# Gluconeogenesis

A human being needs about 160 ± 20 grams per day of glucose for his metabolism. 75% of that is used for the brain. Inside the body there are about 20 gr of glucose circulating in the blood stream and 180/200 gr stored in glycogen.
That means that when the daily intake of glucose is not sufficient, the body must produce it.

**Gluconeogenesis** is a metabolic pathway that results in the generation of glucose from non-carbohydrate carbon substrates.

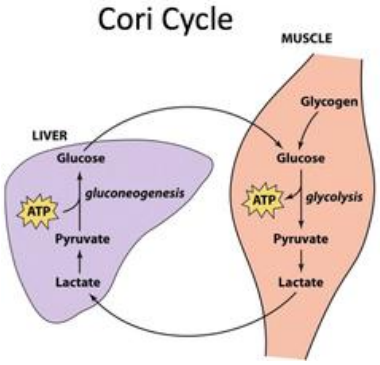
Gluconeogenesis is one of the two main mechanisms used by humans and many other animals to maintain regular blood glucose levels, avoiding low blood glucose level (hypoglycemia) [The other mechanism operates through the degradation of glycogen (glycogenolysis)].
Gluconeogenesis is a ubiquitous process, present in plants, animals, fungi, bacteria, and other microorganisms. In vertebrates, gluconeogenesis takes place mainly in the liver and, to a lesser extent, in the cortex of the kidneys.
In most animals, the process occurs during periods of fasting, starvation, low-carbohydrate diets, or intense exercise.
The process in itself is highly endergonic, but it is coupled to the hydrolysis of ATP or GTP, effectively making the global process exergonic.

In humans the main gluconeogenic precursors are:

- Lactate (transported back to the liver where it is converted into pyruvate by the Cori cycle [#]),
- Glycerol (from triacylglycerols),
- Alanine and glutamine.

Altogether, they account for over 90% of the overall gluconeogenesis.
Other glucogenic amino acids enter their carbon skeleton into the cycle by transamination or deamination, directly (as pyruvate or oxaloacetate), or indirectly via the citric acid cycle.
All TCA cycle intermediates as well, through conversion to oxaloacetate, can also function as substrates for gluconeogenesis.
Odd-chain fatty acids can be converted into glucose too. While there are no evidences of conversion for even-chain fatty acids.

In any case Pyruvate is the start substrate of the gluconeogenic pathway.



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## Location

In mammals, gluconeogenesis is restricted to the liver and the kidneys.
In all species, the formation of oxaloacetate from pyruvate and TCA cycle intermediates is restricted to the mitochondrion, while the enzymes that convert Phosphoenolpyruvate (PEP) to glucose are found in the cytosol.

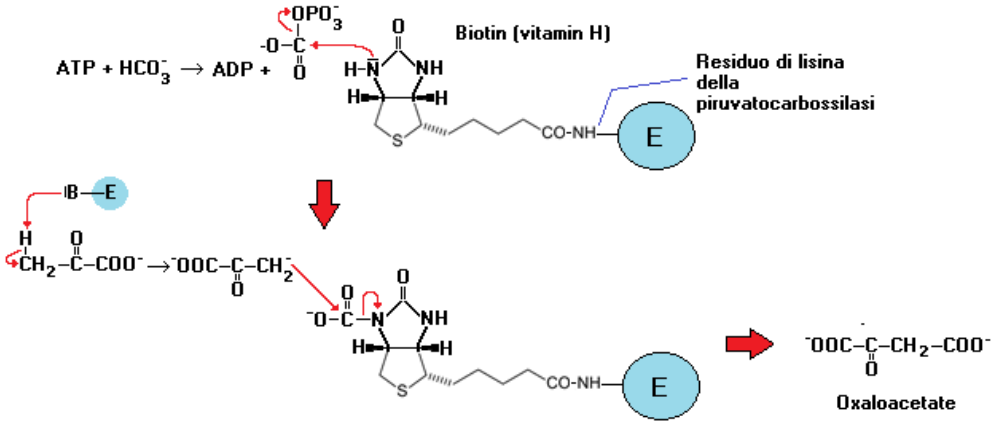
There are dedicated transport proteins accomplishing transport of PEP across the mitochondrial membrane, but no such proteins exist for oxaloacetate. Therefore oxaloacetate cannot exit mitochondria, it must be converted into malate, exported from the mitochondrion, and converted back into oxaloacetate in order to allow gluconeogenesis to continue.

