

GLUCOSE OXIDATION AND SHUTTLES

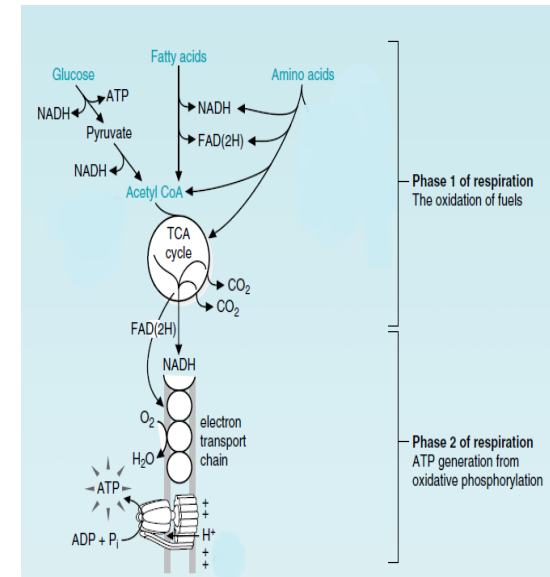
- ✓ All physiologic processes in living cells require energy transformation. Cells convert the chemical bond energy in foods into other forms

CELLULAR RESPIRATION:

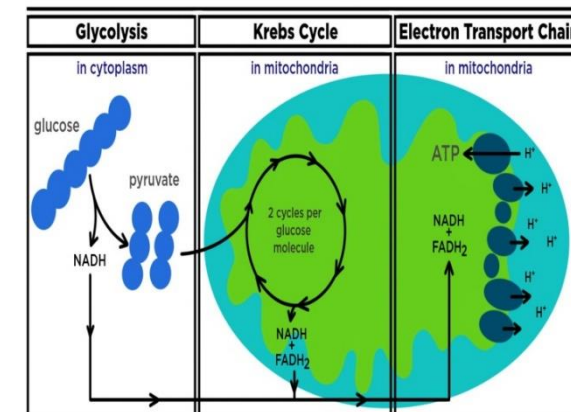
- ✓ The process of using **O₂** and energy-derived from **oxidizing fuels** (CHO, lipids, protein) to generate **ATP**.
- ✓ We breathe principally because Cells require O₂ to generate ATP from the oxidation of fuels to CO₂ and water.
- ✓ Cellular respiration uses over 90% of the O₂ we inhale.

These energy transformations can be divided into three principal phases:

Phase 1 Oxidation of fuels (carbohydrates, lipids and proteins).	1-Oxidation of (glucose, fatty acids, and many amino acids) converge on the generation of acetyl CoA 2- complete oxidation of the acetyl group to CO₂ occurs in the tricarboxylic acid (TCA) cycle , which collects the energy mostly as NADH and FADH₂ .
Phase 2 of cellular respiration (synthesis of ATP)	1-The energy derived from fuel oxidation(NADH and FADH₂) is converted to the high-energy phosphate bonds of ATP by the process of oxidative phosphorylation Electrons are transferred from NADH and FADH ₂ to O ₂ by the electron transport chain (ETC, located in the inner mitochondrial membrane). These series of reactions are coupled with the synthesis of ATP
Phase 3 of cellular respiration (consumption of ATP)	The high-energy phosphate bonds of ATP are used for processes such as muscle contraction (mechanical work), maintaining low intracellular Na concentrations (transport work), synthesis of larger molecules such as DNA in anabolic pathways (biosynthetic work), or detoxification (biochemical work). -ATP is either directly or indirectly hydrolyzed to ADP+ inorganic phosphate (Pi), or AMP + pyrophosphate (PPi).



What is Cellular Respiration?



Mitochondria is the site for cellular respiration

- Almost all of the enzymes for the **TCA cycle** and oxidation of fatty acids located in the **mitochondrial matrix** (phase 1)
- The components of the **ETC** are located in the **inner mitochondrial membrane** (phase 2).

