

Chapter 15

Principles of Metabolic Regulation:
Glucose and Glycogen

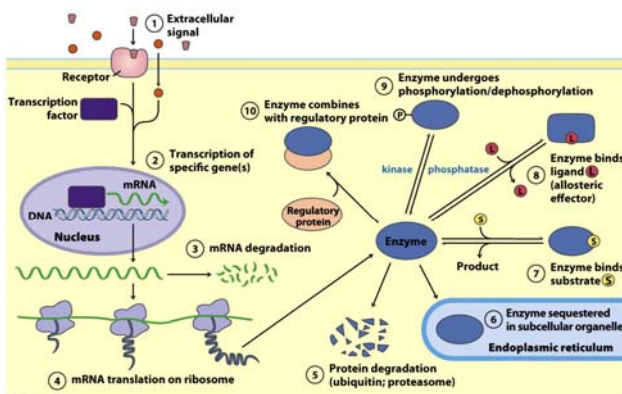
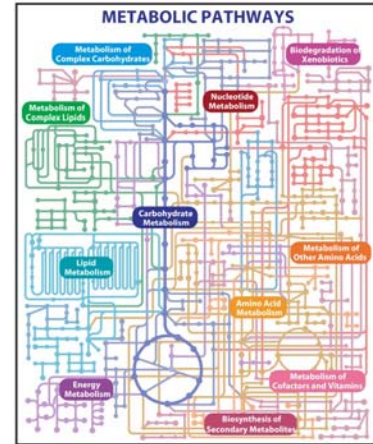
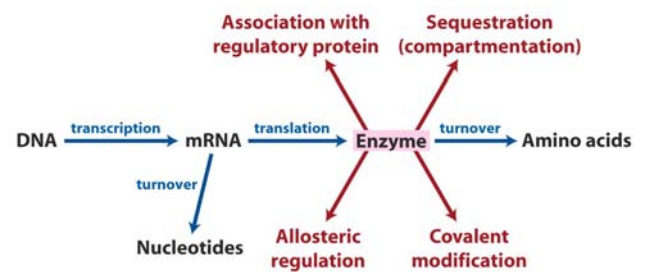


Figure 15-2
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Enzyme Regulation



What is the "BLUE"? *Molecular Biology or Gen Biochem 2*

TABLE 15-1 Average Half-life of Proteins in Mammalian Tissues	
Tissue	Half-life (days)
Liver	0.9
Kidney	1.7
Heart	4.1
Brain	4.6
Muscle	10.7

Table 15-1
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TABLE 15-2 Relationship between Hill Coefficient and the Effect of Substrate Concentration on Reaction Rate for Allosteric Enzymes	
Hill coefficient (n_H)	Required change in [S] to increase V_0 from 10% to 90% V_{max}
0.5	×6,600
1.0	×81
2.0	×9
3.0	×4.3
4.0	×3

Table 15-2
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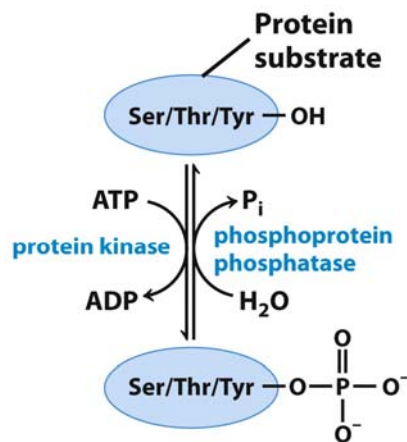


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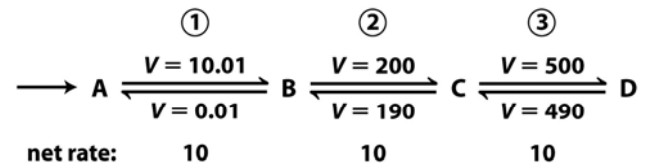


Figure 15-4
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Which reaction is driving this sequence?
Which has the most negative ΔG ?

TABLE 15-3 Equilibrium Constants, Mass Action Coefficients, and Free-Energy Changes for Enzymes of Carbohydrate Metabolism

Enzyme	K'_{eq}	Mass action ratio, Q		Reaction near equilibrium in vivo? ^a	$\Delta G'^{\circ}$ (kJ/mol)	$\Delta G'$ (kJ/mol) in heart
		Liver	Heart			
Hexokinase	1×10^3	2×10^{-2}	8×10^{-2}	No	-17	-27
PFK-1	1.0×10^3	9×10^{-2}	3×10^{-2}	No	-14	-23
Aldolase	1.0×10^{-4}	1.2×10^{-6}	9×10^{-6}	Yes	+24	-6.0
Triose phosphate isomerase	4×10^{-2}	—	2.4×10^{-1}	Yes	+7.5	+3.8
Glyceraldehyde 3-phosphate dehydrogenase + phosphoglycerate kinase	2×10^3	6×10^2	9.0	Yes	-13	+3.5
Phosphoglycerate mutase	1×10^{-1}	1×10^{-1}	1.2×10^{-1}	Yes	+4.4	+0.6
Enolase	3	2.9	1.4	Yes	-3.2	-0.5
Pyruvate kinase	2×10^4	7×10^{-1}	40	No	-31	-17
Phosphoglucose isomerase	4×10^{-1}	3.1×10^{-1}	2.4×10^{-1}	Yes	+2.2	-1.4
Pyruvate carboxylase + PEP carboxykinase	7	1×10^{-3}	—	No	-5.0	-23
Glucose 6-phosphatase	8.5×10^2	1.2×10^2	—	Yes	-17	-5.0

Source: K'_{eq} and Q from Newsholme, E.A. & Start, C. (1973) *Regulation in Metabolism*, Wiley Press, New York, pp.97,263. $\Delta G'$ and $\Delta G'^{\circ}$ were calculated from these data.
^aFor simplicity, any reaction for which the absolute value of the calculated $\Delta G'$ is less than 6 is considered near equilibrium.

