Steps and Pathway of Gluconeogenesis

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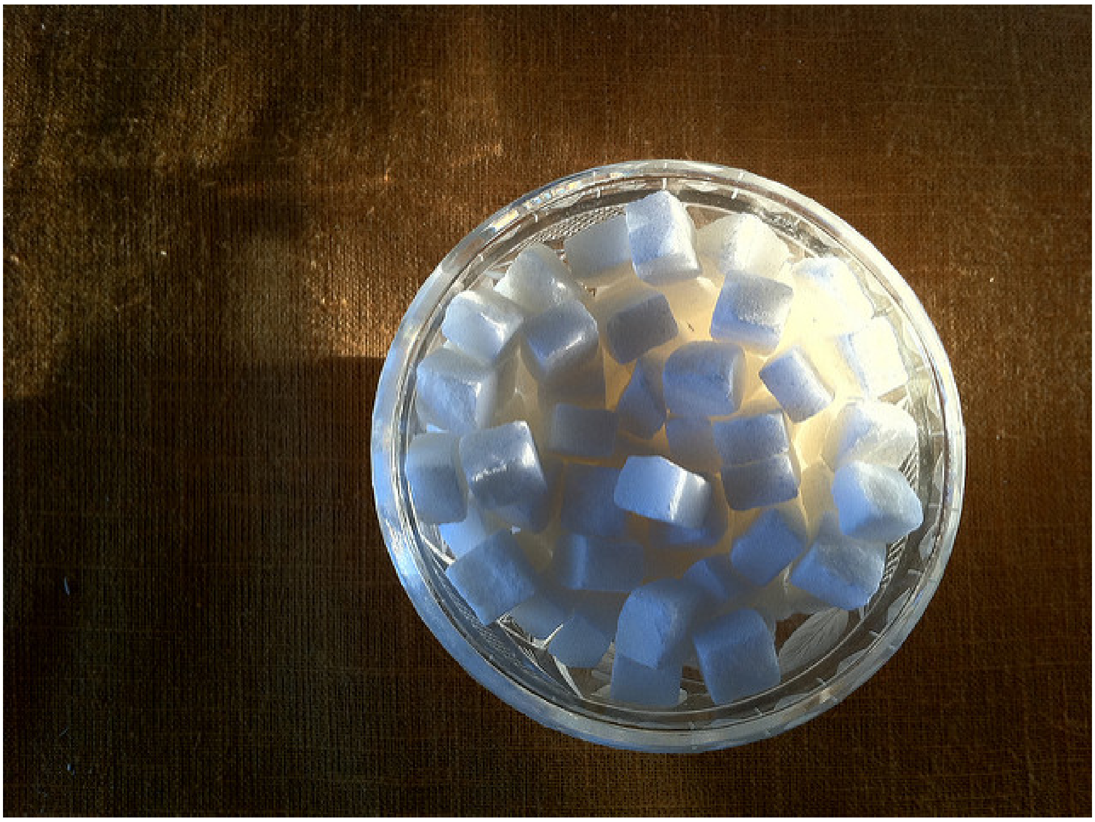
Gluconeogenesis is the process by which the body produces glucose from broken-down components of sugar. This metabolic pathway is more than just a reversal of glycolysis and is essential to human life. The following article provides a comprehensive overview of gluconeogenesis and highlights parts of this process that are essential in examinations.



Function of Gluconeogenesis

Gluconeogenesis provides the body with glucose when this cannot be obtained from food, such as during a fasting period. Some organs and cells, for instance, cannot gain energy from fat. Particularly, the red blood cells, renal medulla, and nervous system depend on glucose as their sole energy source.

Location and Substrates of Gluconeogenesis

The enzymes necessary for gluconeogenesis are located in the human liver, kidneys, and intestinal mucosa. Here, the production of glucose from **lactate** (derived from muscle and erythrocytes), **glycogenic amino acids** (mainly from the muscles), and **glycerol** (especially from fat) is carried out. Lactate and glycogenic amino acids are converted into

pyruvate and introduced to the pathway of gluconeogenesis.