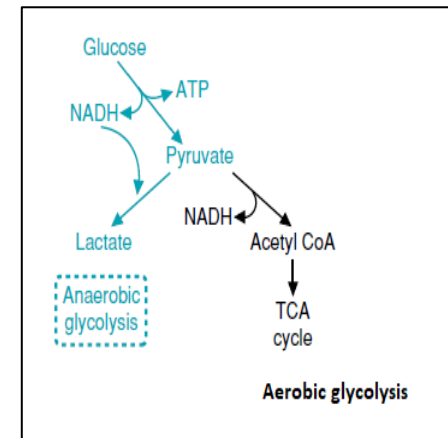
Examples of cellular respiration

❖ **Glucose is a universal fuel used to generate ATP in every cell type in the body**

In glycolysis, 1 mole of **glucose** is oxidized to **2 pyruvate** + **2 NADH** by cytosolic enzymes + **2 ATP** by **substrate-level phosphorylation** from high-energy metabolic intermediates.

In anaerobic glycolysis

- **NADH** is reoxidized by conversion of **pyruvate to lactate**, enters the blood.
- Although **anaerobic glycolysis** has a **low ATP yield**, it is important for tissues that **lack of mitochondria** (e.g., R.B.Cs, the kidney medulla), or **tissues experiencing diminished blood flow** (exercising muscle)



❖ Fate of the end products of aerobic glycolysis (pyruvate and NADH)

- 1- Pyruvate:** In presence of **O₂** and **mitochondria**, pyruvate is transported to **mitochondria** and undergoes **oxidative decarboxylation to acetyl CoA** which is the major fuel of the **TCA** cycle.
 - 2- Cytosolic NADH:** is reoxidized via the **electron transport chain**, but Cytosolic NADH **cannot directly pass** through **inner mitochondrial** membrane to reach the **electron transport chain**.
- **NADH is indirectly transferred to the inside of the mitochondria by what is called the shuttle mechanisms**

A-Malate aspartate shuttle

B-Glycerolphosphate shuttle

- Many tissues contain both the glycerophosphate shuttle and the malate–aspartate shuttle.

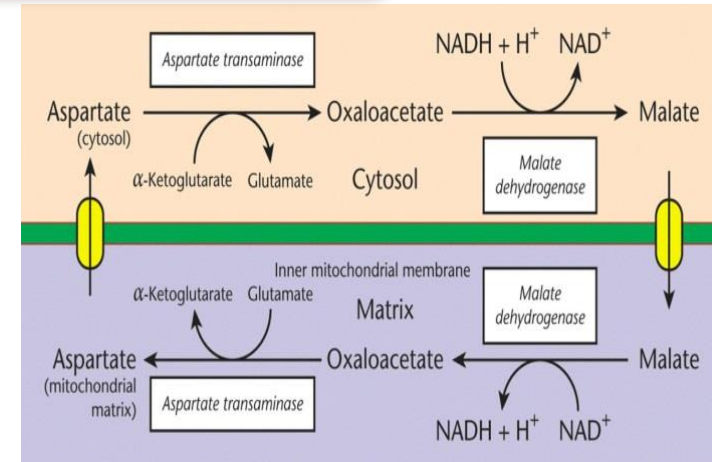
(1) THE MALATE-ASPARTATE SHUTTLE (MALATE SHUTTLE)

- The cytosolic **malate dehydrogenase (MDH)** enzyme transfers electrons from NADH to cytosolic **Oxaloacetate** → **Malate**.
- Malate** is transported across the inner mitochondrial membrane by a specific translocase.
- In the mitochondrial matrix, **Malate** is oxidized back to → **Oxaloacetate** by **mitochondrial malate dehydrogenase**, and **NADH is generated**.

-This NADH can donate electrons to the **electron transport chain** with generation of approximately **3 moles of ATP per mole of NADH**.

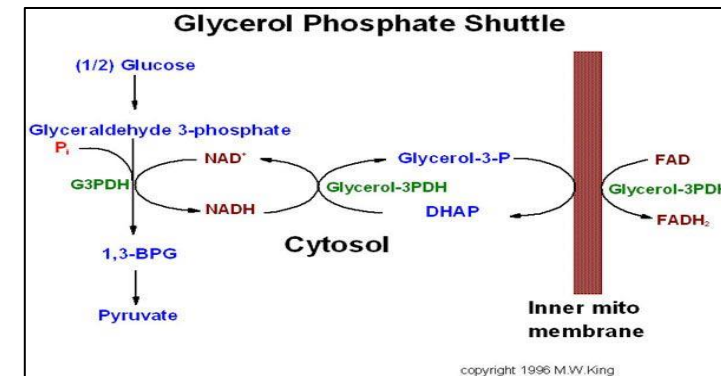
- The newly formed oxaloacetate cannot pass back through the inner mitochondrial membrane under physiologic conditions.

