CHO METABOLISM
(GLUCONEOGENESIS)

By

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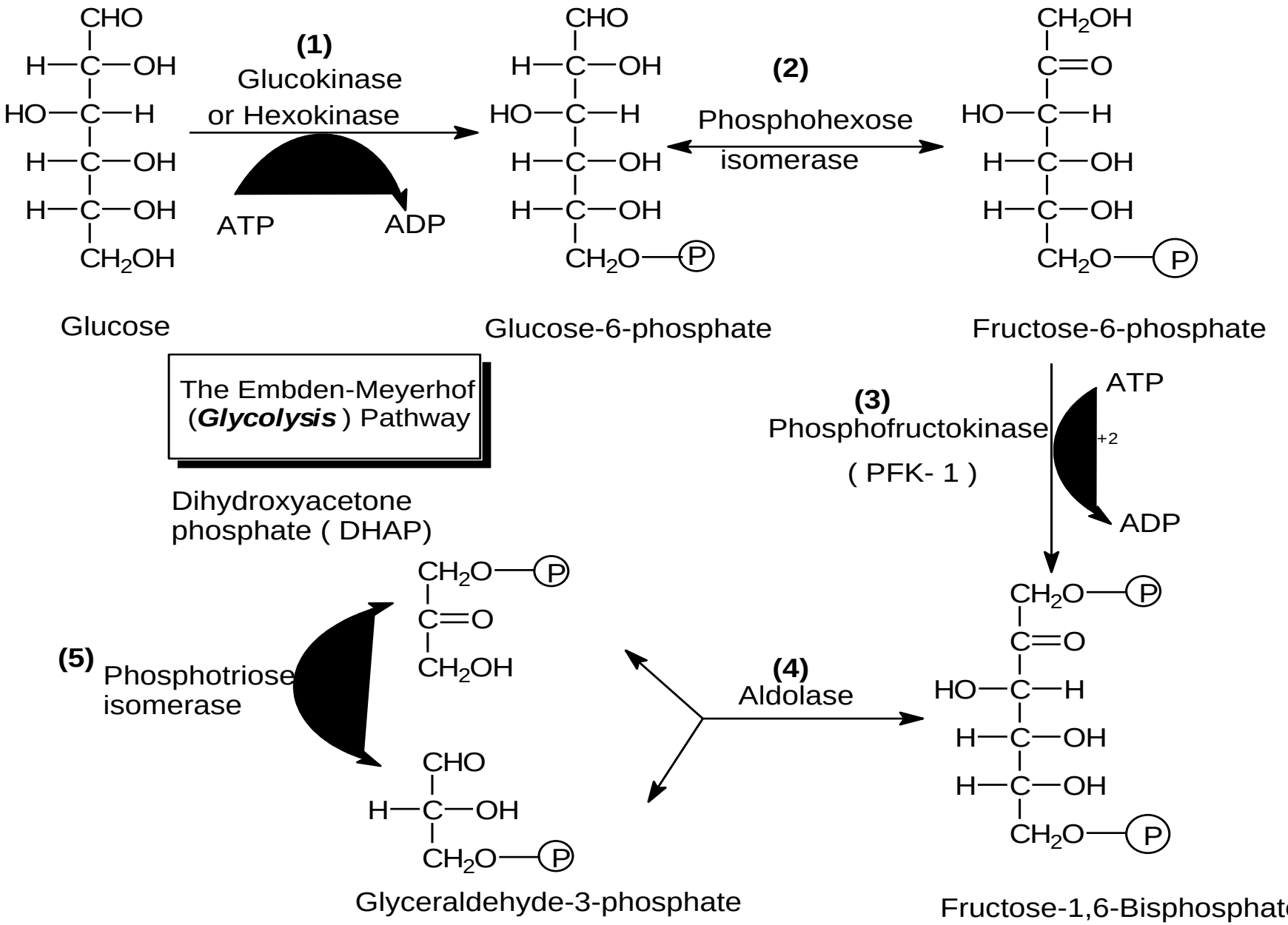
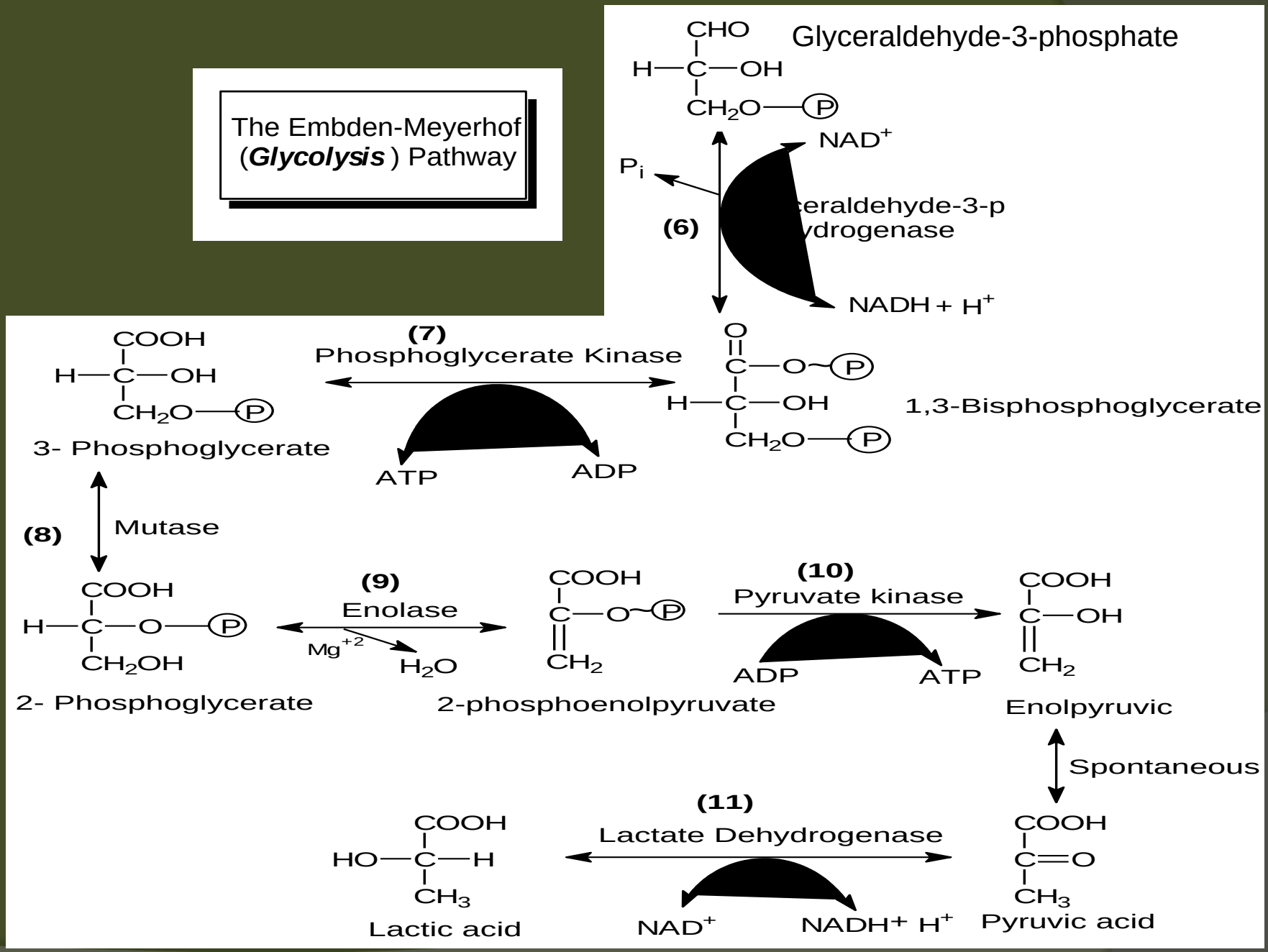
&