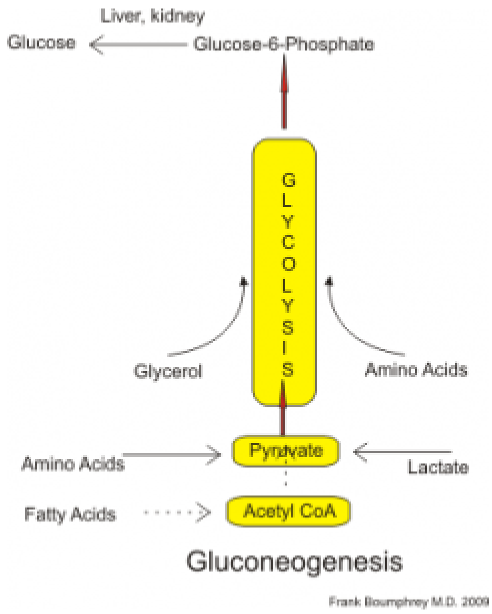


Image: 'Gluconeogenesis summary' by Boumphreyfr.
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As gluconeogenesis is aimed at reversing glycolysis, the reversible steps of the glycolysis pathway simply run in the other direction. However, there are **3 irreversible steps** that cannot run in the other direction for energy-related reasons. These steps must be circumvented using 3 key reactions that make them more energy efficient.

The Steps of Gluconeogenesis

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Step 1: Conversion of pyruvate to phosphoenolpyruvate

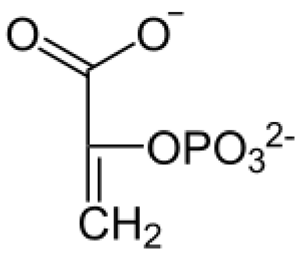

Image: 'Structure of Phosphoenolpyruvate in Fischer projection' by NEUROtiker.
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Pyruvate is carboxylated by **pyruvate carboxylase** to **oxaloacetate** using 1 CO2 and 1 ATP. **Oxaloacetate** is decarboxylated and phosphorylated by **phosphoenolpyruvate carboxykinase** (PEPCK) to **phosphoenolpyruvate** using 1 GTP and by releasing CO2. Here, decarboxylation drives the reaction; the phosphorylation generates a high-energy bond in the **phosphoenolpyruvate**. This energy comes from the GTP used.

Step 2 – 6: Conversion of phosphoenolpyruvate to fructose-1,6-biphosphate

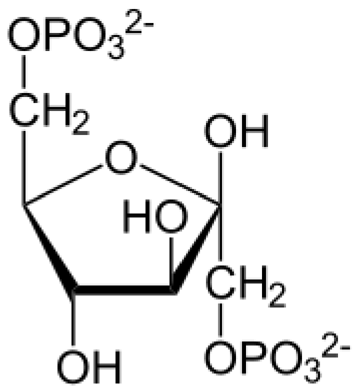


Image: ‘ Structure of beta-D-fructose-1,6-bisphosphate’ by NEUROtiker. License: Public Domain

Steps 2–6 are summarized because they correspond precisely to the process of glycolysis—just in the opposite direction. Via the intermediate products 2-phosphoglycerate, 3-phosphoglycerate, 1,3-bisphosphate, and glyceraldehyde-3-phosphate, **fructose-1,6-biphosphate** is formed. In this process, 1 ATP and 1 NADH + H+ are consumed. The individual reaction steps can be found here. Glycolysis and gluconeogenesis both involve the same enzymes, only the direction of the reaction is different.

Step 7: Dephosphorylation of fructose-1,6-bisphosphate to fructose-6-phosphate

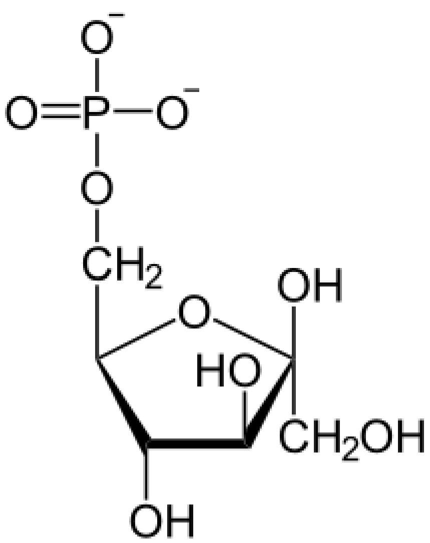


Image: “Structure vof beta-D-fructose-6-phosphate” by NEUROtiker. License: Public Domain

The 2nd key enzyme has to dephosphorylate **fructose-1,6-biphosphate**. In gluconeogenesis, the enzyme **fructose-1,6-bisphosphatase** catalyzes the dephosphorylation of the substrate to **fructose-6-phosphate**, thereby consuming 1 H2O (in glycolysis, it is **phosphofructokinase 1** that catalyzes the phosphorylation).

