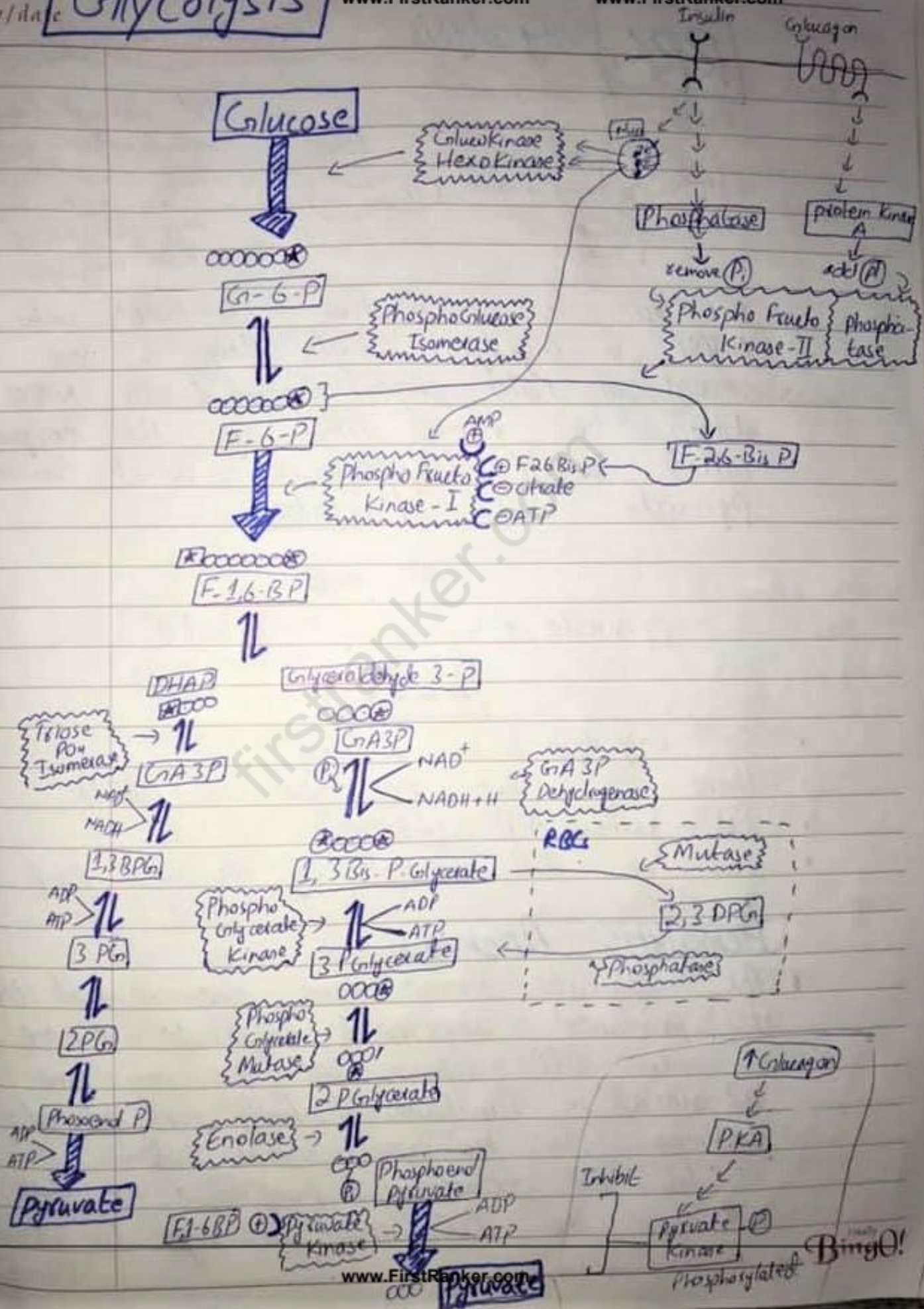
day/date

Glycolysis



Glycolysis

Part ①

⇒ • The metabolic pathway in which you breakdown glucose into two molecule of pyruvate by releasing energy as ATP and NADH

- If there is oxygen and mitochondria available in cell then pyruvate → Kreb's cycle. (Aerobic Glycolysis)
- If there is no mitochondria and O_2 present in cell then pyruvate → Lactic Acid (Anaerobic Glycolysis)

→ • Glycolysis take place in all cell of a body.

