# Biochemistry

# Metabolism

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## Gluconeogenesis

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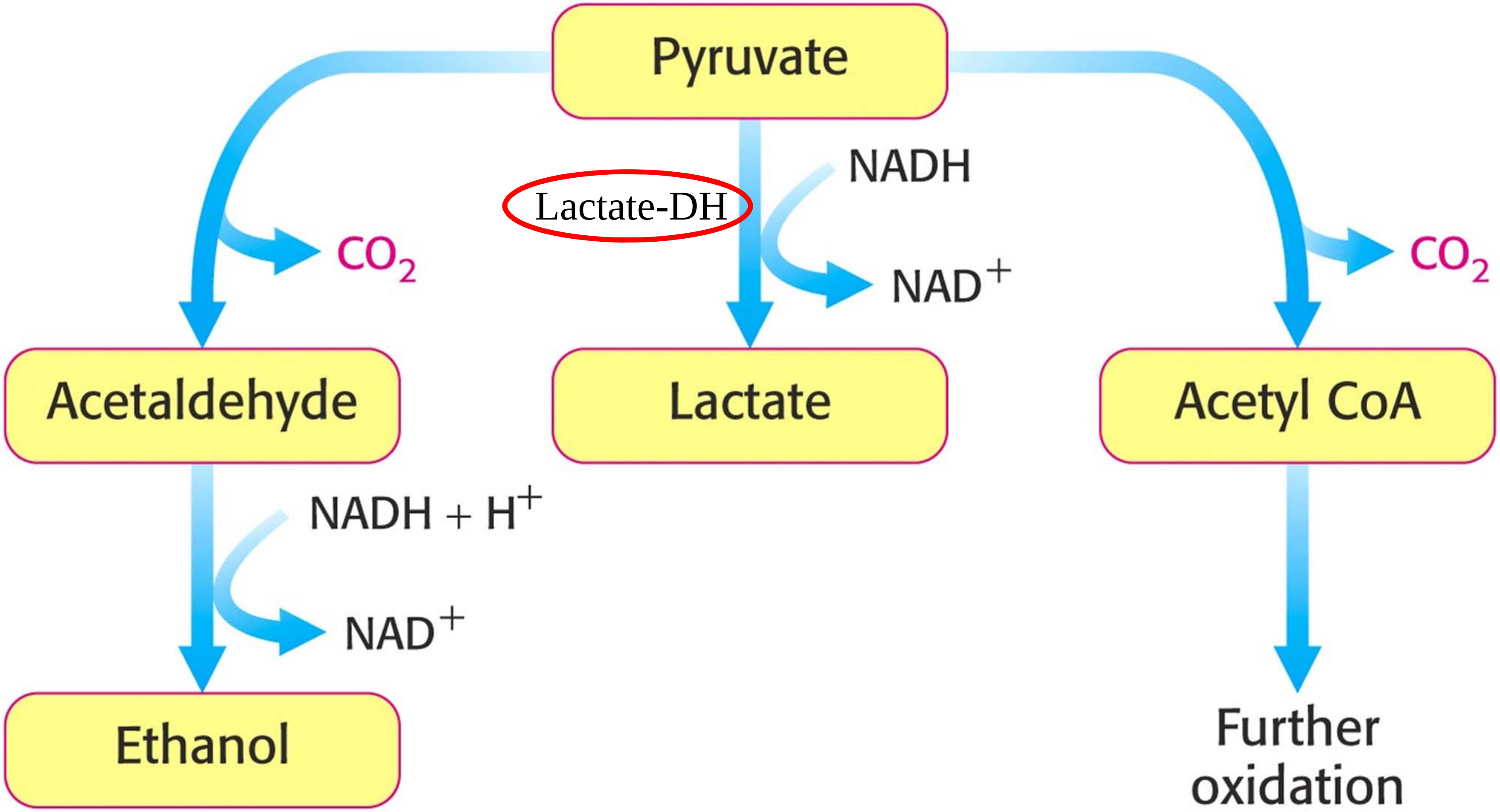
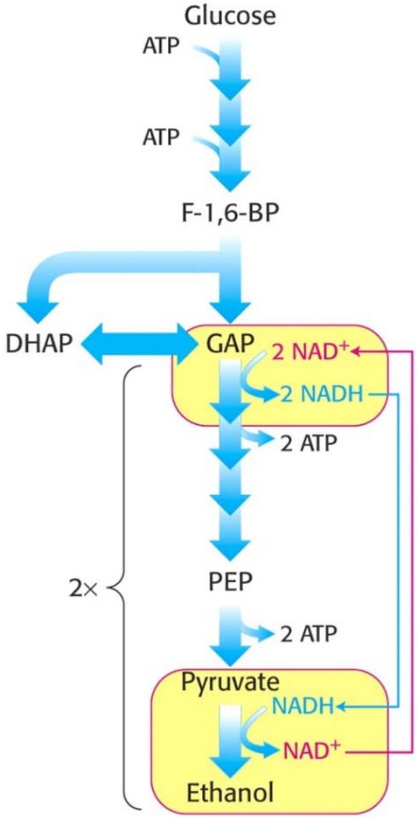
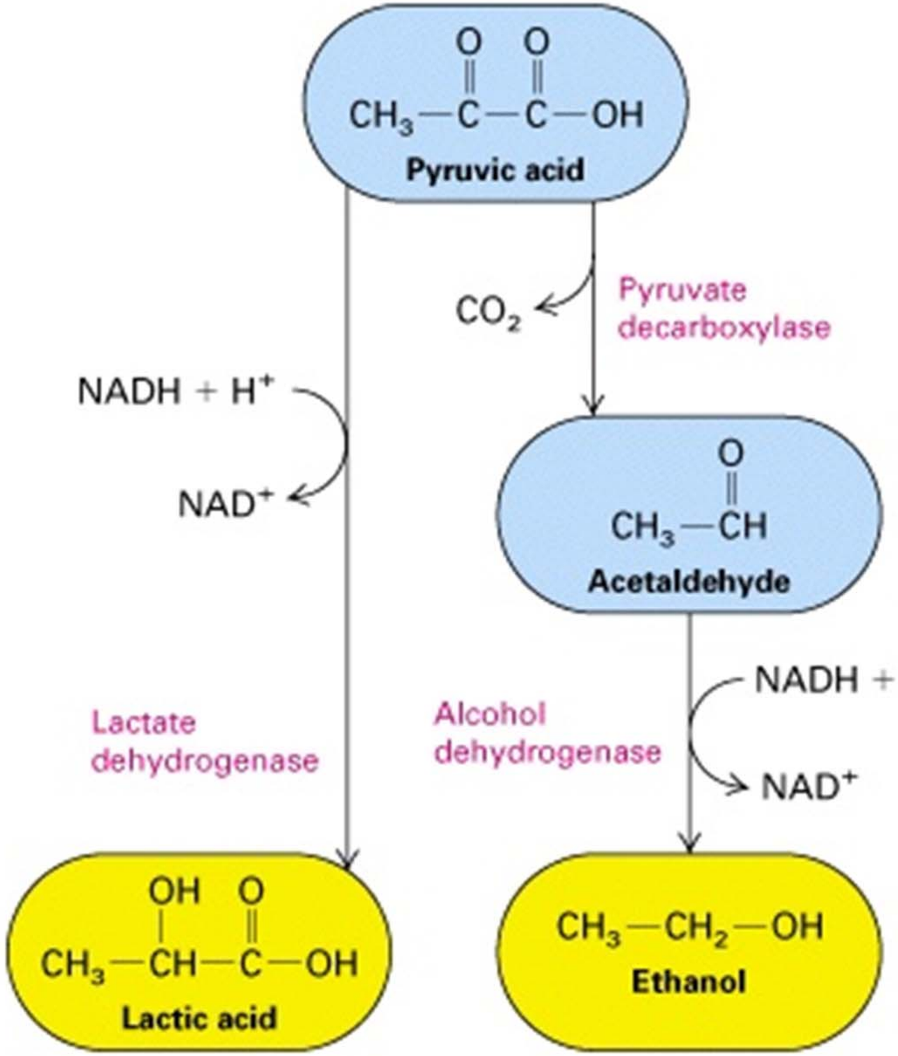
Utilization of pyruvate