Table 15-3
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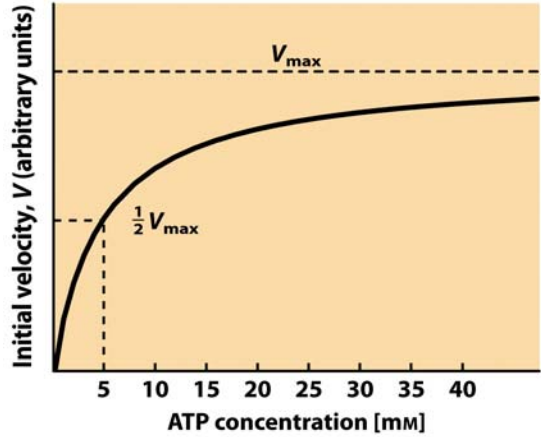


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TABLE 15-4 Relative Changes in [ATP] and [AMP] When ATP Is Consumed

Adenine nucleotide	Concentration before ATP depletion (mM)	Concentration after ATP depletion (mM)	Relative change
ATP	5.0	4.5	10%
ADP	1.0	1.0	0
AMP	0.1	0.6	600%

Table 15-4
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Role of AMP-activated Protein Kinase

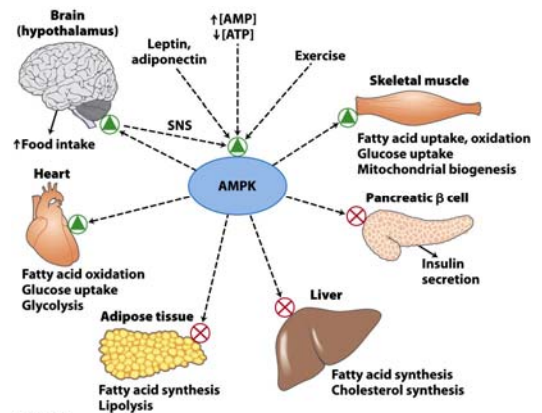


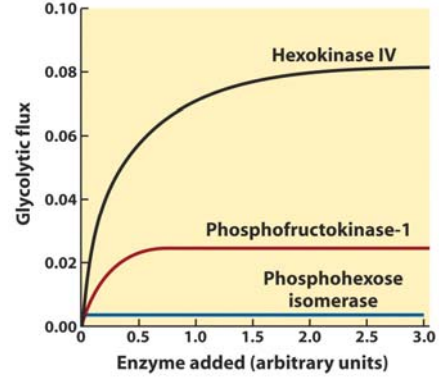
Figure 15-6
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Metabolic Regulation Functions To:

1. Maximize efficiency of energy source use, stops futile cycles.
2. Partitions metabolites and enzymes (Ex alternative pathways – Glycolysis and PPP).
3. Use best suited energy source of the immediate need of the organism (glucose, glycogen, fatty acids, amino acids).
4. Shuts down biosynthesis when products accumulate.

What is a Futile Cycle? Have we seen one already?

Which Enzyme Controls Glycolytic Flux ?



Experiment: purified enzymes added to liver cell extract carrying out glycolysis with own enzymes.

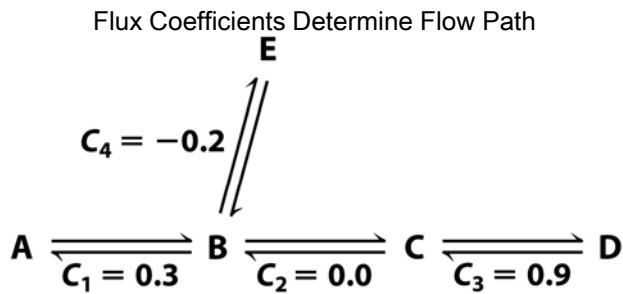


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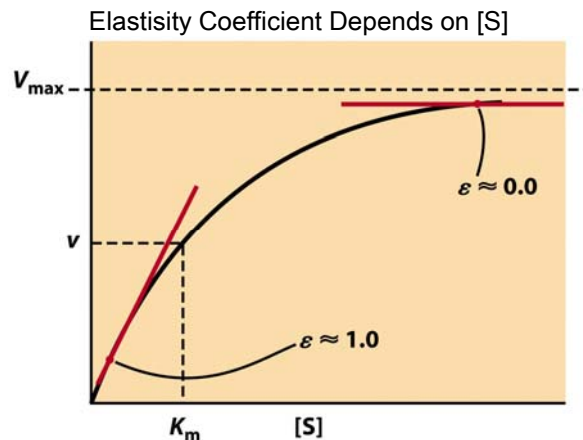


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Metabolic Response Coefficient

$$R = C \cdot \epsilon$$

Insulin Regulation On Muscle Cells

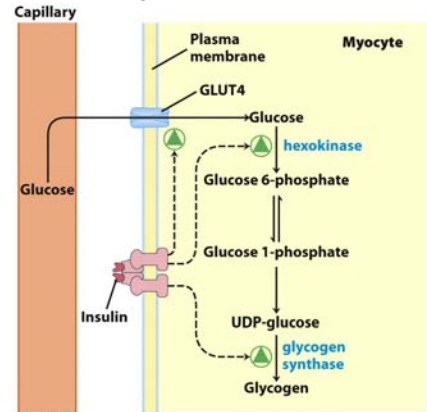
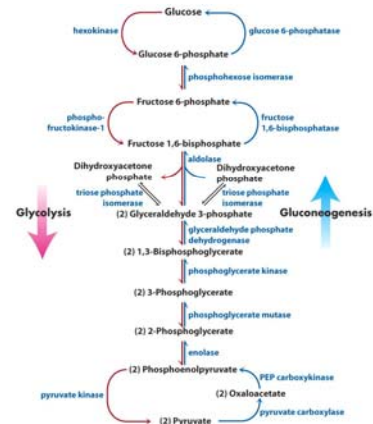


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Potential Futile Cycles between Glycolysis and Gluconeogenesis



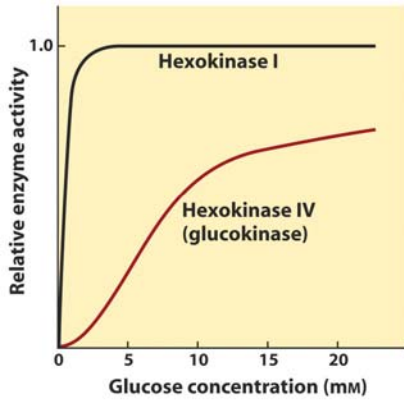
Hexokinase-1 Regulation in Muscles

Glucose-6-Phosphate is a negative allosteric regulator of Hexokinase I and II

So how many binding sites on Hexokinase I and II for Glucose-6-P are there?

