Gluconeogenesis

Gluoconeogenesis

- Is the formation of glucose from non-carbohydrate sources e.g lactic acid ,amino acids , glycerols and propionate.
- Site: liver and kidney.

Gluconeogenesis

Gluconoegenesis is the biosynthesis of new glucose from non carbohydrate substrates.

In the absence of dietary intake of carbohydrate liver glycogen can meet these needs for only 10 to 18 hours

During prolonged fast hepatic glycogen stores are depleted and glucose is formed from precursors such as lactate, pyruvate, glycerol and keto acids.

Approximately 90% of gluconeogenesis occurs in the liver whereas kidneys provide 10 % of newly synthesized glucose molecules,
The kidneys thus play a minor role except during prolonged starvation when they become major glucose producing organs.

- Liver and kidney contains all enzymes of glconeogenesis.
- It does not occur in skeletal muscles due to deficiency of glucose -6-p
- It does not occur in heart muscle,smooth muscles, and dipose tissues due to deficiency of fructose 1-6 dip.

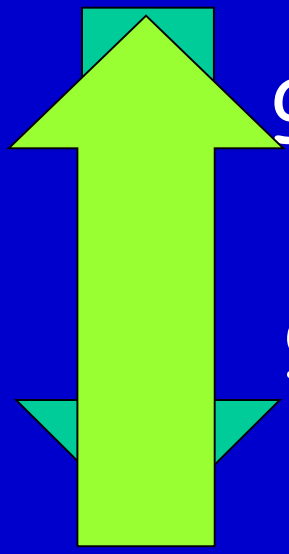
Importance

- Glucose is the only source of energy:
- 1. nervous system
- 2.Skeletal system
- Glucose is required :
- 1. Adipose tissues: as a source of glycerol
- 2.Mammary gland:as a source of lacotse

Advantages of Gluconeogenesis

1) Gluconeogenesis meets the requirements of glucose in the body when carbohydrates are not available in sufficient amounts.
2) Regulate Blood glucose level
3) Source of energy for Nervous tissue and Erythrocytes
4) Maintains level of intermediates of TCA cycle
5) Clear the products of metabolism of other tissues(Muscle)