Berg, Tymoczko, Stryer: Biochemistry

# The „anaerobic fate“ of pyruvate

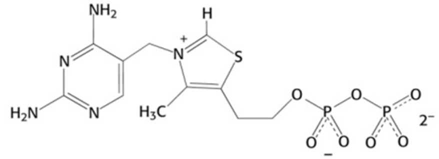


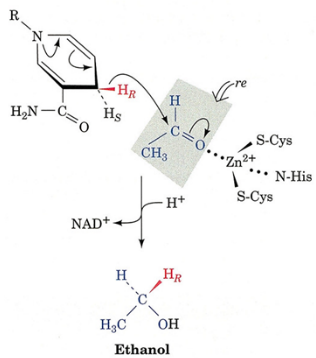

Overall reactions of anaerobic metabolism:

$$\text{Glucose} + 2\,\text{ADP} + 2\,\text{P}_i \longrightarrow 2\,\text{lactate} + 2\,\text{ATP}$$

$$\text{Glucose} + 2\,\text{ADP} + 2\,\text{P}_i \longrightarrow 2\,\text{ethanol} + 2\,\text{CO}_2 + 2\,\text{ATP}$$



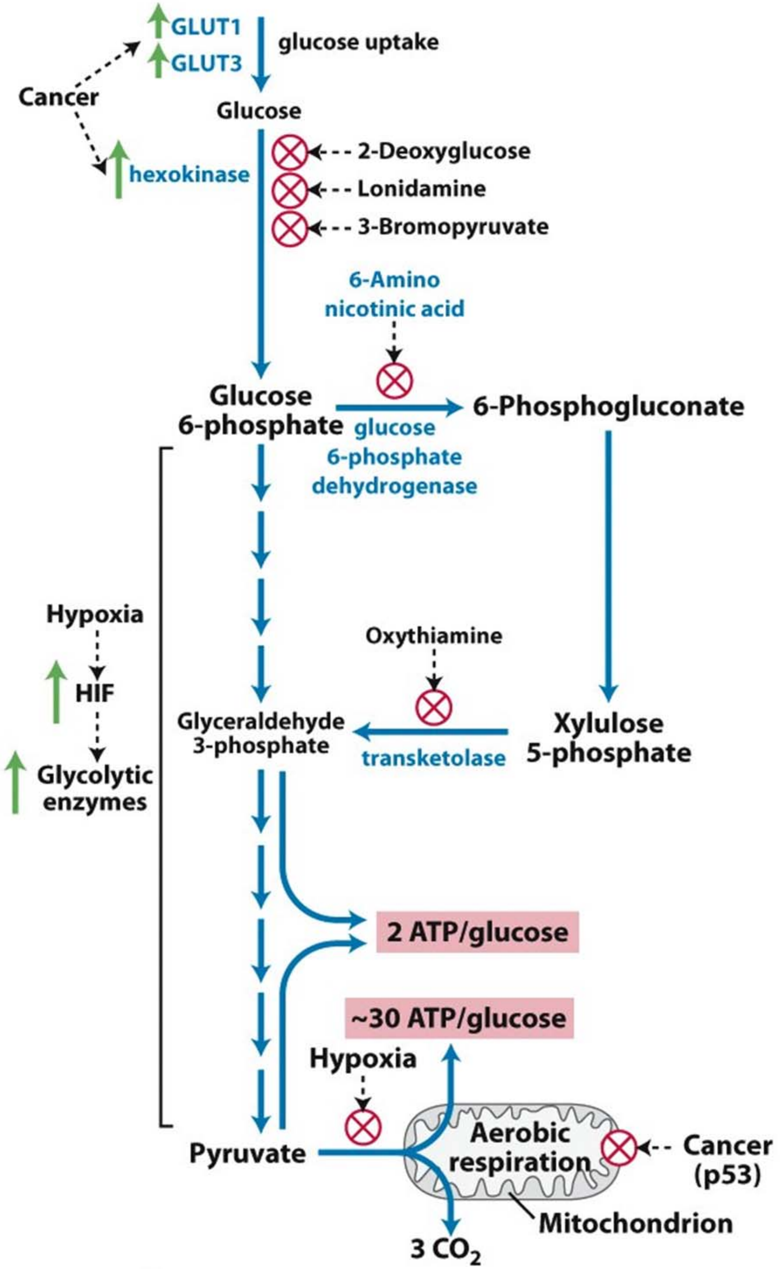
Thiamine pyrophosphate (TPP)



# High rate of glycolysis in tumors suggests targets for chemotherapy and facilitates diagnosis

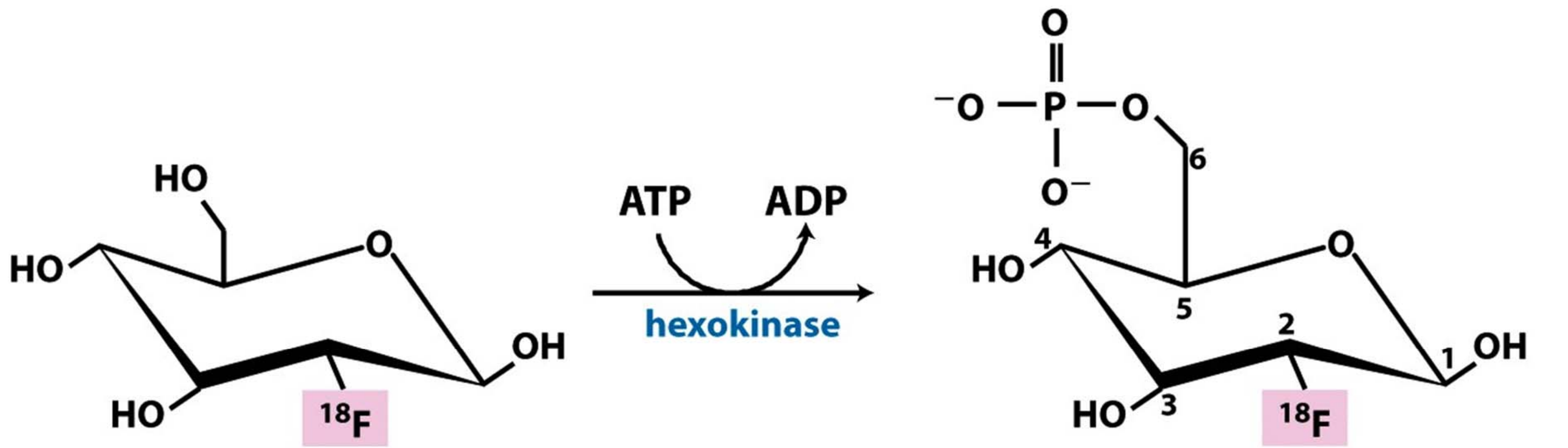
Cell transformation is accompanied by a switch to ATP generation **via glycolysis**. Thus assuring cellular energy homeostasis under hypoxic conditions. Consequently glucose transporters and glycolytic enzymes are overproduced in tumours.

p53: tumor suppressor protein; protects cells against unrestrained growth; is most frequently mutated gene (> 50%) in human cancer.




