Glycolysis

- Glucose is the major energy substrate in certain tissues like brain
- Glycolysis occurs in the cell's cytosol
- it takes place in all organisms both aerobic and anaerobic (mostly!)
- The intermediates either: ① Provide entry points to the cycle ② They are useful directly! (anabolism)

- phosphorylation goals: ① Priming / Activation ② Tricking the cell by changing the glucose's form. ③ Trapping the sugar inside the cell. | keep continous influx!

Glucose

(Step 1) ATP → ADP (phosphorylation) (Priming) (Activation)

Glucose 6-Phosphate

(Step 2) isomaraization

- mediated by ⇒ phosphoglucose isomerase
- mannose + Fructose ⇒ enters glycolytic pathway at this point!.
- Reversibile.

Fructose 6-phosphate

(Step 3) ATP → ADP (phosphorylation)

- Goal ? Destabalize the ring!
- mediated by ⇒ Phosphofructo Kinase (PFK-1)
- rate limiting step (key regulatory step) ⇒ slowest step that determines the speed of the reaction.
- Phosphorylation of (OH) at carbon #1

Fructose 1,6-Biphosphate

(Step 4) Cleavage between C3-C4

- mediated by ⇒ Aldose
- Cleavage into 2 triose phosphates at the bond between C3-C4.

Glyceraldehyde 3-phosphate ⇒ GAP (then ×2)
Dihydroxyacetone phosphate ⇒ DHAP

- Can't go further! → isomerization to GAP! (Step 5) By Triose phosphate isomeraze.
- Precursor for glycerol → used for the formation of triglycerol!!

(Step 6) 2P, 2NAD⁺ → 2 NADH + H⁺

1,3-Biphosphoglycerate (2)

- Super High energy molecule (Storing)
- oxidative phosphorylation.
- by → Glyceraldehyde 3-phosphate dehydrogenase. Goal → making high energy molecule.
- electron donors / Reductants (J ⇒ Jols)!

(Step 7) 2ADP → 2ATP

3-phosphoglycerate (2)

- First ATP forming reaction (Direct Energy) (Substrate level formation)
- by ⇒ phosphoglycerate Kinase!

(Step 8) Reversabile (internal shifting)

2-phosphoglycerate (2)

- Only terminal shifting → C3 to C2
- isomaraization by: phosphoglycerate mutase
- Activation of phosphate group

(Step 9) → 2H₂O (Dehydration Reaction)

Phosphoenolpyruvate (2)

- 2nd super high energy molecule
- by ⇒ Enolase
- increase in the energy stored in phosphate.
- OH from Carbon #3 is gone
- H from Carbon #2 is gone
- Double bond between C3 + C2

(Step 10) 2ADP → 2ATP

- 2nd ATP is generated
- Substrate level formation By pyruvate kinase.

Pyruvate (2)

Regarding the Enzyme used in Step 1 (Hexokinase)

Hexokinase ⇒ different versions/isoforms exist in the Heart, brain and liver. same gene but different expressions

Hexokinase I, II, III:
- non specific
- can phosphorylate variety of hexoses like: ① glucose ② Mannose ... etc
- type I ⇒ is involved in the Catabolic pathways
- type II + III ⇒ involved in anabolic pathways.
- all the time phosphorylation. - allosterically inhibited by G6P at high level (product control mechanism)

Hexokinase IV:
- expressed in the liver and β-cells of pancreas.
- Specific for D-glucose
- Specific phosphorylation only when the blood glucose is high.

Bi → 2 but not close
Di → 2 close (beside eachother)

