# Glyconeogenesis

## Lecture 14

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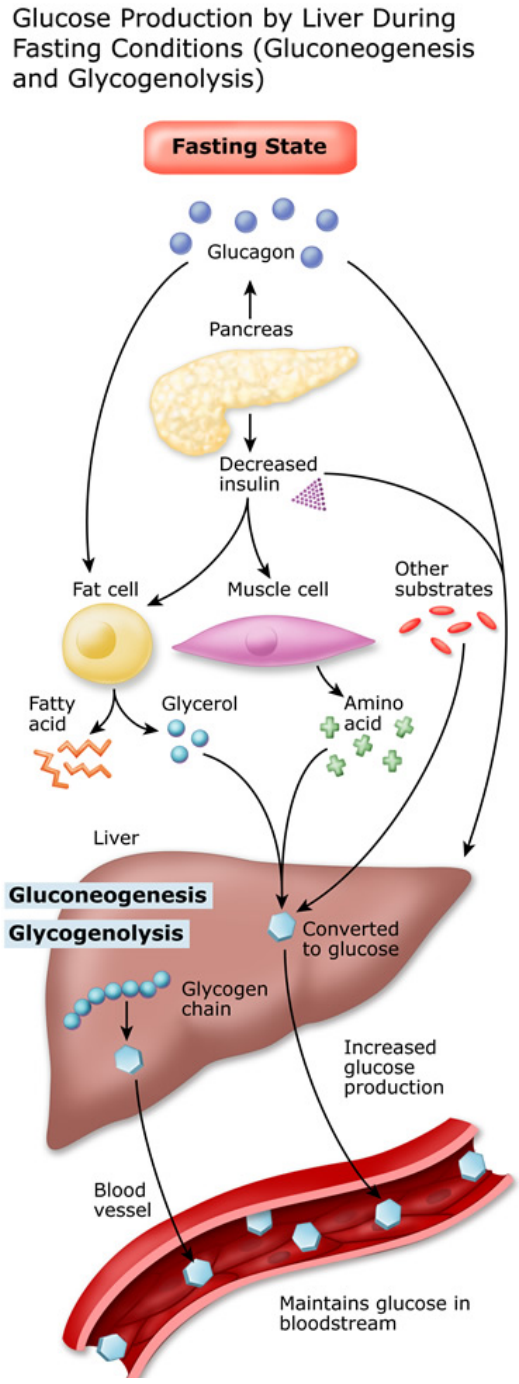
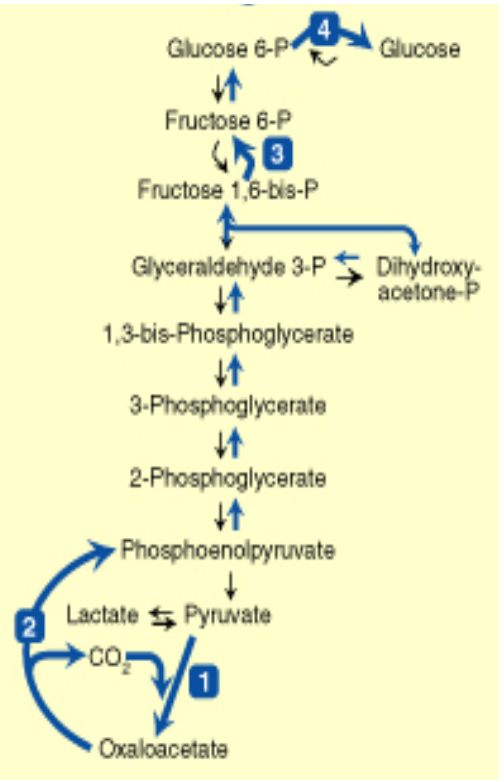
- In the absence of dietary intake of carbohydrate (during fast), liver glycogen is an important source of glucose (through glucogenolysis) to meet the tissue needs for 10-18 hours.
- During prolonged fasting, liver glycogen stores are depleted, and glucose is formed by gluconeogenesis. (Gluco- : glucose, neo-: new, genesis: make or create).
- During Overnight fast:
  - ✓ 90% of gluconeogenesis occurs in liver
  - ✓ 10% of gluconeogenesis occurs in Kidneys
- During Prolonged fast:
  - ✓ 60% of gluconeogenesis occurs in liver
  - ✓ 40% of gluconeogenesis occurs in Kidneys
- Gluconeogenesis requires both mitochondrial & cytosolic enzymes (exception: if gluconeogenesis starts by Glycerol, it will need only the cytosol)
- Gluconeogenesis is an energy consuming. i.e. anabolic process.