**Box 14-1 figure 1**
*Lehninger Principles of Biochemistry, Fifth Edition*

## The high rate of glycolysis in tumor cells is used in diagnosis

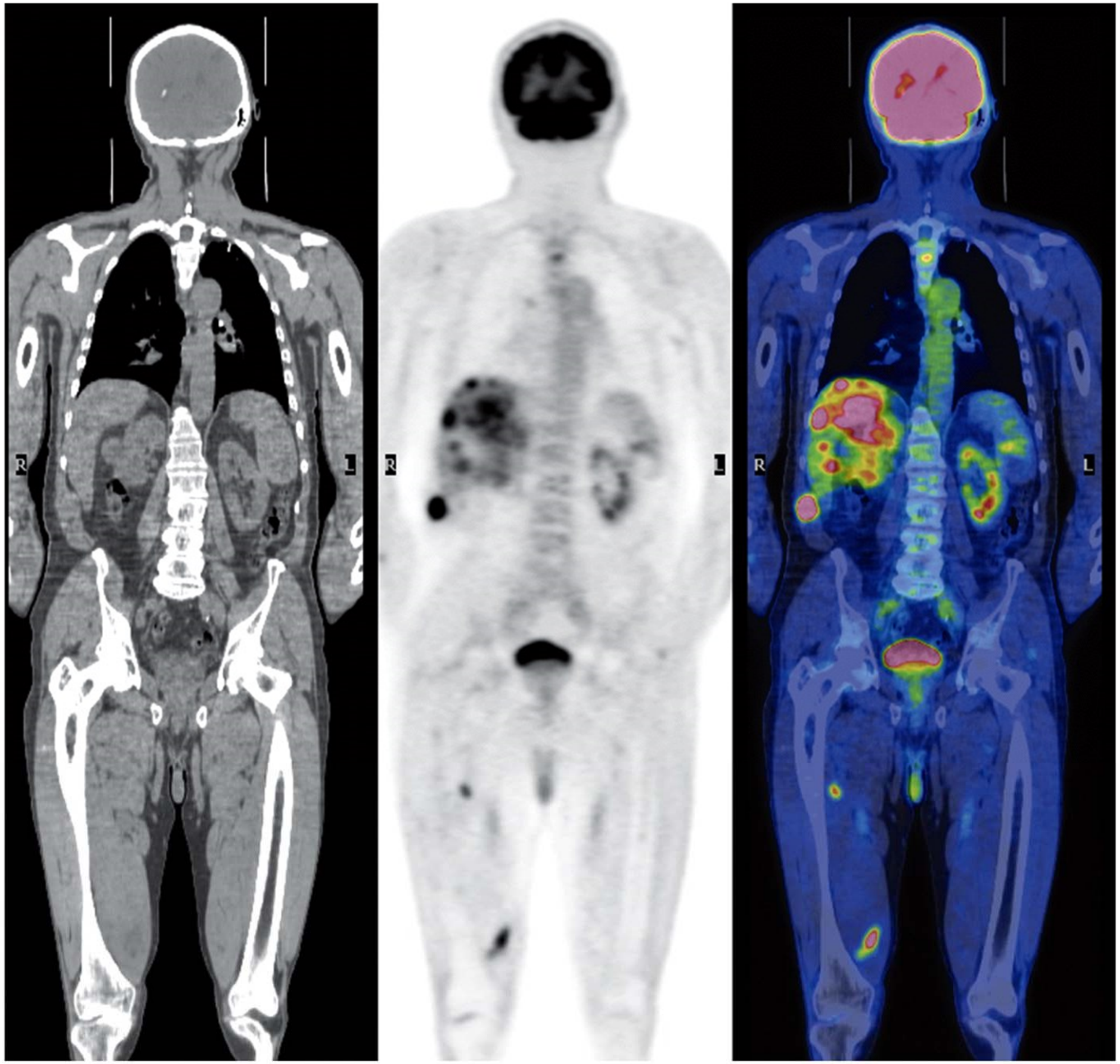



**[18F]2-Fluoro-2-deoxyglucose (FdG)** → **[18F]6-Phospho-2-fluoro-2-deoxyglucose (6-Phospho-FdG)**

**Box 14-1 figure 2**
***Lehninger Principles of Biochemistry, Fifth Edition***


Phosphorylation of $^{18}$F-labelled 2FdG by hexokinase traps the FdG in cells as 6-phosphoFdG, which can be detected by positron emission from $^{18}$F.

# Detection of cancerous tissue by positron emission tomography (PET)




CT

PET

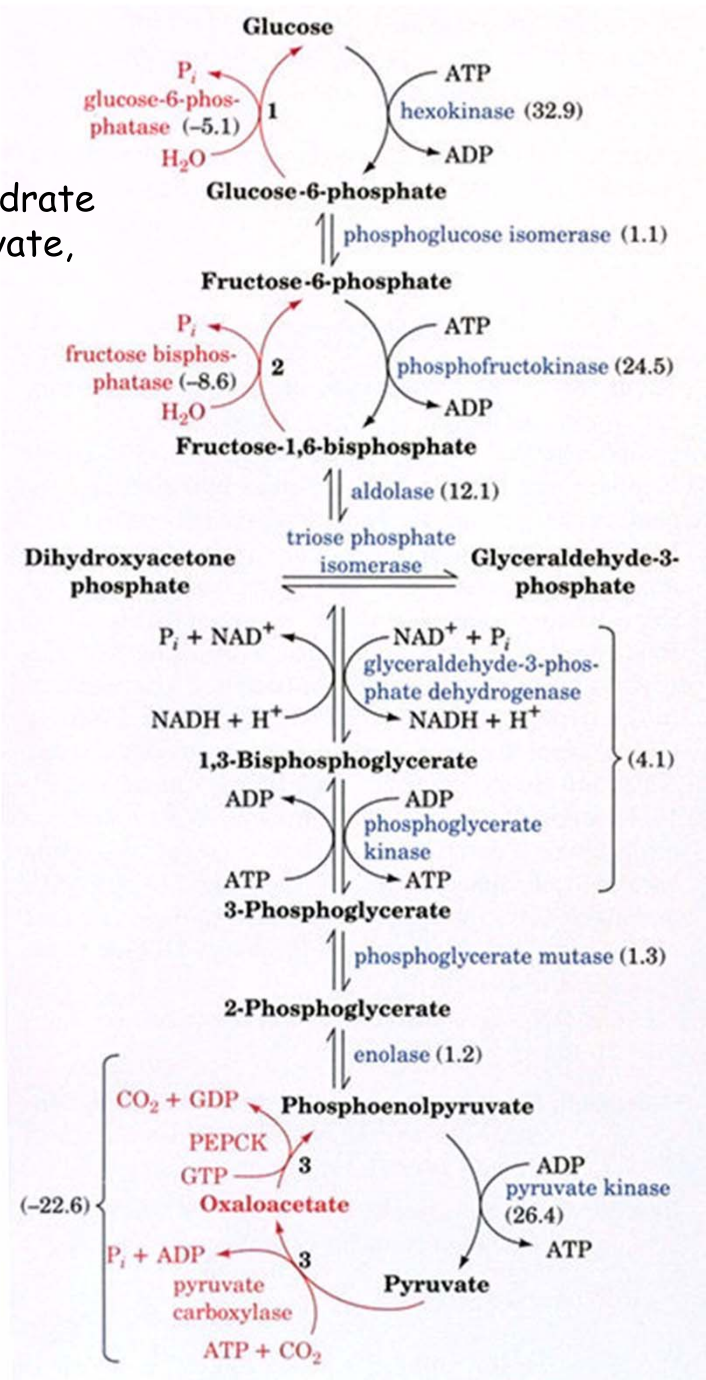
False colour

**Box 14-1 figure 3**
***Lehninger Principles of Biochemistry, Fifth Edition***

# Gluconeogenesis

7 glycolytic enzymes catalyze
the transformation of non-carbohydrate
metabolites including lactate, pyruvate,
glycerol, amino acids into glucose.