- Red blood cell → have anerobic glycolysis b/c no mitochondria present
  - onest transporter of O_2
  - It have high O_2 but RBC doesnot utilized O_2 to itself only transfer lung to tissue.

→ • Glylycolysis is a cytosolic pathway.

Transport of Glucose to cell..

- Glucose coming from GIT, it absorbed through the portal system into liver.
- Hepatocytes are specialized in extracting the Glucose and store it so only small amount of Glucose go to general circulation.
- So high level of Glucose stored in liver cell, so that in General circulation it doesnot produce Hyperglycem
- ~~In fasting~~

- In fasting stage, not high glucose passing through portal system, so liver cell are capable of releasing glucose back to circulation, so blood glucose leve does not drop dangerously

liver cell is bank of Glucose
extra glucose → captured
less glucose → released

- monosaccharides are Glucose, fructose and galactose so liver cell take the fructose and galactose convert them to glucose then pass to circulation.
- Glucose from blood goes into interstitial fluid then into cell.
- Glucose freely moves b/w blood and interstitial fluid, same conc. in both.
- cell is not permeable to large molecule of Glucose, so cell have special type of transporter for Glucose.

Glucose transp across cell

- facilitated diffusion
  - GLUT
    - 14 types
      - ① + ② → most of tissue, eg. CNS or RBC
        - high affinity to ③
      - ④ → skeletal M, adipose tissue
        - dependent of insulin.
      - ② → two way transporter
        - liver, kidney, Beell of pancreas
- ③ high to low by facilitated GLUT.
- ⑤ - Na co-transpo

Liver

- Gluconeogenesis → formation of Glucose from non-carbohydrate product. (also in kidney)
- Glycogenesis → formation of glycogen.
- glycogenolysis → glycogen is broken.

GLUT (5) → fructose transporter
↳ GIT, Testes, sperm

GLUT (7) → Endoplasmic reticulum.

Glycolysis

⇒ (1) → Glucose transport in to cell by GLUT.

⇒ (2) → Make Glucose highly polar by attaching PO_4 phosphate to make it Polar. (G)-6-ph

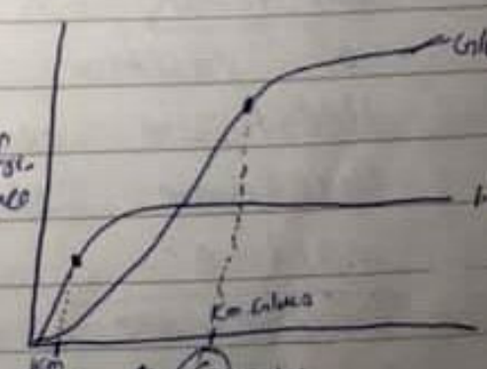
Imp. (3) → Enzyme that capture (G) and bind to PO_4 by called Kinase. → (2) types (Hexo and Gluco

Hexokinase → slightly increase (G) conc., the power of reaction goes very rapidly up, upto plateu.

Glucokinase → little (G) it doesnot perform, as keep increase in (G) conc. it keep perform more.

one way reaction not reversible

- most of the tissue have Hexokinase, have less amount of (G), it Phosphated by it.
- liver and some other have Glucokinase, bc there is high amount of (G) in cell



Add Ⓟ → Kinase

Km of an enzyme :

The conc. of a substrate at which half of the enzyme is saturated, and half is not.