## Pathway

Gluconeogenesis is a pathway consisting of a series of eleven enzyme-catalyzed reactions. Many of the reactions are the reversible steps found in glycolysis.
But the three highly regulated and strongly endergonic reactions (steps 1,3 and 10) are replaced with more kinetically favorable reactions.
Hexokinase/glucokinase, phosphofructokinase, and pyruvate kinase enzymes of glycolysis are replaced with glucose-6-phosphatase, fructose-1,6-bisphosphatase, and PEP carboxykinase. This system of reciprocal control allow glycolysis and gluconeogenesis to inhibit each other and prevent the formation of a futile cycle

## From Piruvate to PEP

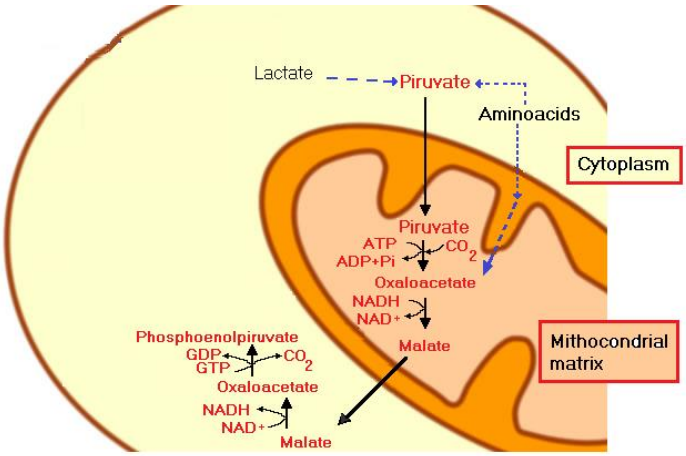
Gluconeogenesis begins in the mitochondria with the formation of oxaloacetate by the carboxylation of pyruvate. This reaction requires one molecule of ATP, and is catalyzed by pyruvate carboxylase.
This enzyme is stimulated by high levels of acetyl-CoA (produced in β-oxidation in the liver) and inhibited by high levels of ADP and glucose.
The carboxyl group comes from $HCO_3^-$ ions and the reaction needs biotin (vitamin H) as cofactor.
The hydrogencarbonate binds to the N atom of biotin ring and after that it is attacked by the negative beta carbon of pyruvate (Perkin condensation).




Oxaloacetate is then reduced to malate using NADH, a step required for its transportation out of the mitochondria.

Malate is oxidized back to oxaloacetate using $NAD^+$ in the cytosol, where the remaining steps of gluconeogenesis take place. The oxidation of malate to OAA in the cytosol generates NADH needed for gluconeogeneis. We could also say that this process is a way of transferring reducing equivalents from the mitochondrion to the cytosol.

In the end Oxaloacetate is decarboxylated and then phosphorylated to form phosphoenolpyruvate using the enzyme PEPCK (PEP carboxykinase). A molecule of GTP is hydrolyzed to GDP during this reaction.




## From PEP to fructose-6-phosphate

The next steps in the reaction are the same as reversed glycolysis until fructose 1,6-bisphosphatase converts fructose 1,6-bisphosphate to fructose 6-phosphate.
Fructose 1,6-bisphosphatase catalyses the reverse of the reaction which is catalysed by phosphofructokinase in glycolysis. These two enzymes only catalyse the reaction in one direction each, and are regulated by metabolites such as fructose 2,6-bisphosphate so that high activity of one of the two enzymes is accompanied by low activity of the other.
More specifically, fructose 2,6-bisphosphate allosterically inhibits fructose 1,6-bisphosphatase, but activates phosphofructokinase-I.
This is the rate-limiting step both of gluconeogenesis and glycolysis.

## From fructose 6-phosphate to glucose

Glucose-6-phosphate is formed from fructose 6-phosphate by phosphoglucoisomerase (the reverse of step 2 in glycolysis).
Glucose-6-phosphate can be used in other metabolic pathways or dephosphorylated to free glucose. Whereas free glucose can easily diffuse in and out of the cell, the phosphorylated form (glucose-6-phosphate) is locked in the cell, a mechanism by which intracellular glucose levels are controlled by cells.
The final reaction of gluconeogenesis, the formation of glucose, occurs when glucose-6-phosphate is hydrolyzed by glucose-6-phosphatase to produce glucose and release an inorganic phosphate.
Like two steps prior, this step is not a simple reversal of glycolysis, in which hexokinase catalyzes the conversion of glucose and ATP into G6P and ADP. Glucose is shuttled into the cytoplasm by glucose transporters located in the endoplasmic reticulum's membrane.

