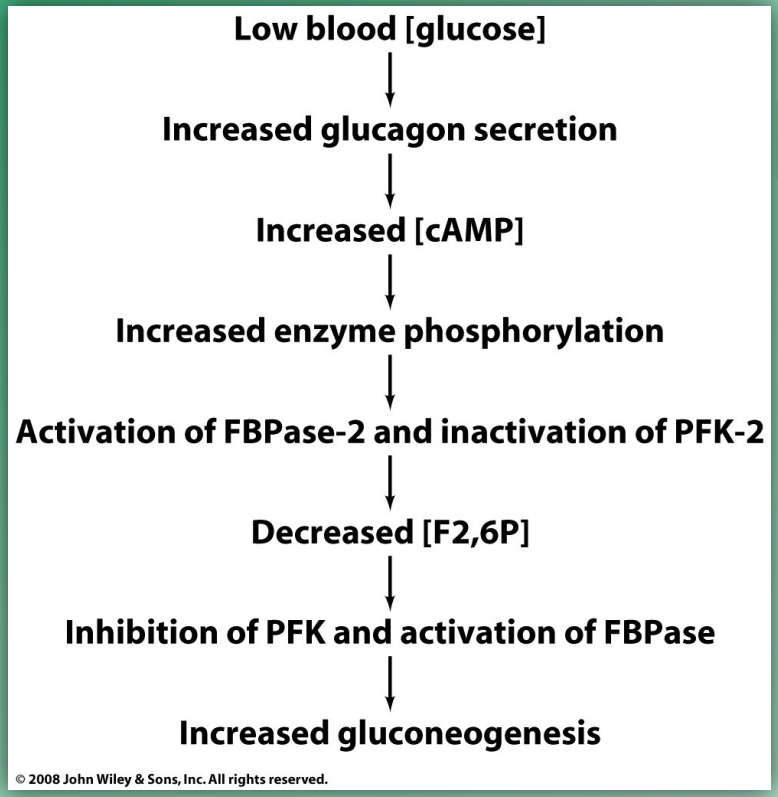


Cellular [F2,6BP] depends on the balance between its rates of synthesis and degradation by *PFK-2* (phosphofructokinase-2) and *FBPase-2* (fructose bisphosphatase-2).

These activities are located on different domains of the same homodimeric protein (a bifunctional enzyme).

The bifunctional enzyme is regulated by allosteric effectors and by phosphorylation/dephosphorylation catalyzed by *PKA* (protein kinase A) and a phosphoprotein phosphatase.

Metabolic events linking low blood [glucose] to gluconeogenesis in liver



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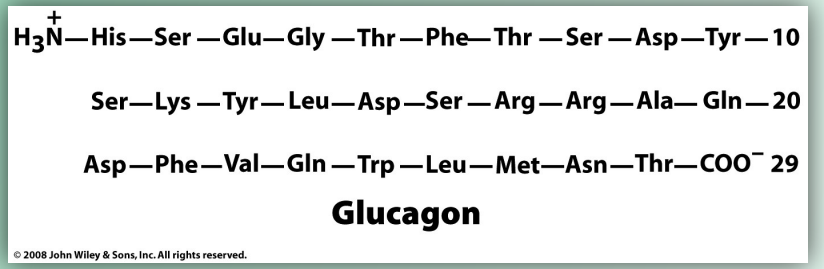
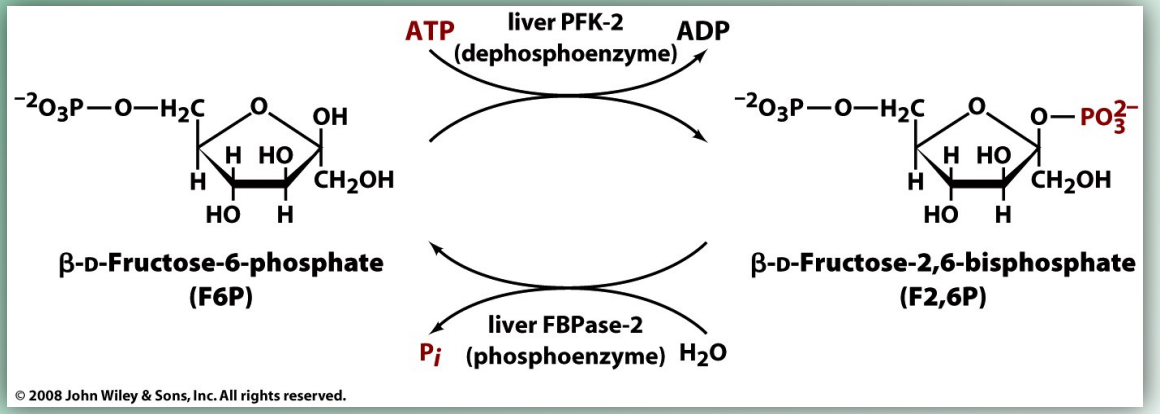
When blood [glucose] is high, cAMP levels decrease, and [F2,6BP] rises, promoting glycolysis.