Molecular Biology


(1)
Glucokinase
or Hexokinase
ATP
ADP
(2)
Phosphohexose
isomerase
Glucose
Glucose-6-phosphate
Fructose-6-phosphate
The Embden-Meyerhof
(Glycolysis) Pathway
(3)
Phosphofructokinase
(PFK- 1)
ATP
+2
ADP
Dihydroxyacetone
phosphate (DHAP)
(5)
Phosphotriose
isomerase
(4)
Aldolase
Glyceraldehyde-3-phosphate
Fructose-1,6-Bisphosphate

The Embden-Meyerhof (*Glycolysis*) Pathway



GLUCONEOGENESIS

Definition: It is the formation of glucose or glycogen from non-carbohydrate sources

Sources:

1. **Proteins:** (58%) **most important**.
2. **Fats**: a) Glycerol (10% of fats).
   b) Odd chain fatty acids (rare).
3. **Lactate**: from RBCs & muscles during exercise

Site: * Chiefly in liver & kidneys.
* Little in skeletal muscles.
* Not in heart, smooth muscles & fat cells (fructose – 1, 6-bisphosphatase deficient).

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Importance of gluconeogenesis:

I. Supplies blood glucose, during fasting >18 hours, which is important for:

* **Energy** in brain, RBCs & muscle exercise.
* **α-glycerol-P** in fat cells for re-esterify fatty acids
* **Oxaloacetate** in all tissues for Krebs' cycle.

II. Removes:

***Lactate & Pyruvate** from RBCs & muscle exercise
***Glycerol** **(absorbed from intestines or produced by adipose tissues)**

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Steps: (essentially the reversal of glycolysis).

