METABOLISM

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ARKAN ACADEMY

Regulation of metabolism

- Metabolism can be regulated by:
  - **Signals within the cells** which is considered as a **rapid** response
    - ✓ It includes Substrate availability, Product inhibition and Allosteric (inhibitors or stimulators)
  - **Intercellular communications** which is **slower** response
    - ✓ It usually involves receptor mediated formation of second messenger such as cAMP, PKA, Ca^{+2}
    - ✓ GPCR is the most common membrane receptor, and it has 7 transmembrane domains
    - ✓ Receptor activation and second messenger formation can be either:
      1) *Synaptic:* Which depends on ***neurotransmitters*** by paracrine secretion
      2) *Endocrine:* Which depends on hormones delivered by the ***blood***
      3) *Direct contact:* by Gap junction and membrane bound ligands

Glycolysis

- It is a catabolic linear pathway
  - Breaks glucose into *2 pyruvates* (without the production of CO_2) with ATP production
  - It is a *universal* pathway occurs in all cell types
  - It is an *anaerobic pathway* (occur with or without Oxygen)
- It consists of 10 steps of 2 phases (preparative and ATP generating phases)

Preparative Phase

- It ***consumes 2 ATP*** molecules per glucose molecule

1) *Hexokinase or Glucokinase*

- Phosphorylates glucose into *glucose 6-phosphate* with the consumption of **ATP**
  - Phosphate is negatively charged so ***traps*** glucose 6 phosphate in the cell
- *Hexokinase:* It is widely distributed (all tissues), less specific (mannose, fructose, glucose) and can act at any sugar concentration (due to its *high affinity*)
- *Glucokinase:* In liver, highly specific (glucose only), act only at high glucose concentration (*low affinity*)

2) *Phosphoglucose Isomerase*

- Converts glucose 6-phosphate into *fructose 6-phosphate*

3) *Phosphofructokinase (PFK)*

- It is the **rate limiting** step and the committed step of glycolysis
- Phosphorylates fructose 6-phosphate into *fructose 1,6-bisphosphate* using **ATP**

4) *Aldolase*

- Cleavage of fructose 1,6-bisphosphate into *DHAP* and *G3P*

DHAP: Dihydroxyacetone Phosphate

G3P: Glyceraldehyde 3 Phosphate

5) *Triose phosphate isomerase*

- Converts DHAP into *G3P*

ATP generating Phase

- It ***Produces 4 ATP*** and ***2 NADH*** molecules per glucose molecule

6) *Glyceraldehyde 3-phosphate dehydrogenase*

- Converts G3P into *1,3 bisphosphoglycerate* and produces *NADH* + H^+

The P used here is **inorganic** phosphate

7) *Phosphoglycerate kinase*

- It phosphorylates ADP into *ATP* producing *3-phosphoglycerate*

8) *Phosphoglycerate mutase*

- Isomerization of 3-phosphoglycerate into *2-phosphoglycerate*

All glycolysis steps are reversible except 1,3, 10 which are catalyzed by kinases

9) *Enolase*

- Forming double bond, producing *phosphoenolpyruvate*

10) *Pyruvate kinase*

- Converts phosphoenolpyruvate into ***pyruvate*** and phosphorylates ADP into ***ATP***
  - Pyruvate is a 3-C molecule
- All the glycolytic steps are **reversible** except steps 1, 3 and 10 which are irreversible

- RBCs are the cells responsible for O_2 transport in the blood
- To *increase the efficiency of O_2 transport* and prevent rebinding of O_2 to hemoglobin, a shunt in ATP production in step 7 could happen
  - Producing *2,3-bisphosphoglycerate* via a mutase instead of 3-phosphoglycerate
  - No net production of ATP

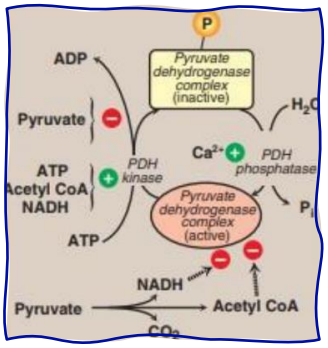
Pyruvate Fates

- Under aerobic conditions, pyruvate is oxidized into acetyl CoA then enters TCA cycle
  - **Pyruvate oxidation** is done by *pyruvate dehydrogenase* (PDH) in the mitochondrial *matrix*
  - Pyruvate is transported into the mitochondria by a specific transporter