Vmax of an enzyme :

all the Ⓖ conc is saturated

Imp ★ So HexoKinase have high affinity for Ⓖ and Glucokinase have less affinity for Ⓖ

★ Hexokinase • low Km and • low Vmax
Glucokinase • high Km and • high Vmax

⇒ Ⓖ → Ⓖ-6 phosphate little change in area in Glucose molecule convert it into Fructose-6-phosphate by enzyme called

Phospho Glucose Isomerase → It is reversible

★ **Regulation of Hexo and Gluco Kinase :-**

Hexokinase and Glucosekinase is very well regulated enzyme.

Hexokinase is inhibited by its product of reaction.

Hexokinase are present in cytoplasm so Ⓖ Hexokinase active and if Ⓖ-6Ⓟ ↑ hexo inactive.

Glucokinase They are extremely well regula Glucokinase are present in Nucleus

Glucokinase regulating protein present in the nucleus of hepatocyte cell of liver where Glucose kinase binds

- ★ • So Ⓖ conc. in liver cell is high, then Ⓖ goes into nucleus and pull out the Glucokinase in cyto, convert Ⓖ to Ⓖ-6Ⓟ but Ⓖ-6-Ⓟ doesnot take Glucokinase back to nucleus to stop its activity it (Ⓕ-6-Ⓟ) → that pushed Glucokinase back into nucleus
- Hexokinase is specific to Ⓖ Ⓕ Gal
- X Glucokinase is specific to Ⓖ X

Glucokinase is specific to Ⓖ Ⓕ and Gal

⇒ (S) → Ⓕ-6-Ⓟ to Ⓕ-1,6-Bis Ⓟ.

phospho fructo kinase enzyme. → one way reaction
↳ well regulated enzyme.

Another enzyme which take back reac
called Phospho Fructos-1,6 Bisphosphatase enzyme.
↳ remove phosphate.

- ★ • If cell is in poor energy then Phosphofructo k enzyme work to take reaction forward. to produce energy.

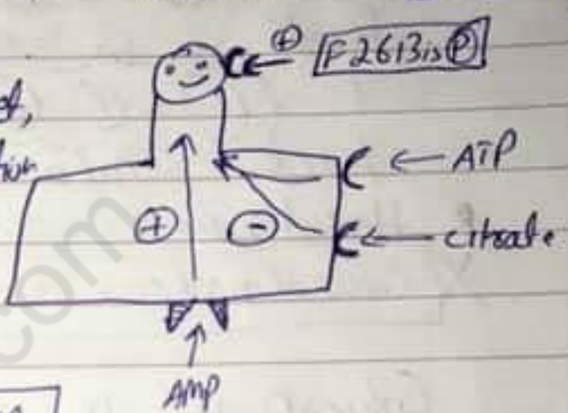
If cell is high in energy then Phospho fructo 1-6 Bisphos enzyme work to take reaction backward and energy is consumed

- Phospho fructo kinase it have multiple point where ATP, citrate and Amp attach to sense whats going on in the cell.

most Imp in Glycolysis

- Cell need energy, ATP less, citrate also less, Amp is very high → mean cell is breakdown of ATP very bad level, then Phospho fructo Kinase become active b/c Amp attached to it. → ⊕ regulator
- More ATP, more citrate, no AMP then cell does not need more energy it have enough energy Then this enzyme become inactive. → ⊖ regulator

- Enzyme have certain packet, due to changes in interaction with this packets, this enzyme work, these type of enzyme called Allosteric regulation enzyme.



ATP, citrate and AMP allosteric regulate the Phospho-Fructo Kinase-1

- Phospho-fructo Kinase-1 also ⊕ regulated by Fructose-2,6-Bisphosphate → It a very strong allosteric regulator. regulator.