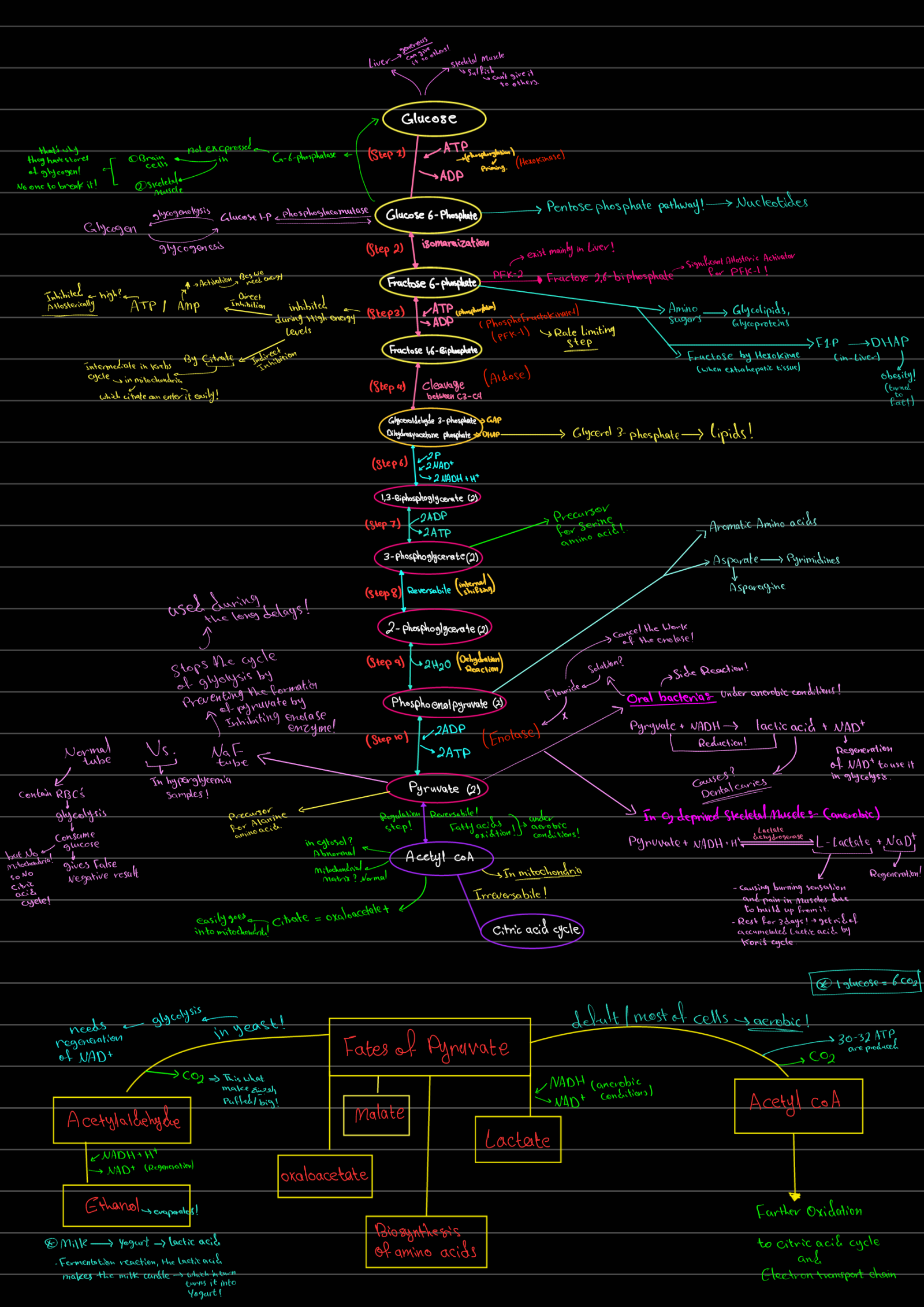
Regarding Step 6: Nicotinoamide Adenine Dinucleotide (NAD)

- NAD ⇒ deravative? Vit B3 (Niacin)
- exist in 2 forms: NAD⁺ (oxidized form), NADH (Reduced form) | - Coenzyme for dehydrogenases
- Energy rich molecule! indirect form of energy!