glucose



glycolysis

gluconeogenesis

pyruvate
lactate

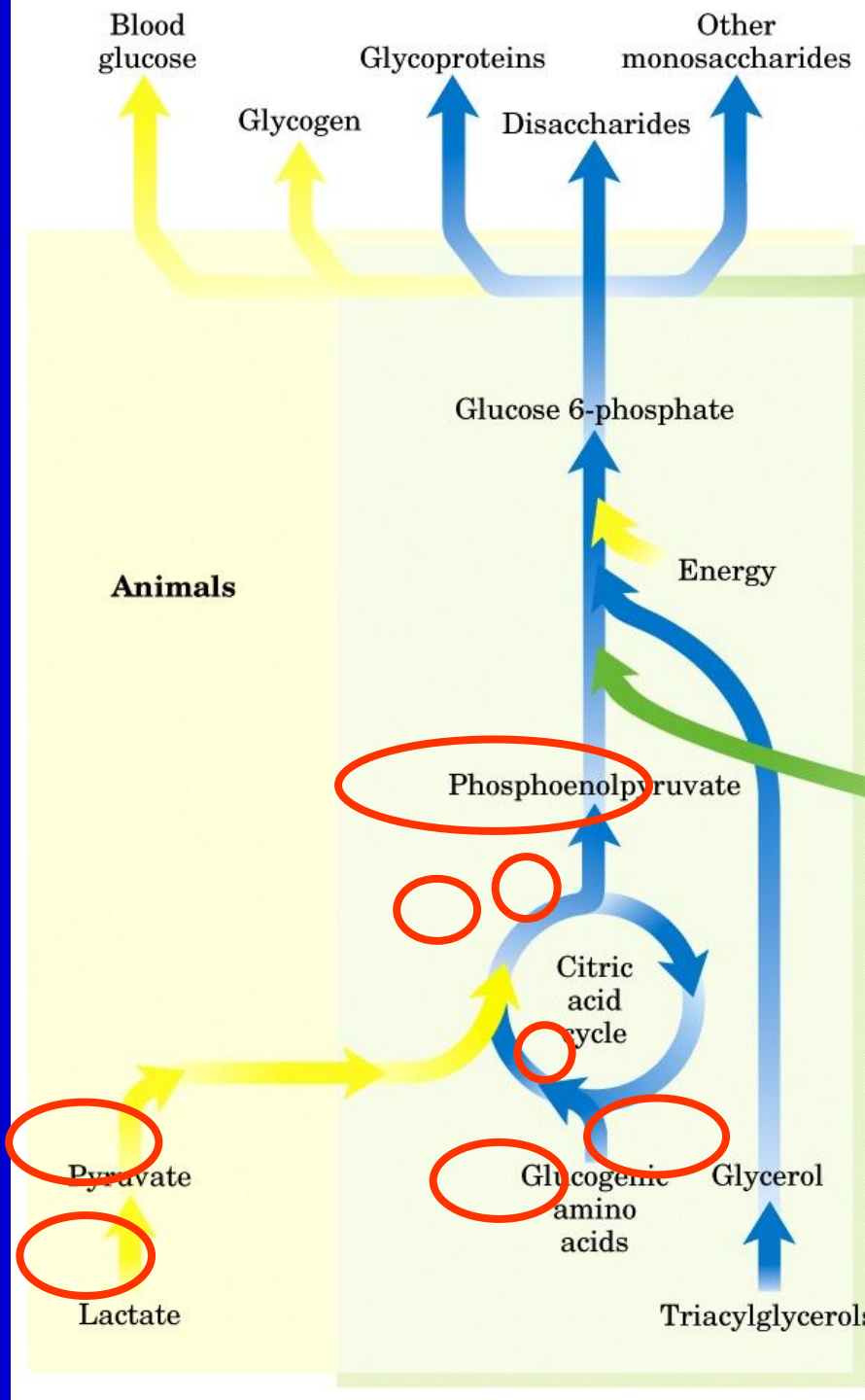
gluco neo genesis

sugar (re)new make/
create

Gluconeogenesis

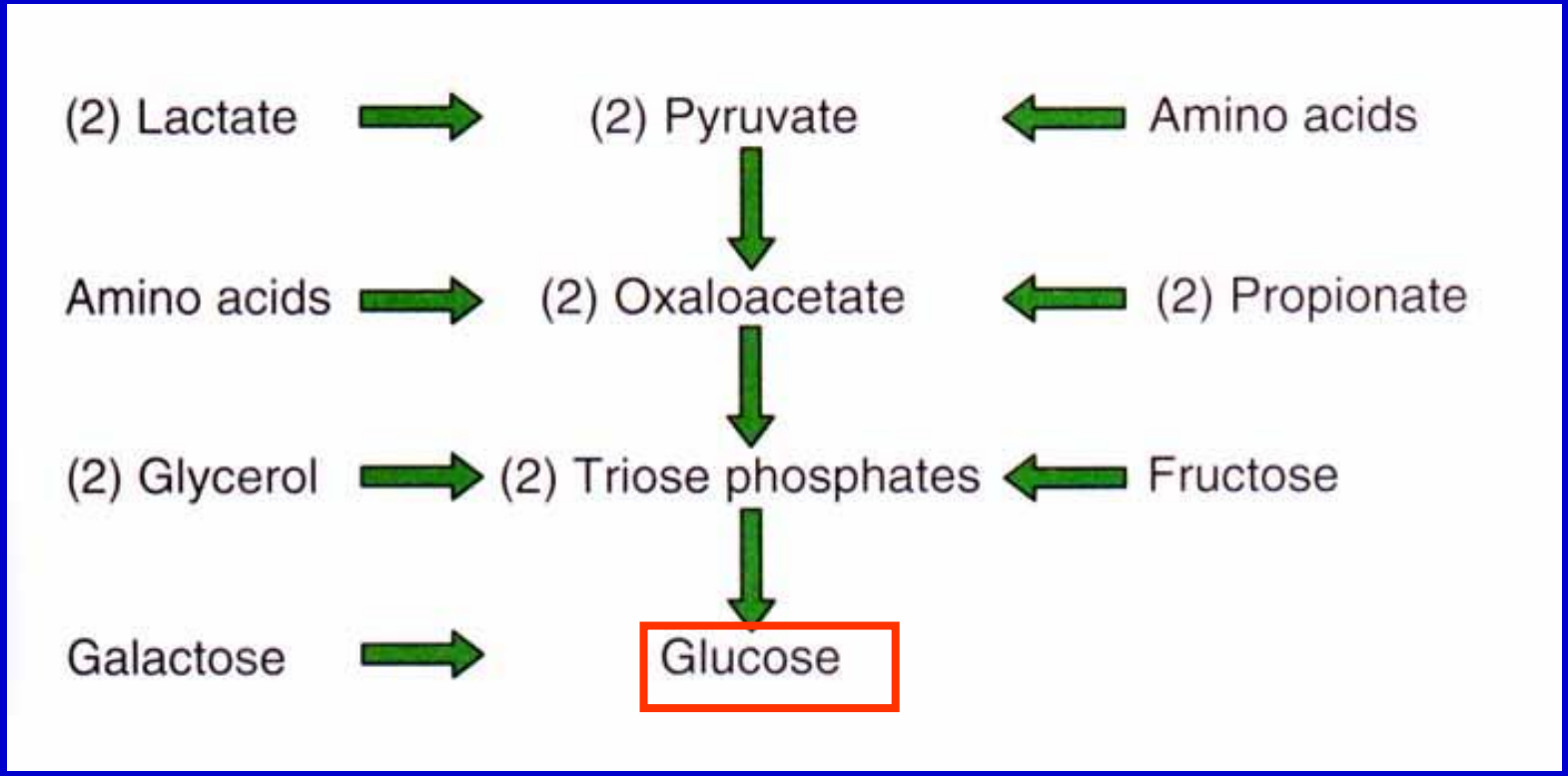
- Occurs in all animals, plants, fungi and microbes
- Occurs largely in the liver; some in renal cortex
- Of 10 enzymatic steps, 7 are reversals of glycolytic reactions

Carbohydrate synthesis from simple precursors



Metabolites feed into gluconeogenesis at various points

main path



All AA can feed into gluconeogenesis except leucine and lysine

table 20–3

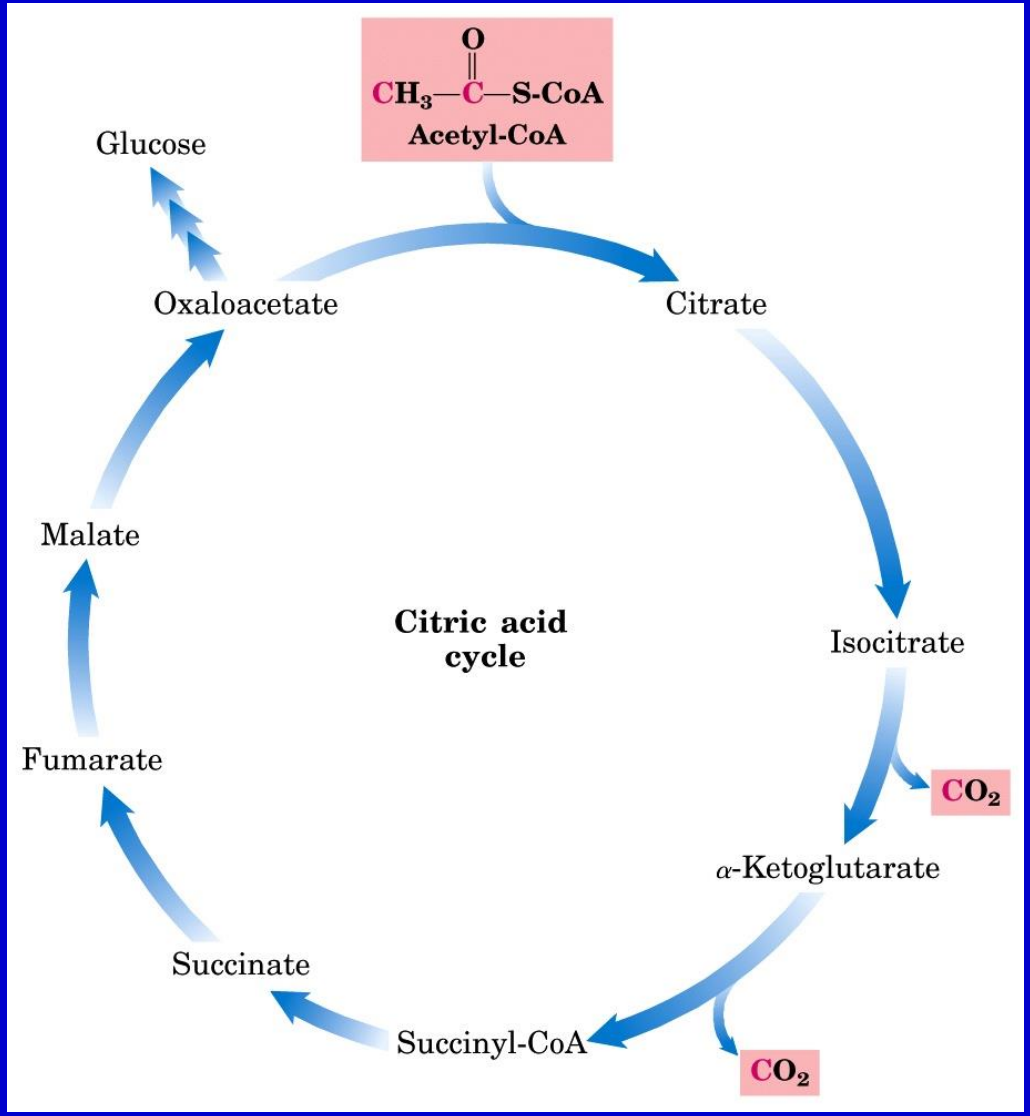
Glucogenic Amino Acids, Grouped by Site of Entry*

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

*These amino acids are precursors of blood glucose or liver glycogen because they can be converted to pyruvate or citric acid cycle intermediates. Only leucine and lysine are unable to furnish carbon for net glucose synthesis.