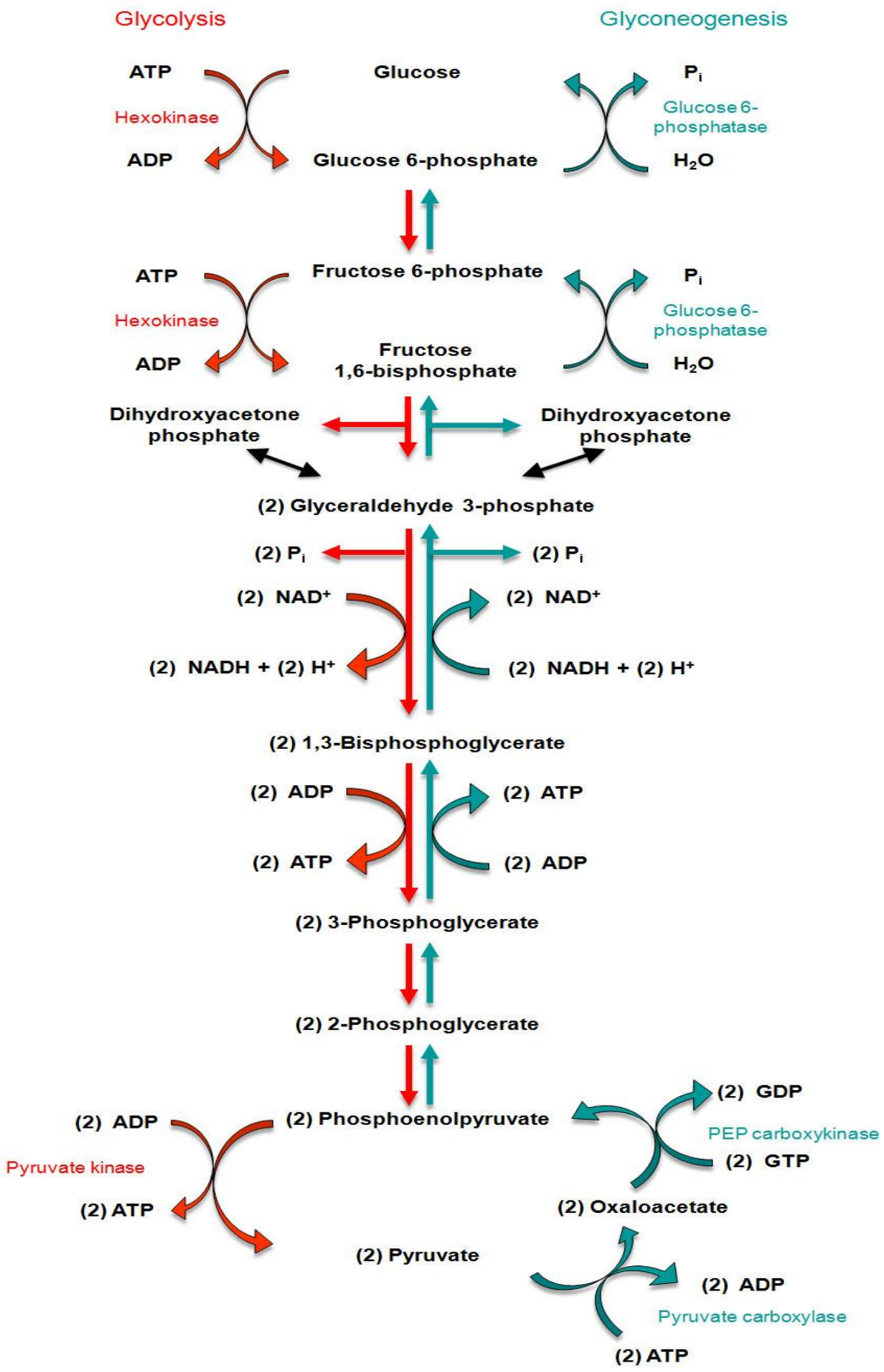
## Regulation

Most factors that regulate the activity of the gluconeogenesis pathway do so by inhibiting the activity or expression of key enzymes.

Global control of gluconeogenesis is mediated by glucagon (*released when blood glucose is low*); it triggers phosphorylation of enzymes and regulatory proteins by Protein Kinase A (a cyclic AMP regulated kinase) resulting in inhibition of glycolysis and stimulation of gluconeogenesis.

The rate of gluconeogenesis is ultimately controlled by the action of a key enzyme, fructose-1,6-bisphosphatase, which is also regulated through its phosphorylation.

Both acetyl CoA and citrate activate gluconeogenesis enzymes (pyruvate carboxylase and fructose-1,6-bisphosphatase, respectively). Due to the reciprocal control of the cycle, acetyl-CoA and citrate also have inhibitory roles in the activity of pyruvate kinase.


Glycolysis
Glyconeogenesis
ATP
Glucose
Hexokinase
ADP
Glucose 6-phosphate
$P_i$
Glucose 6-phosphatase
$H_2O$
Fructose 6-phosphate
ATP
Hexokinase
ADP
Fructose 1,6-bisphosphate
$P_i$
Glucose 6-phosphatase
$H_2O$
Dihydroxyacetone phosphate
Dihydroxyacetone phosphate
(2) Glyceraldehyde 3-phosphate
(2) $P_i$
(2) $P_i$
(2) $NAD^+$
(2) $NAD^+$
(2) NADH + (2) $H^+$
(2) NADH + (2) $H^+$
(2) 1,3-Bisphosphoglycerate
(2) ADP
(2) ATP
(2) ATP
(2) ADP
(2) 3-Phosphoglycerate
(2) 2-Phosphoglycerate
(2) Phosphoenolpyruvate
(2) ADP
Pyruvate kinase
(2) ATP
(2) GDP
PEP carboxykinase
(2) GTP
(2) Oxaloacetate
(2) Pyruvate
(2) ADP
Pyruvate carboxylase
(2) ATP