GLYCOLYSIS

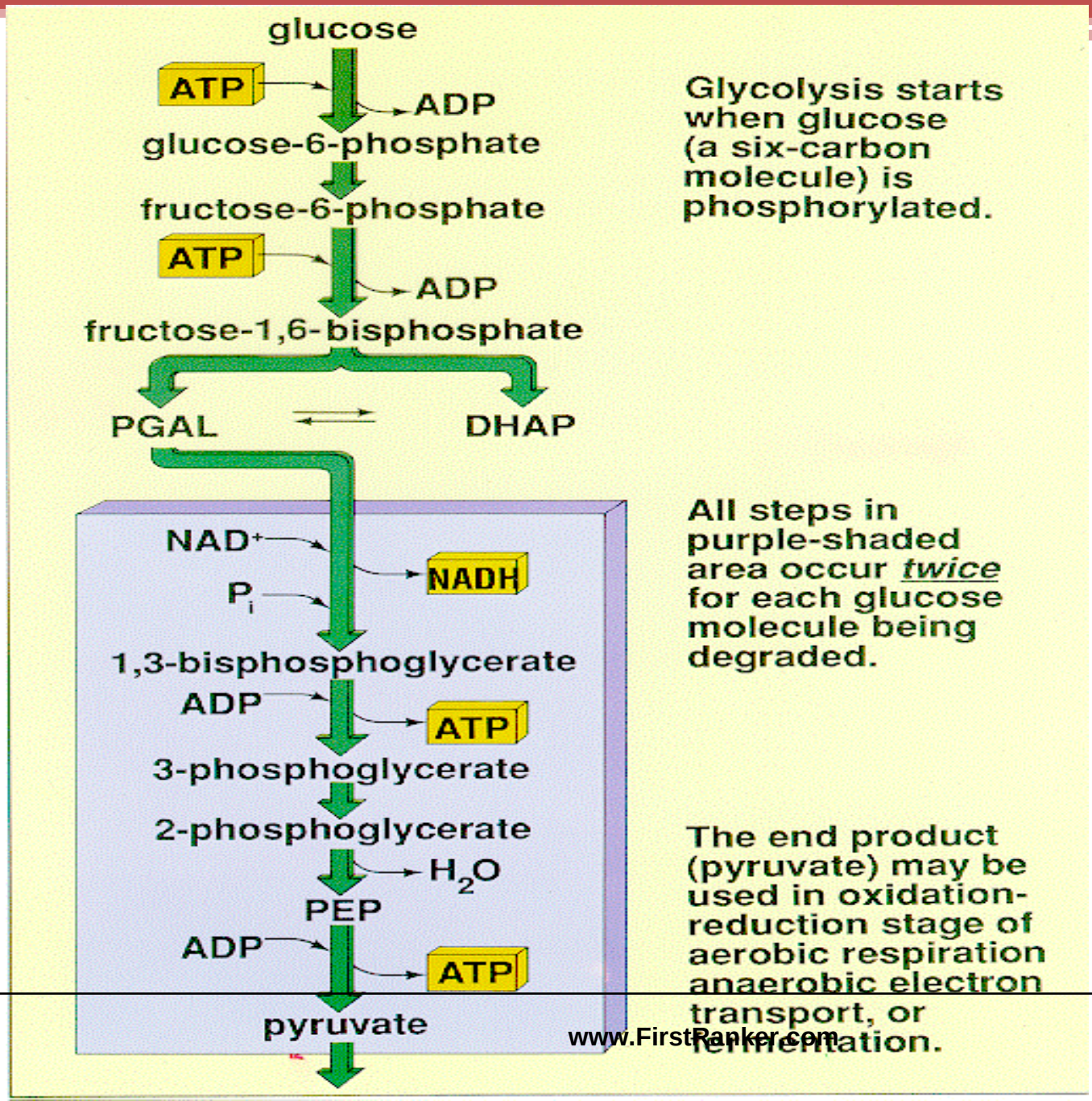
- Also called Embden Meyerhof Pathway.
- It is the oxidation of glucose or glycogen to pyruvate or Lactate.

BIOMEDICAL IMPORTANCE

- It is the major Pathway for Glucose metabolism.
- It occurs in the cytosol of all cells.
- Its unique features is that it can function aerobically or anaerobically, depending on the availability of oxygen and electron transport chain.
- RBCs have no mitochondria and they rely completely on glucose as their metabolic fuel and metabolize it anaerobically.

- Glycolysis is the principle route for glucose metabolism, and is also the main pathway for the metabolism of fructose, galactose and other CHO derived from the diet.
- Glycolysis of glucose to provide ATP anaerobically is especially important, because skeletal muscles can perform under anoxic conditions.
- Cardiac muscles have low glycolytic activity.

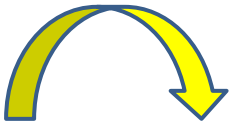
- Diseases in which glycolytic enzymes are deficient are mainly seen as hemolytic anemia's.
- If the defect affects skeletal muscle, then it is seen as fatigue.
- In the cancerous cells Glycolysis proceeds at a very high rate, forming large amounts of pyruvate, which is reduced to lactate, leads to acidic environment and has implications for cancer therapy.