1. From lactate & pyruvate:

***Lactate → pyruvate**

***Reversal of pyruvate kinase reaction:**

(Dicarboxylic acid shuttle)

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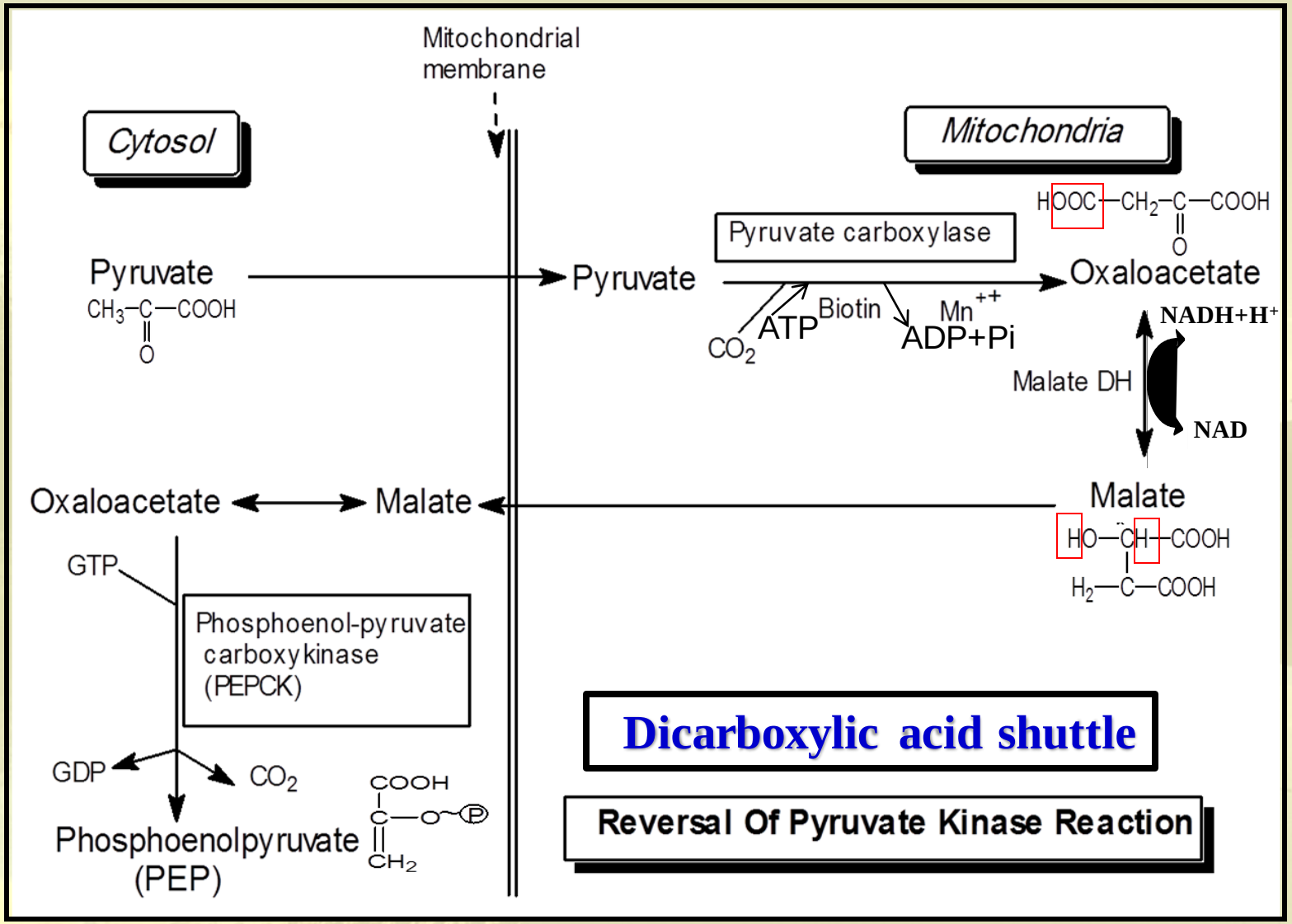
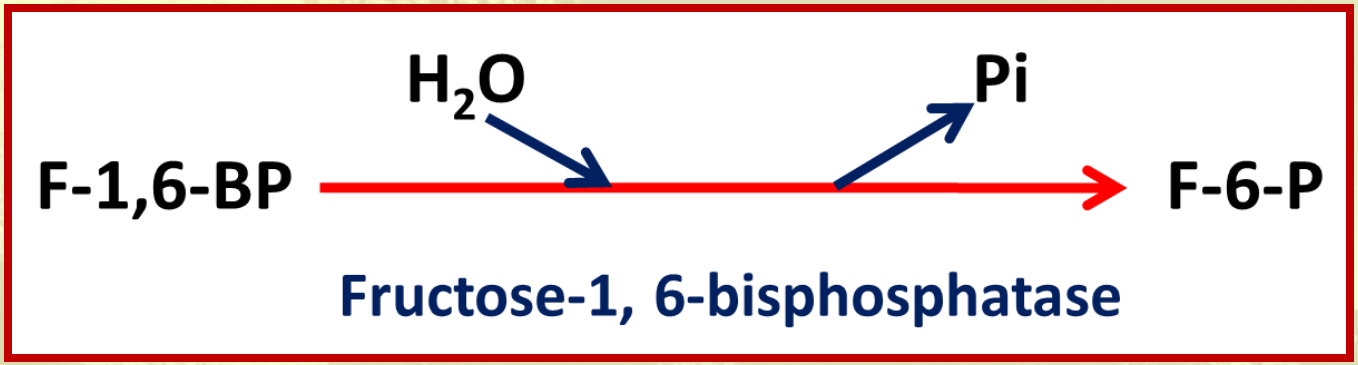