The F2,6BP control system in muscle differs from that in liver.

Hormones that stimulate glycogen breakdown in *heart muscle* lead to phosphorylation of the bifunctional enzyme that stimulates rather than inhibits PFK-2. The increasing [F2,6BP] stimulates glycolysis so that glycogen breakdown and glycolysis are coordinated.

The skeletal muscle PFK-2/PBPase-2 isozyme lacks a phosphorylation site and is thus not subject to cAMP-dependent control.

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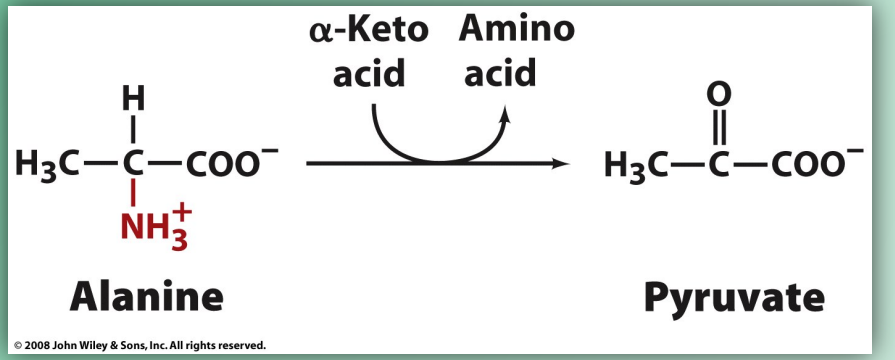
Alanine inhibits pyruvate kinase.

Alanine, a major gluconeogenic precursor, inhibits PK.



Liver PK is also inactivated by phosphorylation. Phosphorylation activates glycogen phosphorylase and FBPase-2: thus the pathways of gluconeogenesis and glycogen breakdown both flow towards G6P, which is converted to glucose for export from the liver.

Hexokinase/glucokinase and G6Pase activities are also controlled.

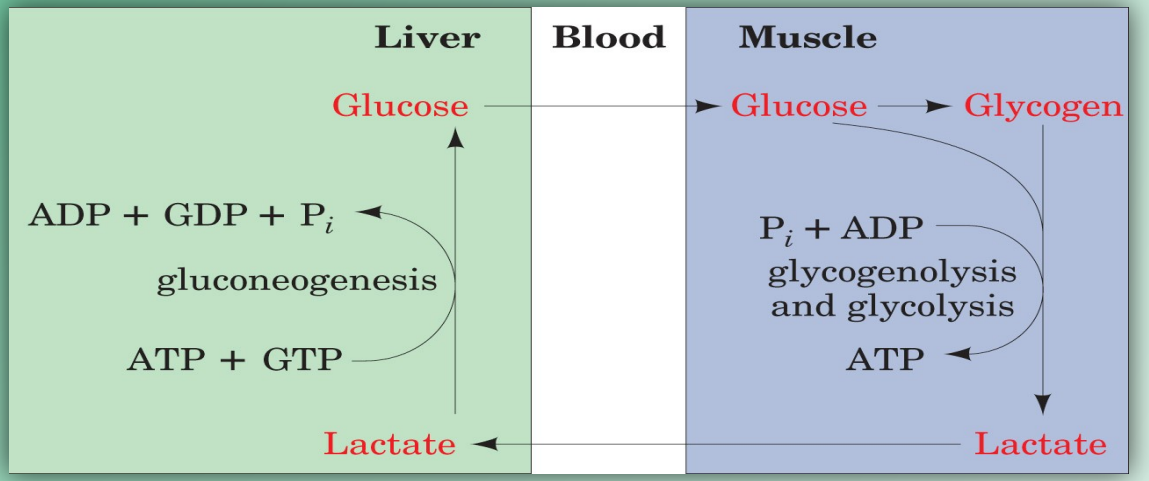
Other control factors

Glucose metabolism is regulated by long-term changes in the *amounts of enzymes* synthesized.

Rates of transcription and mRNA stabilities encoding regulatory enzymes are influenced by hormones.

Insulin (high blood glucose) inhibits transcription of the gene for PEPCK; high [cAMP] (low blood glucose) promotes transcription of the genes for PEPCK, FBPase, and G6Pase (gluconeogenic enzymes), and represses transcription of the genes for glucokinase, PFK (glycolytic enzymes) and PFK-2/FBPase-2.

The Cori cycle: transport of muscle-generated L-lactate to the liver for conversion to glucose



Lactate produced by muscle glycolysis (anaerobic) is transported by the bloodstream to the liver, where it is converted to glucose by gluconeogenesis.

Metabolic interrelationships between brain, adipose tissue, muscle, liver and kidney in humans