Gluconeogenesis

Regulation of Glycolysis & Gluconeogenesis

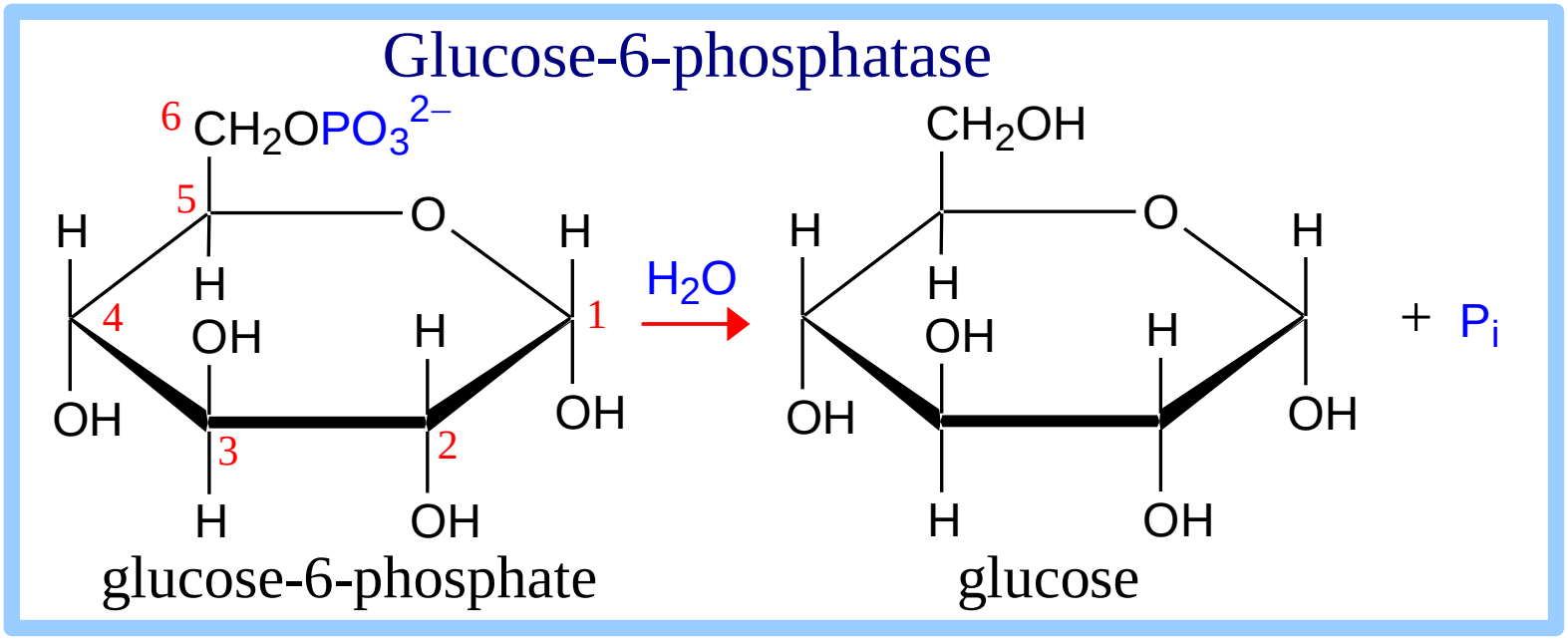
Gluconeogenesis is the process by which glucose is synthesized from non carbohydrate precursors , occurs mainly in the liver under fasting condition .

Synthesis of glucose from pyruvate utilizes many of the same enzymes as **Glycolysis**.

Three Glycolysis reactions have such a large negative ΔG that they are essentially **irreversible**.

- **Hexokinase** (or Glucokinase)
- **Phosphofructokinase**
- **Pyruvate Kinase.**

These steps must be **bypassed** in gluconeogenesis. **Two** of the bypass reactions involve simple **hydrolysis** reactions.