**Gluconeogenic pathway** is the opposite way from glycolysis (lectures 11&12). It consists of nine steps:

- ✓ Seven glycolytic reactions are reversible & are used in gluconeogenesis from lactate or pyruvate.
- ✓ Three glycolytic reactions are irreversible & must be reversed (by 4 alternate reactions) in gluconeogenesis. These reaction are:

| Glycolysis | Gluconeogensis |
|---|---|
| Pyruvate kinase | 1) Pyruvate carboxylase<br>2) PEP-CK |
| PFK-1 | 3) Fructose 1,6 bisphosphate |
| Glucokinase | 4) Glucose 6-phosphatase |




1

Pyruvate —(Pyruvate carboxylase)→ Oxaloacetat → Malate

- -caboxylase = add $CO_2$ to pyruvate
- This reaction requires ATP and Co-enzyme (Biotin).
- This reaction occurs in mitochondria
- Acetyl CoA induced this reaction.

2

Malate —(PEP-CK)→ Phosphoenolpyruvate (PEP)

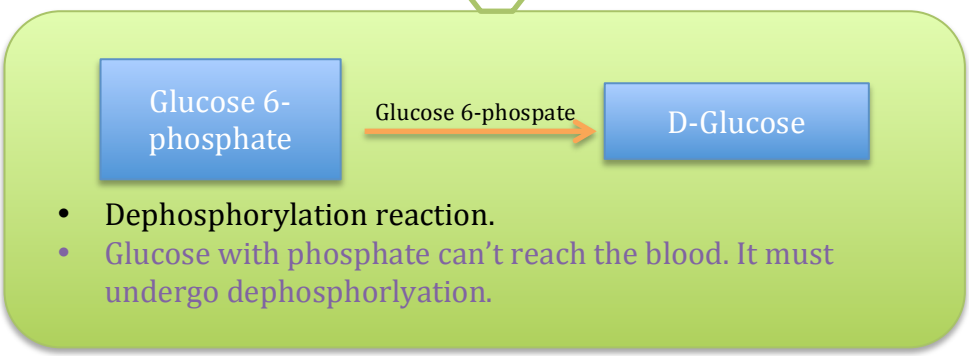
- Decarboxylation & phosphorylation reaction.
- This reaction requires energy (GTP).
- This reaction occurs in cytosol.
- It is represented by insulin & reduced by glucagon.

