Lecture 1
Session 3
Tricarboxylic Acid Cycle & Gluconeogenesis

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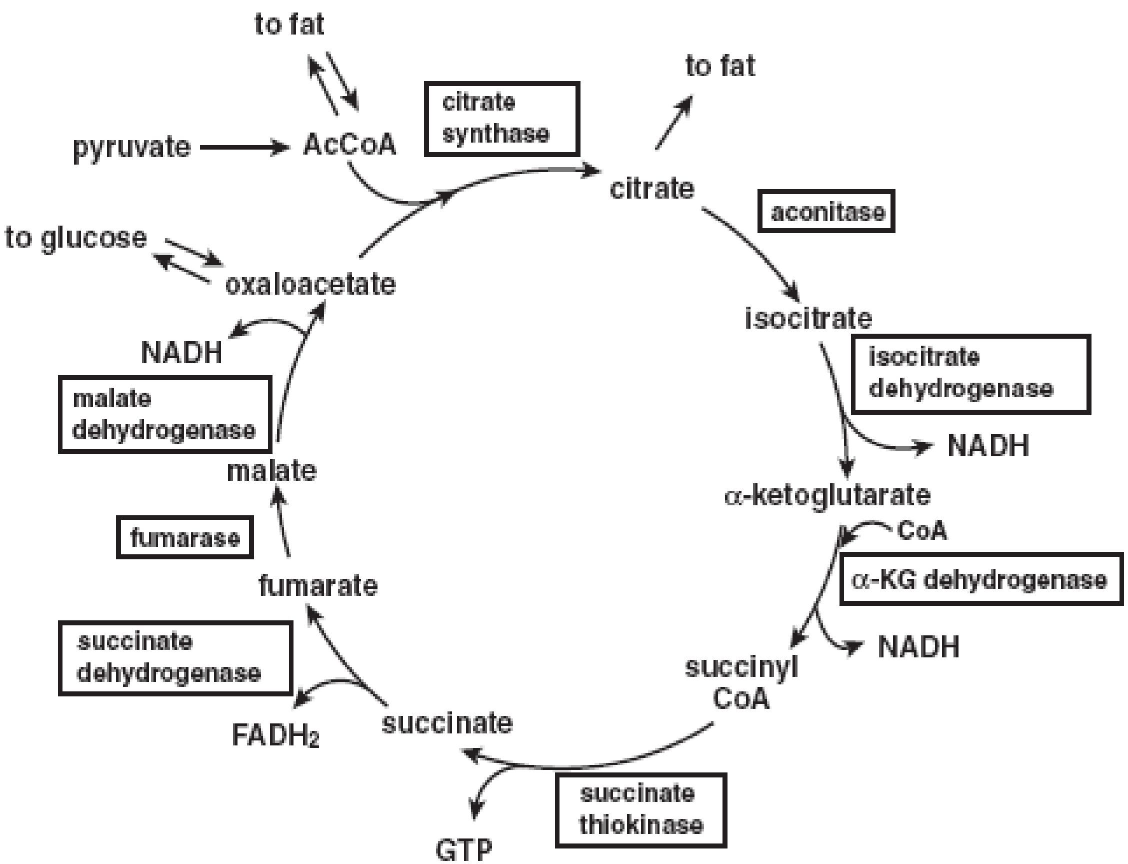
Tricarboxylic Acid Cycle (TCA)

- **This is the stage 3 of CHO metabolism. It is an** oxidative pathway that occurs in **mitochondria** The overall equation for the pathway is:



Functions of TCA

- **Catabolism** of sugars, fatty acids, ketone bodies, alcohol and amino acids leads to formation of acetyle CoA and CO_2. (Main function)
- The H+ and e- removed from **acetate** are transferred to NAD+ and FAD (stage 4 **energy production**) .
- **Anabolic** (**biosynthetic**) of the intermediates include:
- α-ketoglutarate, succinate, fumarate and malate used for the synthesis of nonessential **amino acids**.
- Succinate and oxaloacetate used in synthesis of **heme and glucose**
- Citrate used in synthesis of **fatty acids.**

Regulation of the TCA cycle

- **Two major signals feed information on the rate of utilization of ATP to the TCA cycle:**
    - ATP/ADP ratio
    - NADH/NAD+ ratio
- **One of the early irreversible steps of the TCA cycle (catalysed by *isocitrate dehydrogenase*) is**
- inhibited by the high-energy signal NADH and
- activated by the low-energy signal ADP.