1 NADH = 2.5 ATP → only in aerobic conditions!

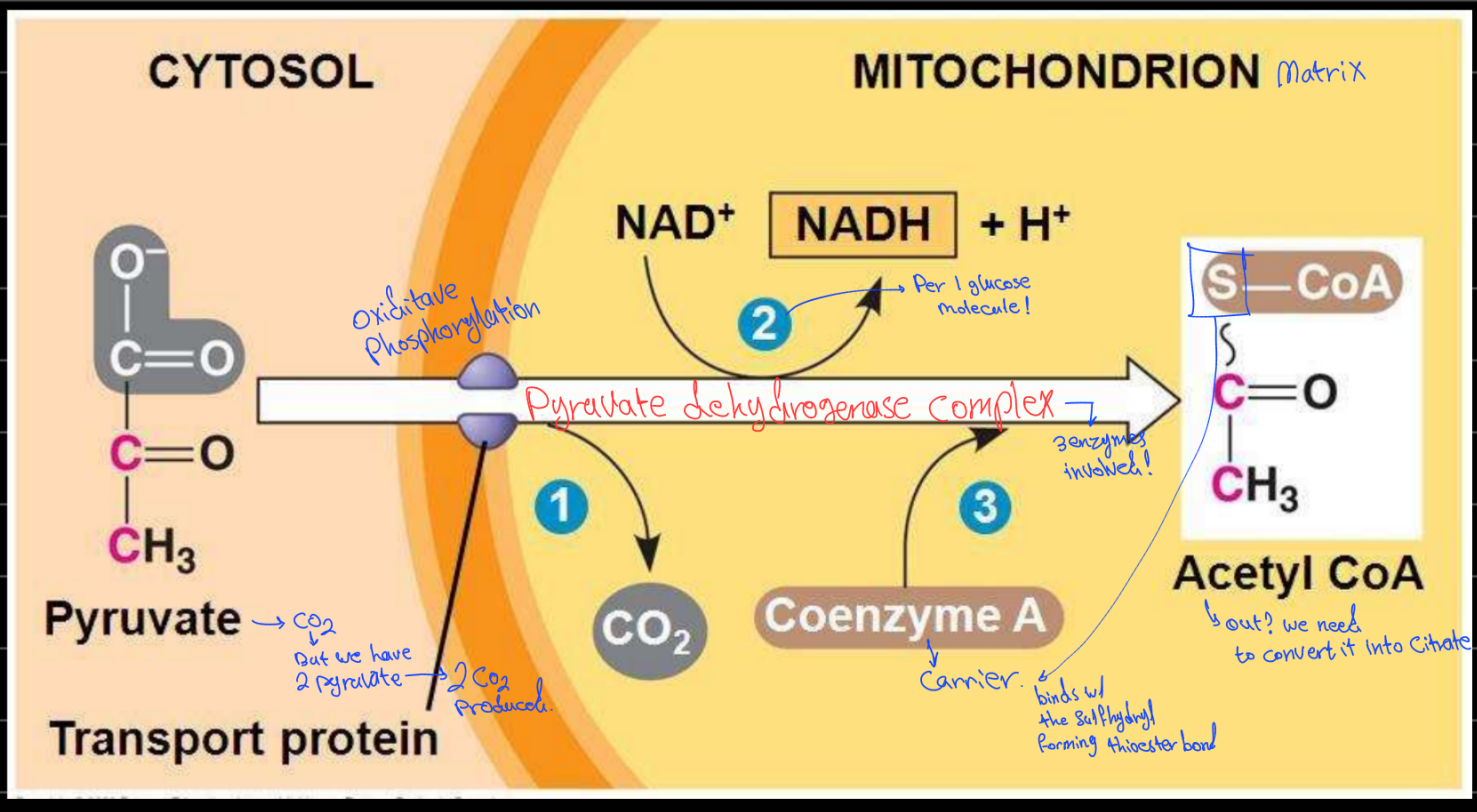
Net result of Glycolysis:

- 2 ATP (Steps 7, 10: 4 − 2 = 2 (steps 1, 3))
- 2 Pyruvate → End result
- 2 NADH → step 6


Liver → generous can give it to others!
Skeletal Muscle → Selfish → can't give it to others
Glucose
(Step 1)
ATP → ADP
(Phosphorylation) priming. (Hexokinase)
Not expressed in
Brain cells
Skeletal Muscle
G-6-phosphatase
that's why they have stores of glycogen! No one to break it!
Glucose 6-Phosphate
Pentose phosphate pathway! → Nucleotides
Glycogen
glycogenolysis
Glucose 1-P
phosphoglucomutase
glycogenesis
(Step 2) isomarization
exist mainly in Liver!
Fructose 6-phosphate
PFK-2
Fructose 2,6-biphosphate
Significant Allosteric Activator for PFK-1!
Inhibited Allosterically
high?
ATP / AMP
Activation
Because need energy
Direct Inhibition
inhibited during High energy levels
(Step3)
ATP → ADP
(Phosphofructokinase) (PFK-1)
Rate limiting step
Amino Sugars → Glycolipids, Glycoproteins
Fructose 1,6-Biphosphate
Fructose by Hexokinase (when extrahepatic tissue)
F-1-P → DHAP (in Liver)
obesity! (turned to fat!)
Intermediate in Krebs cycle → in mitochondria
By Citrate
Indirect Inhibition
which citrate can enter it easily!
(Step 4) cleavage between C3-C4 (Aldose)
Glyceraldehyde 3-phosphate → GAP
Dihydroxyacetone phosphate → DHAP
Glycerol 3-phosphate → Lipids!
(Step 6)
2P
2 NAD+ → 2 NADH + H+
1,3-Biphosphoglycerate (2)
(Step 7)
2ADP → 2ATP
Precursor for Serine amino acid!
3-phosphoglycerate (2)
Aromatic Amino acids
Asparate → Pyrimidines
Asparagine
(Step 8) Reversabile (internal shifting)
used during the long delays!
2-phosphoglycerate (2)
Stops the cycle of glycolysis by preventing the formation of pyruvate by inhibiting enolase enzyme!
(Step 9) 2H2O (Dehydration Reaction)
Cancel the Work of the enolase!
Fluoride
Solution?
Side Reaction!
Oral bacteria: Under anerobic conditions!
Phosphoenolpyruvate (2)
(Step 10) 2ADP → 2ATP (Enolase)
Pyruvate + NADH → lactic acid + NAD+
Reduction!
Regeneration of NAD+ to use it in glycolysis.
Causes? Dental caries
Normal tube
Vs.
NaF tube
In hyperglycemia samples!
Contain RBCs → glycolysis → Consume glucose → gives False Negative result
but No mitochondria! so No citric acid cycle!
Pyruvate (2)
Precursor for Alanine amino acid.
Regulation step!
Reversible!
Fatty acids oxidation! → under aerobic conditions!
In O2 deprived Skeletal Muscle = (Anerobic)
Pyruvate + NADH + H+ → (Lactate dehydrogenase) L-Lactate + NAD+
Regeneration!
- Causing burning sensation and pain in Muscles due to build up from it.
- Rest for 3days! → get rid of accumulated Lactic acid by Kori's cycle.
in cytosol? Abnormal
Mitochondrial Matrix? Normal
Acetyl coA
In mitochondria
Irreversabile!
easily goes into mitochondria!
Citrate = oxaloacetate +
Citric acid cycle
1 glucose = 6 CO2
Fates of Pyruvate
default / most of cells → aerobic!
needs regeneration of NAD+
glycolysis
in yeast!
30-32 ATP are produced
CO2
CO2 → This what make bread fluffed / big!
Acetylaldehyde
Acetyl coA
NADH + H+ → NAD+ (Regeneration)
Malate
NADH → NAD+ (anerobic conditions)
Lactate
Ethanol → evaporates!
oxaloacetate
Biosynthesis of amino acids
Further Oxidation
to citric acid cycle and Electron transport chain
Milk → Yogurt → lactic acid
- Fermentation reaction, the Lactic acid makes the milk curdle → which in turn turns it into Yogurt!