†These amino acids are also ketogenic (see Fig. 18–19).

TCA intermediates are gluconeogenic; funnel through oxaloacetate



Reactions Unique to Gluconeogenesis

Seven of the reactions of glycolysis are reversible and are used in the synthesis of glucose from lactate or pyruvate. However three of the reactions are irreversible and must be bypassed by four alternate reactions that energetically favored the synthesis of glucose.

Bypass of irreversible steps in glycolysis

Bypassed Reactions in Gluconeogenesis

1. **Phosphoenolpyruvate is formed from pyruvate** *by way of oxaloacetate* through the action of ***pyruvate carboxylase*** and ***phosphoenolpyruvate carboxykinase.***

Pyruvate + CO_2 + ATP + H_2O → oxaloacetate + ADP + P_i + $2H^+$
Oxaloacetate + GTP → phosphoenolpyruvate + GDP + CO_2

2. **Fructose 6-phosphate is formed from fructose 1,6-bisphosphate.**
Enzyme - ***fructose 1,6-bisphosphatase.***

Fructose 1,6-bisphosphate + H_2O → fructose 6-phosphate + P_i

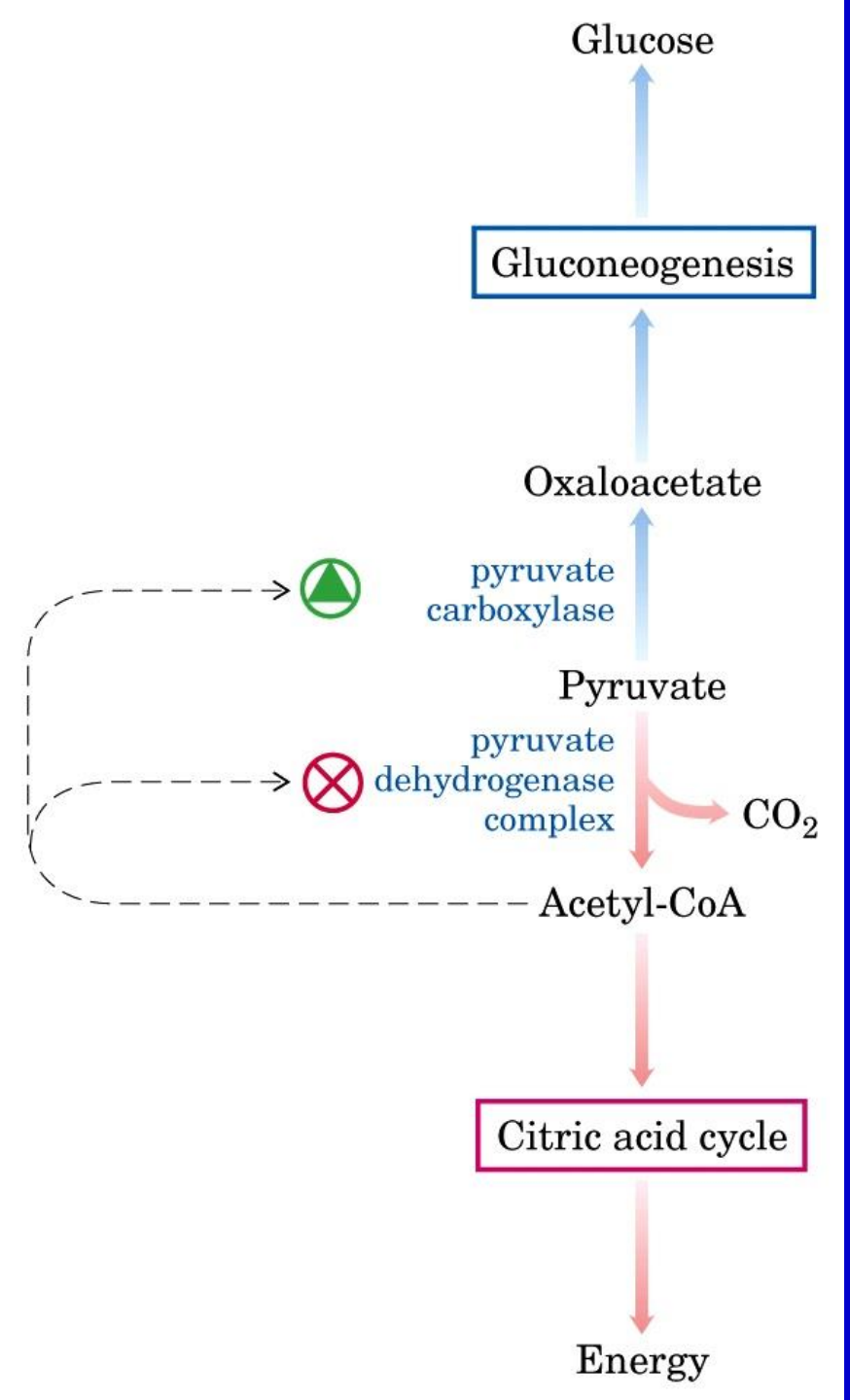
3. Glucose is formed by hydrolysis of glucose 6-phosphate in a reaction catalyzed by ***glucose 6-phosphatase.***