Mitochondrial membrane
Cytosol
Mitochondria
Pyruvate
Pyruvate
Pyruvate carboxylase
Oxaloacetate
CO2
ATP
Biotin
Mn++
ADP+Pi
NADH+H+
Malate DH
NAD
Oxaloacetate
Malate
Malate
GTP
Phosphoenol-pyruvate carboxykinase (PEPCK)
GDP
CO2
Phosphoenolpyruvate (PEP)
Dicarboxylic acid shuttle
Reversal Of Pyruvate Kinase Reaction

*Reversal of the phosphofructokinase reaction



Fructose-1, 6-bisphosphatase is the ***KEY ENZYME*** of gluconeogenesis.

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*Reversal of the Hexokinase reaction

- G-6-phosphatase is present in the liver, kidney, & intestines.
- **Glucose-6-phosphatase is** absent from skeletal muscles that makes gluconeogenesis ends in glycogen formation.

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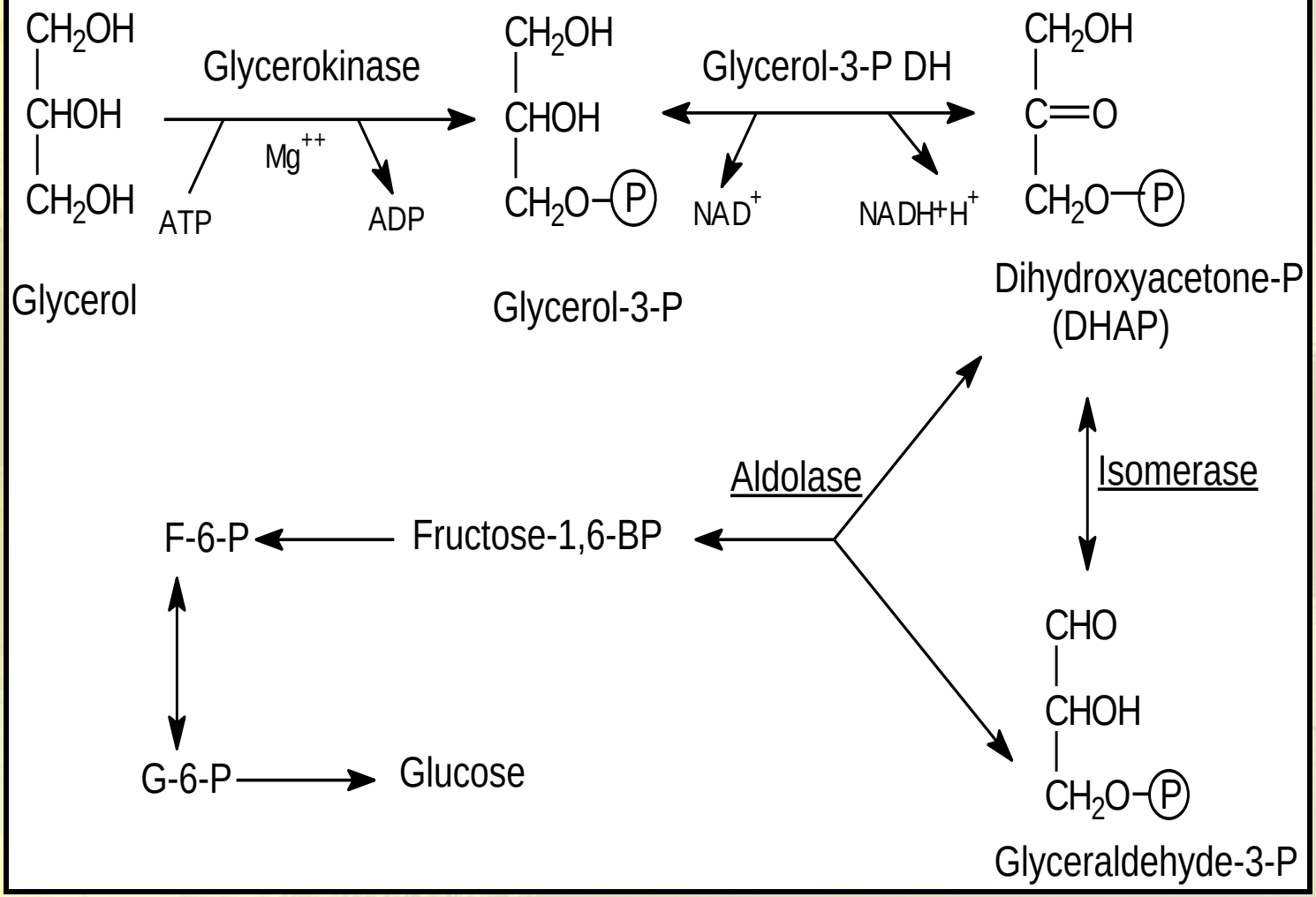
2. From glycerol: (10% of fat)



