

# Gluconeogenesis : An overview

-The biosynthesis of new glucose

-Substrates for gluconeogenesis include lactate, pyruvate, glycerol and glucogenic amino acids

-Under normal circumstances, the liver is responsible for 85%-95% of the glucose that is made

\*\* during starvation or metabolic acidosis, the kidney is capable of making glucose and may contribute up to 50% of the glucose formed

\*\* the only other tissue capable of gluconeogenesis is the epithelial cell of the small intestine, which contributes  $\leq 5\%$  of total glucose formation

- Energetics: the conversion of 2 moles of pyruvate to 1 mole of glucose requires 4 moles of ATP, 2 moles of GTP and 2 moles of NADH

- Functions:

1. During starvation, liver glycogen levels fall , gluconeogenesis is important in maintaining adequate blood sugar concentrations
2. During extended exercise, when carbohydrate and lipid reserves are mobilized, gluconeogenesis allows the use of lactate from glycolysis and glycerol from fat breakdown
3. During metabolic acidosis, gluconeogenesis in the kidney allows the excretion of an increased number of protons ??
4. Gluconeogenesis allows the use of dietary protein in carbohydrate pathways

# SUBSTRATES FOR GLUCONEOGENESIS

## A. Lactate:

1. **interconversion of lactate and pyruvate** is catalyzed by lactate dehydrogenase (LDH), an oxidized  $\text{NAD}^+$ -dependent enzyme



**a.** In gluconeogenic tissues (liver), LDH usually runs this reaction in the direction of pyruvate formation

**b.** In muscle cells and erythrocytes, LDH usually runs this reaction in the direction of lactate formation

**c.** The direction in which the reaction proceeds depends on

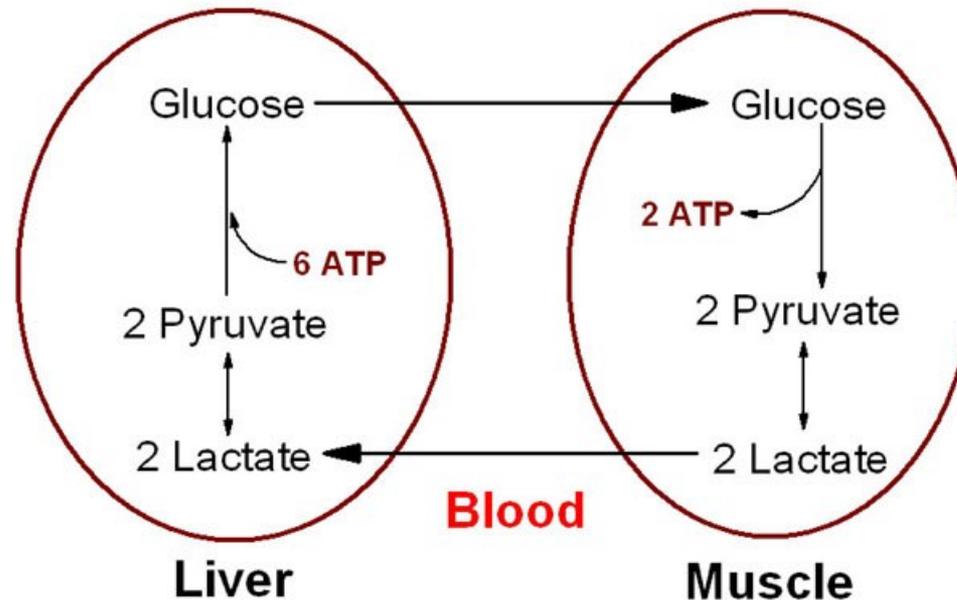
**i )** The ratios of  $\text{NAD}^+$  to  $\text{NADH}$  and lactate to pyruvate

**ii)** The isozyme of LDH that is present

## 2. Cori cycle

- Pyruvate formed from glucose by glycolysis in the muscle cells and erythrocytes is converted to lactate by LDH
- Lactate is released into the blood, taken up by the liver, and converted to pyruvate by LDH
- Pyruvate is converted to glucose via gluconeogenesis in the liver and is released into the blood where it can be used as an energy source for muscle as well as other tissues

The Cori Cycle



## B. ALANINE

1. Pyruvate formed from glycolysis in the muscle converted to alanine by a transamination reaction
2. Alanine also may be formed in muscle during degradation of protein, which occurs during starvation
3. Alanine is released by the muscle into the blood, taken up by the liver, and converted back to pyruvate by the reverse of the transamination reaction that occurred in the muscle
4. Pyruvate is then used to produce glucose via gluconeogenesis