Glucose 6-phosphate + H_2O → glucose + P_i

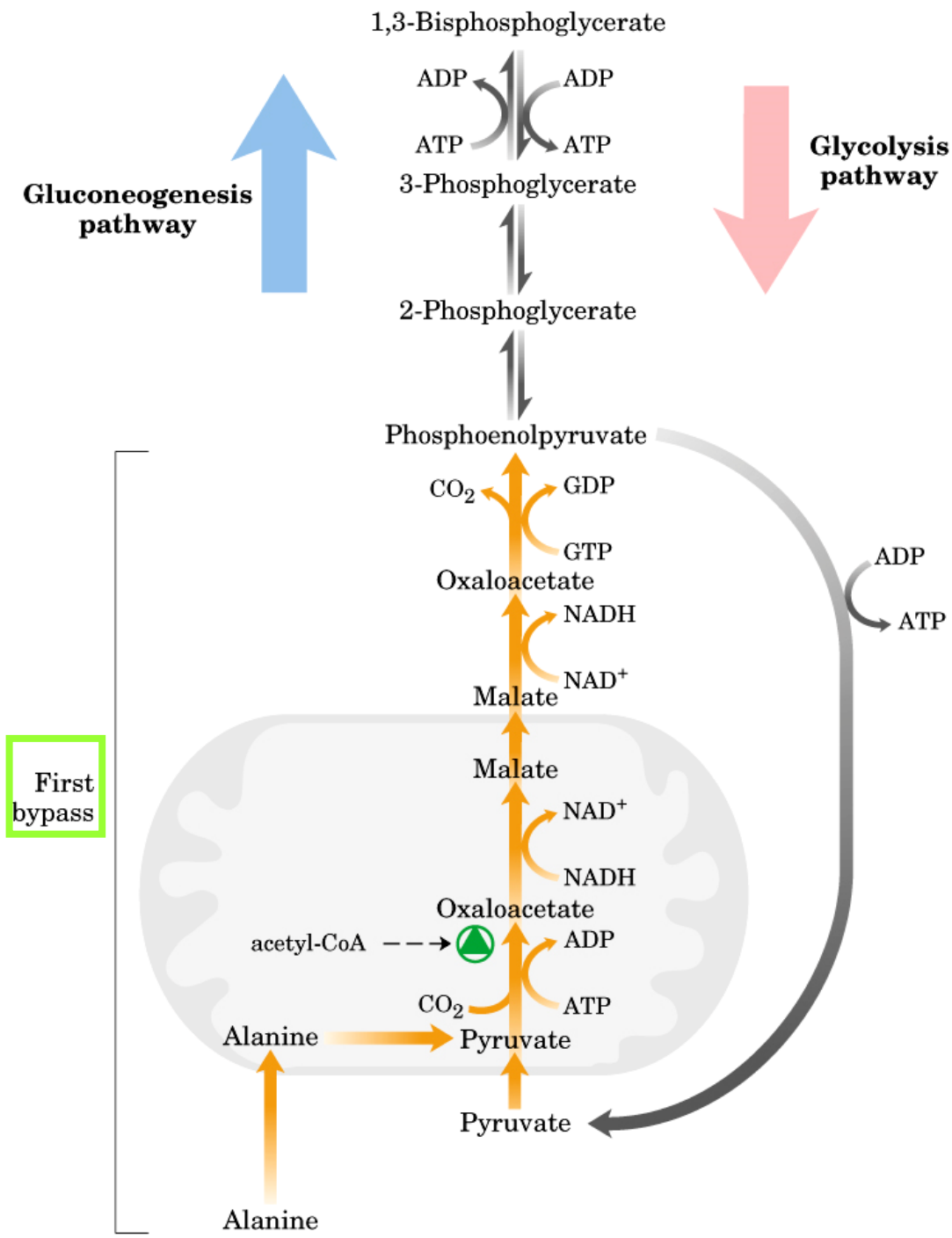
Irreversible glycolytic steps bypassed

glycolysis	gluconeogenesis
1. Hexokinase (hexK)	by Glucose-6-phosphatase
2. Phosphofructokinase-1 (PFK-1)	by Fructose 1,6-bisphosphatase (FBP-1)
3. Pyruvate kinase (PyrK)	by Pyruvate Carboxylase & Phosphoenolpyruvate carboxykinase (PEPCK)

These 3 key enzymes



Pyruvate can go "up" or "down" depending upon energy needs



First bypass step is generation of PEP from pyruvate via oxaloacetate

*Note:

In order to cross the mito membrane, oxaloacetate must:

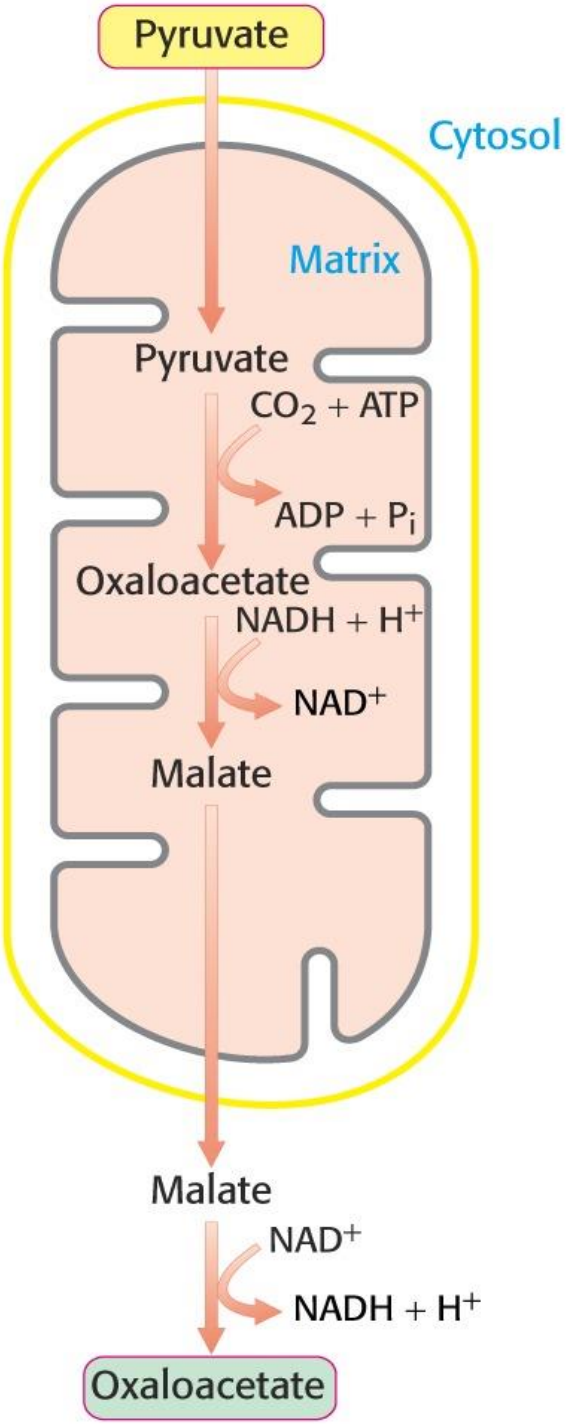
1. Be reduced to malate
2. Go through the malate shuttle
3. Be reoxidized to oxaloacetate

Oxaloacetate is polar molecule and can not pass through the mitochondria membrane into cytoplasm