Acetyl CoA Formation ⇒ in aerobic conditions!

- occurs in the Mitochondrial matrix.
- Pyruvate (3C) ⟶ acetyl coA (2C)
- Shuttling of pyruvate from the cytosol is facilitated by Pyravate translocase, exists in the inner mitochondrial membrane!



Pyruvate Dehydrogenase Complex:

E1 E2 E3

CoEnzymes:

- Thiamine pyrophosphate (TPP) a prosthetic group of E1
- Lipoic acid (lipoamide) a prosthetic group of E2
- Flavin adenine dinucleotide (FAD) a prosthetic group of E3
- Coenzyme A (CoA or CoA-SH)
- Nicotinamide adenine dinucleotide (NAD+)

At the End of Kreb's Cycle, the products are:

4 ATP + 6 CO2 + 10 NADH + 2 FADH2

- 4 ATP → 2 glycolysis, 2 Kreps cycle.
- 6 CO2 → 3 glycolysis; 1 → Converting from Pyruvate to Acetyl coA; 2 → Kreb's cycle
- 10 NADH → 2 glycolysis; 2 Acetyl coA Production; 6 Kreb's cycle
- 2 FADH2 → Kreb's cycle.

In Cytosol

Glucose
(Step 1)
ATP
ADP
(phosphorylation) (Priming) (Activation)
Glucose 6-Phosphate
(Step 2)
isomaraization
Fructose 6-phosphate
(Step 3)
ATP
ADP
(phosphorylaltion)
Fructose 1,6-Biphosphate
(Step 4)
Cleavage between C3-C4
Glyceraldehyde 3-phosphate
Dihydroxyacetone phosphate
(Step 6)
2P
2NAD+
2 NADH + H+
1,3-Biphosphoglycerate (2)
(Step 7)
2ADP
2ATP
3-phosphoglycerate (2)
(Step 8)
Reversabile
(internal shifting)
2-phosphoglycerate (2)
(Step 9)
2H2O
(Dehydration Reaction)
Phosphoenolpyruvate (2)
(Step 10)
2ADP
2ATP
Pyruvate (2)
in mitochondria (aerobic)
CO2
Pyruvate dehydrogenase
Acetyl coA
(2C)

Cytosolic NADH Shuttling:

⇒ it can't go into the matrix, so where the e^- would go? by:

1. DHAP/G3P shuttle: (gives 1.5 ATP)
   - is active in brain and skeletal muscle.
   - it delivers the $2e^-$ from cytosolic NADH to mitochondrial FAD.
2. Asparate/Malate shuttle: (gives 2.5 ATP)
   - is active in liver and heart.
   - it delivers the $2e^-$ from cytosolic NADH to mitochondrial NAD^+, "by the membrane catching".