- PDH complex consists of ***3 enzymes***, E1 (decarboxylase), E2 (dihydrolipoyl transacetylase) and E3 (dihydrolipoyl dehydrogenase) which is similar to α-Ketoglutarate dehydrogenase
  - ✓ E1 requires ***TPP*** as a coenzyme
  - ✓ E2 requires ***CoA*** and ***Lipoic*** acid as coenzymes
  - ✓ E3 requires ***NAD***$^{+}$ and ***FAD*** as coenzymes

- Pyruvate oxidation results in the production of *1 CO_2*, *1 NADH* and *acetyl CoA*

- PDH is regulated by many ways:
  - ✓ It is activated by PDH *Phosphatase*
  - ✓ It is inhibited by PDH *Kinase*, *NADH* and *acetyl CoA*
  - ✓ Indirect activation: *Ca^{+2}* (activate phosphatase), *Pyruvate* (inhibit kinase)
  - ✓ Indirect inhibition: *ATP*, NADH and acetyl CoA (activate kinase)



- PDH disorders and deficiency can cause ***lactic acidosis*** due to the accumulation of pyruvate then converted into lactic acid it can be caused by:
  - ✓ Deficient coenzyme
  - ✓ Deficient regulator
  - ✓ Deficient enzyme component
    - *E1 deficiency* is X-linked genetic disorder and the most common cause of congenital lactic acidosis which has no treatment
    - The most sensitive organ for this issue is: ***Brain***
    - It can cause neurodegeneration, muscle spasticity and can cause early death
    - Can be relieved by ***dietary restriction on carbohydrates***
    - ***TPP supplementary*** can reduce symptoms
    - ***Arsenic poisoning*** cause E1 disorders

- In the anaerobic conditions, it undergoes **fermentation** (recycle NAD^{+} from NADH)

1) Lactic acid fermentation

- Pyruvate is converted into *lactate* by *lactate dehydrogenase* which converts *NADH into NAD^{+}*
- Occurs in *RBCs*, rigorous *muscle exercising* and *hypoxia*
  - Hypoxia can be caused due to collapse of circulatory system (impaired O_2 transport), respiratory failure, uncontrolled hemorrhage (hypovolemic shock, causing decrease in hemoglobin)
  - It occurs during inhibition of oxidative phosphorylation (aerobic) directly
  - It occurs during alcohol intoxication which increases the ratio of NADH/NAD^{+}
  - Accumulation of pyruvate due to decreased Gluconeogenesis and pyruvate carboxylase activity or Decreased pyruvate dehydrogenase and TCA cycle activity

- Lactate accumulation causes fatigue
  - ***Lacic acidosis*** causes decrease in the pH (high production of lactic acid, or low utilization of it)

2) Alcohol fermentation

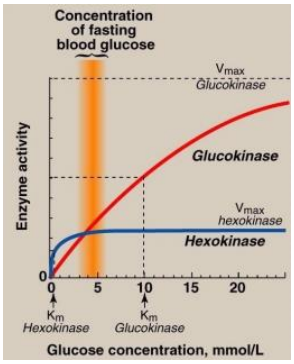
- It occurs in the *yeast*
- Pyruvate is decarboxylated into acetaldehyde and then reduced into *ethanol* which involves the conversion of *NADH into* NAD^+

Glycolysis Regulation

- Activators of the glycolysis are inhibitors of the gluconeogenesis and vice versa
- ATP inhibits glycolysis enzymes and AMP activates them
- Regulation is done mainly for the irreversible steps (1,3 and 10):

1) Glucokinase and Hexokinase Activity

- Hexokinase is <u>active</u> at low glucose concentration, but glucokinase is <u>inactive</u>
- At ***low glucose level***, glucokinase is *sequestered in the nucleus* bound to glucokinase regulatory protein (GKRP), which dissociate from it when glucose level increases after a meal
- After the activation of glycolysis, when ***fructose 6-phosphate*** level is high, sequestration is activated