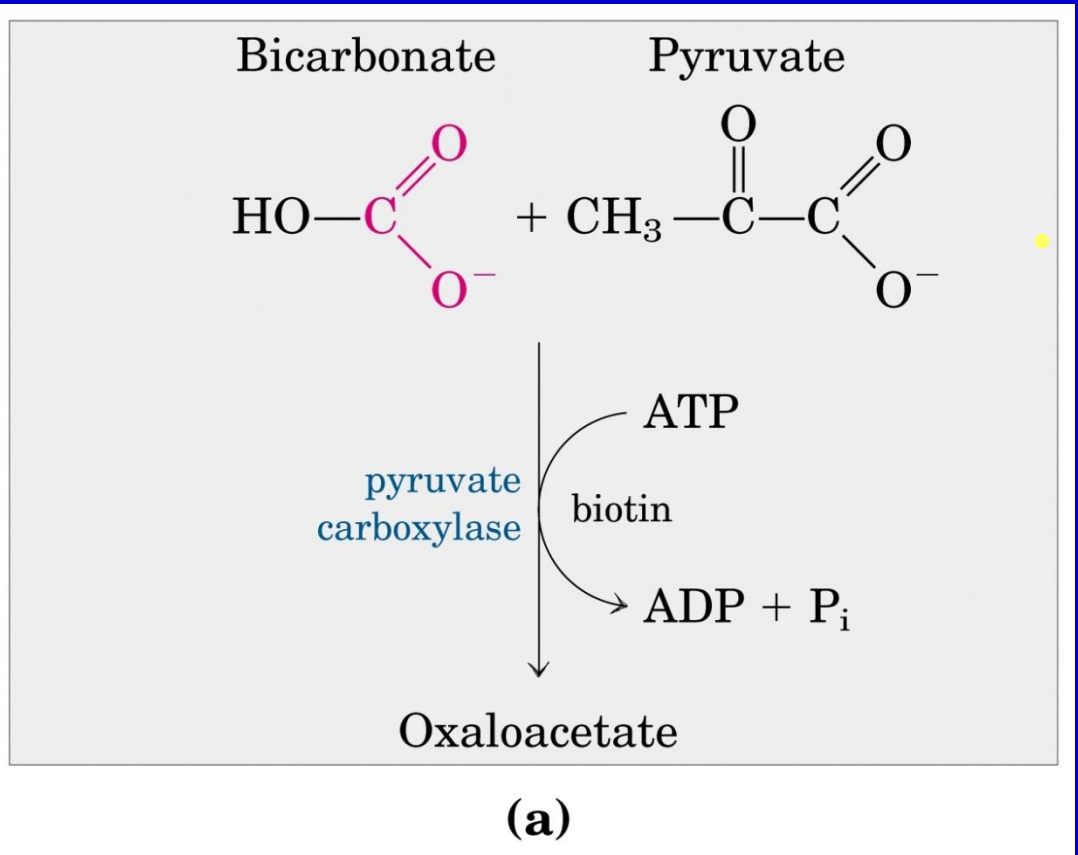
Therefore it is reduced:
oxaloacetate + $NADH_2$ → malate + NAD^+
Enzyme – ***malate dehydrogenase***

Malate passes through the mitochondria membrane into cytoplasm and again oxidized to oxaloacetate (enzyme ***malate dehydrogenase***):
malate + NAD^+ → oxaloacetate + $NADH_2$

Cytoplasmic **oxaloacetate** is decarboxylated to **phosphoenolpyruvate** by ***phosphoenolpyruvate carboxykinase***