? - Fructose-⑥-phosphat also convert in Fructose, 2-6 Bisphoate when there is a million of Fructose⑥-6 Bisphosphate present some of them convert into Fructos, 2-6 Bisphate. then reaction goes in forward direction. to so ~~ce~~ then Fructose ⑥ phosphate convert to Fructose 1-6 Bis ph

- First small amount of F⑥P convert to F②⑥ Bis P then it stimulate the phospho fructo Kinase Then F⑥P convert to F 1-6 Bis P.

day/date

How the ⓖ level in blood determine Glycolysis?

Most power activator of Phospho fructo kinase is F-2,6-Bis P* [Thermophectict enzyme]?

- The enzyme which convert F-6-P to F 2-6 Bis P ~~Gated~~ is double action Enzyme.

opposite action enzyme
- one component → Phospho fructo Kinase-2 (b/c ⓟ add at 2nd posit
- 2nd component → phosphatase → It reverse the rxn by removing ⓟ.

F-6-P —PF Kinase 2→ F-2-6 Bis P

ⓟ F-2-6 Bis P —Phosphatase→ F-6-P

- ⓖ ↑ in blood Glycolysis ↑, ⓖ ↓ Glycolysis ↓

→ Glucose is low in blood → Insuline ↓, Glucagon ↑

- Glucagon high it stimulate receptor in cell act ~~from~~ Gs-stimulatory become active inside cell, then this stimulate Adenalyl cylase, then it convert ATP into ⓒ CAMP., then CAMP will stimulate Protein Kinase A, then this become active.
- Then Protein Kinase A Phosphoryl the double actior enzyme, so enzyme Kinase activity becom inactive and Phosphatase activity become active so Glycolysis stop.

→ • Glucose is high in blood → insuline ↑, Glucagon ↓.

The insuline stimulate Protein phosphatase in the cell that remove phosphate from double actior enzyme, then Kinase activity become activ Glycolysis move forward.

- F 2.6 Bis Ⓟ stimulate PFK-1 and break down phosphatase activity.

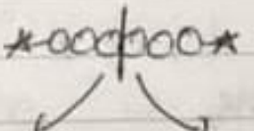
- Some of the signal of insulin go into nucleus and stimulate genes and then gene expression are increases mean that genes are more transcribed and mRNA produced, from that protein produced
  * some of these protein are ① Glucokinase and Hexokinase, ② Phosphofructose kinase 1 also produced these enzyme are irreversible enzyme.

Insulin ↑ → activate of enzyme
→ production of enzyme

③ Pyruvate Kinase enzyme are also produced on insulin ↑.
this is also irreversible enzyme.

⇒ ⑥ → F 1,6 Bis Ⓟ ⟶ (reversible rxn) DHAP + Glyceraldehyde 3. Ⓟ

Aldolase enzyme cut F 1,6 Bis Ⓟ and make product



DHAP
Dihydro acetone phosphate

Ⓟ at C ① — not same — Ⓟ at C ③

DHAP — Glyceraldehyde 3 Ⓟ

It doesn't involve in Glycolysis so it convert into Glyceraldehyde 3 Ⓟ by enzyme called

Triose Por isomerase

Glucose $\xrightarrow[HK,\ GK]{ATP\ \ ADP}$ G-6-Ⓟ → This Ⓟ comes from ATP

F.6 Ⓟ $\xrightarrow[PFK-I]{ATP\ \ ADP}$ F. 1.6 Bis Ⓟ

⇒ ⑦ → Glyceraldehyde 3-Ⓟ $\xrightarrow[NAD \rightarrow NADH+H]{Pi}$ 1,3-Bisphosphoglycera

- In this reaction aldehyde group convert into carboxylic group and lot of energy released some these energy is traped in form of NA and there also extra energy, this energy is traped by binding of phosphate to carbon no. 1.
- The enzyme which involves in this rxn called **Glyceraldehyde 3-Ⓟ Dehydrogenase** this enzyme have three pocket carrying Ⓟi, ~~G3P~~ GA3Ⓟ, NAD^+.
- 2NADH → ETC → **6 ATP** indirectly produced.