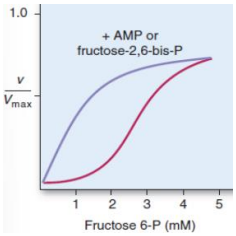
2) Phosphofructokinase-1

- Activated by *Fructose-2,6-bisphosphate* and *AMP*
- *ATP*, *Citrate* and *protons* inhibits glycolysis

3) Pyruvate Kinase

- Activated by *fructose 1,6-bisphosphate* (feed forward activation)
- Inhibited by *ATP* and *alanine* (a precursor of pyruvate)

- Insulin activates glycolysis but glucagon inhibits it
  - Both of them act on the GPCR that increases cAMP, and activates PKA
  - Insulin leads to inhibit PKA but glucagon activates it
  - Active PKA, it phosphorylates bifunctional enzyme (PFK-2, fructose 2,6-bisphosphate phosphatase)



- When *insulin is high*: the bifunctional enzyme **isn't** phosphorylated and Kinase is active causing the production of fructose-2,6-bisphosphate causing activation of glycolysis
- When *Glucagon is high*: the bifunctional enzyme is phosphorylated and *phosphatase is active* causing the break down of fructose-2,6-bisphosphate causing *no activation* of glycolysis

- ***Pyruvate Kinase Deficiency:*** The most common among glycolytic enzyme deficiencies
  - ATP is required for the Na^+/K^+ pump activity which maintains the flexibility of RBC shape
  - When ATP is deficient, mild to severe chronic hemolytic anemia and premature death of RBCs occur

- Inorganic Inhibitors of Glycolysis:
  - *Fluoride:* used as a **toothpaste**, inhibits bacterial ***Enolase*** which prevents dental carries
  - *Pentavalent Arsenic (Arsenate):* competes phosphate as a substrate for ***GA3PDH*** (decrease ATP)
  - *Trivalent Arsenic (Arsenite):* Forms stable complex with -SH of lipoic acid, inhibiting ***Pyruvate Dehydrogenase*** and α ketoglutarate Dehydrogenase
    - ✓ Arsenic poisoning causes neurologic disturbances which can cause death

Past Papers

1. The effect of arsenate poisoning:
   A. Inhibits PDH
   B. Inhibits G3P dehydrogenase
   C. Activates bifunctional enzyme
   D. All of the above

2. When pyruvate is converted to lactate one statement is correct:
   A. NADH is oxidized into NAD+
   B. NAD+ is reduced into NADH
   C. CoA is attached
   D. It involves the formation of acetaldehyde as an intermediate of the reaction

3. One is wrong about PFK- 2 (bi-functional enzyme):
   A. Protein kinase A phosphorylates the enzyme and activates it
   B. Protein kinase A phosphorylates the enzyme and inhibits it
   C. Activated by glucagon
   D. All of the above

4. How many CO2 molecules result from the oxidation of one mole of glucose?
   A. 4
   B. 2
   C. 3
   D. 1
   E. 6

5. Net of ATP that results of glycolysis:
   A. 4
   B. 2
   C. 1
   D. 0
   E. 6

6. Which of the following inhibits pyruvate kinase activity?
   A. Fructose 1-phosphate
   B. AMP
   C. NAD+
   D. Alanine

7. Rate limiting step of glycolysis is catalyzed by:
   A. Glucokinase
   B. Phosphofructokinase 2
   C. Phosphofructokinase 1
   D. Hexokinase