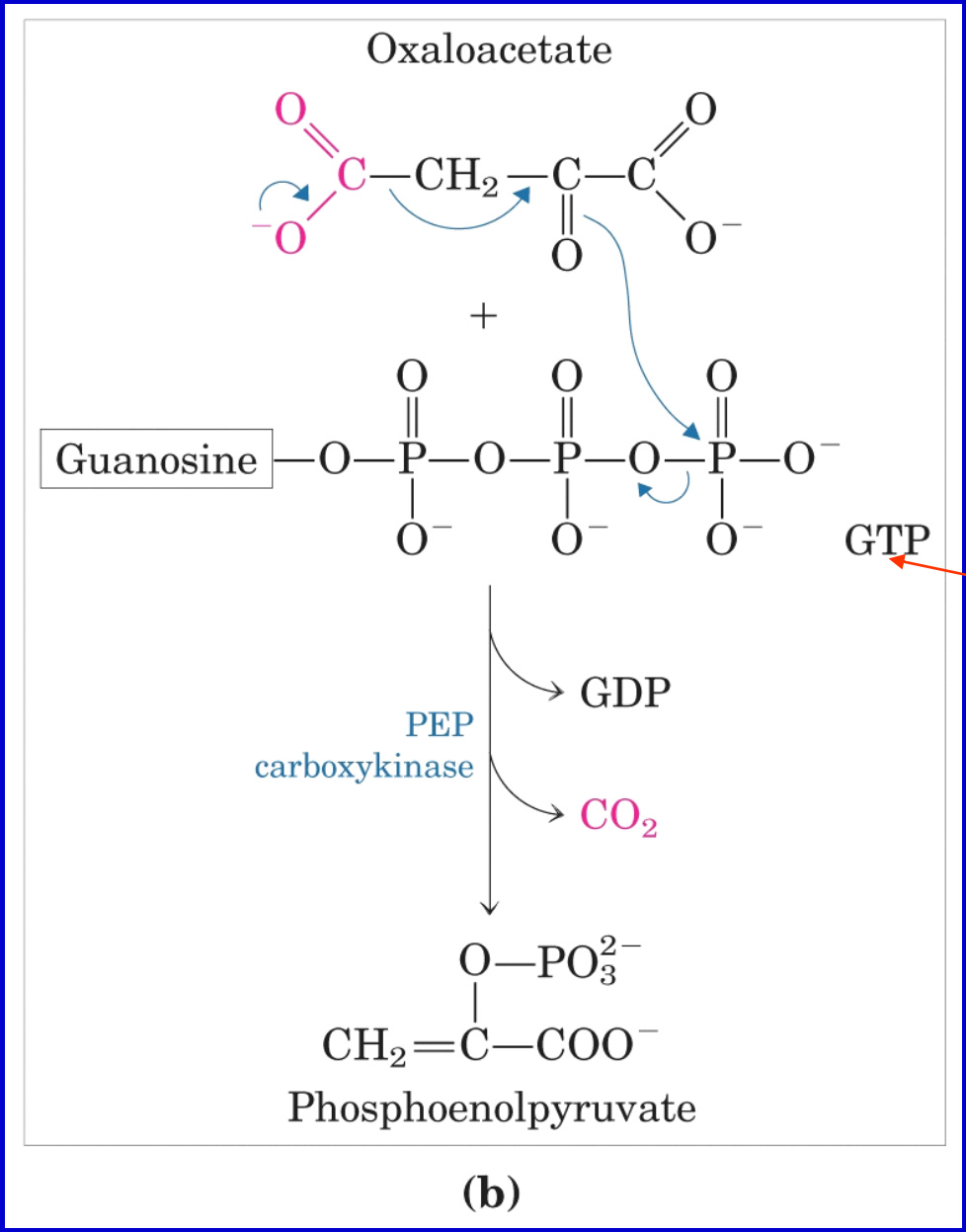


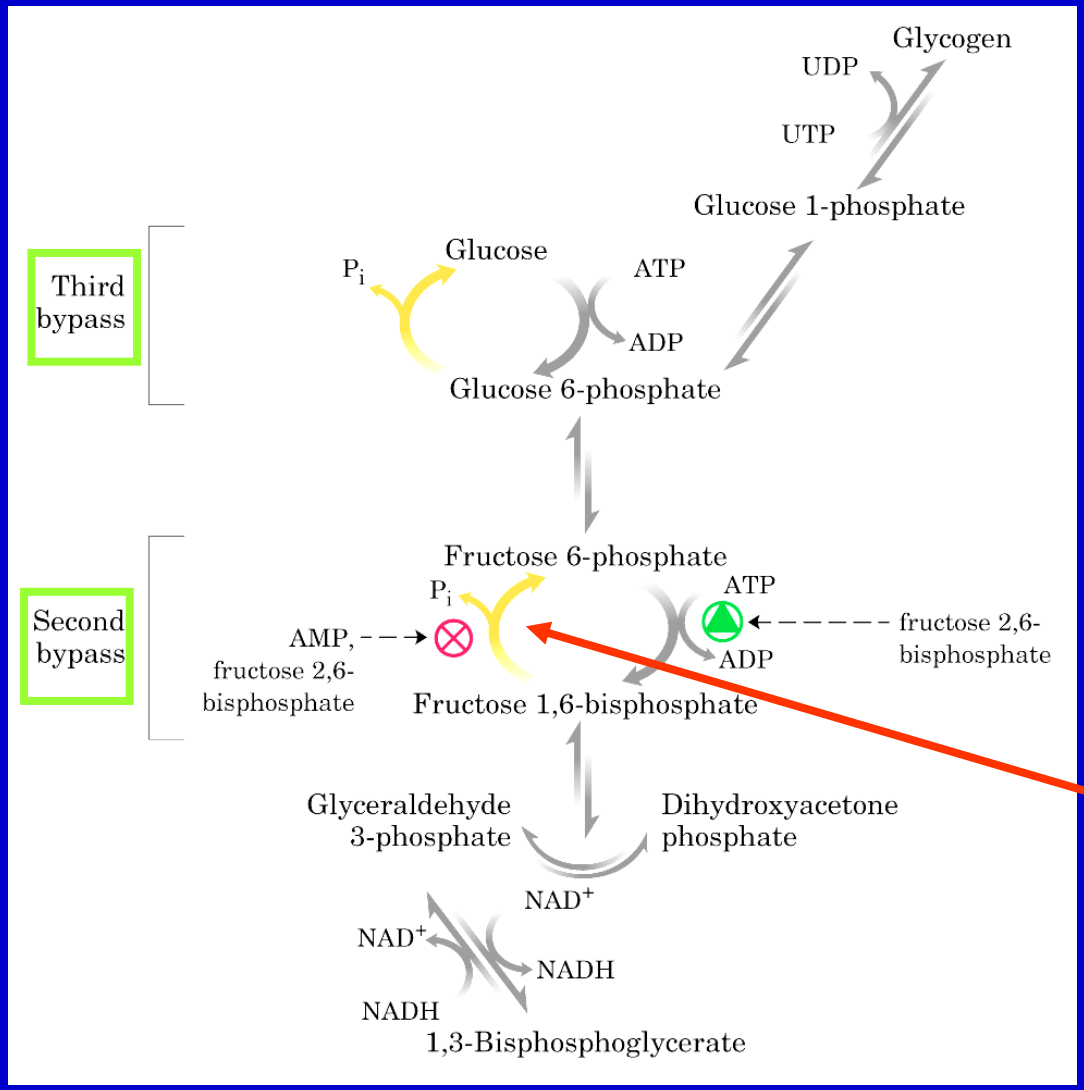
Addition of CO_2 to pyruvate to form oxaloacetate



- Hydrolysis of ATP

Decarboxylation and phosphorylation to PEP





2nd & 3rd bypass steps are near the end of gluconeogenesis ("top" of glycolysis)

Regulation of FBP-1 by AMP and F2,6P

Dephosphorylation of G6P, 3rd bypass reaction

Glucose 6-phosphatase removes the phosphate to liberate free glucose

$$\text{glucose-6-P} + H_2O \xrightarrow{\text{G6Pase}} \text{glucose} + P_i$$

- This is primarily a function of the liver to buffer blood glucose levels
- G6Pase is NOT present in brain and muscle! (Gluconeogenesis does not occur in these tissues)

Subcellular Locations of Gluconeogenic Enzymes

- Gluconeogenesis enzymes are cytosolic except:

(1) ***Glucose 6-phosphatase*** (endoplasmic reticulum)

(2) ***Pyruvate carboxylase*** (mitochondria)

(3) ***Phosphoenolpyruvate carboxykinase*** (cytosol and/or mitochondria)

Gluconeogenesis is energetically expensive to cells (hepatocytes)

table 20–2

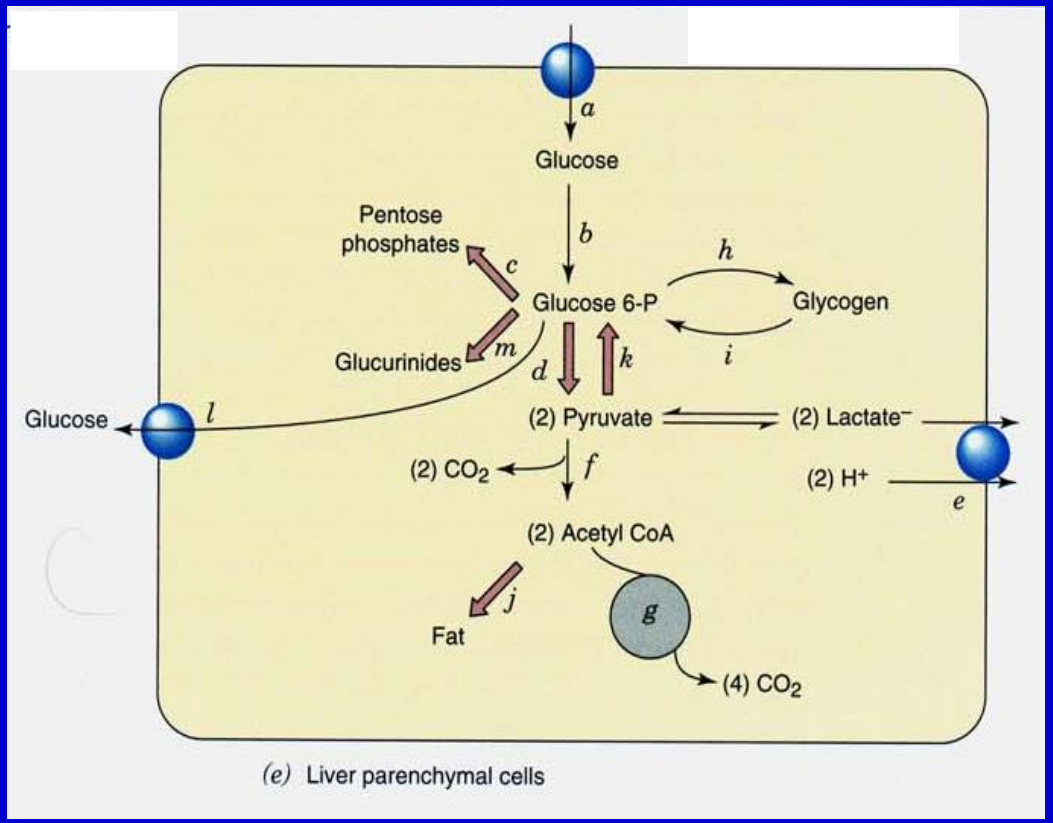
Sequential Reactions in Gluconeogenesis Starting from Pyruvate*

Pyruvate + HCO_3^- + ATP ⟶ oxaloacetate + ADP + P_i + H^+	×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 + H^+	×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 + H_2O ⟶ 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 + $4H_2O$ ⟶ glucose + 4ADP + 2GDP + $6P_i$ + $2NAD^+$ + $2H^+$

cost

Liver is the major source of blood glucose from GN



(e) Liver parenchymal cells

Is the primary gluconeogenic organ

Produces glucose for export to brain, muscle, RBC's

Uses many small metabolites and fatty acids to feed GN

Liver function is highly sensitive to insulin & glucagon

Regulation of Gluconeogenesis

Gluconeogenesis and glycolysis are altemately **regulated** - within a cell one pathway is relatively inactive while the other is highly active.