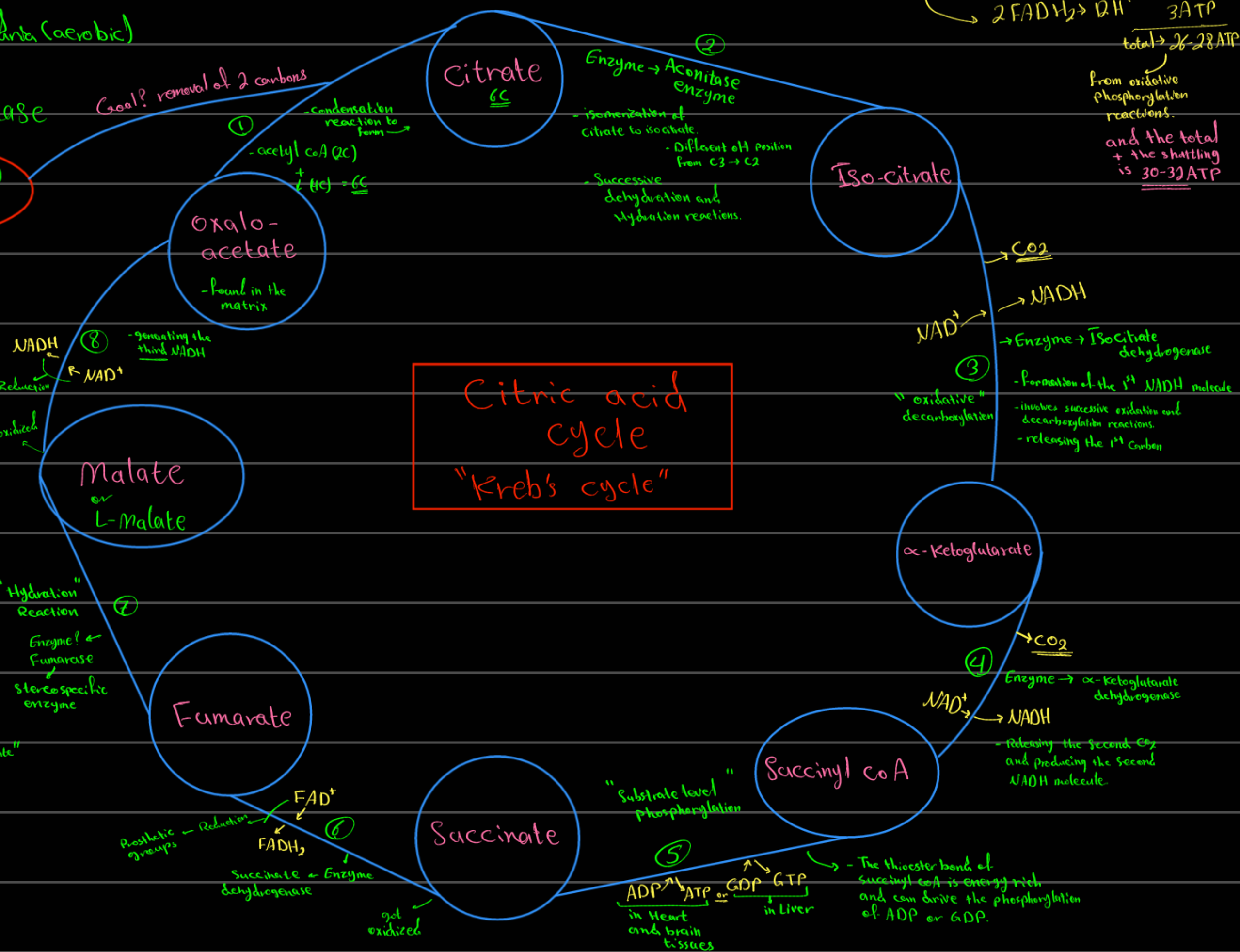
- Biosynthetic Role of TCA intermediates:

1. Succinyl coA is used in synthesis of Heme and other porphrins.
2. Oxaloacetate is converted by transamination to the amino acid Asparate. α-ketoglutamate " " " " " " " glutamate. } → Anaploretic Pathways.
3. Citrate in some tissues is transported to the cytosol where it is converted back to Acetyl coA for fatty acids biosynthesis.

ATP count ⇒
1. Glycolysis — 12-20 H^+ pumped — 3-5 ATP
2. Acetyl coA Production — 20 H^+ " — 5 ATP
3. Kreb's cycle
   - 6 NADH → 60 H^+ — 15 ATP
   - 2 $FADH_2$ → 12 H^+ — 3 ATP

total → 26-28 ATP from oxidative phosphorylation reactions.