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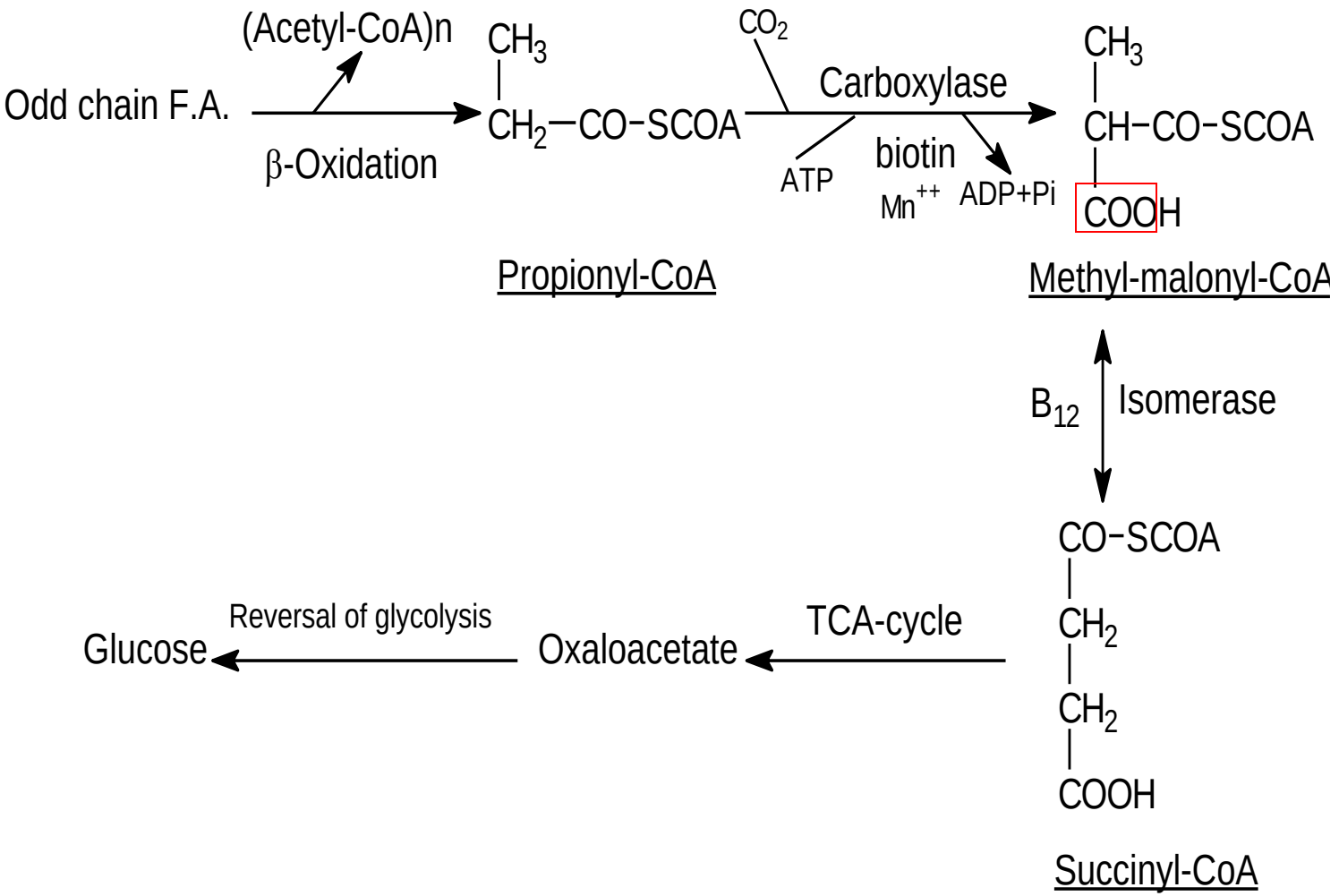
3. From odd chain fatty acids: rare



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3. From proteins (58%):

- All glucogenic and mixed amino acids can give glucose (i.e. all amino acid except leucine).
- **Dextrose / Nitrogen ratio:** D/N = 3.65/1
- Amino acids give pyruvic acid or intermediate of Krebs' cycle, both can be converted to oxaloacetate which by PEPCK can give phosphoenolpyruvate (PEP). PEP by reversal of glycolysis can form glucose or glycogen.

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How to proof that 58% of proteins give glucose (D/N ratio):

An experimental animal is:

1) Starved: - No external source of glucose.