3

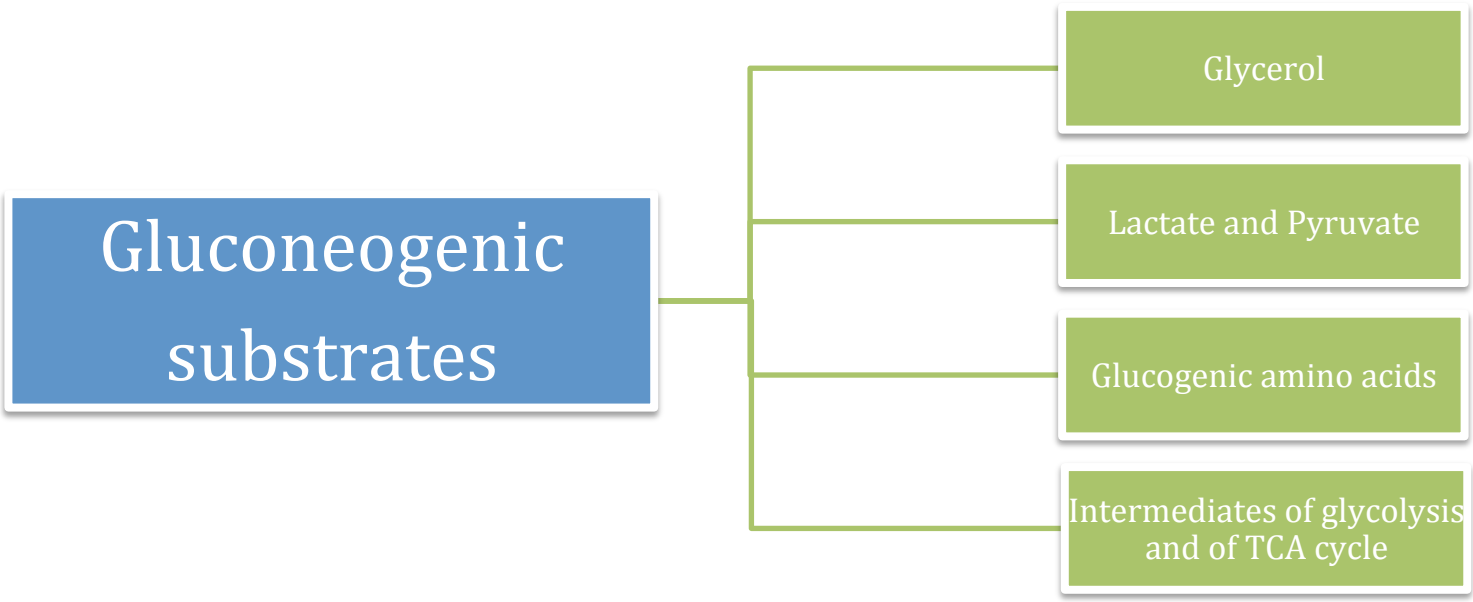
Fructose 1,6-bisphosphate —(Fructose 1,6 bisphosphatase)→ Fructose 6-phosphate

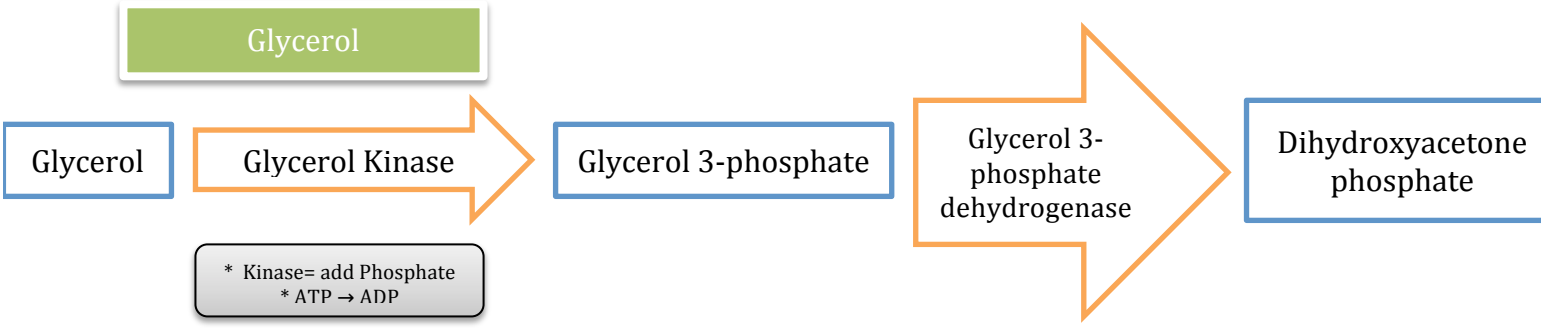
- Dephosphorylation reaction.
- This reaction inhabited by high levels of AMP and induced by ATP or low level of AMP.
- This reaction is reciprocal reaction with glycolysis.