The **amounts and activities of** the distinctive **enzymes** of each pathway **are controlled**.

The rate of glycolysis is determined by the **concentration of glucose.**

The rate of gluconeogenesis is determined by the **concentrations of precursors of glucose**.

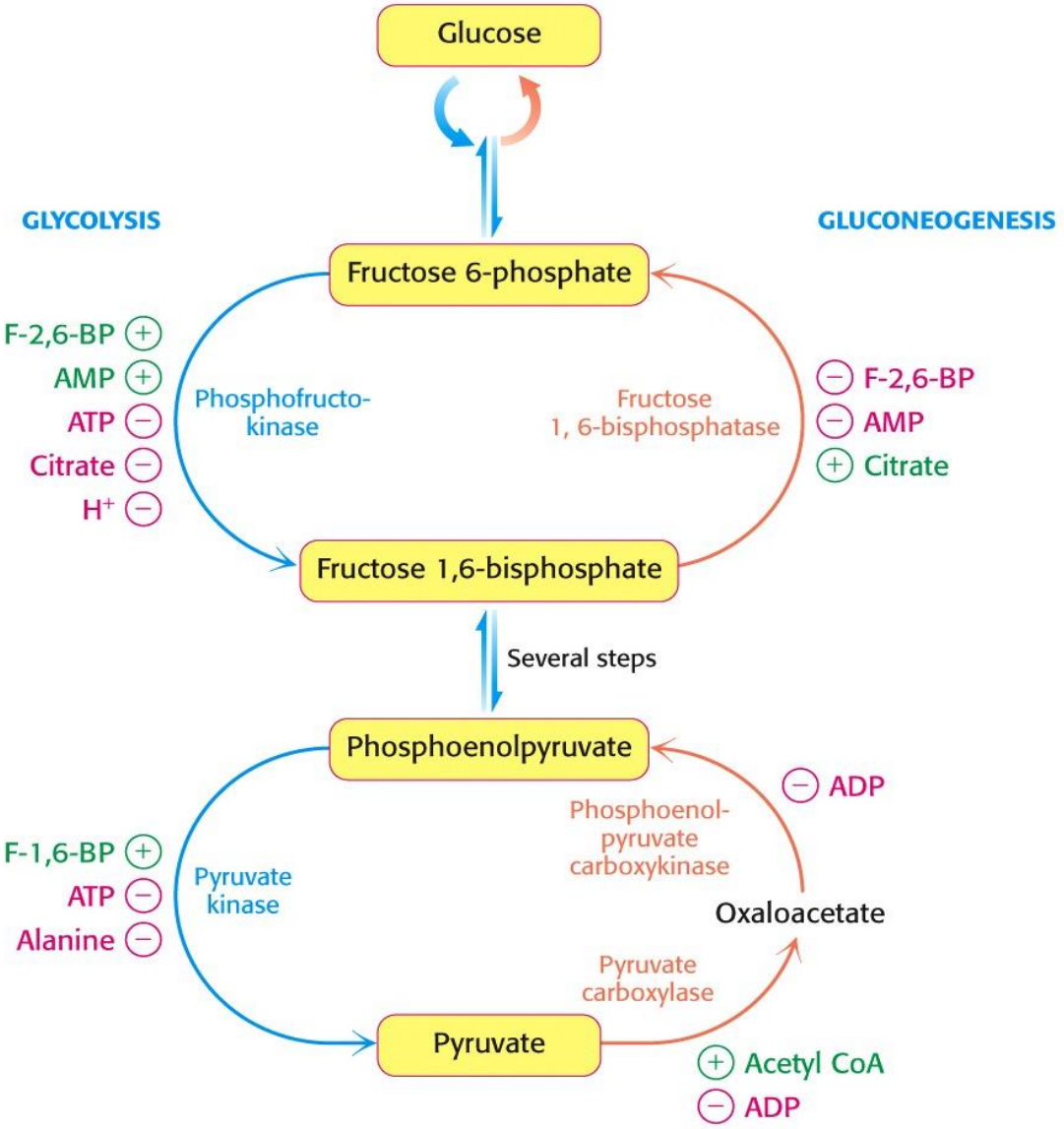
AMP stimulates ***phospho-fructokinase***, whereas **ATP** and **citrate** inhibit it. ***Fructose 1,6-bisphosphatase*** is inhibited by ***AMP*** and activated by **citrate**.

Fructose 1,6-bisphosphate strongly stimulates ***phospho-fructokinase 1*** and inhibits ***fructose 1,6-bisphosphatase***.

During starvation, gluconeo-genesis predominates because the level of **F-1,6-BP** is very low.

High levels of **ATP** and **alanine**, which signal that the energy charge is high and that building blocks are abundant, inhibit the ***pyruvate kinase***.

Pyruvate carboxylase is activated by **acetyl CoA** and inhibited by **ADP**.



phosphoenol-pyruvate carboxykinase

Gluconeogenesis is favored when the cell is rich in biosynthetic precursors and ATP.

Regulation of the Enzymes Amount by Hormones

Hormones affect gene expression primarily by changing the rate of transcription.

Insulin, which rises subsequent to eating, **stimulates** the expression of ***phosphofructokinase*** and ***pyruvate kinase***.

Glucagon, which rises during starvation, **inhibits** the expression of these enzymes and stimulates the production of ***phosphoenolpyruvate carboxykinase*** and ***fructose 1,6-bisphosphatase.***