- Liver glycogen is depleted.
- Gluconeogenesis (proteins becomes the only source of glucose.)

2) Pancreatectomized or given phlorrhizin:

The animal becomes completely diabetic so, glucose utilization is inhibited. Glucose formed from proteins cannot be utilized by the animal & is excreted in urine

N.B. Phlorrhizin inhibits renal tubular reabsorption of glucose.

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Collect urine & determine D/N ratio (Dextrose / Nitrogen):

D/N = 3.65/1 (it is normally = zero, no glucose in urine)

Since 100 gm protein contains 16 gm nitrogen and 1 gram N_2 gives 3.65 grams glucose, hence, 100 grams of protein gives about 58 grams of glucose.

100 grams proteins→ 3.65 x 16 = 58.4

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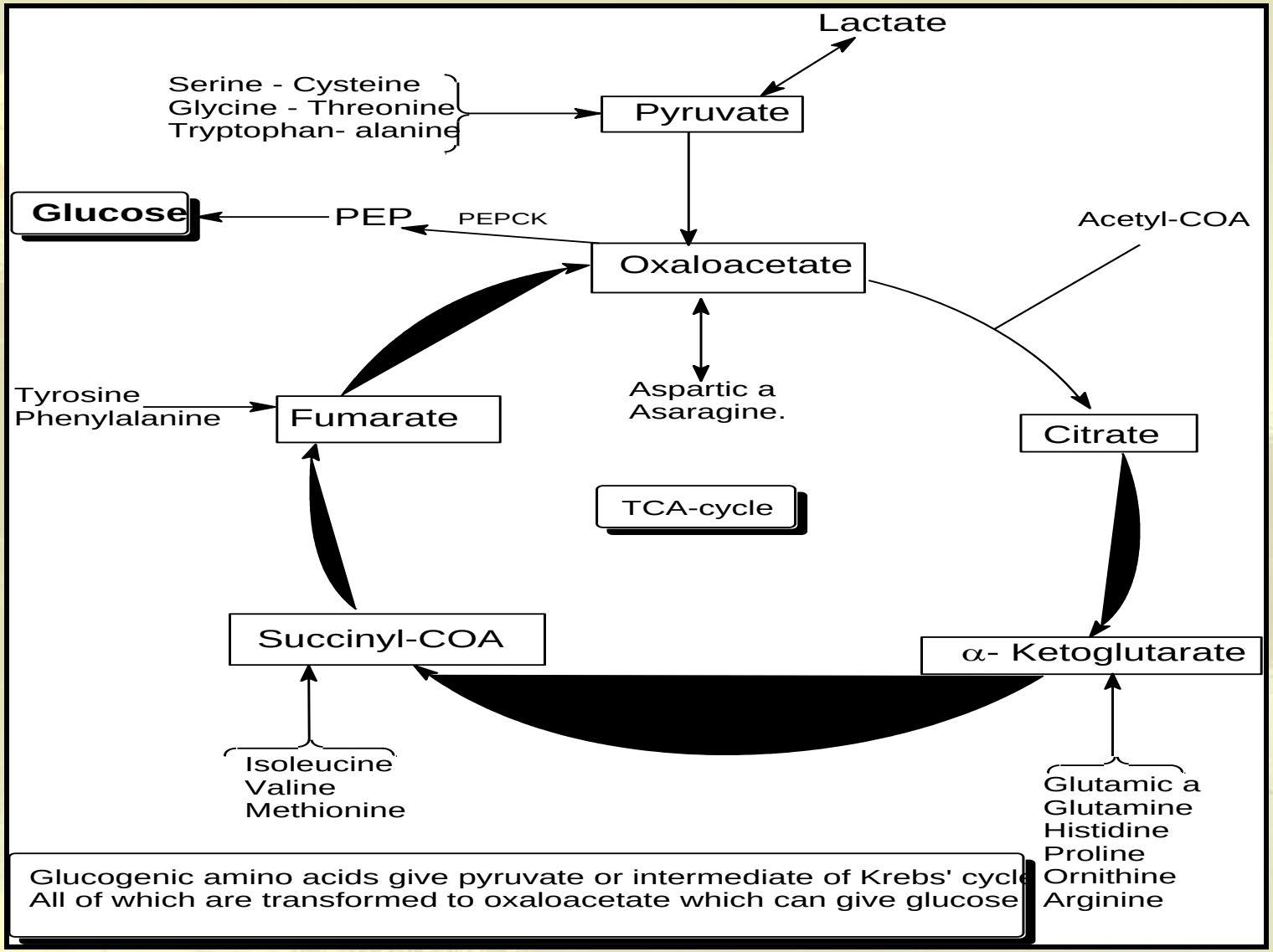

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The opposing enzymatic differences between Glycolysis and Gluconeogenesis

Enzymes	Glycolysis	Gluconeogenesis
1	Glucokinase (or Hexokinase)	Glucose – 6 – phosphatase
2	Phosphofructokinase-1 **(the key enzyme)**	Fructose -1,6 - bisphosphatase **(the key enzyme)**
3	Pyruvate kinase	Pyruvate carboxylase & phosphoenolpyruvate carboxykinase (**PEPCK**).