Gluconeogenesis (GNG)

- Is a metabolic pathway that results in the generation of glucose from non- carbohydrate carbon substrates

such as:

- pyruvate,
- lactate,
- Glycerol,
- glucogenic amino acids and
- Odd chain fatty acids (propionate)

Gluconeogenesis (GNG)

- It is one of the two main mechanisms humans use to keep blood glucose levels from dropping too low (hypoglycemia).
- The other means of maintaining blood glucose levels is through the degradation of glycogen (glycogenolysis).

Gluconeogenesis (GNG)

- In vertebrates, gluconeogenesis takes place mainly in the **liver** and, to a lesser extent, in the cortex of **kidneys**.
- The process occurs during periods of **fasting**, **starvation**, **low** – carbohydrate diet or severe **exercise**.
- Gluconeogenesis is also a target of therapy for type II diabetes, such as **metformin**, which inhibits glucose formation and stimulates glucose uptake by cells.

Gluconeogenesis

Check point

- **Why Gluconeogenesis process occur in the liver only ?**
- **What is the importance of this process in kidney cortex?**

Why Gluconeogenesis is important?

1. Glucose is necessary as a **source of energy**, especially for the brain and RBCs.

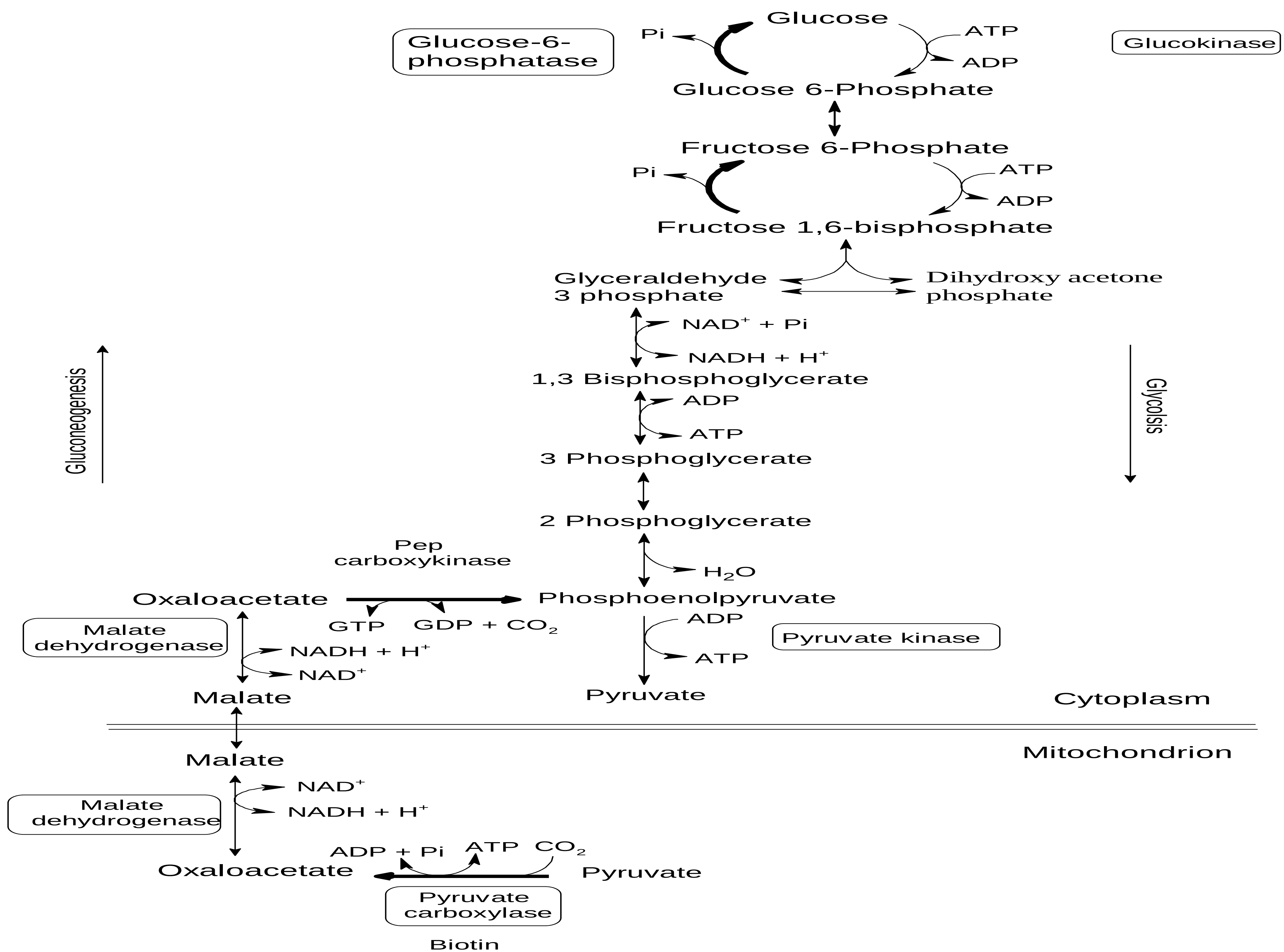
- Below the critical glucose level (＜45mg/dL) there is brain dysfunction which can lead to coma and death.