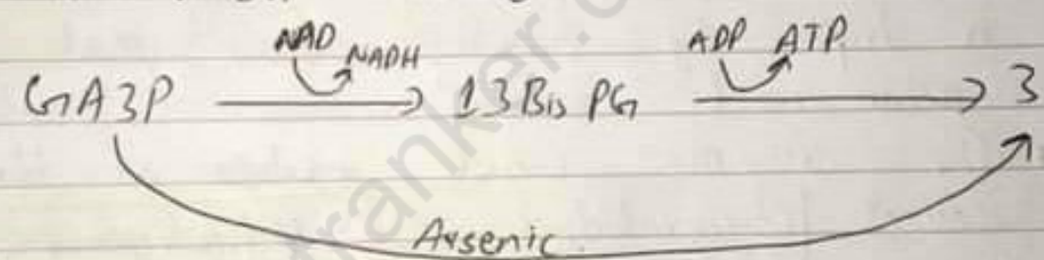
⇒ ⑧ → 1,3-Bisphosphoglycerate $\xrightarrow[ADP \rightarrow ATP]{}$ 3-phosphoglycer

Ⓟi remove from Carbon no. 1.

- ~~2~~ 2 ATP molecules produced from each side by removing 8Ⓟi from substrate and add into ADP by the help of enzyme.
- The enzyme which convert is called **phospho Glycerate Kinase**

- **Toxic drugs**
  - **Arsenic** → interfering enzyme function
    - → G.A.3P Dehydrogenase
    - → Pyruvate Dehydrogenase.

- Arsenic binds or GA3P Dehydrogenase where inorganic (Pi) binds.
- So Glyceral aldehyde 3 (P) directly convert into 3 Phosphoglycerate without the step of 1,3 Bisphosphoglycerate, so there is no ATP and NADH formed.



so glycolysis going on but energy not formed

In Red blood cell

1,3-Bisphosphoglycerate —(1,3 Bis PG Mutase)→ 2,3-DPG (2,3-Diphospho glycerate)

- 2,3-DPG increase the capacity of hemoglobin to release oxygen.
- 2,3 DPG cross linked the β chain of Hb A then Hb became narrow to release more oxygen to tissue.

2,3 DPG ——Phosphatase——→ 3PGlycerate

- ATP which is formed by oxidative phosphorylation in Electron transport chain
- ATP which is formed in Glycolysis step 1,3 Bis Phosphoglycerate ⟶ 3P Glycerate there ADP convert to ATP, this type of phosphorylation called substrate level phosphorylation

⇒ (9) → 3-phospho Glycerate ⟶ 2-phospho Glycerate
(Phospho Glycerate Mutase enzyme)

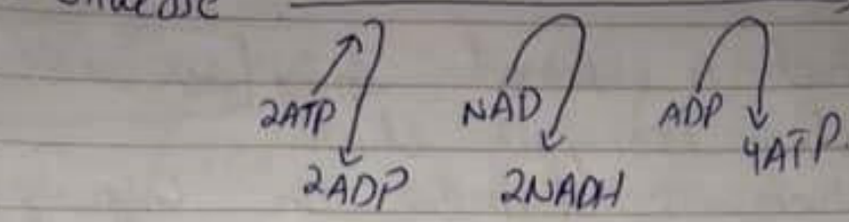
phosphate change its position from C3 to C2.

⇒ (10) → 2-phosphoGlycerate —Enolase enzyme→ Phosphoenol pyruvate + H_2O

From 2PG, we remove H_2O and loose the phosphate group, but not ~~dead~~ dealtach it.

⇒ (11) → phosphoenol pyruvate ⟶ Pyruvate
(ADP → ATP)

- The enzyme called Pyruvate Kinase
- This is 3rd irreversible rxn. regulated
- Pyruvate Kinase activated, ~~by the~~ Fructose 1-6. Bisphosphate so it increase its rxn.