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REGULATION OF GLUCONEOGENESIS:

1- Induction and Repression of the key enzymes:

- ***CHO feeding*** increases insulin secretion. This ***represses enzymes of gluconeogenesis*** **(↓ synthesis).**

- ***Fasting*** decreases insulin secretion but it increases glucagon and adrenaline secretions. This ***induces enzymes of gluconeogenesis*** **(↑synthesis).**

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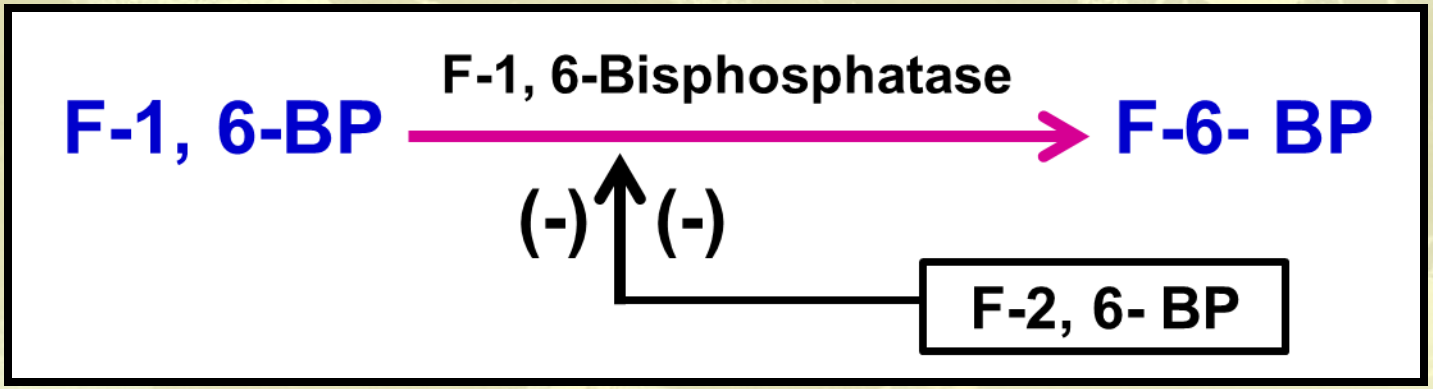
REGULATION OF GLUCONEOGENESIS:

2-Allosteric regulation:

- **F-1, 6-Bisphosphatase (key enzyme),** is allosterically inhibited by ***F-2, 6–BP***.

(F-2, 6–BP allosterically inhibits F-1, 6- Bis-Ptase)



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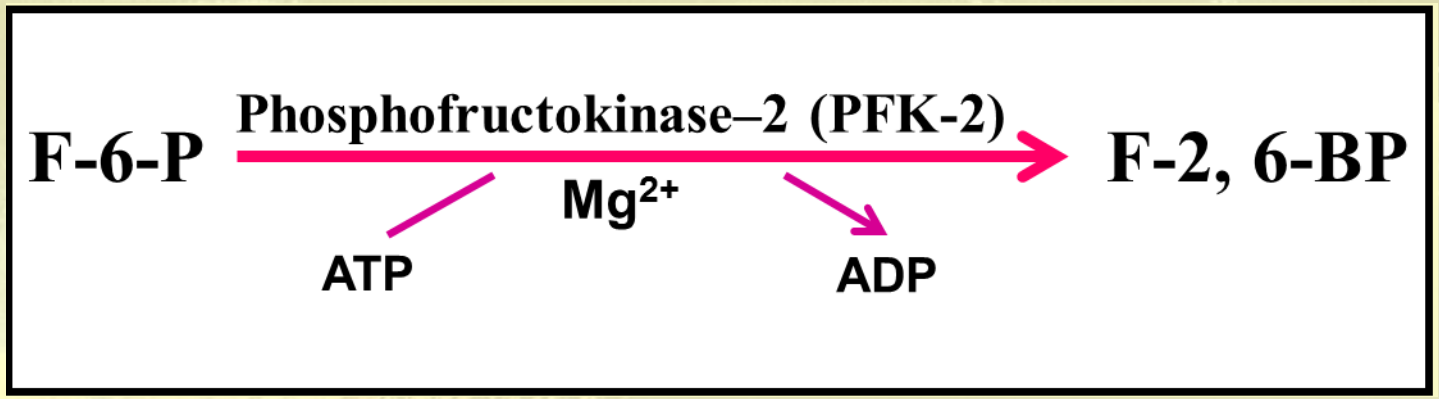
REGULATION OF GLUCONEOGENESIS:

- Fasting →↑↑ adrenaline & glucagon →↑ cAMP → ↓↓ F-2, 6-BP → Stimulation of F-1, 6-BPtase → Stimulation of gluconeogenesis.
- Fructose-2, 6-Bisphosphate: [F-2, 6–BP] is formed by phosphorylation of F-6-P by the enzyme phosphofructokinase–2 (PFK-2).