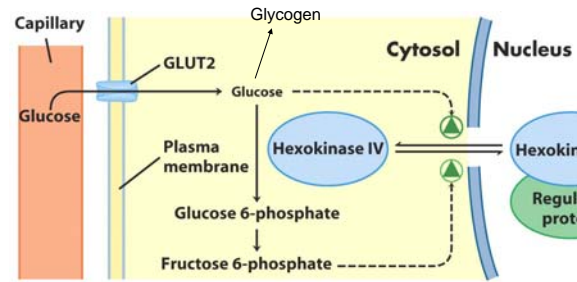


1. Hexokinase Isozymes



Check out Box 15-2 : ISOZYMES, the example is Lactic Acid Dehydrogenase (LDH)

Hexokinase IV Regulation in Liver



Hexokinase IV is also called Glucokinase

Glucokinase=Hexokinase IV

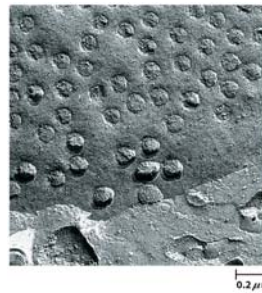
Signal Sequences: 300-310 ELVRLVLLKLV
says export me to the cytoplasm.
347-358 QIHNILSTGLR
says associate with GGRP

Glucokinase Regulatory Protein = GGRP

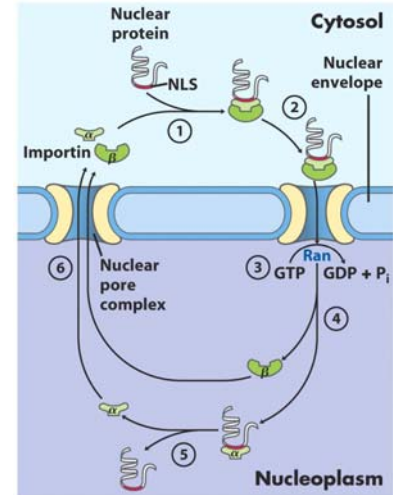
Nuclear Localization Sequence: PKKKRKV (prototype)

+ Importins α and β

Fig 27-42
pgs 1104-1105



NLS = Nuclear Localization Sequence.
4-8 aa's of which there are consecutive K's and R's.



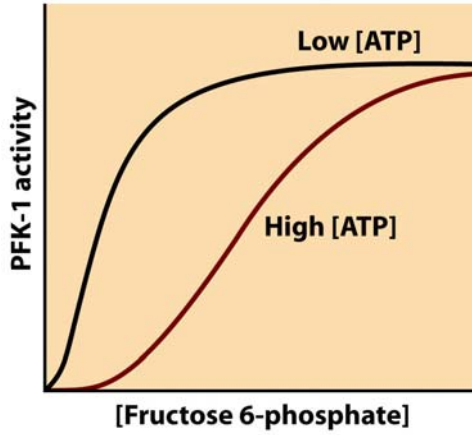


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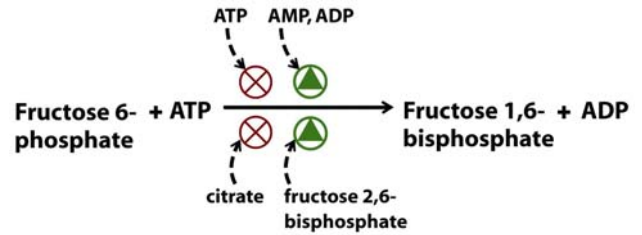


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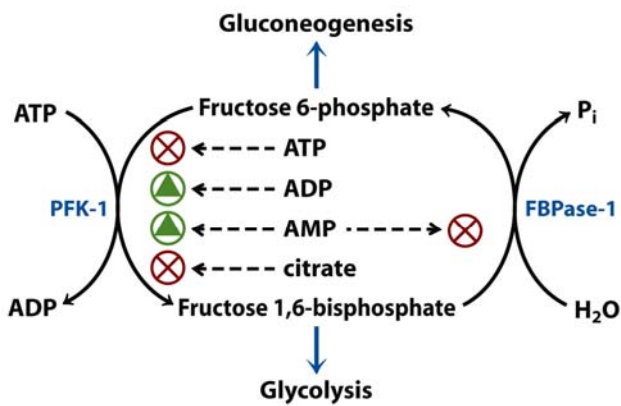
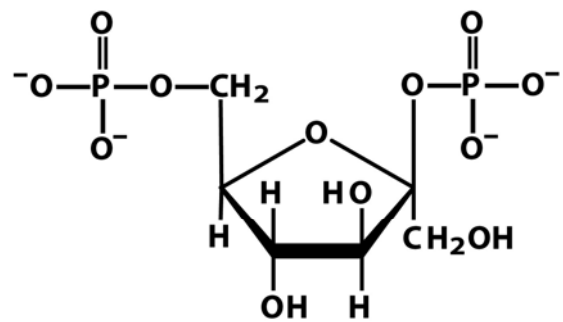


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Fructose 2,6-bisphosphate

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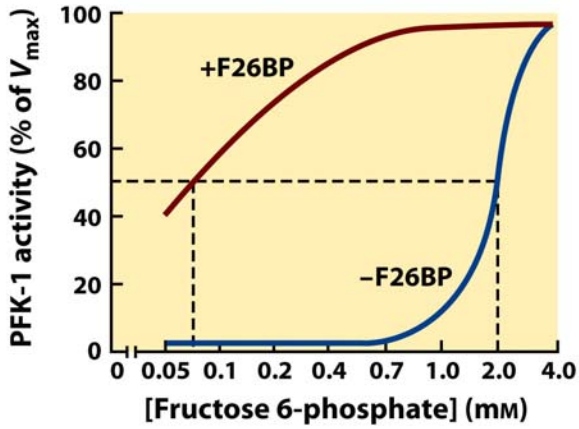