**3 energy consuming bypass reactions are the prize for an independent regulation of the two opposing pathways**




# Glycolysis

Lehninger Principles of Biochemistry
Nelson & Cox

# Glucose 6-phosphatase is active at the lumen of the ER

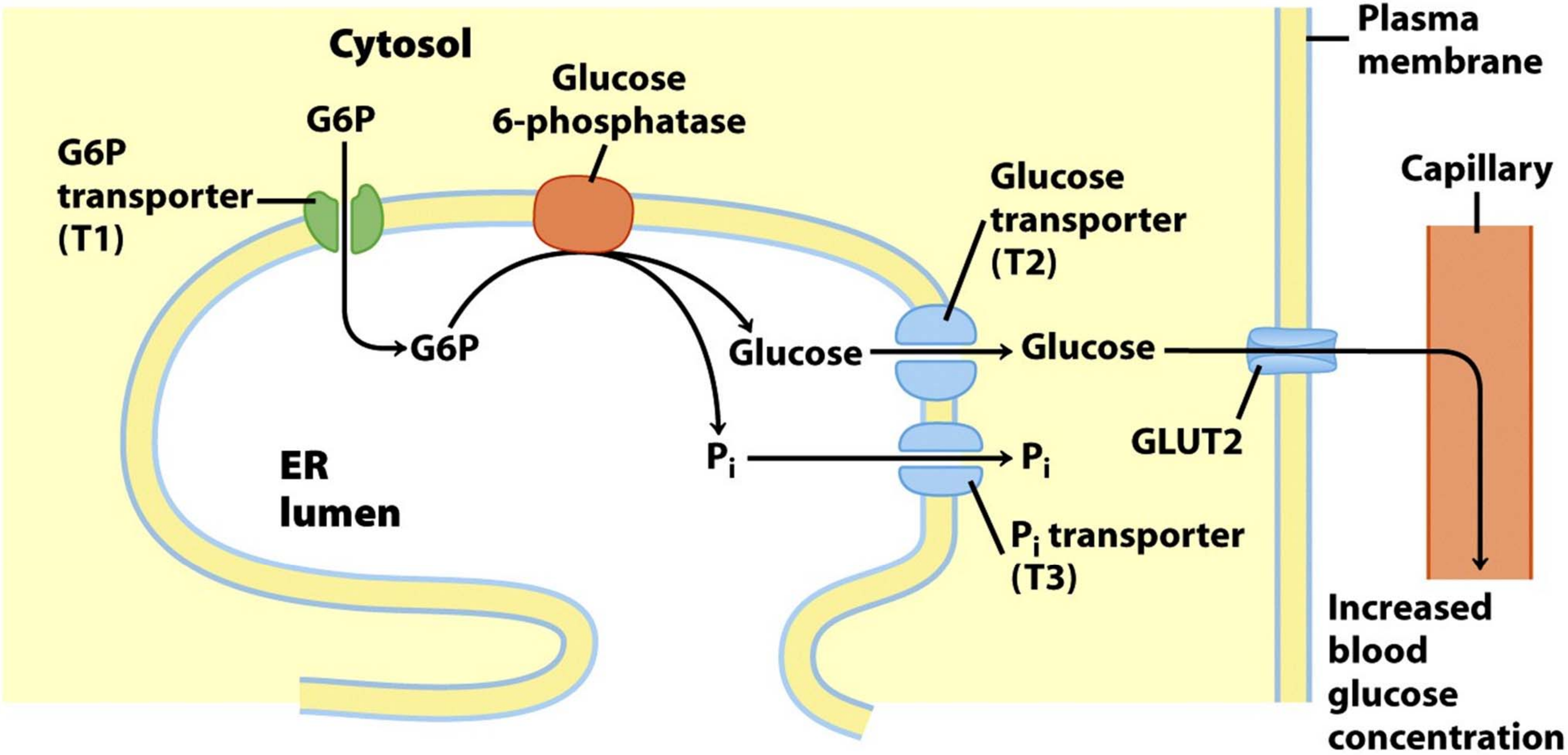
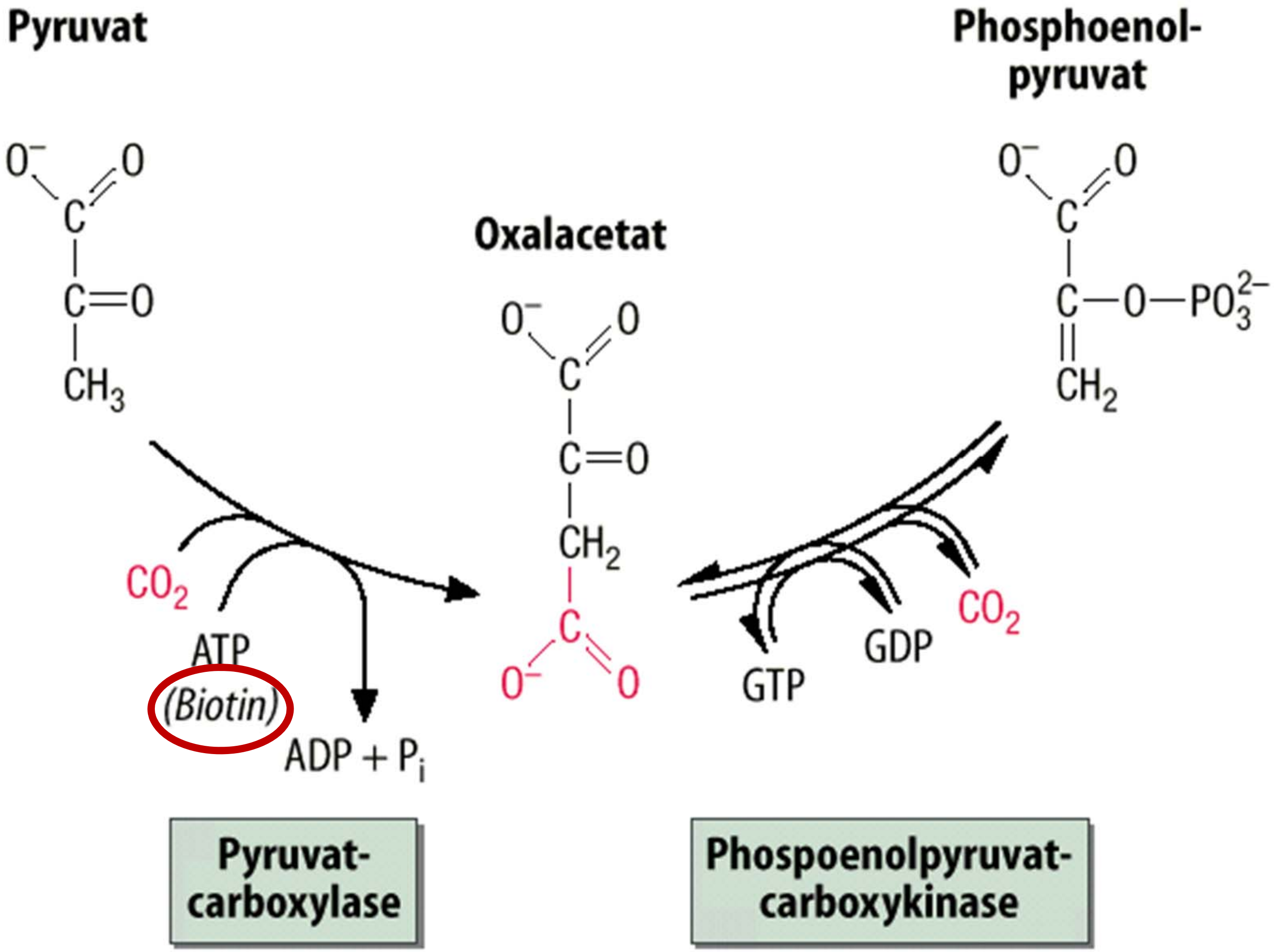


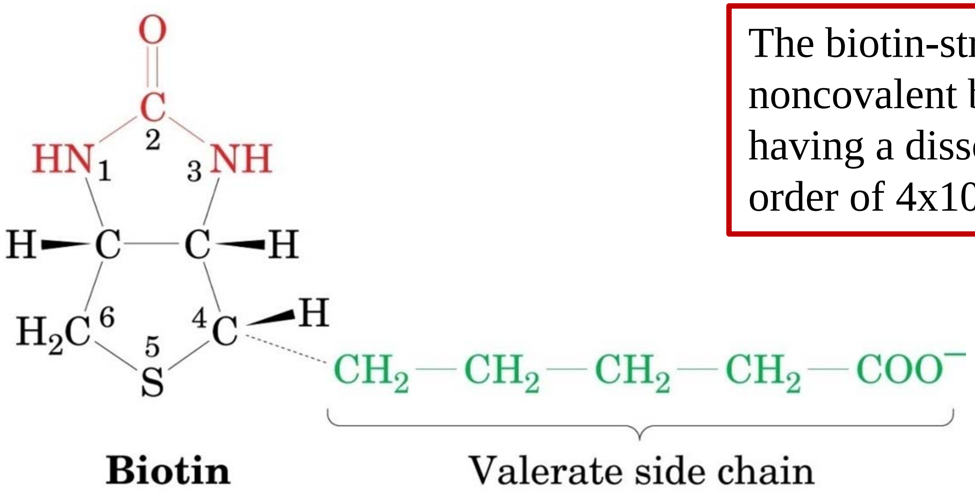

**Figure 15-28**
***Lehninger Principles of Biochemistry, Fifth Edition***

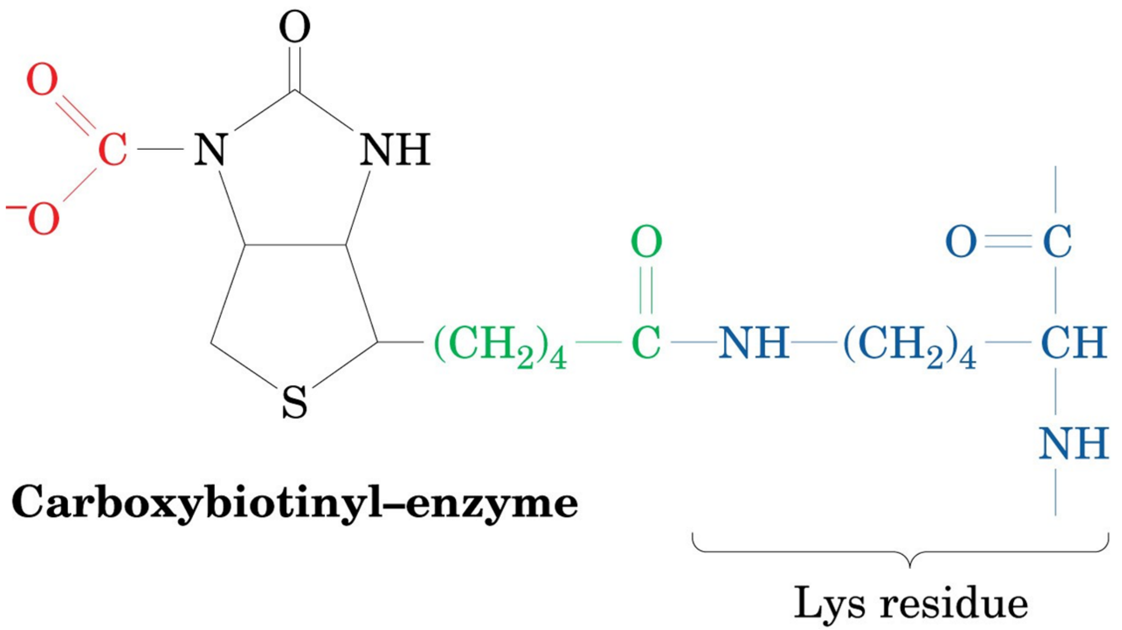
# Conversion of pyruvate into PEP is mediated by oxaloacetate