and the total + the shuttling is 30-32 ATP



Goal? removal of 2 carbons
1
- condensation reaction to form
- acetyl coA (2C) + (4C) = 6C
Citrate
6C
2
Enzyme → Aconitase enzyme
- isomerization of citrate to isocitrate.
- Different OH position from C3 → C2
- Successive dehydration and hydration reactions.
Iso-citrate
CO2
NAD+
NADH
→ Enzyme → Isocitrate dehydrogenase
3
" oxidative " decarboxylation
- Formation of the 1st NADH molecule
- involves successive oxidation and decarboxylation reactions.
- releasing the 1st Carbon
α-Ketoglutarate
CO2
4
Enzyme → α-Ketoglutarate dehydrogenase
NAD+
NADH
- Releasing the second CO2 and producing the second NADH molecule.
Succinyl coA
- The thioester bond of succinyl coA is energy rich and can drive the phosphorylation of ADP or GDP.
" Substrate level phosphorylation "
5
ADP
ATP
or
GDP
GTP
in Heart and brain tissues
in Liver
Succinate
got oxidized
FAD+
FADH2
6
Prosthetic groups ← Reduction
Succinate ← Enzyme dehydrogenase
Fumarate
" Hydration " Reaction
7
Enzyme? ← Fumarase
stereospecific enzyme
Malate or L-Malate
oxidized
Reduction
NADH
NAD+
8
- generating the third NADH
Oxalo-acetate
- found in the matrix
Citric acid cycle
"Kreb's cycle"

Notes on the Steps:

Step 1)

Pyruvate —(Pyruvate Carboxylate)→ oxaloacetate (→ Anaploretic Pathway)

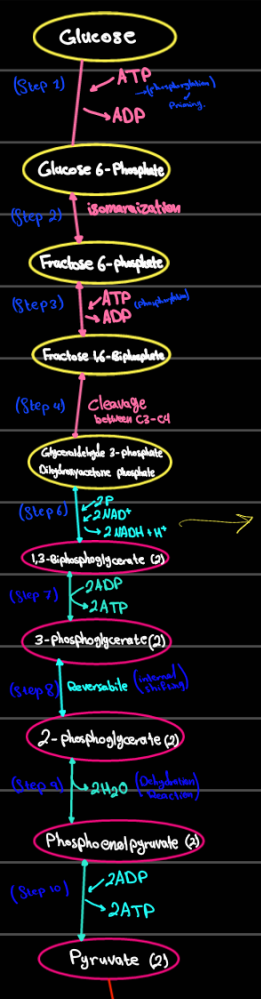
Step 6)

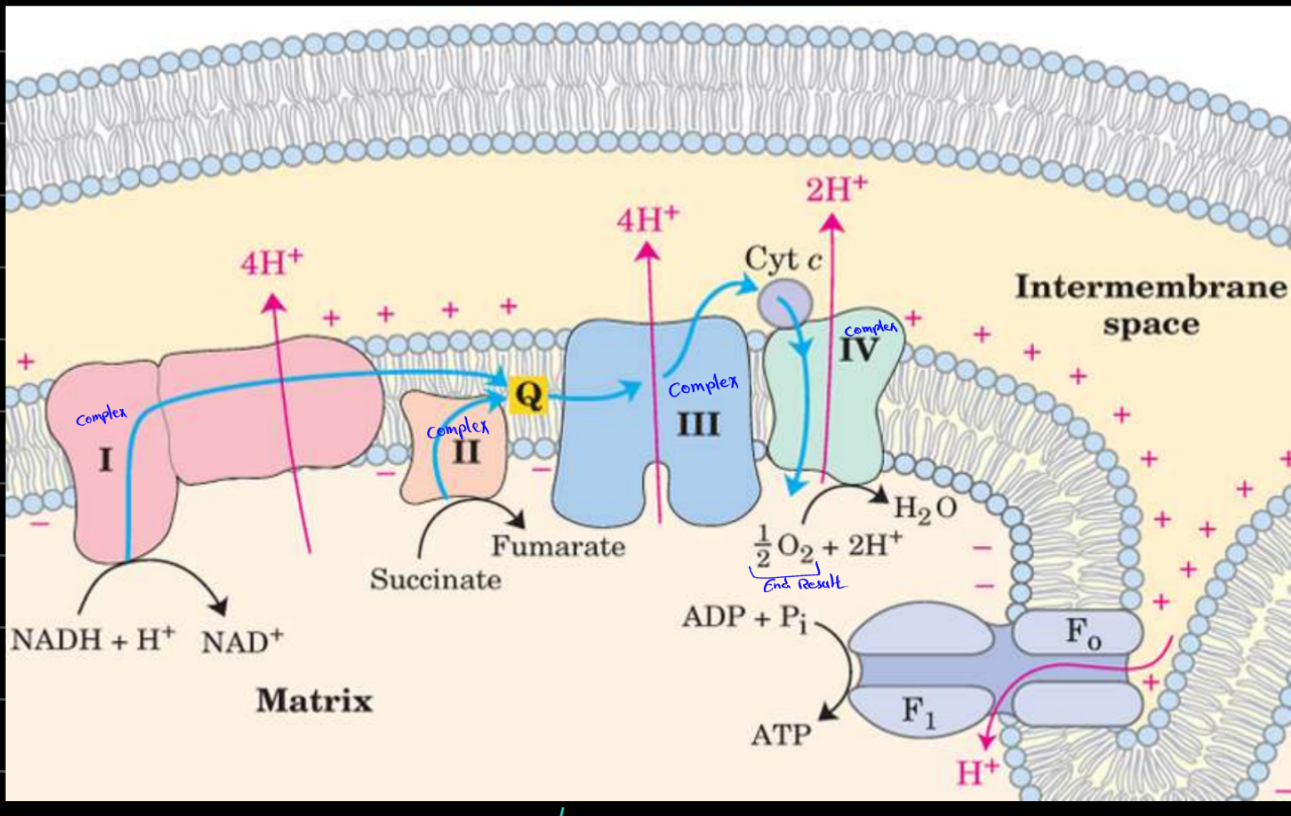
- Succinate dehydrogenase (→ exist in the membrane) is the only enzyme in the inner membrane of Mitochondria.
- FAD is more powerful oxidizing agent than NAD^+
- it is stereoselective enzyme and only the trans isomer "fumarate" is formed but not the cis isomer "maleate"