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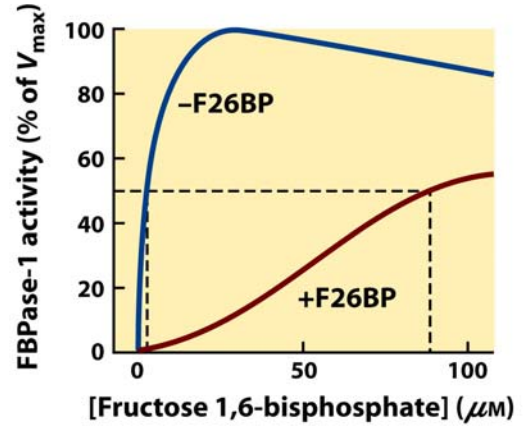


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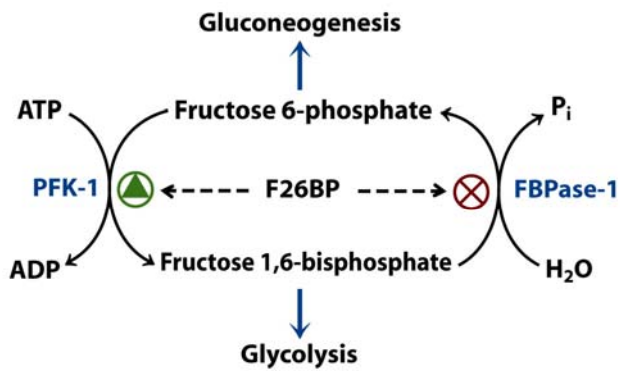


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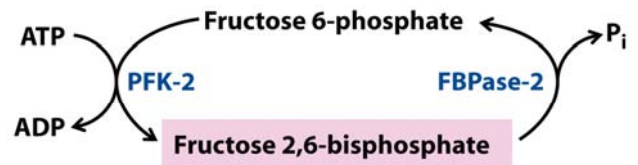


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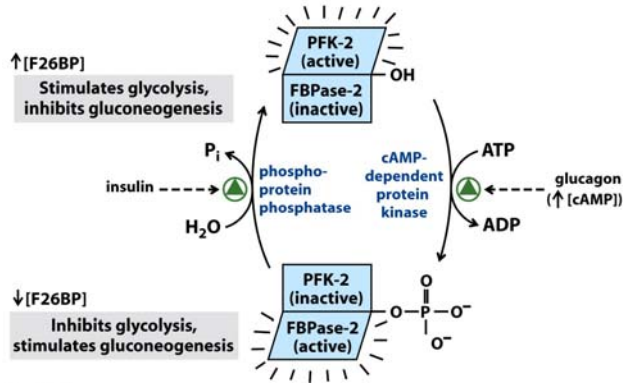


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Phosphoprotein Phosphatase is Stimulated by Xylulose-5-P

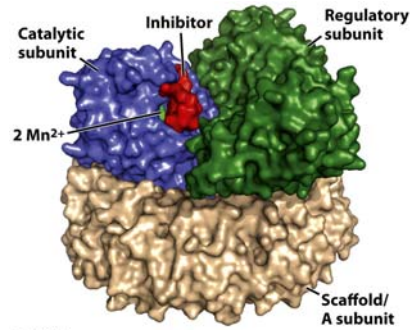


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Xylulose-5-P also stimulates fatty acid synthesis

Phosphoprotein Phosphatase can Recognize Different Proteins

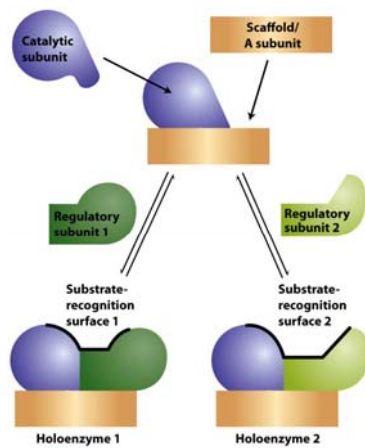


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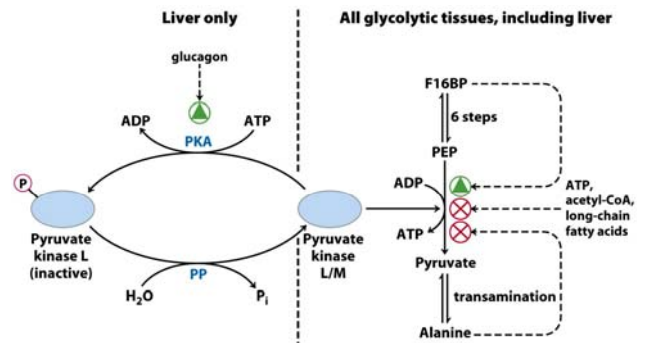


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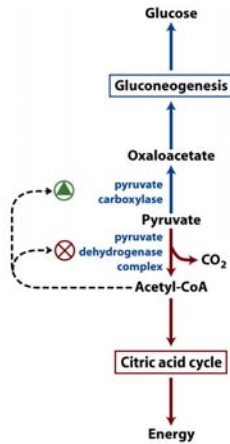


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TABLE 15-5 Some of the Genes Regulated by Insulin	
Change in gene expression	Pathway
Increased expression	
Hexokinase II	Glycolysis
Hexokinase IV	Glycolysis
Phosphofruktokinase-1 (PFK-1)	Glycolysis
Pyruvate kinase	Glycolysis
PFK-2/FBPase-2	Regulation of glycolysis/gluconeogenesis
Glucose 6-phosphate dehydrogenase	Pentose phosphate pathway (NADPH)
6-Phosphogluconate dehydrogenase	Pentose phosphate pathway (NADPH)
Pyruvate dehydrogenase	Fatty acid synthesis
Acetyl-CoA carboxylase	Fatty acid synthesis
Malic enzyme	Fatty acid synthesis (NADPH)
ATP-citrate lyase	Fatty acid synthesis (provides acetyl-CoA)
Fatty acid synthase complex	Fatty acid synthesis
Stearyl-CoA dehydrogenase	Fatty acid desaturation
Acyl-CoA-glycerol transferases	Triacylglycerol synthesis
Decreased expression	
PEP carboxykinase	Gluconeogenesis
Glucose 6-phosphatase (catalytic subunit)	Glucose release to blood