# Biotin is the prosthetic group of pyruvate carboxylase (Vitamin $B_7$/Vitamin H)

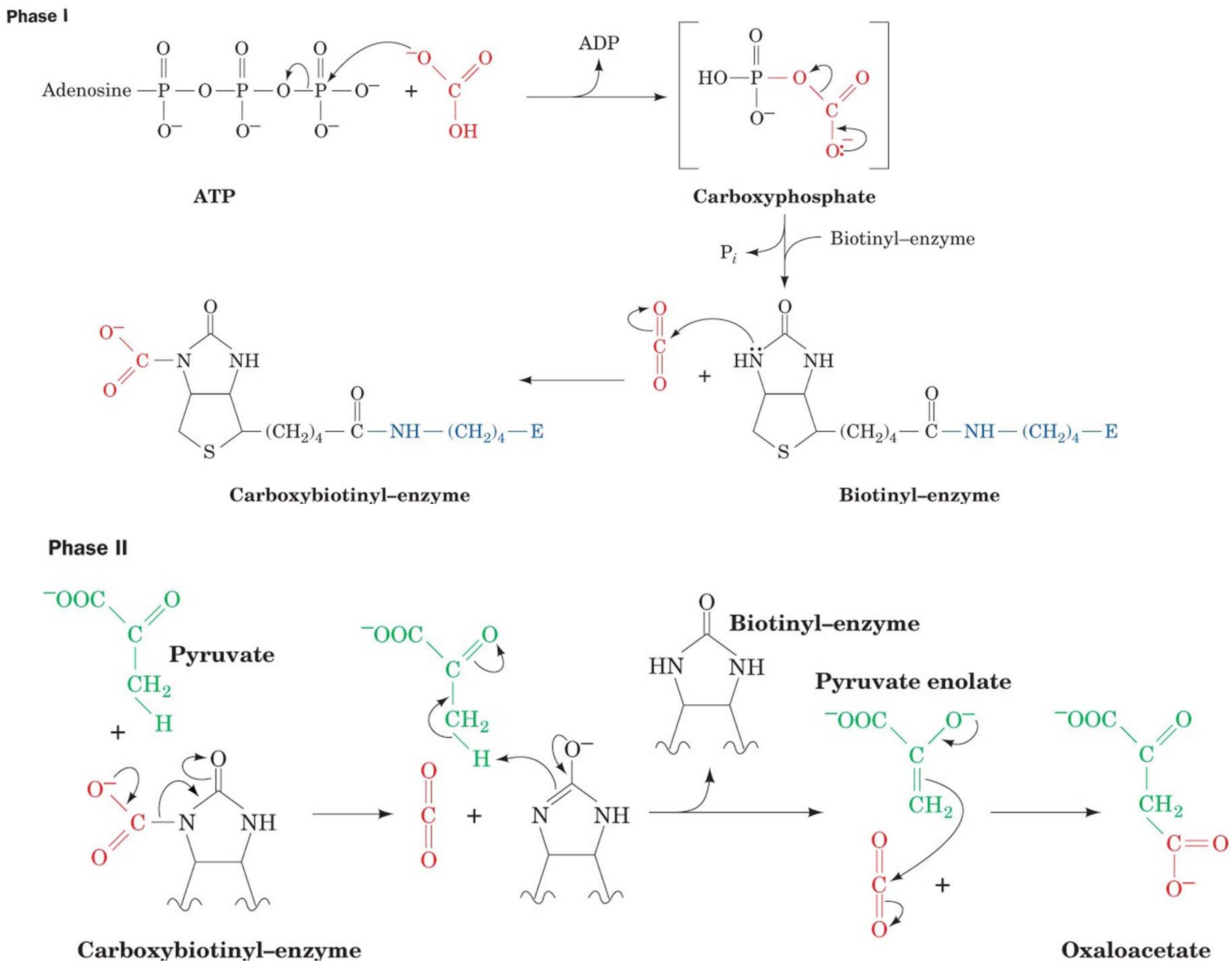
The biotin-streptavidin system is the strongest noncovalent biological interaction known, having a dissociation constant, K(d), in the order of 4x10(-14) M.




Biochemistry. Voet & Voet

# Two-phase reaction mechanism of pyruvate carboxylase




Biochemistry. Voet & Voet

# The reaction mechanism of PEPCK

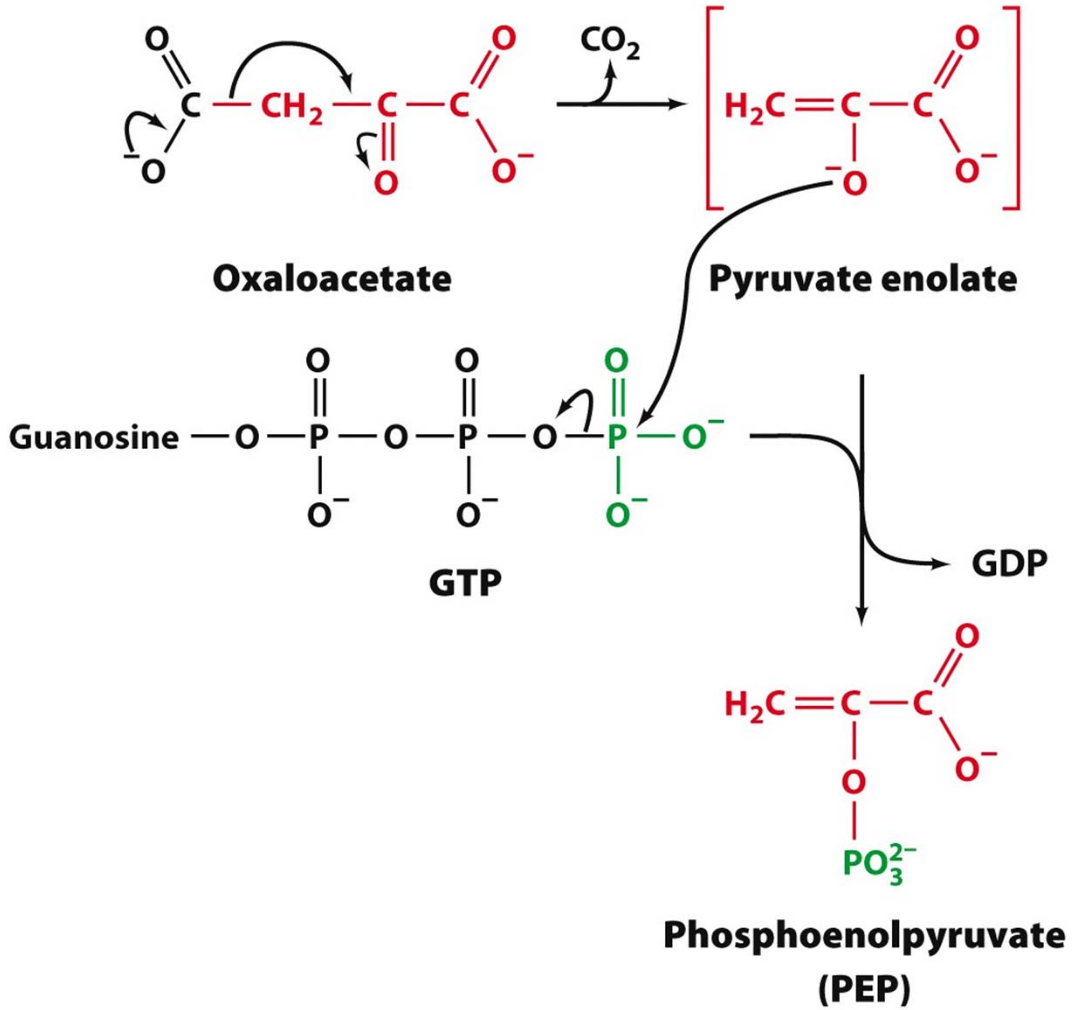



Figure 23-6

# Alternative paths from pyruvate to PEP

Note:
Carboxylation of pyruvate occurs in the mitochondrion

The relative importance of the 2 pathways depends on the availability of pyruvate or lactate and the cytosolic requirements for NADH for gluconeogenesis.