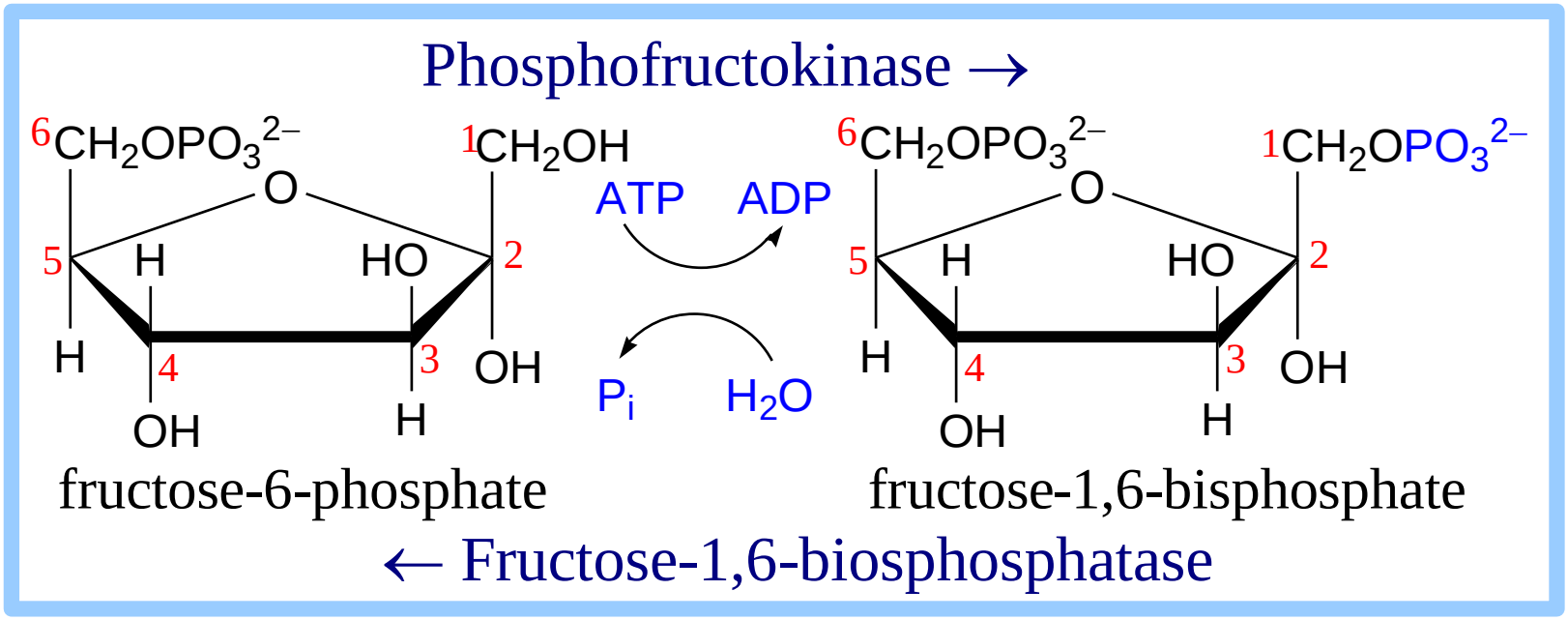


Hexokinase or Glucokinase (Glycolysis) catalyzes:

glucose + ATP → glucose-6-phosphate + ADP

Glucose-6-Phosphatase (Gluconeogenesis) catalyzes:

glucose-6-phosphate + H_2O → glucose + P_i

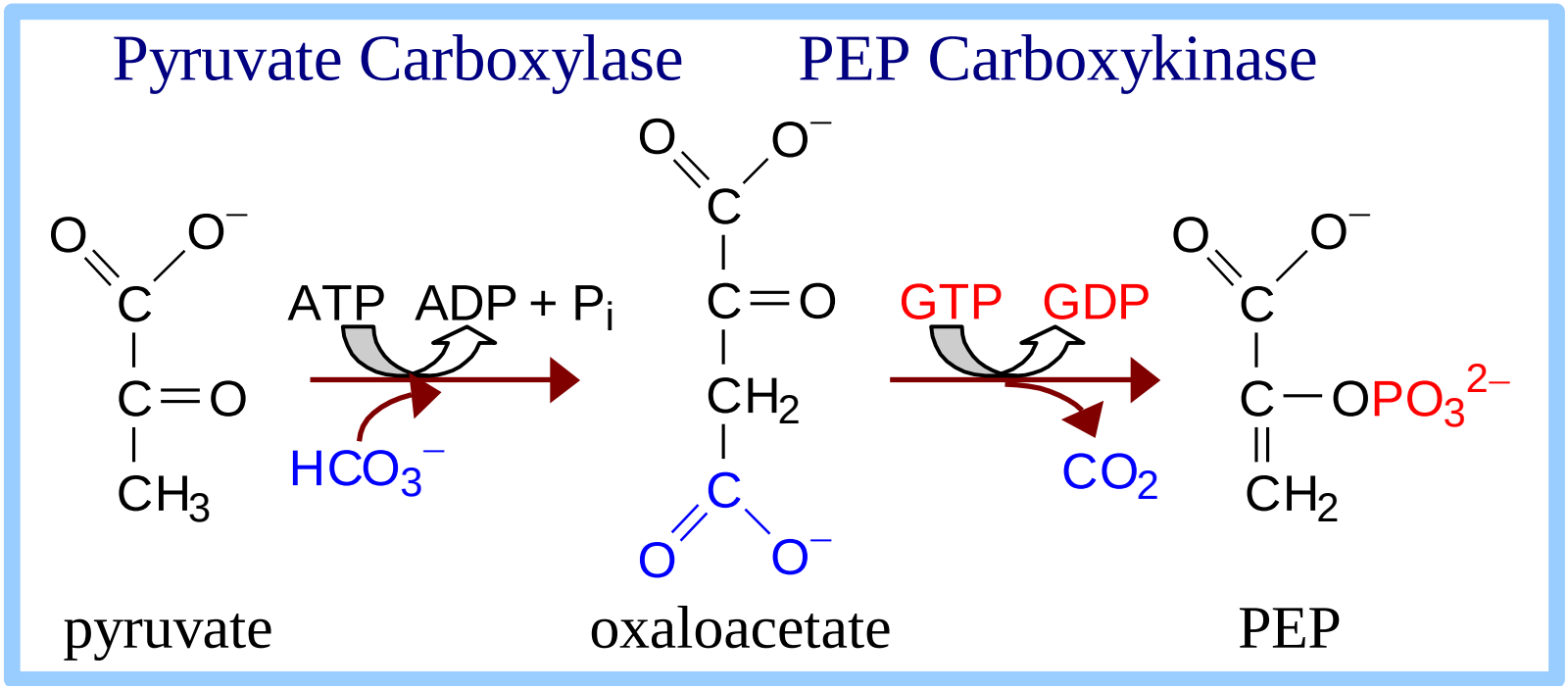


Phosphofructokinase (Glycolysis) catalyzes:

fructose-6-P + ATP → fructose-1,6-bisP + ADP

Fructose-1,6-bisphosphatase (Gluconeogenesis) catalyzes:

fructose-1,6-bisP + H_2O → fructose-6-P + P_i



Bypass of Pyruvate Kinase (2 enzymes):

Pyruvate Carboxylase (Gluconeogenesis) catalyzes:

pyruvate + HCO_3^- + ATP → oxaloacetate + ADP + P_i

PEP Carboxykinase (Gluconeogenesis) catalyzes:

oxaloacetate + GTP → PEP + GDP + CO_2

Gluconeogenesis take place when :

1 . During fasting or starvation or when the level of liver glycogen is low . Gluconeogenesis is important in keeping the blood glucose conc.

2 . During long exercise, lactate is used as precursor.

3 . When ATP is avialable in the cell (or we need minmum energy requirment) .

Gluconeogenes is occurs under conditions in which pyruvate dehydrogenase , pyruvate kinase , PFK and (GK or HK) are relatively inactive .

Regulation of gluconeogenesis

1 . Under fasting conditions , glucagon is elevated and stimulates gluconeogenesis .

2 . Gluconeogenesis is inhibited by insulin and after carbohydrates feeding .

3 . Gluconeogenesis is stimulate in starvation .

4 . Glucocorticoids are steroid hormones stimulates gluconeogenesis by increasing protein catabolism in the peripheral tissues .