Table 15-5
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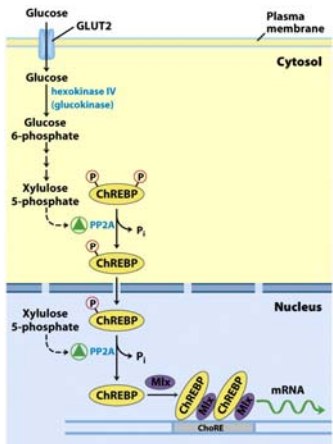


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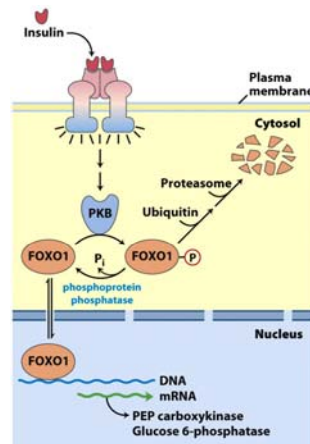
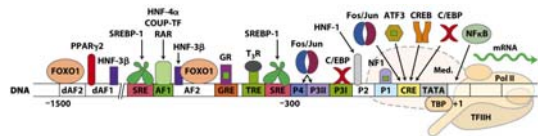


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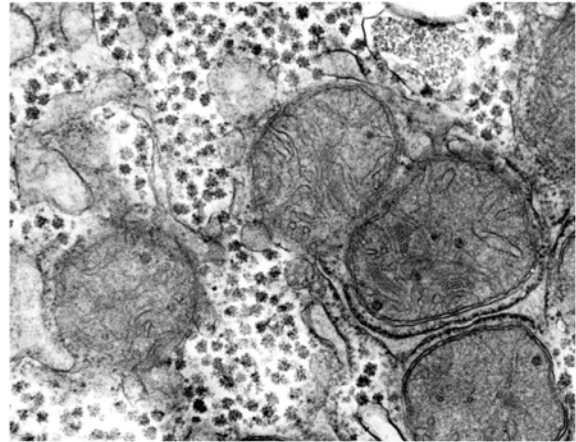
PEP Carboxykinase Regulatory Region is Complex



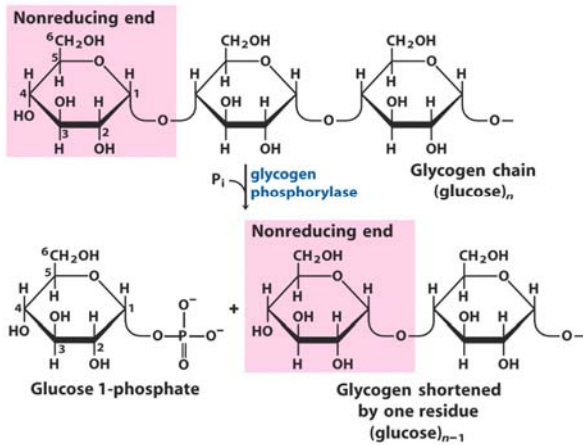
Transcription factors	Response elements and regulatory binding sites in promoter
FOXO1	forkhead box other 1
PPAR-gamma2	peroxisome proliferator-activated receptor gamma2
HNF-3B	hepatic nuclear factor-3B
SREBP-1	sterol regulatory element binding protein-1
HNF-4a	hepatic nuclear factor-4a
COUP-TF	chicken ovalbumin upstream promoter-transcription factor
RAR	retinoic acid receptor
GR	glucocorticoid receptor
T3R	thyroid hormone receptor
C/EBP	CAAT/enhance binding protein
HNF-1	hepatic nuclear factor-1
NF1	nuclear factor 1
ATF3	activating transcription factor 3
CREB	cAMP regulatory element binding protein
NF-kB	nuclear factor kappa B
TBP	TATA-box binding protein
Med.	mediator
TFIIB	transcription factor IIB
dAF2	distal accessory factor 2
dAF1	distal accessory factor 1
SRE	sterol regulatory element
AF1	accessory factor 1
AF2	accessory factor 2
GRE	glucocorticoid regulatory element
TRE	thyroid hormone regulatory element
CRE	cAMP regulatory element

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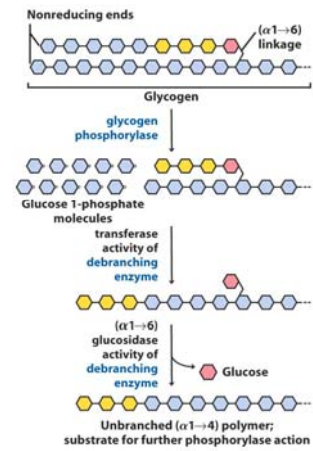
Glycogen Granules, Liver Cell



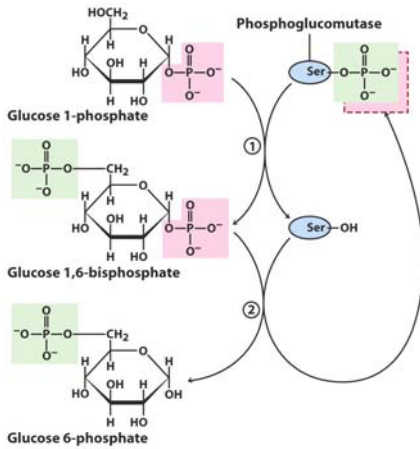
Glycogen Phosphorylase



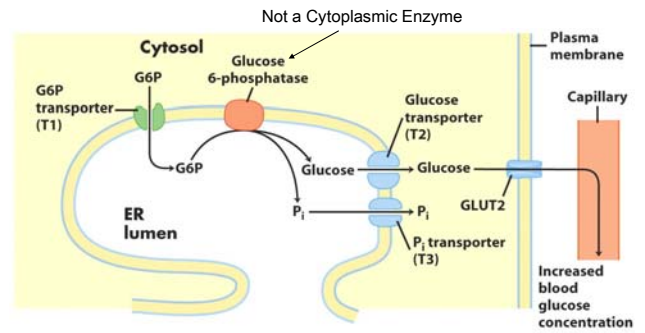
Glycogen Phosphorylase and Debranching Enzyme