Step 8: Conversion of fructose-6-phosphate to glucose-6-phosphate

This step occurs without any use of energy as in glycolysis.

Step 9: Dephosphorylation of glucose-6-phosphate to glucose

In the 3rd and final key reaction, glucose-6-phosphate is dephosphorylated to **glucose,** consuming 1 H2O. This reaction is catalyzed by **glucose-6-phosphatase** and takes place in the endoplasmic reticulum.

Note: The key enzymes in gluconeogenesis are:

1. Pyruvate carboxylase and phosphoenolpyruvate carboxykinase (PEPCK)
2. Fructose-1,6-bisphosphatase
3. Glucose-6-phosphatase

These enzymes are found almost exclusively in the kidney, liver, and intestinal mucosa, which is why gluconeogenesis only takes place in these locations.

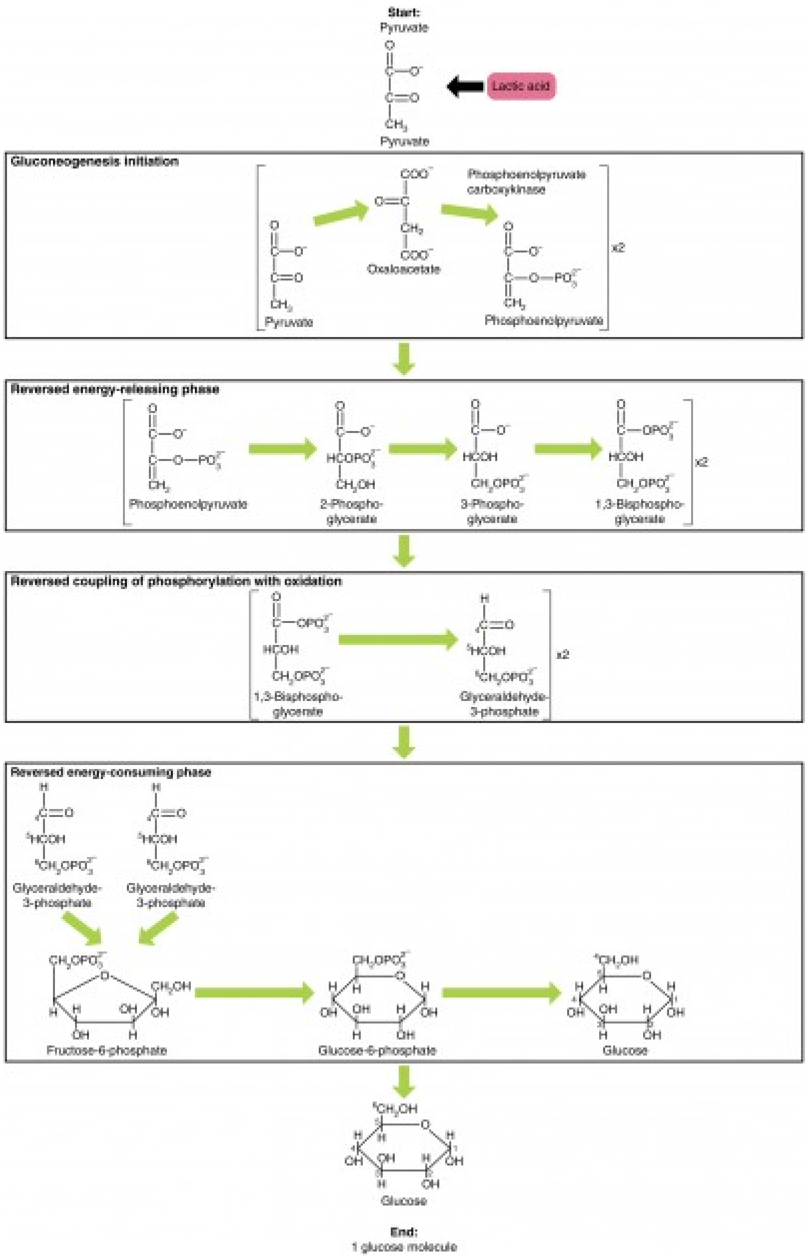


Image: 'Gluconeogenesis' by Phil Schatz. License: CC BY 4.0

Cell Compartments of Gluconeogenesis – Mitochondrial Shuttles

Other than in glycolysis, one of the enzymes of gluconeogenesis, the biotin- and ATP-dependent **pyruvate carboxylase**, is located inside the mitochondria.

Its substrate—pyruvate—is transported into the mitochondrial matrix through a carrier and is converted to **oxaloacetate**. Now, there are 2 possible paths for the oxaloacetate:

1. Oxaloacetate is converted by a **mitochondrial PEPCK** and leaves the mitochondrion as **phosphoenolpyruvate** through an electroneutral transport.
2. **Malate-aspartate shuttle**: oxaloacetate is reduced to **malate** by the mitochondrial **malate dehydrogenase**, resulting in 1 **NADH**. The **malate** then enters the cytosol using an exchanger protein and is oxidized by the cytosolic **malate dehydrogenase** to oxaloacetate. This oxidizes NADH to NAD+. Therefore,

it is also transported out of the mitochondrion and is now available for gluconeogenesis (consumed in step 5).

The 2nd path probably represents the main path since only the cytosolic PEPCK can be regulated.

Energy Balance of Gluconeogenesis

With pyruvate as a starting substrate, the synthesis of **1 molecule of glucose** consumes **4 ATP, 2 GTP, and 2 NADPH + H+**. Considering the whole process, a direct reversal of the glycolytic pathway would be more efficient. However, as mentioned above, 3 steps in glycolysis have to be bypassed since, with regard to thermodynamics, the required amount of energy would be too great.

With their circumvention, glucose synthesis becomes possible but is **always endergonic**. If this were not the case, the body could build and consume glucose in an endless cycle in order to produce energy. However, gluconeogenesis will only be used by the body when an insufficient glucose supply makes it absolutely necessary.