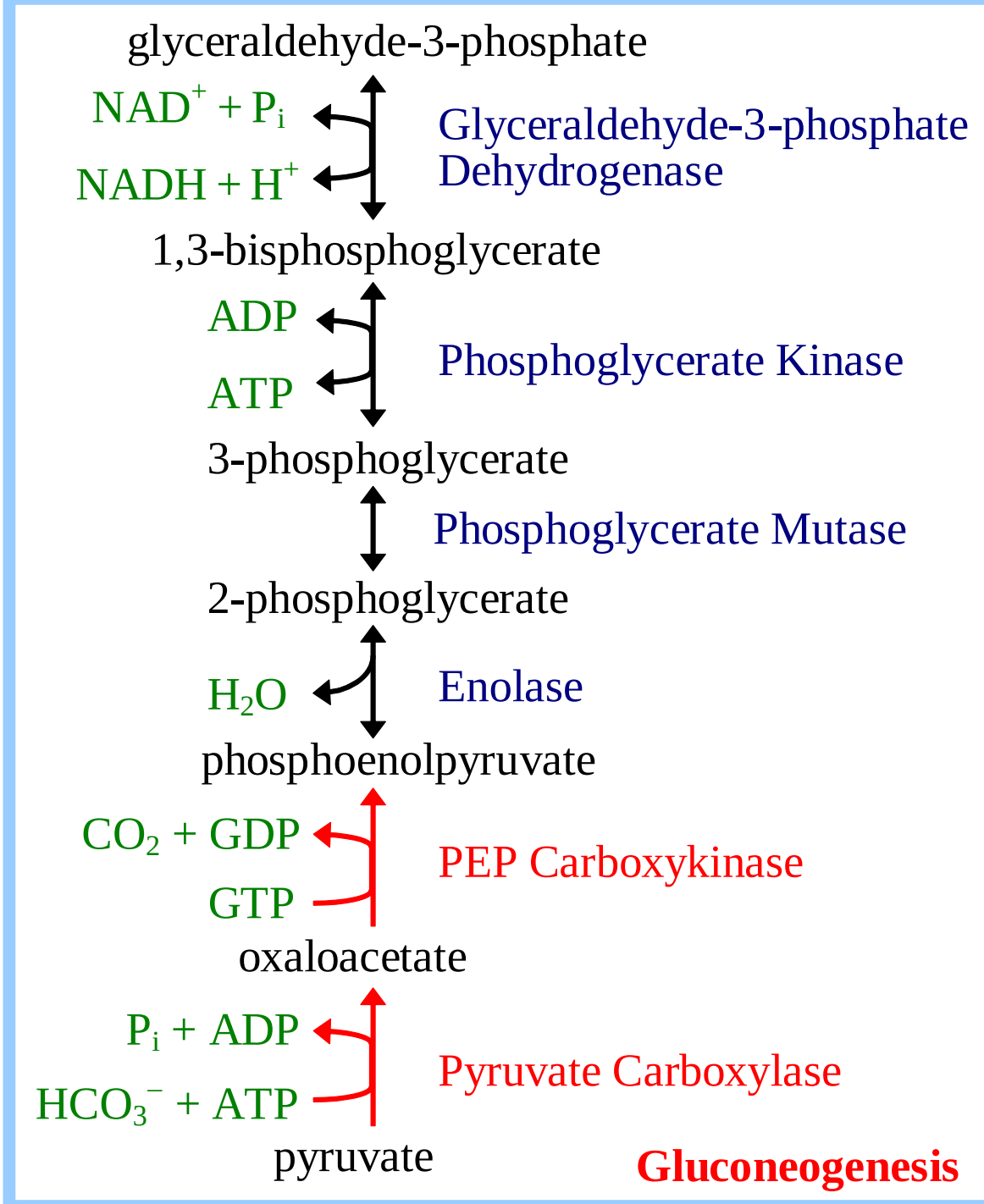
The major substrates of gluconeogenesis are lactate , glycerol , propionate and glucogenic amino acids .