4

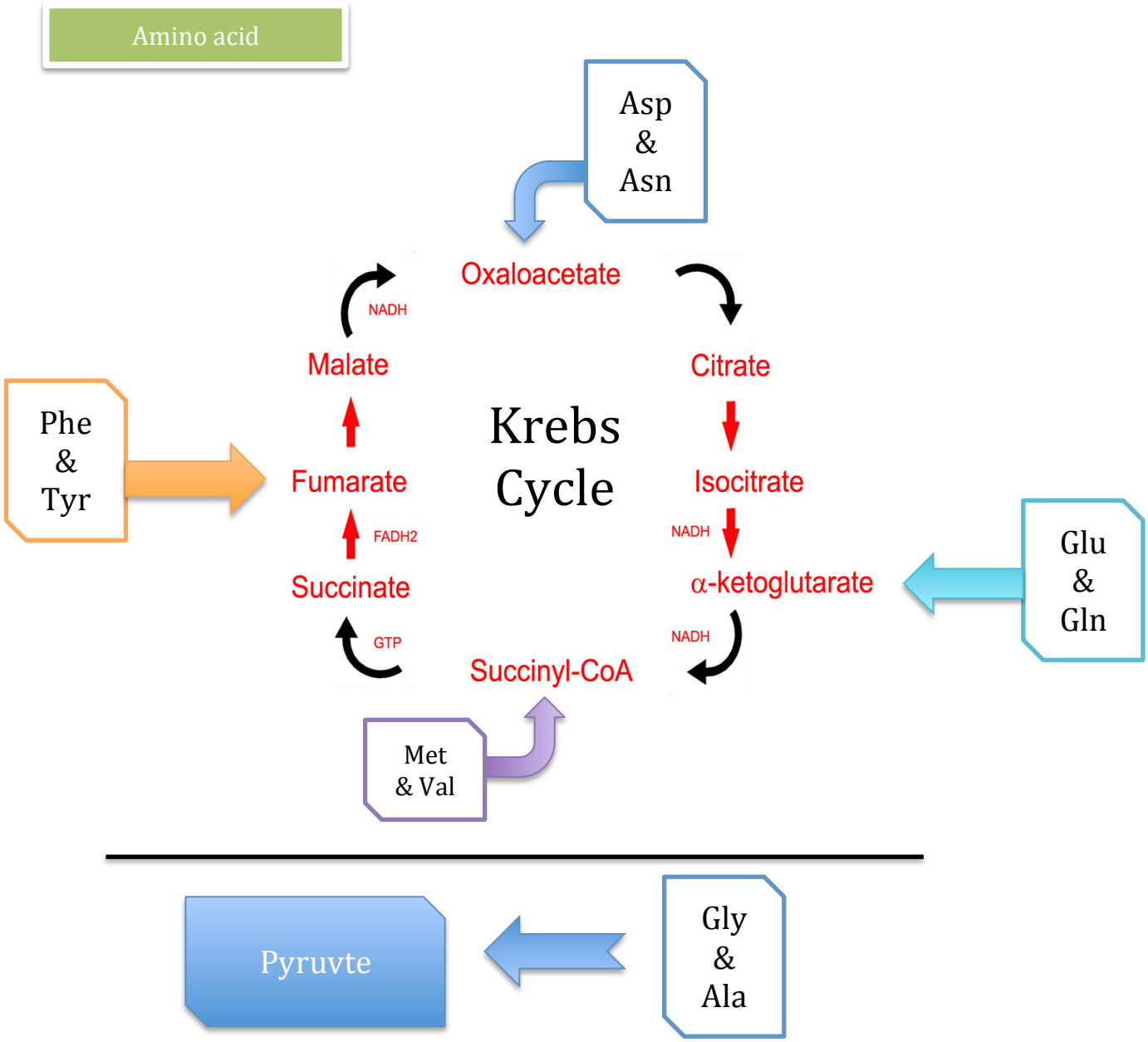



- Dephosphorylation reaction.
- Glucose with phosphate can't reach the blood. It must undergo dephosphorlyation.