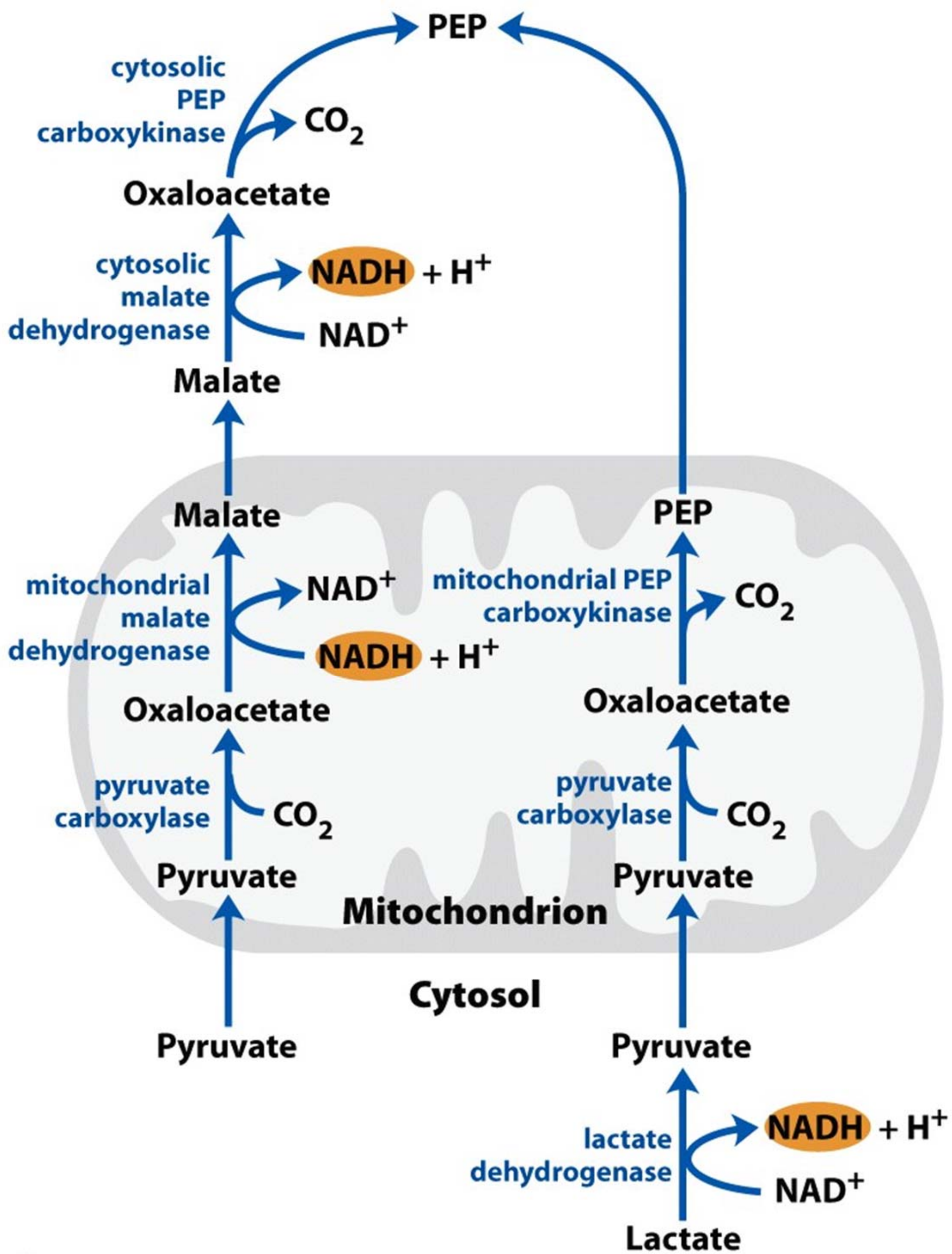



**Figure 14-19**
*Lehninger Principles of Biochemistry, Fifth Edition*

## TABLE 14–4 Glucogenic Amino Acids, Grouped by Site of Entry

| Pyruvate | Succinyl-CoA |
| --- | --- |
| Alanine | Isoleucine* |
| Cysteine | Methionine |
| Glycine | Threonine |
| Serine | Valine |
| Threonine | **Fumarate** |
| Tryptophan* | Phenylalanine* |
| **α-Ketoglutarate** | Tyrosine* |
| Arginine | **Oxaloacetate** |
| Glutamate | Asparagine |
| Glutamine | Aspartate |
| Histidine | |
| Proline | |

**Note:** All these amino acids are precursors of blood glucose or liver glycogen, because they can be converted to pyruvate or citric acid cycle intermediates. Of the 20 common amino acids, only leucine and lysine are unable to furnish carbon for net glucose synthesis.

*These amino acids are also ketogenic (see Fig. 18–21).

Table 14-4
*Lehninger Principles of Biochemistry, Fifth Edition*

# The Cori Cycle: Metabolic cooperation between skeletal muscle and liver

**Anaerobic utilization of pyruvate** converted to lactate (acidic). At pH 7.35 lactate disassociates to carboxylate anion, lactate and H+.
The **lactate and H+** are transported out of the cell, diffuse into the blood and can cause lactic acidosis.
But most lactate is taken up by the liver and heart muscle and oxidized back to pyruvate.

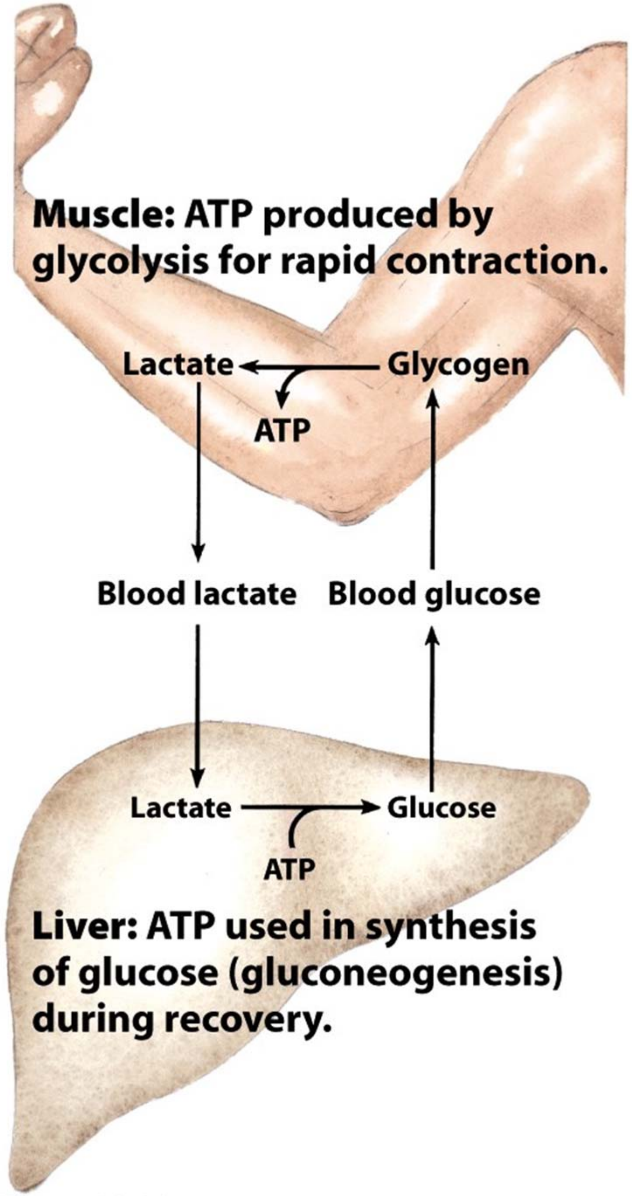



**Figure 23-20**
*Lehninger Principles of Biochemistry, Fifth Edition*


**Muscle** – under anaerobic conditions makes lactate

**Liver** – picks up the lactate made in the muscle

| TABLE 14–3 Sequential Reactions in Gluconeogenesis Starting from Pyruvate | |
|---|---|
| Pyruvate + $HCO_3^-$ + ATP ⟶ oxaloacetate + ADP + $P_i$ | ×2 |
| Oxaloacetate + GTP ⇌ phosphoenolpyruvate + $CO_2$ + GDP | ×2 |
| Phosphoenolpyruvate + $H_2O$ ⇌ 2-phosphoglycerate | ×2 |
| 2-Phosphoglycerate ⇌ 3-phosphoglycerate | ×2 |
| 3-Phosphoglycerate + ATP ⇌ 1,3-bisphosphoglycerate + ADP | ×2 |
| 1,3-Bisphosphoglycerate + NADH + $H^+$ ⇌ glyceraldehyde 3-phosphate + $NAD^+$ + $P_i$ | ×2 |
| Glyceraldehyde 3-phosphate ⇌ dihydroxyacetone phosphate | |
| Glyceraldehyde 3-phosphate + dihydroxyacetone phosphate ⇌ fructose 1,6-bisphosphate | |
| Fructose 1,6-bisphosphate ⟶ fructose 6-phosphate + $P_i$ | |
| Fructose 6-phosphate ⇌ glucose 6-phosphate | |
| Glucose 6-phosphate + $H_2O$ ⟶ glucose + $P_i$ | |
| *Sum:* 2 Pyruvate + 4ATP + 2GTP + 2NADH + $2H^+$ + $4H_2O$ ⟶ glucose + 4ADP + 2GDP + $6P_i$ + $2NAD^+$ | |

**Note:** The bypass reactions are in red; all other reactions are reversible steps of glycolysis. The figures at the right indicate that the reaction is to be counted twice, because two three-carbon precursors are required to make a molecule of glucose. The reactions required to replace the cytosolic NADH consumed in the glyceraldehyde 3-phosphate dehydrogenase reaction (the conversion of lactate to pyruvate in the cytosol or the transport of reducing equivalents from mitochondria to the cytosol in the form of malate) are not considered in this summary. Biochemical equations are not necessarily balanced for H and charge (p. 501).