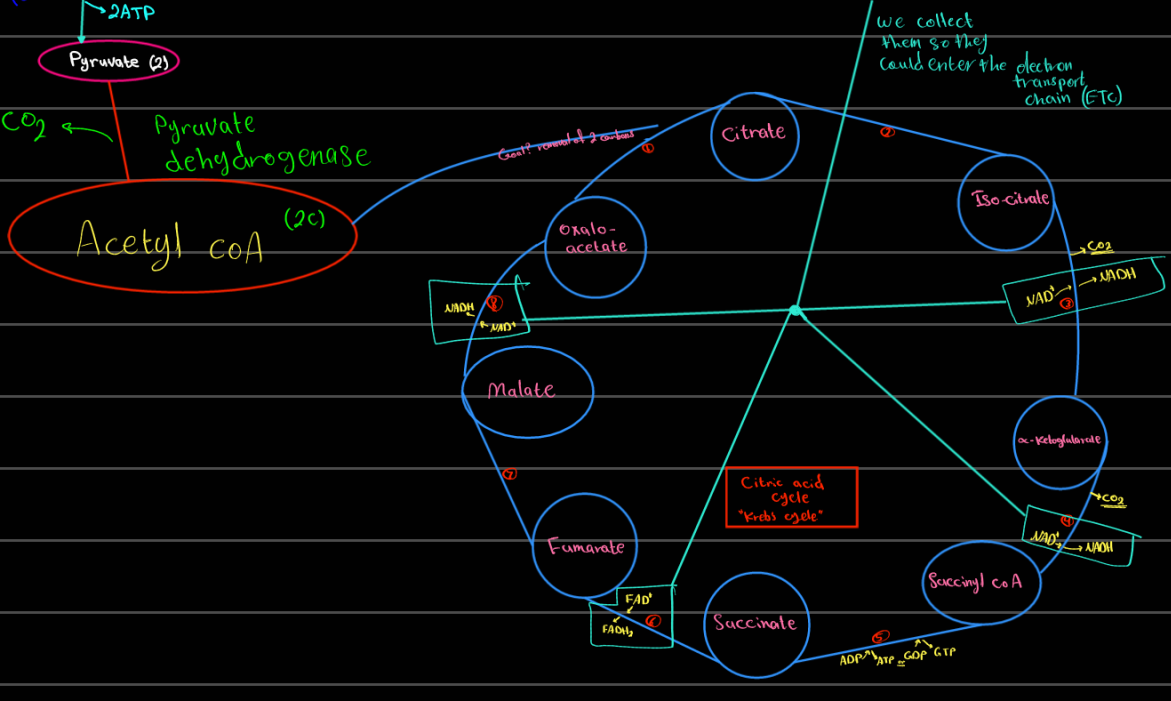
The Goal of the ETC is to pass the electrons From The FAD and NAD molecules to the innner miochondrial membrane where there is 4 complexes that the electrons pass from 1st to the 4th complex. then the 4th complex gives the electrons to the O2 forming H2O.

Oxiditave Phosphorylation: when FAD and NAD molecules loses their electrons in the chain, the free energy is lost too, so it got captured and stored by the production of ATP from ADP and inorganic phosphate. The remainder of the free energy which isn't trapped as ATP is released as heat.

Remember: NADH made in cytosol , it Can't get into mitochondrial matrix.