Phosphoglucomutase

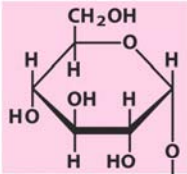


Liver Transports Glucose to Blood

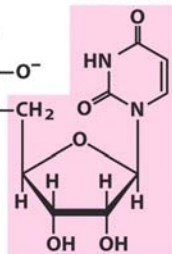


Glycogen Synthase uses UDP-glucose

D-Glucosyl group



Uridine



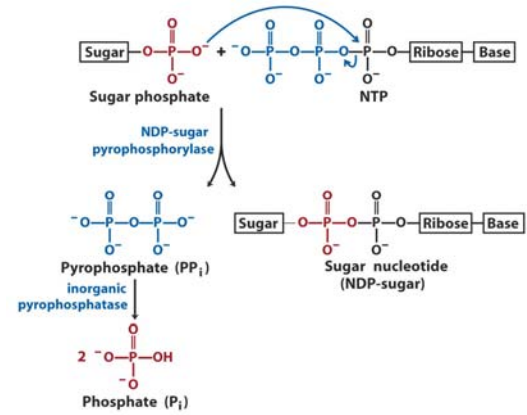
UDP-glucose

(a sugar nucleotide)

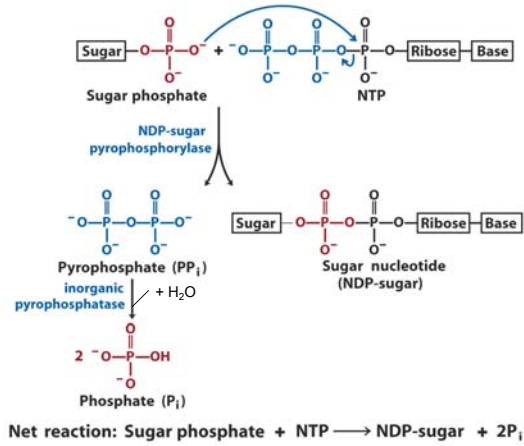
Synthase
or
Synthetase

There is a
difference!

NDP-sugar Pyrophosphorylase



NDP-sugar Pyrophosphorylase



The Cori's



Discovered Various Glycogen Diseases

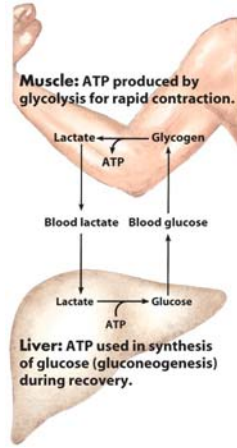
TABLE 1 Glycogen Storage Diseases of Humans

Type (name)	Enzyme affected	Primary organ affected	Symptoms
Type 0	Glycogen synthase	Liver	Low blood glucose, high ketone bodies, early death
Type Ia (von Gierke's)	Glucose 6-phosphatase	Liver	Enlarged liver, kidney failure
Type Ib	Microsomal glucose 6-phosphate translocase	Liver	As in Ia; also high susceptibility to bacterial infections
Type Ic	Microsomal P _i transporter	Liver	As in Ia
Type II (Pompe's)	Lysosomal glucosidase	Skeletal and cardiac muscle	Infantile form: death by age 2; juvenile form: muscle defects (myopathy); adult form: as in muscular dystrophy
Type IIIa (Cori's or Forbes's)	Debranching enzyme	Liver, skeletal and cardiac muscle	Enlarged liver in infants; myopathy
Type IIIb	Liver debranching enzyme (muscle enzyme normal)	Liver	Enlarged liver in infants
Type IV (Andersen's)	Branching enzyme	Liver, skeletal muscle	Enlarged liver and spleen, myoglobin in urine
Type V (McArdle's)	Muscle phosphorylase	Skeletal muscle	Exercise-induced cramps and pain; myoglobin in urine
Type VI (Hers's)	Liver phosphorylase	Liver	Enlarged liver
Type VII (Tarui's)	Muscle PFK-1	Muscle, erythrocytes	As in V; also hemolytic anemia
Type VIIb, VIII, or IX	Phosphorylase kinase	Liver, leukocytes, muscle	Enlarged liver
Type XI (Fanconi-Bickel)	Glucose transporter (GLUT2)	Liver	Failure to thrive, enlarged liver, rickets, kidney dysfunction

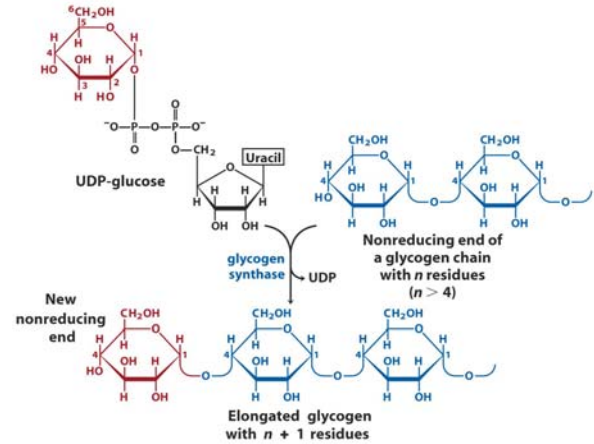
Cori Cycle in Rapid Exercising Muscle and other ways Muscle becomes Anaerobic