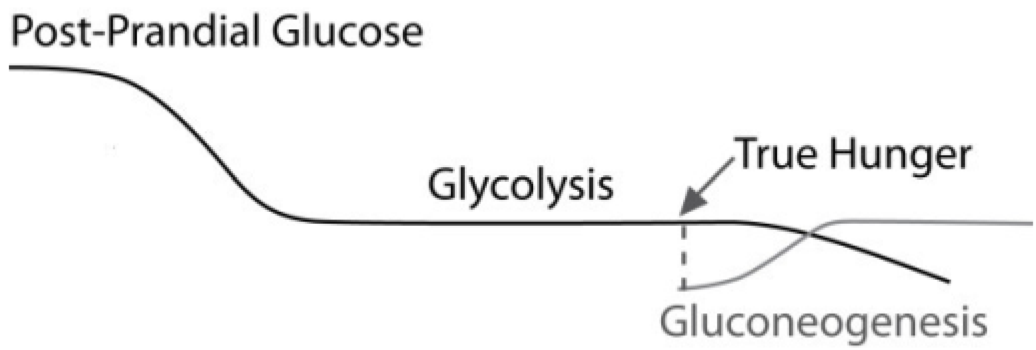


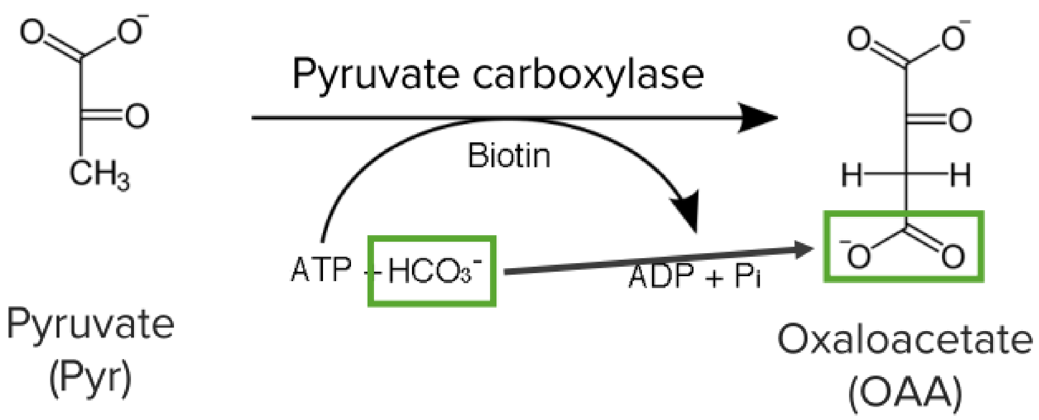
Image: “The Glucose Response Curve” by openi. License: CC BY 2.0

Reactions of Gluconeogenesis

	Gluconeogenesis enzymes		Glycolysis enzymes
	Glucose		
11	Glucose-6-phosphatase	1	Hexokinase
	G6P		
10	Phosphoglucoisomerase	2	Phosphoglucoisomerase
	F6P		
9	F1,6 Bisphosphatase	3	PFK1
	F1,6BP		
8	Aldolase	4	Aldolase
	DHAP + GA3P		
7	Triose phosphate isomerase	5	Triose phosphate isomerase
	GA3P + GA3P		
6	GA3PDH	6	GA3PDH
	1,3 BPG + 1,3 BPG		
5	Phosphoglycerate kinase	7	Phosphoglycerate kinase
	3-PG + 3-PG		
4	Phosphoglycerate mutase	8	Phosphoglycerate mutase
	2-PG + 2-PG		
3	Enolase	9	Enolase
	PEP + PEP		
2	PEPCK	10	Pyruvate kinase
	OAA + OAA		PYR + PYR
1	Pyruvate carboxylase		
	PYR + PYR		

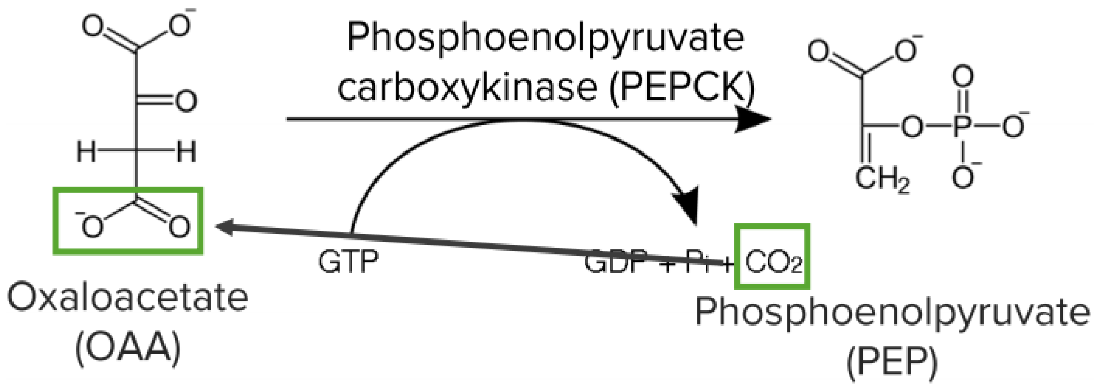
Reaction #1

- Step 1 of bypassing pyruvate kinase
- Occurs in the mitochondrion.