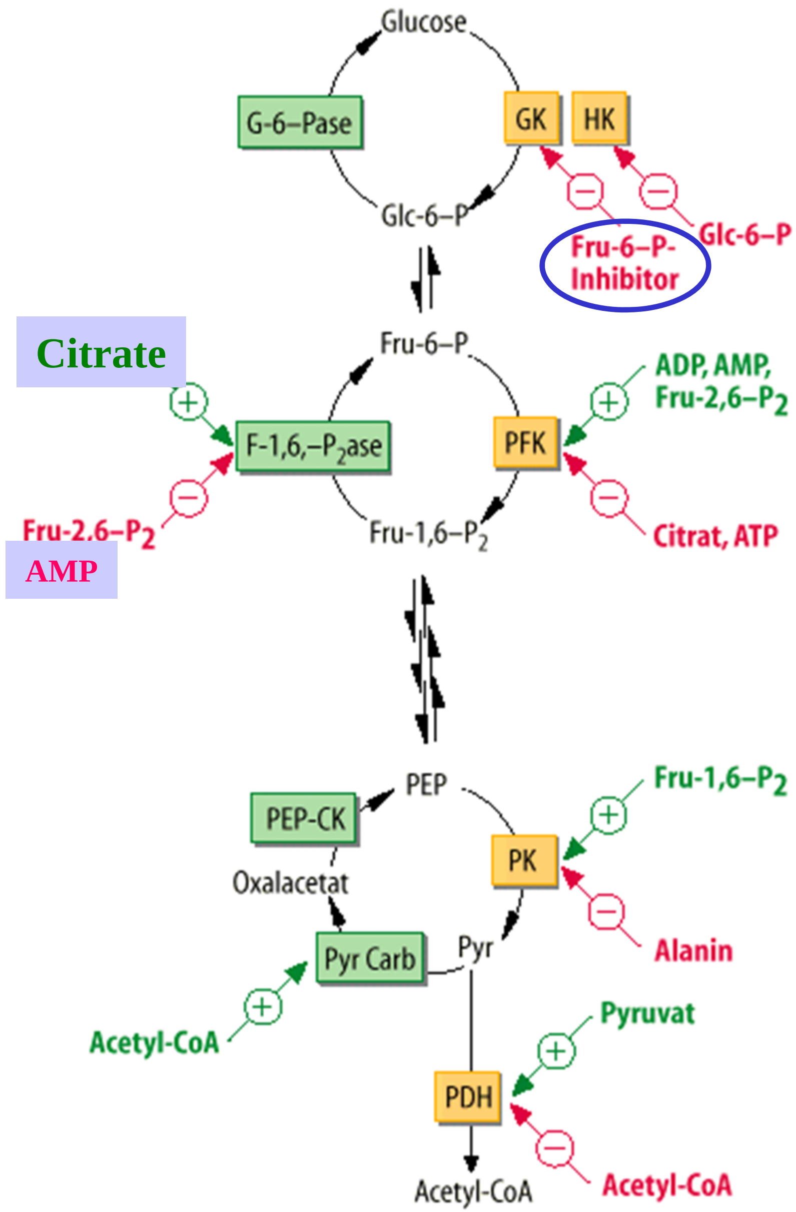
Table 14-3
*Lehninger Principles of Biochemistry, Fifth Edition*


**Sum of glycolysis:**
**Glucose + $2NAD^+$ + 2ADP + $2P_i$ → 2pyruvate + 2NADH + $2H^+$ +2ATP + $2H_2O$**

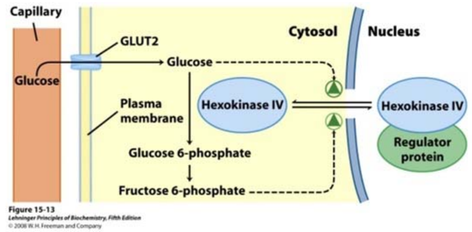
**2ATP + 2GTP + $4H_2O$ → 2ADP + 2GDP + $4P_i$ Prize for independent regulation**

# The allosteric modulation of key enzymes of Gluconeogenesis and Glycolysis

## Gluconeogenesis



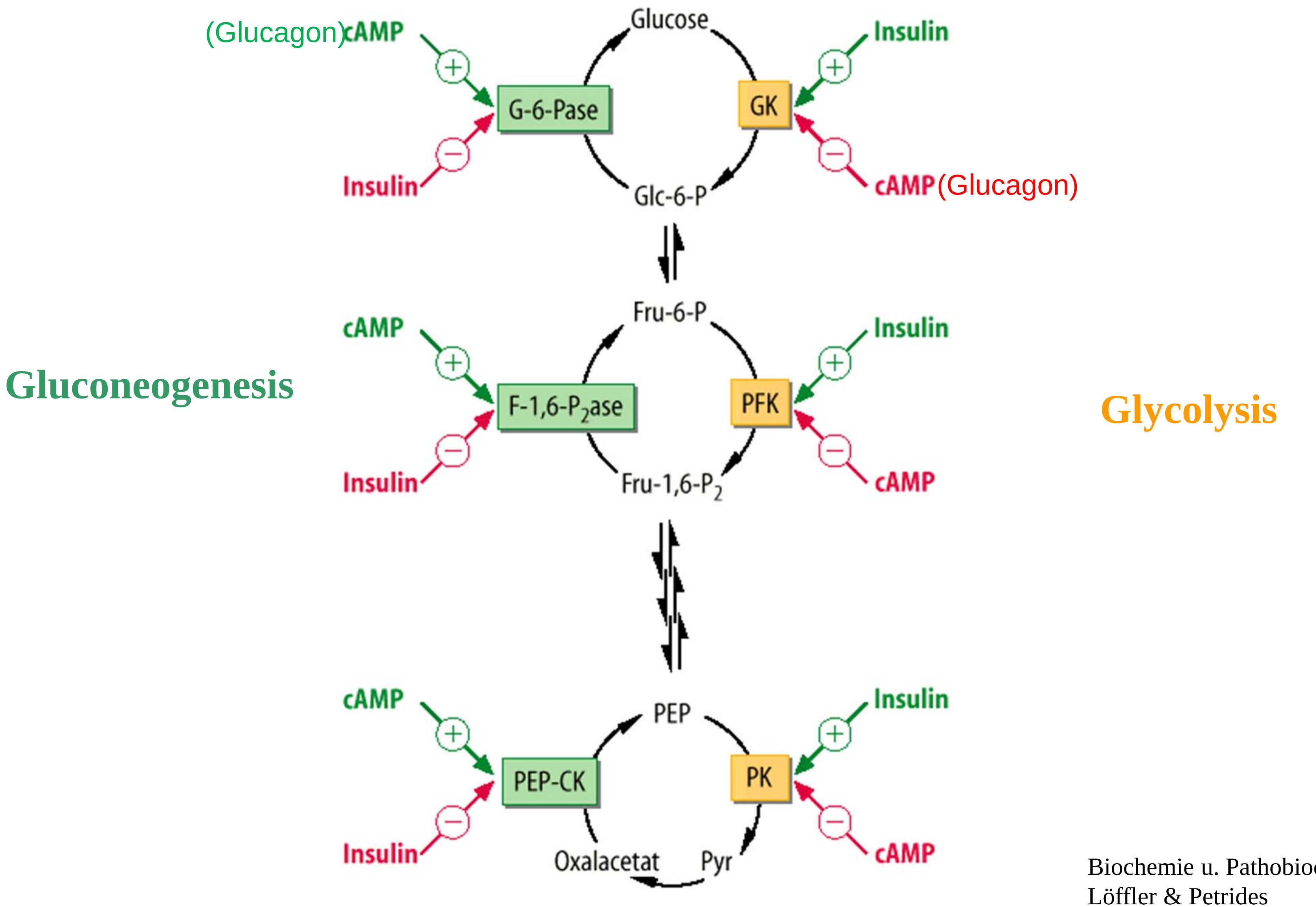

## Glycolysis




Glucokinase = Hexokinase IV

Biochemie u. Pathobiochemie.
Löffler & Petrides

# Coordinated transcriptional regulation of Gluconeogenesis and Glycolysis by insulin and cAMP in liver

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## Hormonal Regulation of Gene Expression

Regulation of glycolysis by **allosteric** activation or inhibition, or the **phosphorylation/ dephosphorylation** of rate-limiting enzymes, is **short term**, i.e., min or h.