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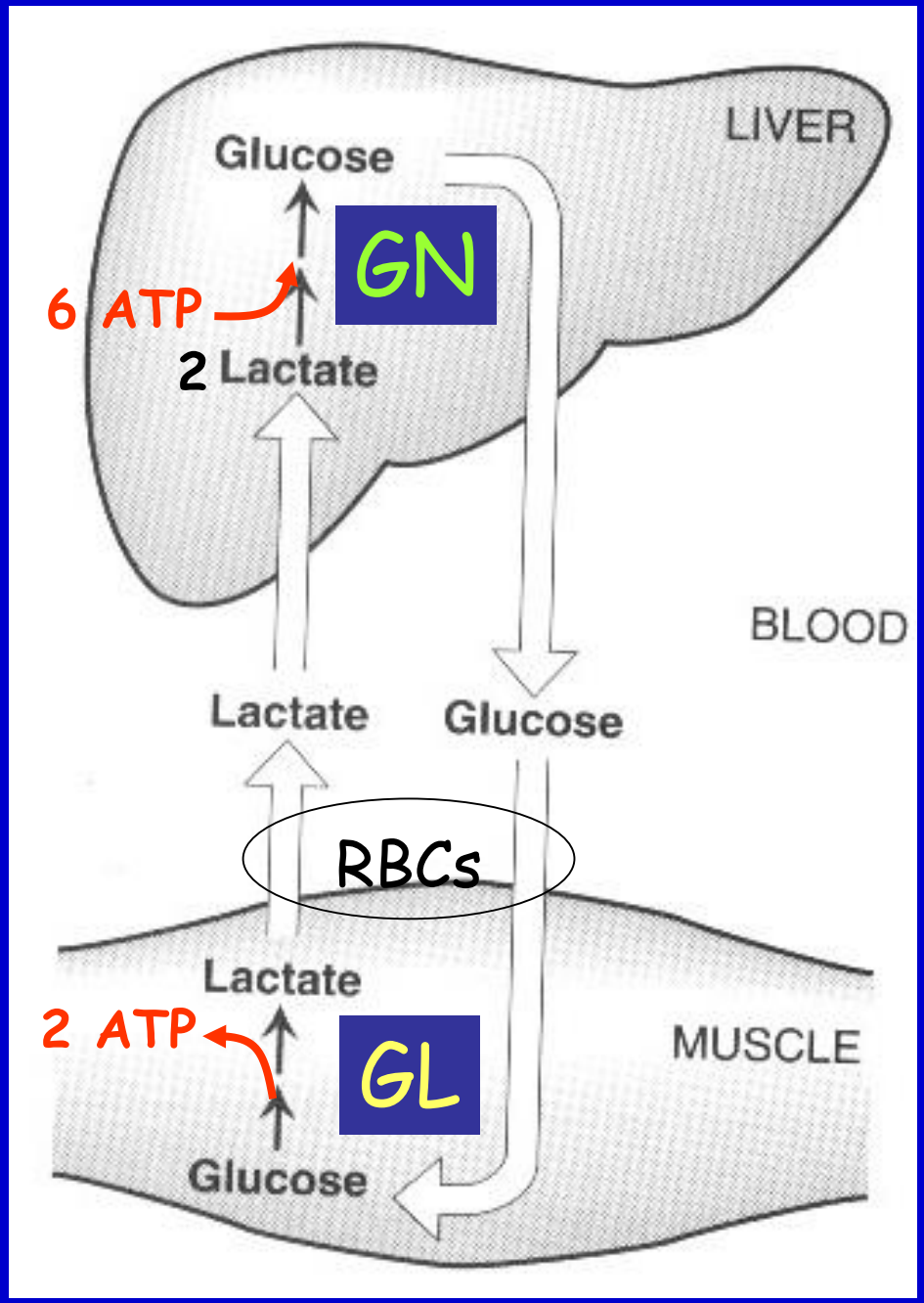


The Cori Cycle

Lactate and glucose shuttle between active muscle/RBC and liver (glucagon/insulin reg.)

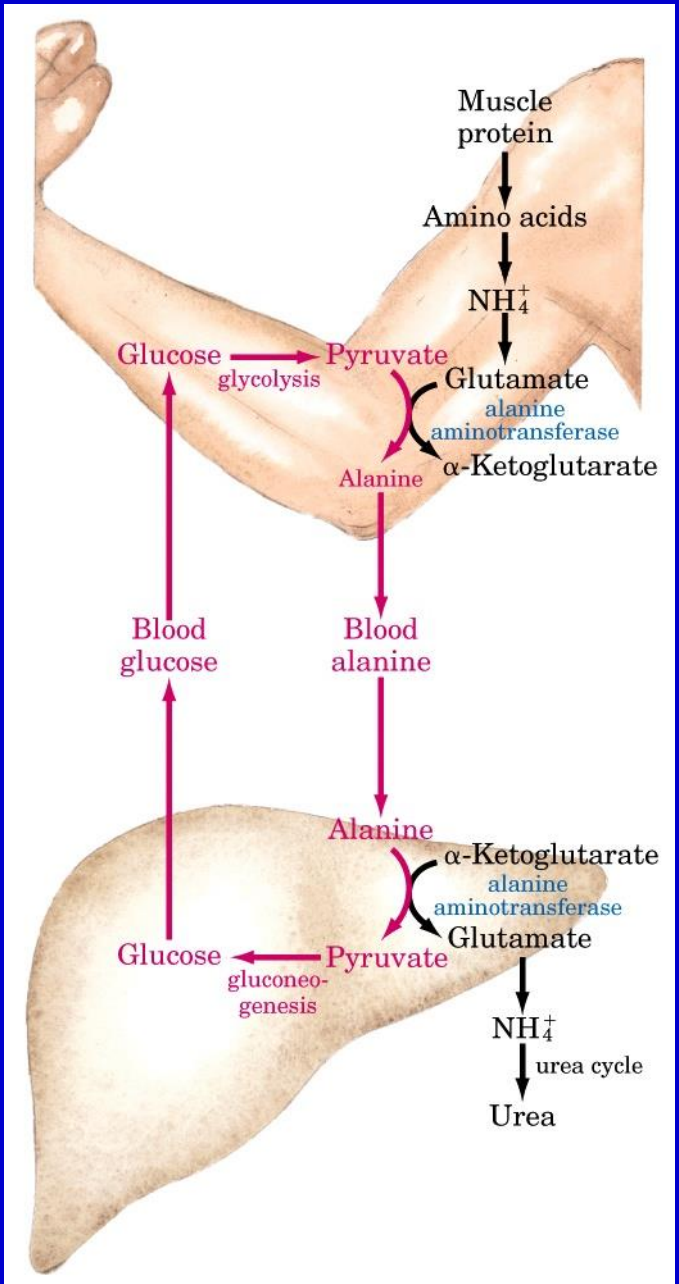
Liver gluconeogenesis buffers the blood glucose for use by muscle, RBC's and brain (120 g/day)

*Note: the brain fully oxidizes glucose, so it does not funnel back lactate

Coris Cycle or Lactic Acid Cycle

In an actively contracting muscle, only about 8% of the pyruvate is utilized by the citric acid cycle and the remaining is, therefore, reduced to lactate. The lactic acid thus generated should not be allowed to accumulate in the muscle tissues. The muscle cramps, often associated with strenuous muscular exercise are thought to be due to lactate accumulation. This lactate diffuses into the blood.

During exercise, blood lactate level increases considerably. Lactate then reaches liver where it is oxidized to pyruvate. It is then taken up through gluconeogenesis pathway and becomes glucose, which can enter into blood and then taken to muscle. This cycle is called cori's cycle, by which the lactate is efficiently utilized by the body.



The Alanine Cycle

The liver can also use the amino acid Alanine similarly to Lactate

Following transamination to pyruvate, gluconeogenesis allows the liver to convert it to glucose for secretion into the blood