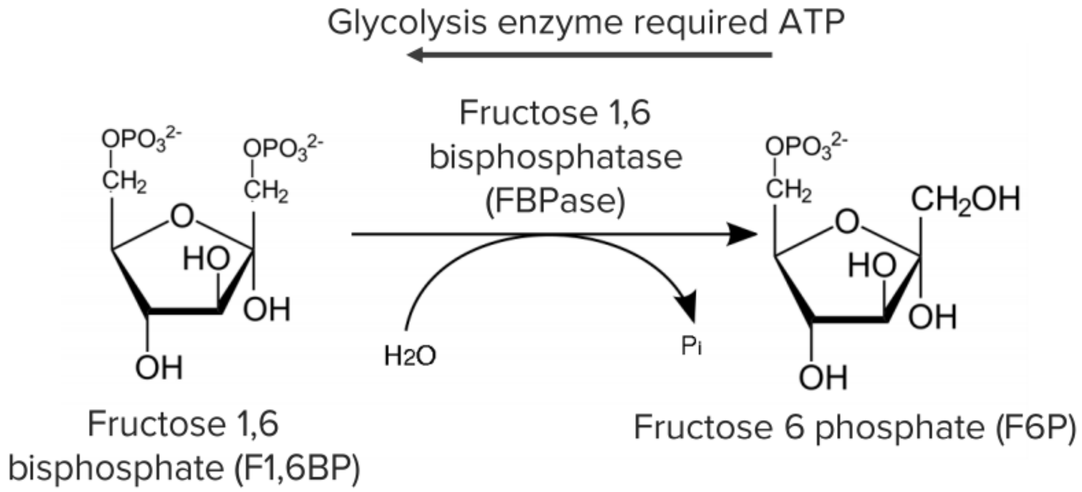
Reaction #2

- Occurs in the cytoplasm.
- Second triphosphate necessary



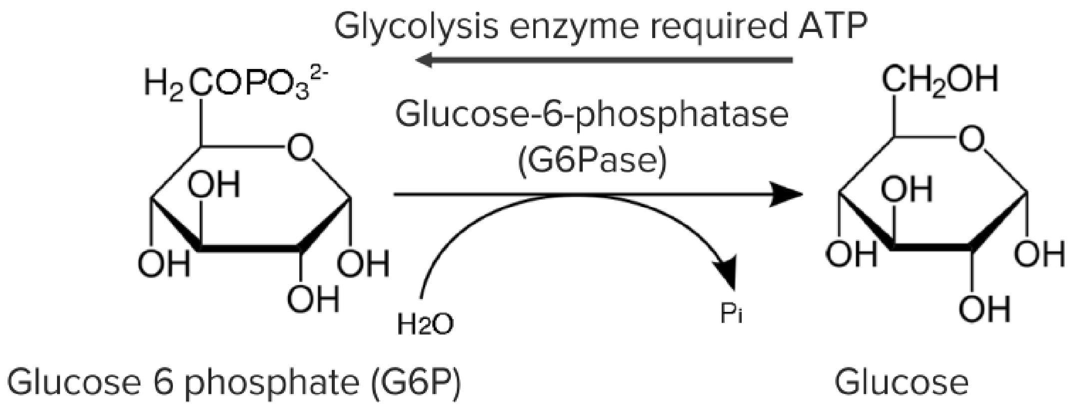
Reaction #9

- Is not the reversal of the phosphofructokinase reaction.
- Energy realized by not regenerating ATP



Reaction #11

- Is not the reversal of the hexokinase reaction.
- Energy realized by not regenerating ATP.
- Occurs in the endoplasmic reticulum.



Regulation of Gluconeogenesis

Since glycolysis and gluconeogenesis run in exactly opposite directions, it is important that they do not run simultaneously. Rate-controlling steps (effective within minutes) include:

Conversion of pyruvate to phosphoenolpyruvate

Pyruvate carboxylase catalyzes this 1st important step of gluconeogenesis. It is activated by acetyl-CoA so that more oxaloacetate is produced and available for further reaction steps.

Conversion of fructose-1,6-bisphosphate to fructose-6-phosphate

Fructose-1,6-bisphosphatase is responsible for this step. It is allosterically controlled by fructose-2,6-bisphosphate, just like its 'opponent' – phosphofructokinase. The regulatory enzyme is **phosphofructokinase 2** (not to be confused with phosphofructokinase 1 of glycolysis).

When active, it synthesizes **fructose-2,6-bisphosphate,** which has an inhibitory effect on gluconeogenesis and a promoting effect on glycolysis. This kind of contrary regulation is also called **reciprocal regulation.** Stimulator of phosphofructokinase 2 is a low cAMP level in the cell, which, for example, is provided by insulin. Citrate and ATP have a positive effect on the new synthesis of glucose.

In the long term, the expression of key enzymes can be regulated. **cAMP and glucocorticoids** stimulate this expression whereas **insulin** represses the expression.

References

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Notes