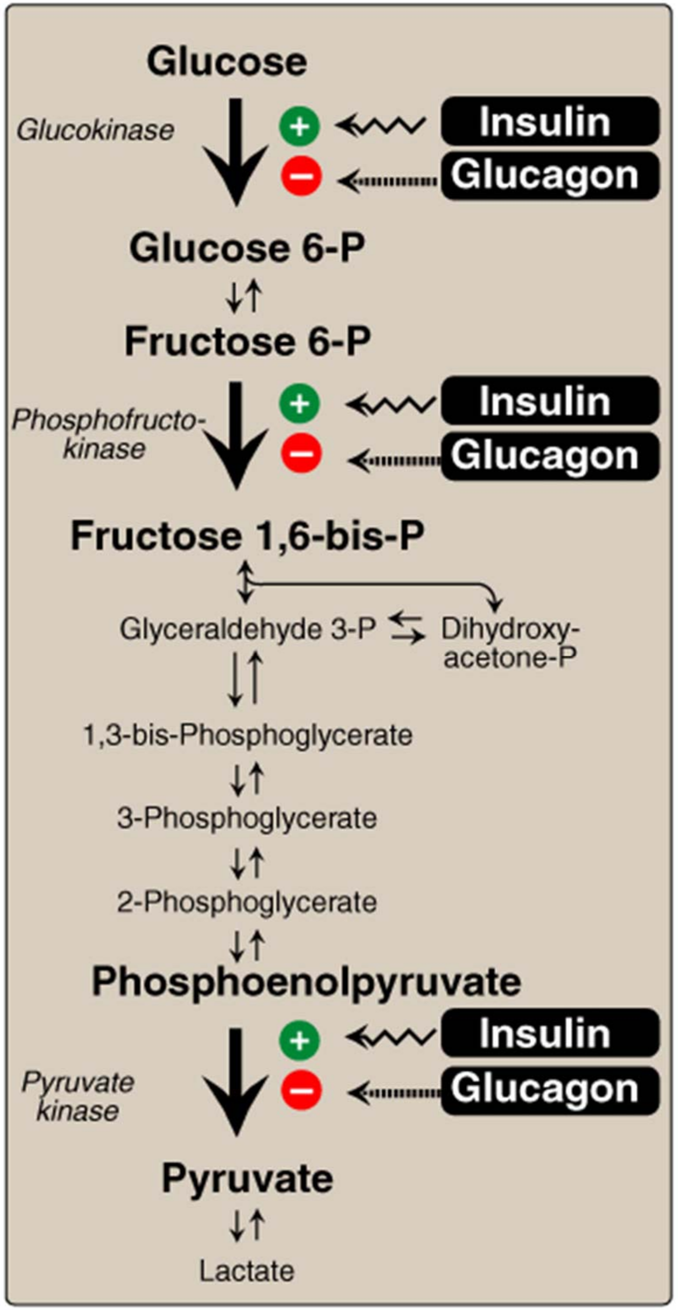
Slower, and more profound, **hormonal** influences on [enzyme protein] **synthesized** result in 10-20-fold increases in enzyme activity over h to days.

Current focus is on **glycolysis**, reciprocal changes also occur in the rate-limiting enzymes of **gluconeogenesis (synthesis of glucose)**.

Regular consumption of **carbohydrate-**rich meals or administration of **insulin** initiates increase in **glucokinase, phosphofructokinase**, and **pyruvate kinase** in liver reflecting increases in gene transcription, and increased enzyme synthesis.

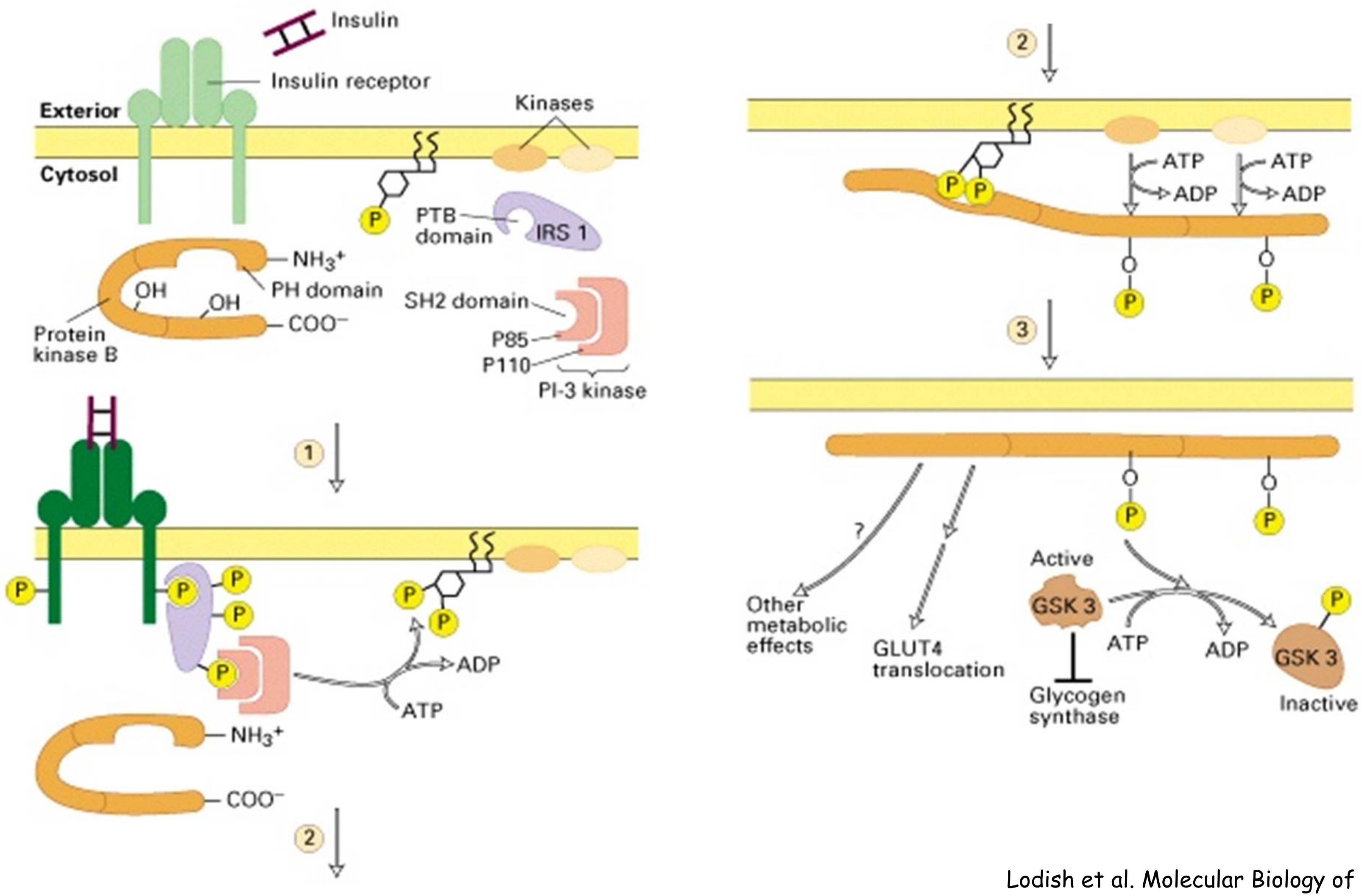
High activity of these 3 enzymes favors conversion of glucose to pyruvate.

Conversely, gene transcription and synthesis of **glucokinase, PFK**, and **pyruvate kinase** are **decreased** when plasma glucagon is high and insulin is low, as seen in fasting or diabetes.



# Insulin activates PKB via PI-3 kinase

## A Ras independent pathway activates Protein Kinase B




Lodish et al. Molecular Biology of the Cell