8. Where does Pyruvate Dehydrogenase reaction occur?

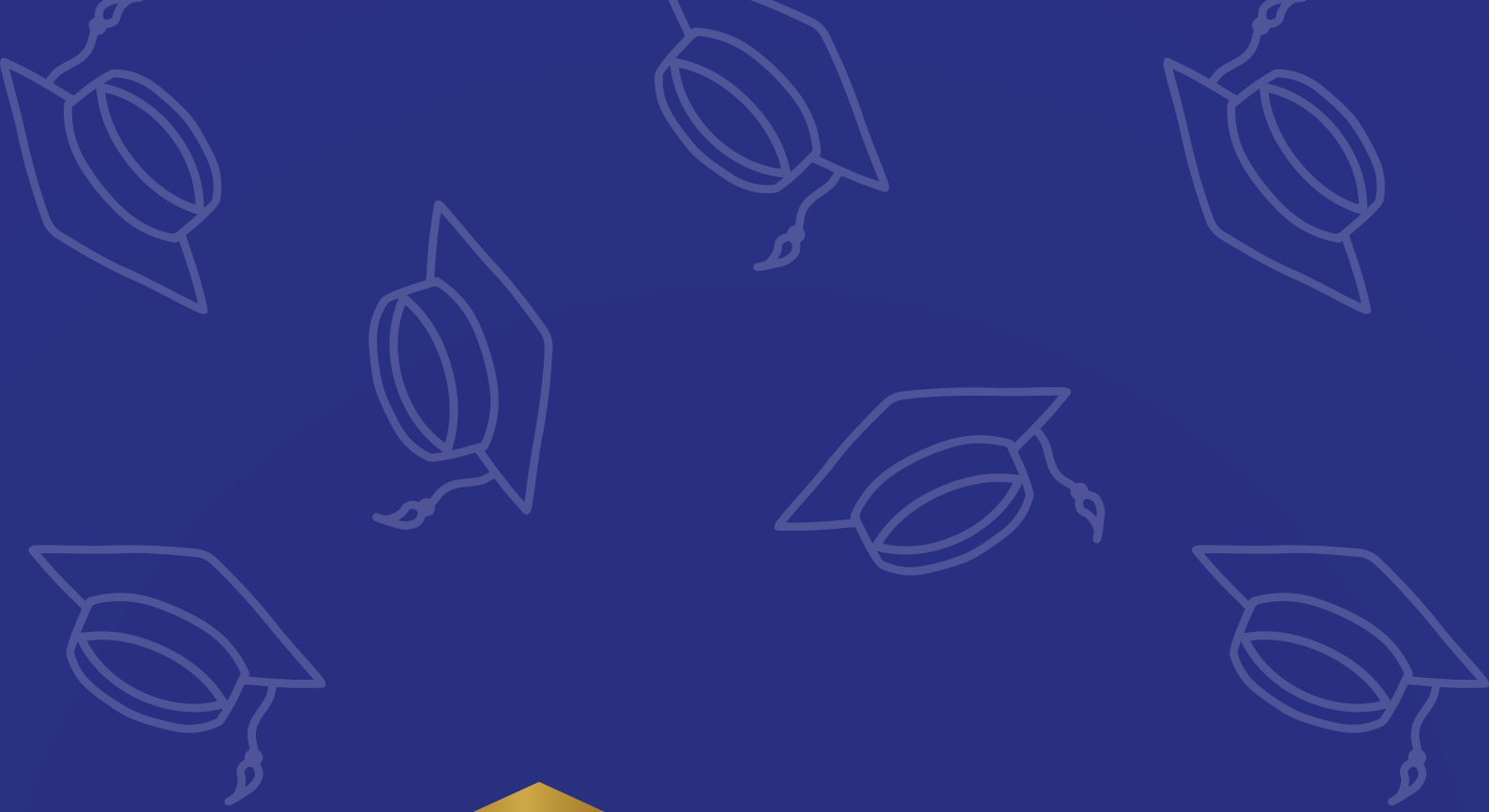
   A. Cytosol
   B. Mitochondrial Matrix
   C. Intermembrane Space

9. Which enzyme deficiency causes hemolytic anemia?

   A. Glucokinase
   B. Phosphofructokinase 2
   C. Phosphofructokinase 1
   D. Hexokinase
   E. Pyruvate kinase

10. All of the following cause lactic acidosis, except:

   A. Deficiency of pyruvate dehydrogenase
   B. Inhibition of electron transport chain
   C. Inhibition of Phosphofructokinase-1
   D. Low blood absorption of O_2 in lungs



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