-Therefore, oxaloacetate is converted by **Aspartate transaminase (AST)** into **aspartate**. Then, transported out to the cytosol using an **aspartate/glutamate exchange translocase**



(2) THE GLYCEROLPHOSPHATE SHUTTLE:

- The glycerolphosphate shuttle is the **major shuttle** in most tissues.
- Cytoplasmic **glycerol 3-phosphate dehydrogenase** transfers electrons from NADH to **DHAP** to form **glycerol 3-phosphate**
- Glycerol 3-phosphate** then diffuses to the inner mitochondrial membrane, where the electrons are donated to **FAD forming FADH₂**.
- FADH₂** by using the **ETC** results in the synthesis of **approximately 2 ATP**.
- Dihydroxyacetone phosphate returns to the cytosol to continue the shuttle.



OXIDATIVE DECARBOXYLATION OF PYRUVATE BY PYRUVATE DEHYDROGENASE COMPLEX (PDH) COMPLEX

- Pyruvate is transported to the **inside of the mitochondria** to be completely oxidized in the **TCA cycle**
- Within the mitochondria, pyruvate undergoes **oxidative decarboxylation** catalyzed by the enzyme **pyruvate dehydrogenase complex (PDH)** to form **acetyl CoA**

✓ The complex contains three enzymes:

- Pyruvate dehydrogenase, dihyrolipoyl transacetylase and dihydrolipoyl dehydrogenase

✓ PDH complex needs five coenzymes: ~~pyruvate~~

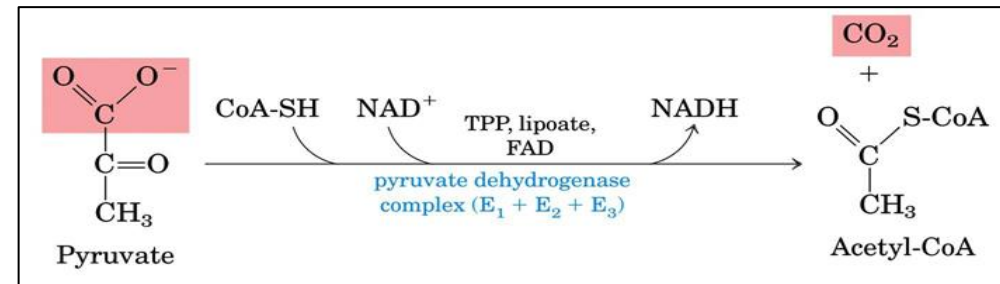
1-Thiamin pyrophosphate (TPP)

2-Lipoic acid

3-COASH

4-FAD

5-NAD⁺

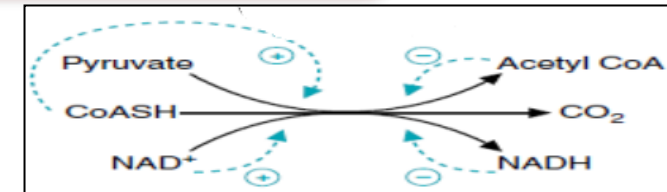


- Now, the **acetyl CoA** formed from pyruvate is ready to be completely oxidized in the **TCA cycle**.

REGULATION OF PYRUVATE DEHYDROGENASE COMPLEX: *مهم*

1- Allosteric regulation

PDH is **inhibited** by its products, **acetyl CoA** and **NADH**.
stimulated by **pyruvate** and **NAD**



2- Covalent Modification:

- ✓ PDH is **activated** through **Dephosphorylation** by **pyruvate dehydrogenase phosphatase**
- ✓ PDH is **inhibited** through **phosphorylation** by **pyruvate dehydrogenase kinase** (PDH kinase).