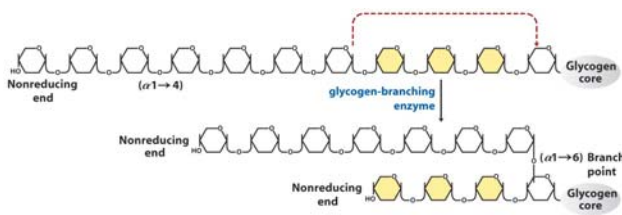
Cori Cycle



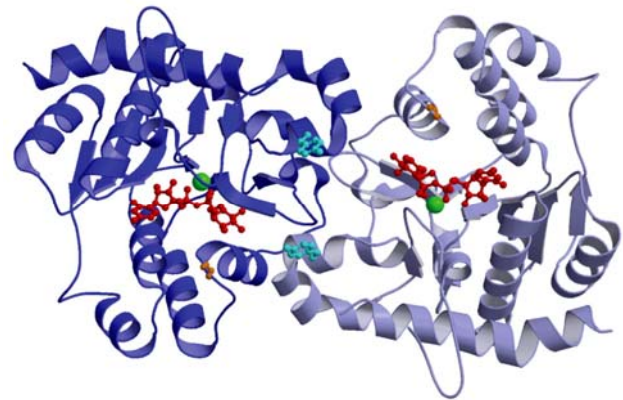
Glycogen Synthase

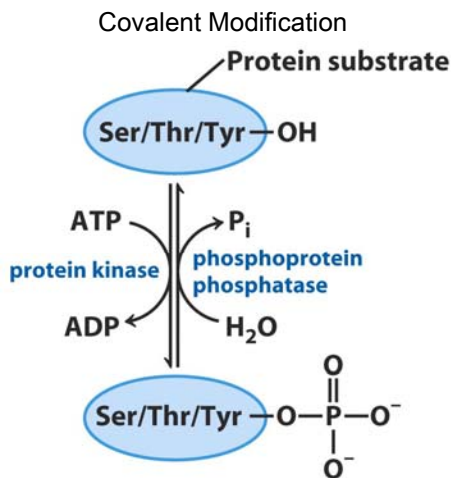
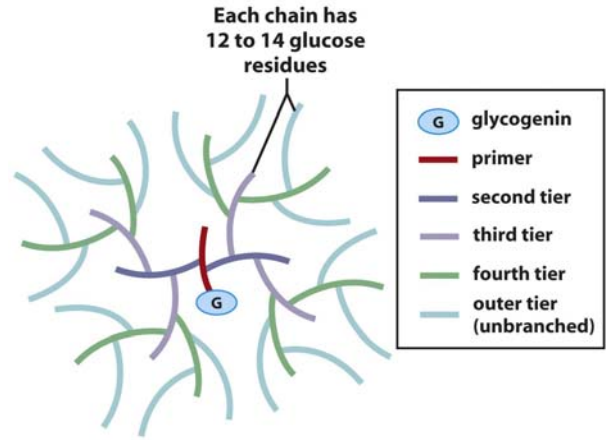
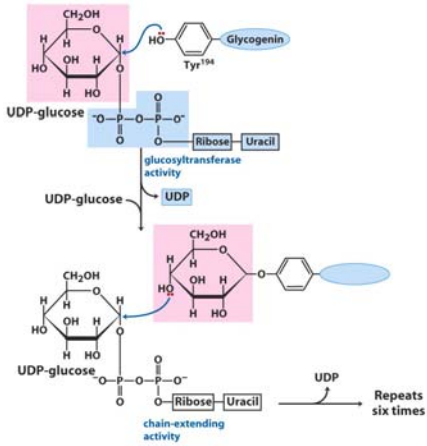


Branching Enzyme
Amylo ($1 \rightarrow 4$) to ($1 \rightarrow 6$) Transglycosylase



Glycogenin





Discovery of c-AMP

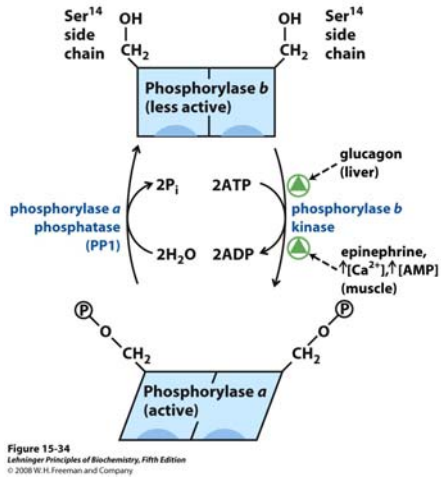


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1915-1074

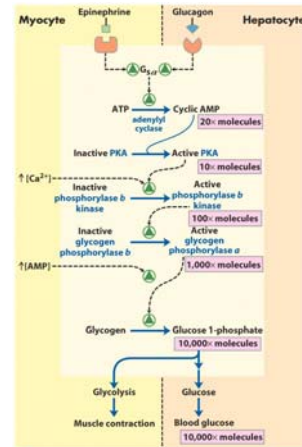


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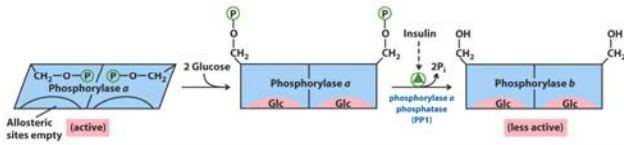
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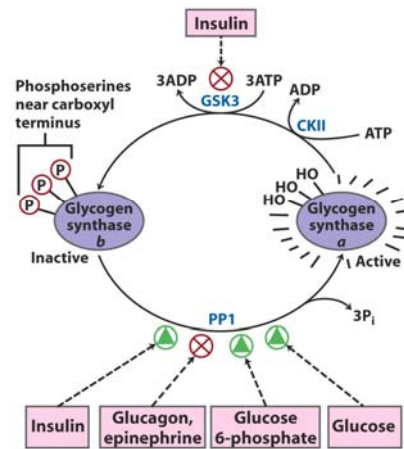
Phosphorylation Cascade with Ca⁺⁺ and AMP