2. **Even under conditions where fat may be supplying most of the calorie requirements, there is, always basal requirements for glucose for example:**

- glucose is the **only** fuel that supplies energy to the skeletal muscles under anaerobic conditions.
- Also, glucose is the precursor of **milk sugar** (lactose) in lactating mammary glands.

3. **Gluconeogenesis used to clear the products of metabolism of other tissues from the blood e.g.**

- **lactate** (produced by muscles and RBCs) and
- **glycerol** (produced by adipose tissue in glycolysis).



Glucose
Pi
ATP
ADP
Glucose-6-phosphatase
Glucokinase
Glucose 6-Phosphate
Fructose 6-Phosphate
Pi
ATP
ADP
Fructose 1,6-bisphosphate
Glyceraldehyde 3 phosphate
Dihydroxy acetone phosphate
NAD+ + Pi
NADH + H+
1,3 Bisphosphoglycerate
ADP
ATP
3 Phosphoglycerate
2 Phosphoglycerate
H2O
Gluconeogenesis
Glycolsis
Pep carboxykinase
Oxaloacetate
Phosphoenolpyruvate
GTP
GDP + CO2
ADP
ATP
Pyruvate kinase
Malate dehydrogenase
NADH + H+
NAD+
Malate
Pyruvate
Cytoplasm
Mitochondrion
Malate
NAD+
NADH + H+
Malate dehydrogenase
ADP + Pi
ATP
CO2
Oxaloacetate
Pyruvate
Pyruvate carboxylase
Biotin

Regulation of gluconeogenesis

- Gluconeogenesis occurs as part of the response to stress situations (e.g. fasting, starvation, prolonged exercise) and is largely under hormonal control.
- The major control sites are *PEPCK* and *Fructose 1,6-bisphosphatase*. The activity of *PEPCK* is **increased** by glucagon and cortisol and **decreased** by insulin
- The activity of *Fructose 1,6- bisphosphatase* is also increased by glucagon and decreased by insulin
- The insulin/glucagon ratio plays a major role in determining the rate of gluconeogenesis.
- In the absence of adequate levels of biologically effective insulin, such as occurs in **diabetes**, increased rates of gluconeogenesis contribute significantly to the hyperglycaemia.