REACTIONS OF GLYCOLYSIS

- In glycolysis glucose is converted to pyruvate in two stages:
- First five reactions of glycolysis correspond to an energy investment phase.
- Subsequent reactions correspond to energy generation phase .

- Glucose → Glucose -6-phosphate

ATP  ADP

Hexokinase/ glucokinase

- Glucose -6-phosphate ↔ Fructose-6- phosphate

Phosphoglucose isomerase

- Fructose-6- phosphate → Fructose -1,6 bisphophate

ATP  ADP

Phosphofructo kinase-1

– ATP, citrate
+ AMP
+ Fructose 2 6 bisphosphate

- Fructose -1,6 bisphophate

↙ ↘

Glyceraldehyde-3 PO_4 phosphate ↔ Dihydroxyacetone

Triose phosphate isomerase

- Glyceraldehyde -3- $PO_4 \leftrightarrow$ 1,3 bisphosphoglycerate

NAD  $NADH+H^+$

Glyceraldehyde -3- PO_4 dehydrogenase

- 1,3 bisphosphoglycerate ↔ 3- phosphoglycerate
  ↓(2) ↑(3) (1)
  2,3 bisphosphoglycerate

ADP ⟷ ATP

Phosphoglycerate kinase (1)

Mutase (2)

Phosphatase (3)

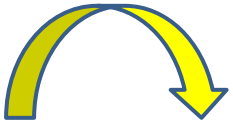
- 3- phosphoglycerate ↔ 2- phosphoglycerate

  Phosphoglycerate mutase

- 2- phosphoglycerate $\leftrightarrow$ Phosphoenolpyruvate
  $\searrow H_2O$

Enolase

- Phosphoenolpyruvate → Pyruvate



ADP ATP

Pyruvate kinase

+ Fructose 1,6 bisphosphate

- The three regulatory enzymes are:

1. Hexokinase
2. Phosphofructokinase
3. Pyruvate kinase

- Phosphorylation of glucose:
- Hexokinase / Glucokinase:
- Features are as follows:

HEXOKINASE

1. In most tissues
2. Broad specifity
3. Low Km
4. High affinity
5. Low Vmax
6. Inhibited by G6P

GLUCOKINASE

1. In hepatocytes/Beta cells of pancreas
2. Specific for glucose
3. High Km
4. Low affinity
5. High Vmax
6. Function as a glucose sensor in pancreas. liver-phosphorylate glucose.
7. Indirectly inhibited by F6P
8. Indirectly stimulated by glucose

Regulation by F6P & glucose

- Glucokinase regulatory Protein exists in the nucleus of hepatocytes.
- In the presence of F6P, glucokinase is translocated to the nucleus and binds tightly to the regulatory protein, thus rendering the enzyme inactive.

- When blood glucose levels increases, the glucose causes the release of glucokinase from the regulatory protein and the enzyme enters the cytosol.