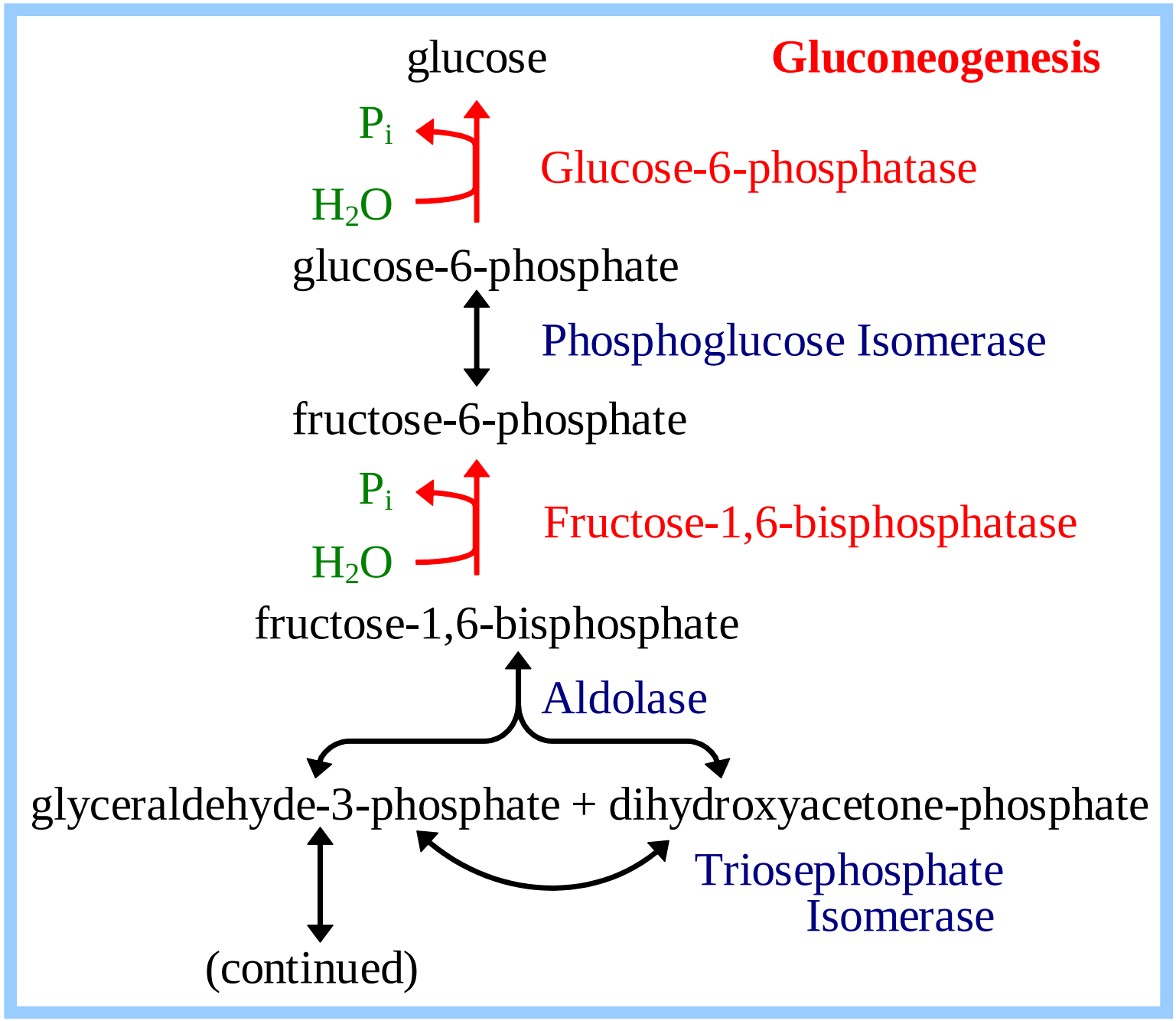
Glucogenic amino acids (Amino acids are derived from the dietary proteins , tissues proteins or from the breakdown of skeletal muscle proteins during starvation)

After deamination or transamination , glucogenic amino acids yield either pyruvate or intermediates of the TCA cycle . Amino acids that are degraded to acetyl CoA or acetoacetyl CoA are termed ketogenic amino acids because they can give rise to ketone bodies .

The hydrolysis of triacylglycerols in fat cells yield glycerol and fatty acids . Glycerol may enter glycolytic pathway at dihydroxy acetone phosphate .

Summary of Gluconeogenesis Pathway




Gluconeogenesis
glucose
P_i
H_2O
Glucose-6-phosphatase
glucose-6-phosphate
Phosphoglucose Isomerase
fructose-6-phosphate
P_i
H_2O
Fructose-1,6-bisphosphatase
fructose-1,6-bisphosphate
Aldolase
glyceraldehyde-3-phosphate + dihydroxyacetone-phosphate
Triosephosphate Isomerase
(continued)

Glycolysis & **Gluconeogenesis** are **both spontaneous**.

Glycolysis:

$$\text{glucose} + 2\,NAD^+ + 2\,ADP + 2\,P_i \rightarrow 2\,\text{pyruvate} + 2\,NADH + 2\,ATP$$

Gluconeogenesis:

$$2\,\text{pyruvate} + 2\,NADH + 4\,ATP + 2\,GTP \rightarrow \text{glucose} + 2\,NAD^+ + 4\,ADP + 2\,GDP + 6\,P_i$$

Why gluconeogenesis is nececssary in the body ?

1 . Gluconeogenesis meets the requirments of glucose in the body when CHO are not avialable in sufficient amount from the diet . Even in conditions , where fat is utilized for energy still certain basal level of glucose is required to meet the need for glucose for special uses , e.g.

- Source of energy for nervous tissues and erytherocytes .
- It is a precursor of milk sugar (lactose) for lactating mammary gland .
- It serves as only fuel for skeletal muscles in anaerobic conditions .

2 . Gluconeogenesis mechanisms are required to clear the products of metabolism of other tissues from the blood , e.g.

- Lactic acid produced by muscles and erytherocytes .
- Glycerol which is continuously produced by adipose tissue by lipolysis of TG .