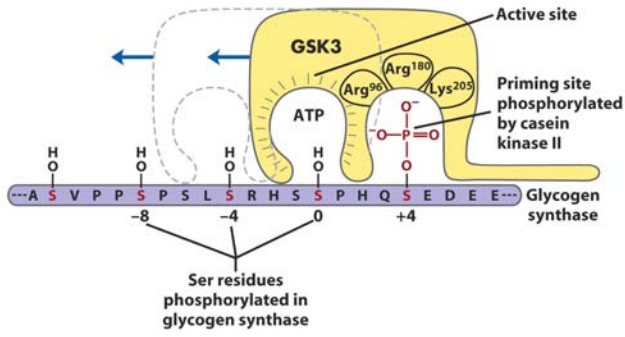


Phosphorylase is *Also* Regulated by Glucose Allosterically

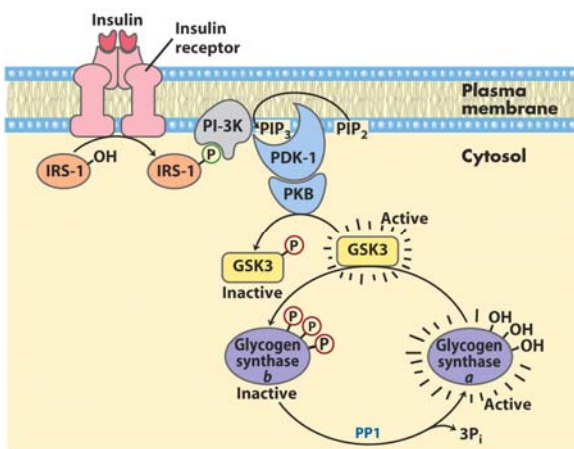
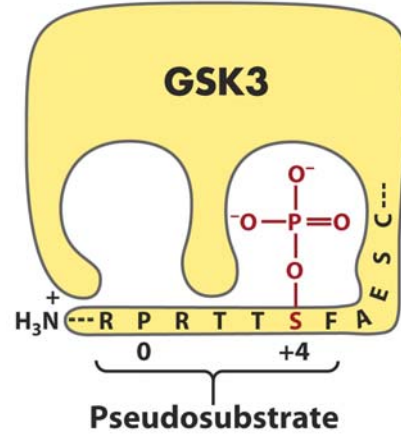


Glycogen Synthase Regulation

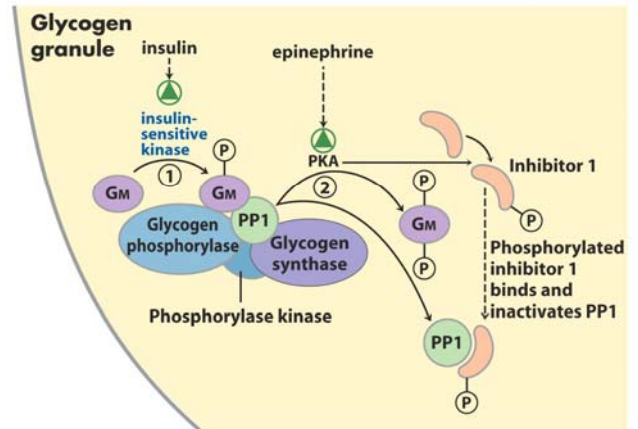




GSK3 in Phosphorylated to Inactivity



Glycogen Synthase and Phosphorylase Are a Protein Module



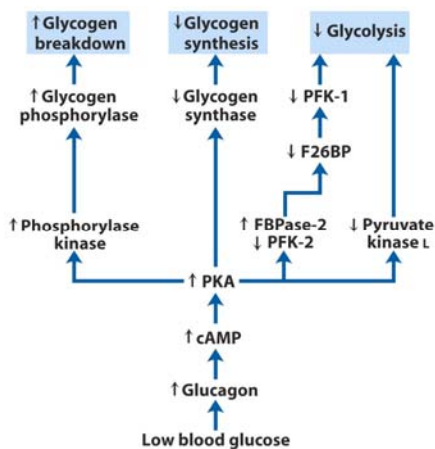
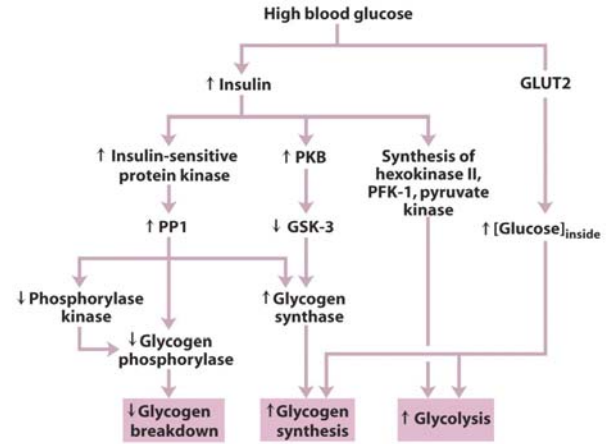
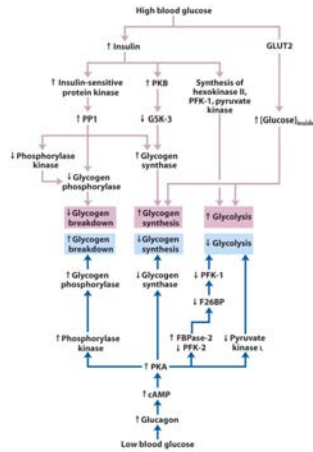


TABLE 15-3 Some of the Genes Regulated by Insulin

Change in gene expression	Pathway
Increased expression	
Hexokinase II	Glycolysis
Hexokinase IV	Glycolysis
Phosphofructokinase-1 (PFK-1)	Glycolysis
Pyruvate kinase	Glycolysis
PFK-2/FBPase-2	Regulation of glycolysis/gluconeogenesis
Glucose 6-phosphate dehydrogenase	Pentose phosphate pathway (NADPH)
6-Phosphogluconate dehydrogenase	Pentose phosphate pathway (NADPH)
Pyruvate dehydrogenase	Fatty acid synthesis
Acetyl-CoA carboxylase	Fatty acid synthesis
Malic enzyme	Fatty acid synthesis (NADPH)
ATP-citrate lyase	Fatty acid synthesis (provides acetyl-CoA)
Fatty acid synthase complex	Fatty acid synthesis
Stearyl-CoA dehydrogenase	Fatty acid desaturation
Acyl-CoA-glycerol transferases	Triacylglycerol synthesis
Decreased expression	
PEP carboxykinase	Gluconeogenesis
Glucose 6-phosphatase (catalytic subunit)	Glucose release to blood

Difference Between Liver and Muscle