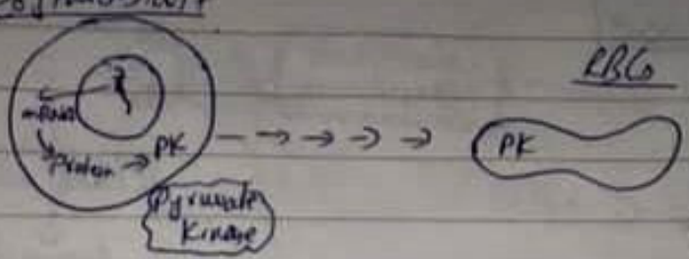


~~Net~~ ATP gain = 2ATP → Put 2ATP and 2ATP out
NADH = 2 mol. → 6ATP

Net gain of ATP 8ATP

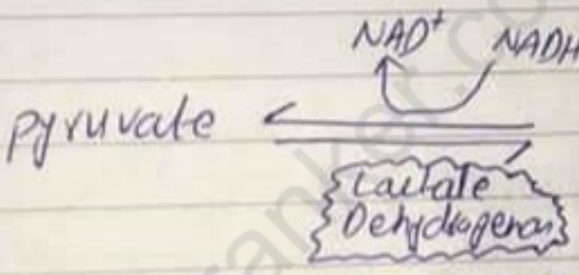
RBCs Glycolysis (Anaerobic Glycolysis)

Erythroblast



RBC do not have mitochondria. So there is no ETC, Citric cycle, so only get energy from Glycolysis.

- So there is conversion of NAD^+ into NADH in Glycolysis but there is less amount of NAD^+ present in RBC, so NADH utilized to formed NAD^+ by the enzyme called lactate dehydrogenase which convert Pyruvate into lactate.



- So Glycolysis is working.
- There is not net gain in NADH.
- Net gain ATP = 2ATP
- Some of ATP utlized by the Na^+K^+ pump in ATP.

Hemolytic Anemia

- The Pyruvate Kinase gene are mutant then it produced abnormal Pyruvate Kinase so in RBC PK are less in conc. abnormal in function ↓affinity for substrate, ↓ Vmax. so the rxn become slow. so less ATP produced, → pump ATPase not work well then the RBCs shape changes to spheric

it stuck into the capillaries in liver, where these eaten by macrophages it cause the pre-mature hemolysis of RBCs.

Hemolytic Anemia
↓ ↓
Breakdown of RBCs reduced RBCs count

Circumstance Anaerobic Glycolysis occur:-

Glycolysis

Anaerobic Gly
normally { RBCs, Leukocytes
Renal medulla
Testes, lens
invest → 2ATP
Recovery → 4ATP
Net NADH → 0
Net ATP → 2ATP

Aerobic
• mitochondria present in cell
• have O_2 in cell
invest → 2ATP
recovery → 4ATP
net → 2ATP
2NADH → 6ATP
Total net → 8ATP

- In Exercise, doing lot of work, utilizing more O_2 cause deficiency of O_2, it convert Pyruvat to lactate because NADH accumulated in NADH b/c of less O_2, so lactic acid accumulate in muscle cause cramp in muscle,
lactic acid accumulation → {lactic acidosis}

- Shock → heart is unable to pump due to MI, bleeding, blockage.
  → generalized hypoxia cause.

excessive muscle → lactate → heart → lactate → Pyruvate → Krebs cycle.
(NAD → NADH)

lactate → liver → NAD NADH → ETC.
lactate → Pyruvate → Krebs cycle gluconeogenesis

PEP
PK
NAD NADH
Lactate ⇌ Pyruvate
L.DH
Microbes
Acetaldehyde → Ethanol
CO_2
Pyruvate dehydrogenase
Acetyl CO.A

CO_2
Pyruvate → oxaloacetate
Pyruvate carboxylase