PDH KINASE:

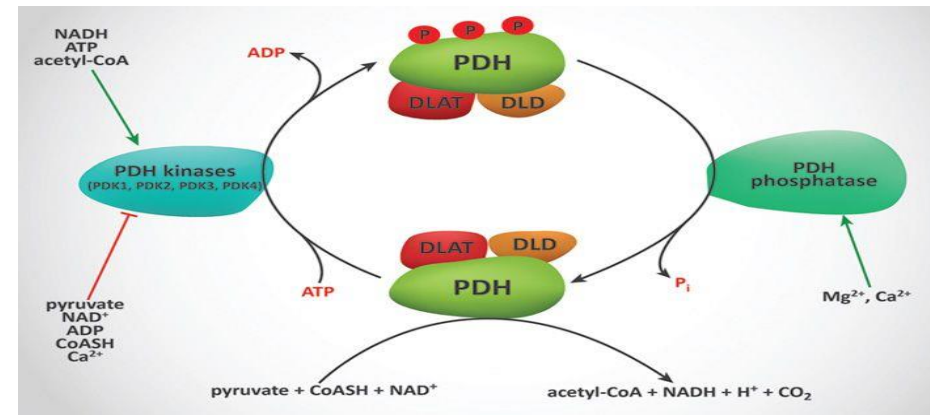
PDH kinase is, itself, **inhibited** allosterically by **ADP** and **pyruvate**. (Thus, when rapid ATP utilization results in an **increase of ADP**, or when activation of glycolysis **increases pyruvate levels**, **PDH kinase is inhibited**, and **PDH remains in the active form (non-phosphorylated form)**. i.e. (Inhibition of inhibitor) → stimulation

PDH kinase is activated by Both **acetyl CoA** and **NADH** which results in **phosphorylation of PDH and inactivation**. i.e. stimulation of inhibitor → inhibition

PDH PHOSPHATASE:

- ✓ Requires calcium for its full activity.

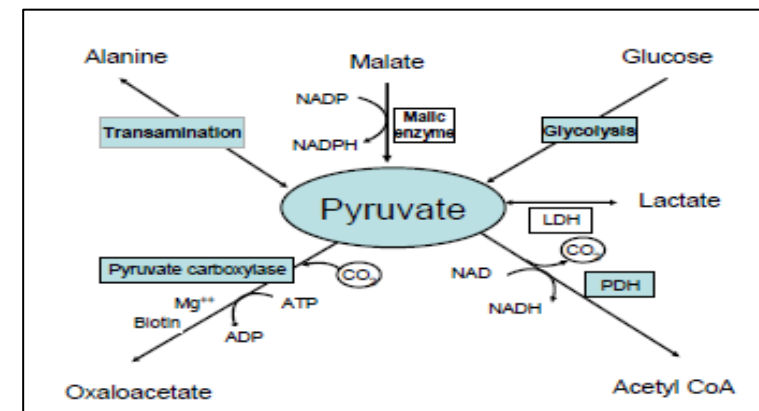
(In the heart, increased intramitochondrial Ca^{2+} during rapid contraction activates the phosphatase, thereby increasing the amount of active, non-phosphorylated PDH).



N.B. **Insulin** favor the **active, dephosphorylated** form while **glucagon** favors the **phosphorylated, inactive** form

Other Fates of Pyruvate:

- ✓ Pyruvate is a central molecule in metabolism. It has several metabolic fates
- ✓ **N.B.** *Pyruvate carboxylase, malic and PDH catalyze irreversible reactions, while lactate dehydrogenase (LDH) and transamination reactions are reversible*



may be due to

1. **Congenital deficiency of the enzyme** (which is rare). The defect may be in one or more of the components of the enzyme complex.
2. **Dietary deficiency of thiamin pyrophosphate (TPP)** in populations that use **white polished rice** as a main source of carbohydrates.
 - This explains the symptoms and signs noted in patients suffering from **Beriberi**.
3. **Alcohol addiction** is accompanied by nutritional deprivation of **thiamin pyrophosphate** because of impaired intestinal absorption of thiamin. Some individuals with alcoholism develop **Wernicke-Korsakoff syndrome** because brain depends on glucose as a preferred fuel, so it is a prominent tissue where these metabolic defects manifest themselves.
4. **Arsenite**: Inhibits enzymes require **lipoic acid** as a **cofactor** as **PDH and α -ketoglutarate dehydrogenase complex** (a TCA cycle enzyme). When arsenite binds to lipoic acid in PDH, pyruvate and consequently lactate accumulate.

LACTIC ACIDOSIS:

abnormalities of the PDH lead to accumulation of lactate.

Blood lactate accumulation results in lowering of blood pH (a serious condition).