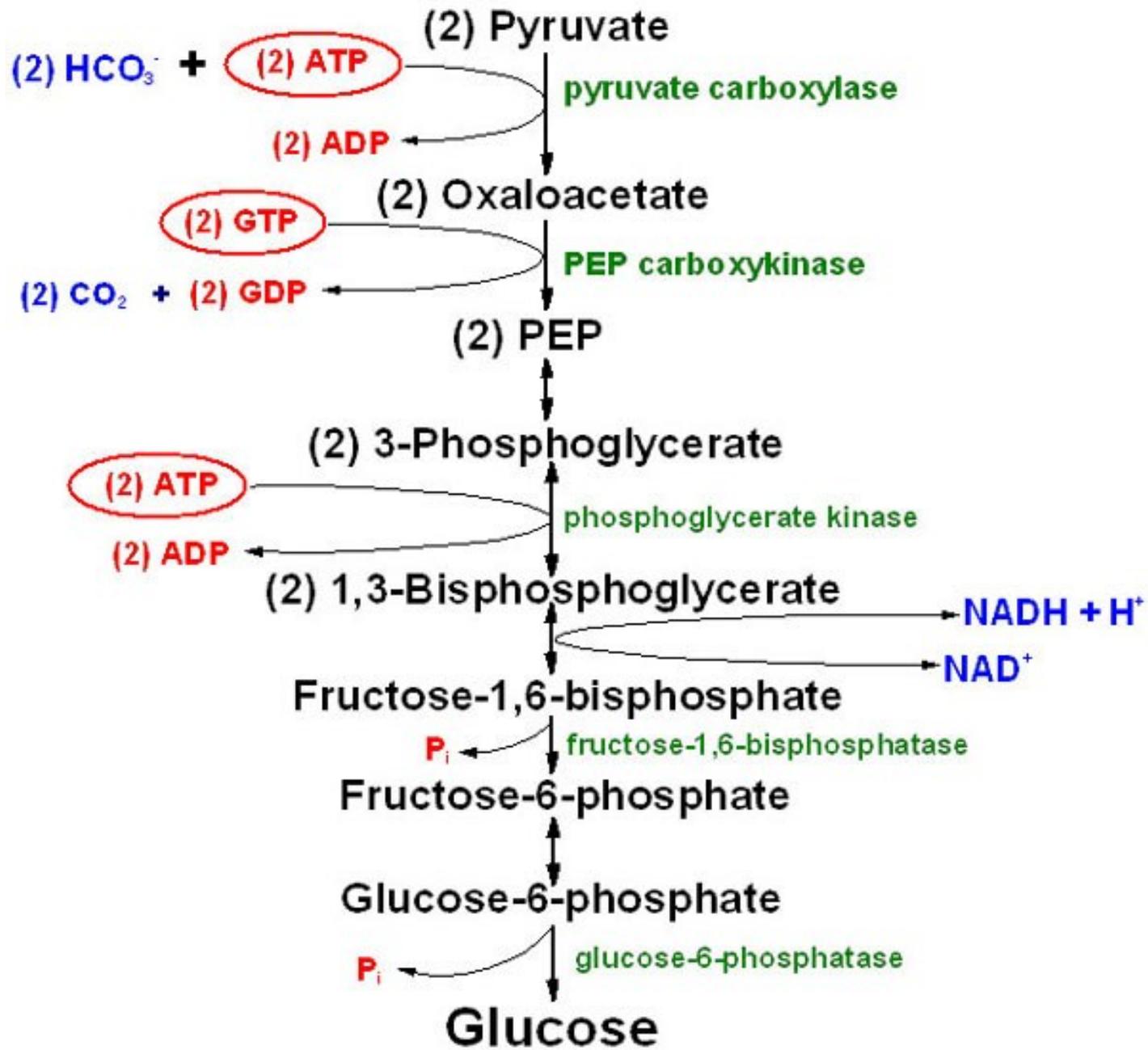
## C. GLYCEROL

1. Glycerol is formed in adipose tissue by lipolysis of triacylglycerols
2. Glycerol is released into the blood and taken up by the liver where it is phosphorylated to 3-phosphoglycerate, which is an intermediate in gluconeogenesis

## D. AMINO ACIDS

- Glucogenic amino acids other than alanine may be converted to citric acid cycle intermediates that are metabolized to oxaloacetate, an intermediate in gluconeogenesis

# Reactions of gluconeogenesis:



## A. PYRUVATE TO OXALOACETATE

1. ATP hydrolysis provides energy for the carboxylation of pyruvate
2. Reaction is catalyzed by carboxypeptidase, the prosthetic group is biotin, magnesium and manganese also required for activity, acetyl CoA is required as an activator and regulates activity in a concentration-dependent manner
3. Occurs in mitochondrial matrix

## B. INTERCONVERSION OF OAA TO MALATE

OAA cannot permeate the mitochondrial membrane well, and must be transported across the membrane in the form of malate

## C. OAA TO PHOSPHOENOLPYRUVATE (PEP)

- Reaction occurs in cytosol
- Hydrolysis of GTP provides the energy for the carboxylation of OAA

## D. PEP to fructose-1,6-bisphosphate (F1,6BP)

- This conversion occurs by six sequential reactions that are simply the reverse of those that occur in glycolysis and are catalyzed by the same enzymes

## E. F1, 6BP to F6P and Pi

- This reaction is the reverse of the reaction catalyzed by phosphofructokinase during glycolysis
- Activator of the kinase is citrate

F. F6P TO G6P

-Reverse reaction in glycolysis

G. G6P TO GLUCOSE AND Pi

- Reverse reaction of glucokinase and hexokinase during glycolysis, however in gluconeogenesis, this reaction is catalyzed by G6Pase which is present only in gluconeogenic tissues

# CONTROL:

## 1. Non-hormonal regulation

- Substrate concentration: pyruvate, lactate and alanine levels are important in determining flux thru gluconeogenic pathway
- Allosteric regulation: acetyl CoA is a concentration-dependent regulator of the activity of pyruvate carboxylase, the first enzyme in the pathway

## 2. Hormonal regulation

- Glucagon, epinephrine and glucorticoids can stimulate the synthesis of enzymes of the gluconeogenic pathway which are used to bypass the irreversible steps of glycolysis
- insulin suppresses the synthesis of these enzymes and is pro glycolysis i.e support syn. Of e.g. hexokinase, PFK etc