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The role of F-2, 6-BP in regulation of gluconeogenesis

- CHO Feeding $\rightarrow\uparrow\uparrow$ insulin $\rightarrow\uparrow\uparrow$ F-2,6-BP leading to inhibition of gluconeogenesis.
- It plays an important role in regulation of glycolysis and gluconeogenesis.
- CHO feeding $\rightarrow\uparrow\uparrow$ F-2,6-BP$\rightarrow$ it allosterically stimulates PFK-1 and inhibits F-1, 6-BPtase $\rightarrow$ (+) Glycolysis & (-) Gluconeogenesis.
- So, glycolysis and Gluconeogenesis can't occur at the same time.

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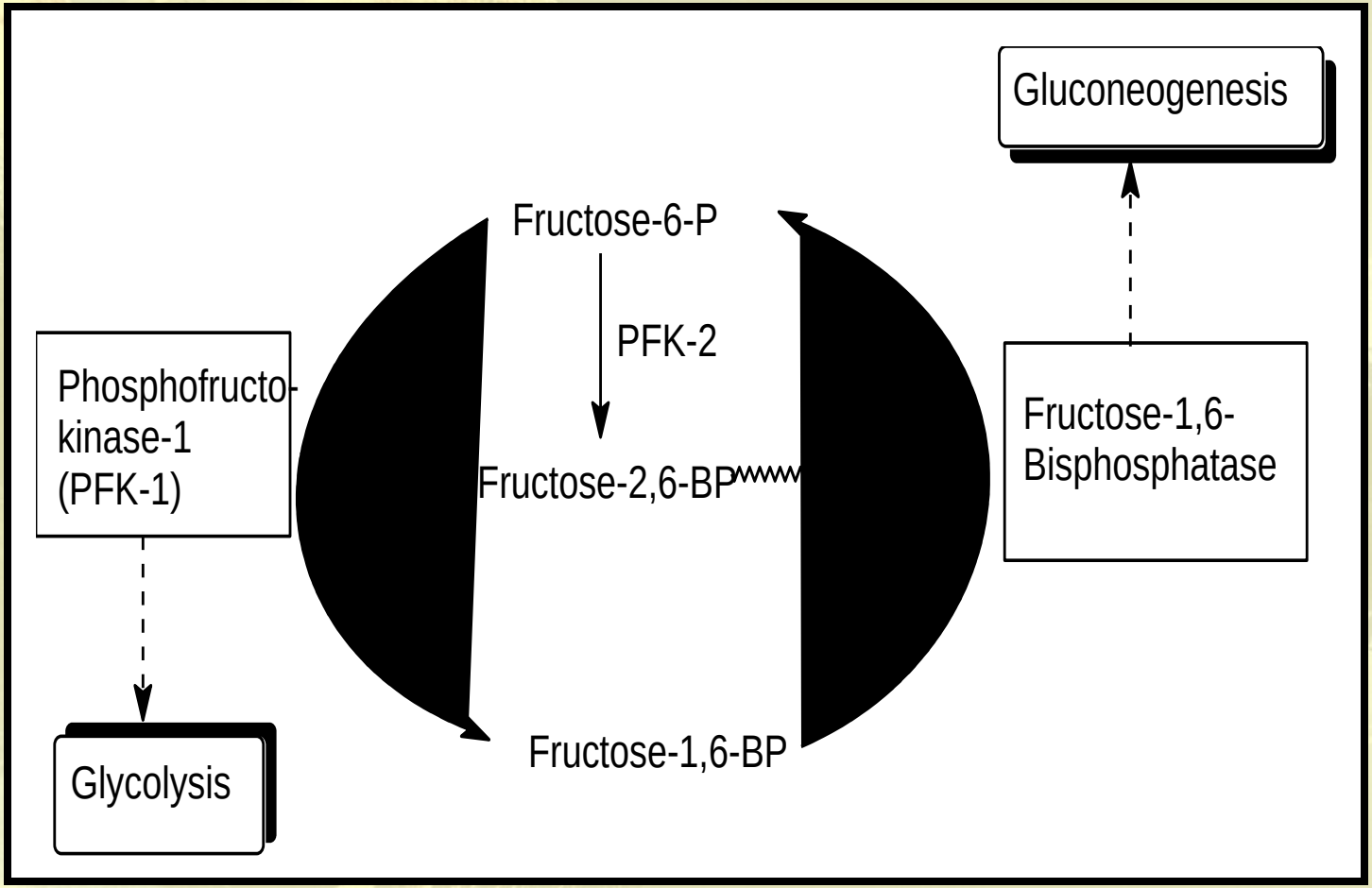
The role of F-2, 6-BP in regulation of gluconeogenesis



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Thank You