1) Glycerol is released during the hydrolysis of Triacylglycerol (TAG) in adipose tissue.
2) In liver and kidney, glycerol will be phosphorylated by glycerol kinase to glycerol-P.
3) Glycerol-P will be oxidized by glycerol-P dehydrogenase to dihydroxyacetone phosphate(DHAP: an intermediate of glycolysis).
4) Then Dihydroxyacetone will go to the cycle and complete its way to glucose.
5) All steps were done in **CYTOSOLL**. (NOT mitochondria)

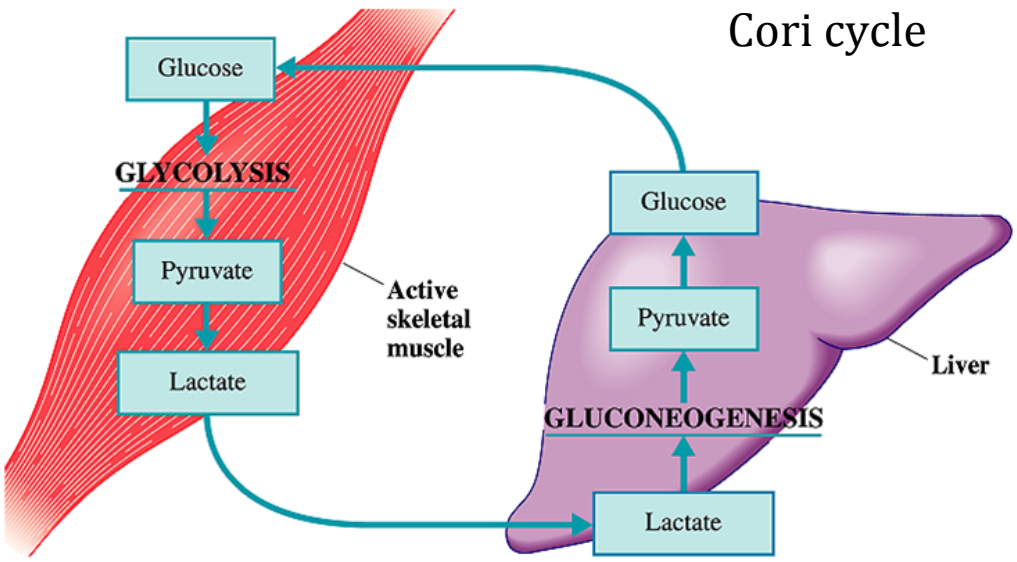



1) Amino acids can be derived from hydrolysis of tissue proteins.
2) Amino acids enter Krebs cycle (except Ala & Gly) then complete its way to glucose.

| Amino Acids | Sites of entrance to the Krebs Cycle |
|---|---|
| Glutamate (Glu) and Glutamine (Gln) | Alpha keto Glutarate (αKG) |
| Methionine (Met) & Valine (Val) | Succinyl CoA |
| Phenylalanine (Phe) & Tyrosine (Tyr) | Fumarate |
| Aspartate (Asp) & Asparagine (Asn) | Oxaloacetate (OAA) |

Alanine (Ala) & Glycine (Gly) amino acids are gluconeogenic substrates through conversion to Pyruvate.

Lactate




1) Lactate is released into the blood by exercising skeletal muscle & by cells lacking mitochondria (Anaerobic glycolysis of glucose).
2) Lactate is taken up by the liver and reconverted to glucose (gluconeogenesis).
3) Glucose will then be released to the circulation to be used by skeletal muscles.

## Gluconeogenesis Regulation :

| Inhibitor /inducer | Outcome |
|---|---|
| ↑ **Acetyl CoA** | ↑ Pyruvate carboxilation |
| ↑ **ATP or** ↓ **AMP** (energy-rich state in cells) | ↑ F 1,6-bisphospatase |
| ↓ **F 2,6-bisphosphate** | |
| ↑ **AMP** (energy-poor state in cells) | Inhibit F 1,6-bisphospatase |
| ↓ **Insulin** | ↓ Gluconeogenesis |
| ↑ **Glucagon** | |
| ↑ **Gluconeogenesis** | ↓ F 2,6-bisphosphate |
| | ↑ PEP-CK |

Glucolysis & Gluconeogenesis are Reciprocal reaction