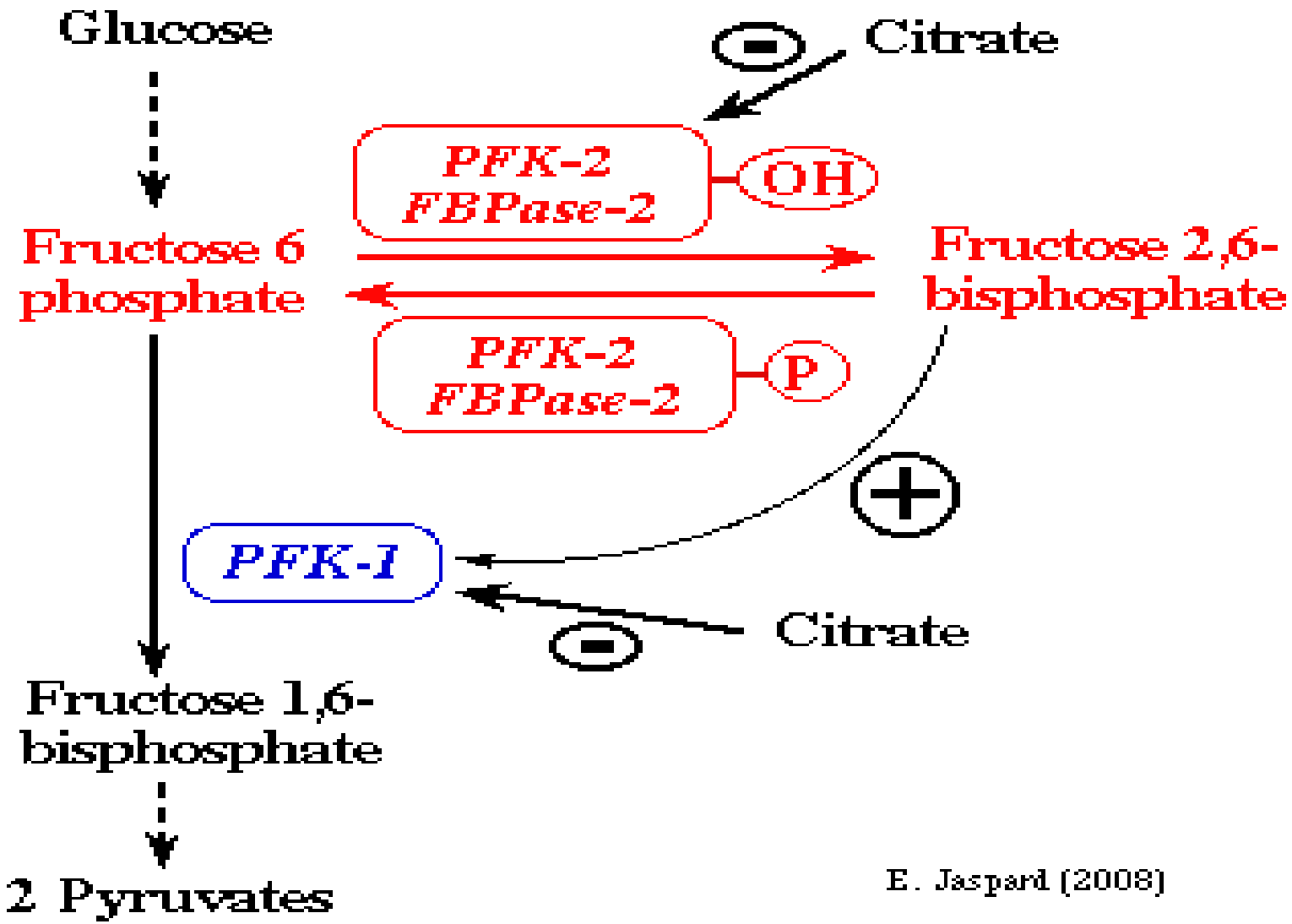
Regulation by Insulin

- Glucokinase activity is increased by insulin.
- Increase blood glucose→ insulin release
- Insulin→ increase transcription of glucokinase

- PFK-I is the second regulatory enzyme.
- It is responsible for the irreversible phosphorylation of F6P.
- It is the most impt control point, the rate limiting and committed step of glycolysis.
- PFK-I is controlled by ATP, F6P, F26BP

- Regulation by energy levels:
- PFK-I is inhibited by elevated levels of ATP, which acts as an energy rich signals
- Inhibited by elevated levels of Citrate.
- Activated by high levels of AMP.
- Most potent activator is F26BP.

- F26BP is formed by PFK-2.
- It is a bifunctional enzyme.
- It has got a kinase as well as a phosphatase activity.
- Increase levels of insulin activate it, and increase levels of Glucagon inhibit it.



E. Jaspard [2008]

- The conversion of G3PO4 to 1,3 BPG is the first oxidation reduction reaction.
- NAD → NADH+H
- Oxidation of NADH by two methods

1. By conversion of Pyruvate to lactate
2. Via Electron transport chain

- 1,3BPG → 3 PG, ATP is formed at substrate level.
- 2,3 BPG is also formed.
- Enzyme- Phosphoglycerate kinase

- Phosphoenolpyruvate → Pyruvate
- Pyruvate kinase is the enzyme. Its deficiency is the second most common cause of hemolytic anemia.
- cAMP dependent protein kinase leads to phosphorylation of pyruvate kinase, which becomes inactive.
- Elevated levels of glucagon are responsible for the phosphorylation.

- Reduction of pyruvate to lactate.
- It is the major fate for Pyruvate in retina, lens, cornea, kidney medulla, testes, leukocytes and RBC, skin,GIT.
- Lactate formation in exercising muscles.
- Lactate consumption (liver, heart).

- **Liver** – lactate converted to pyruvate. Pyruvate converted to glucose by gluconeogenesis, or oxidized to CO_2 in TCA cycle.

- **Heart** – exclusively oxidizes lactate to CO_2 and H_2O in TCA cycle.

- **Lactic Acidosis** – collapse of circulatory system
- Severity of shock can be assessed by measuring the levels of lactic acid.

Energy yield of glycolysis

1. G3PO4 dehydrogenase 6 ATP
2. Phosphoglycerate kinase 2 ATP
3. Pyruvate kinase 2 ATP

Total 10 ATP

Consumed 2 ATP in Hexokinase/glucokinase step.

Net 8 ATP

Hormonal Regulation

1. Allosteric regulation by phosphorylation and dephosphorylation of rate limiting enzymes is short term.
2. Hormonal regulation, is slow and more profound.

Alternate Fates of Pyruvate

1. Oxidative decarboxylation of pyruvate to acetyl CoA
2. Carboxylation of pyruvate to Oxaloacetate
3. Reduction to Ethanol (microorganisms)

Learning Resources

- Lippincott's Biochemistry
- Harper's Biochemistry
- Teacher Notes