Metabolism of other sugars: | Fructose:

Abnormalities in fructose Metabolism:

① **Essential fructosuria:** Deficiency of the hepatic fructokinase enzyme. (No treatement required)
Leads to incomplete metabolism of fructose in the liver
excretion of the urine unchanged. Asymptomatic (benign condition)

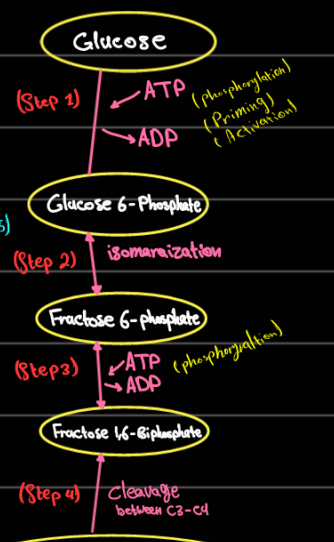
② **Hereditary fructose intolerance:** Deficiency of the aldolase B enzyme which results in accumulation of fructose 1-phosphate.
(severe condition)
Symptoms: Vomiting, Abdominal pain, Hypoglycemia, Jaundice, Hemorrhage
Hepatomegaly and renal failure.
Treatement: limiting fructose intake.

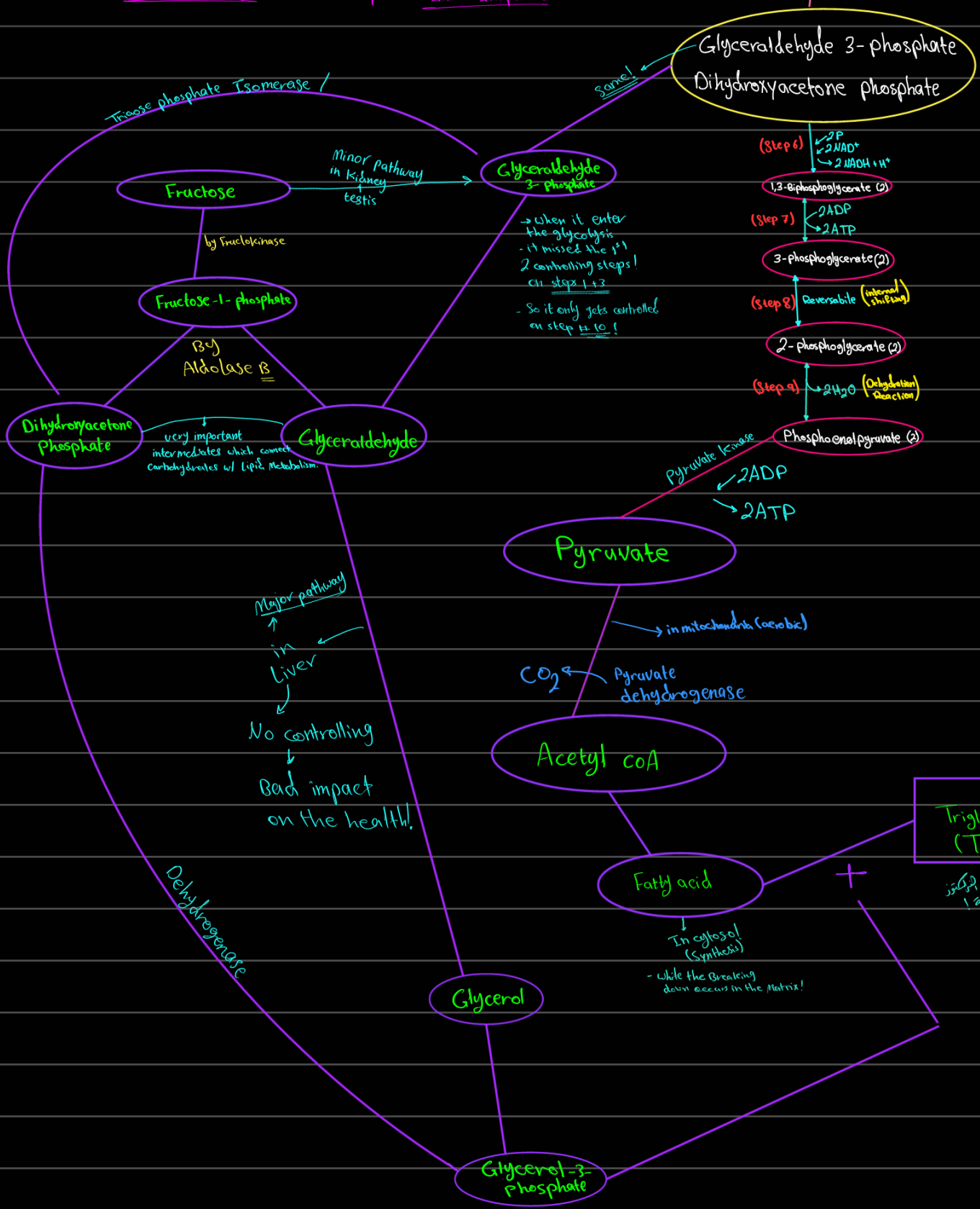
Dietary fructose intolerance:
also know fructose malabsorption, due to impaired absorption of fructose from small intestine as a result of deficiency in fructose carriers (GLUT5)
Symptoms: ① Abdominal pain ② Cramps ③ diarrhea ④ bloating ⑤ flatulence ⑥ Nausea.

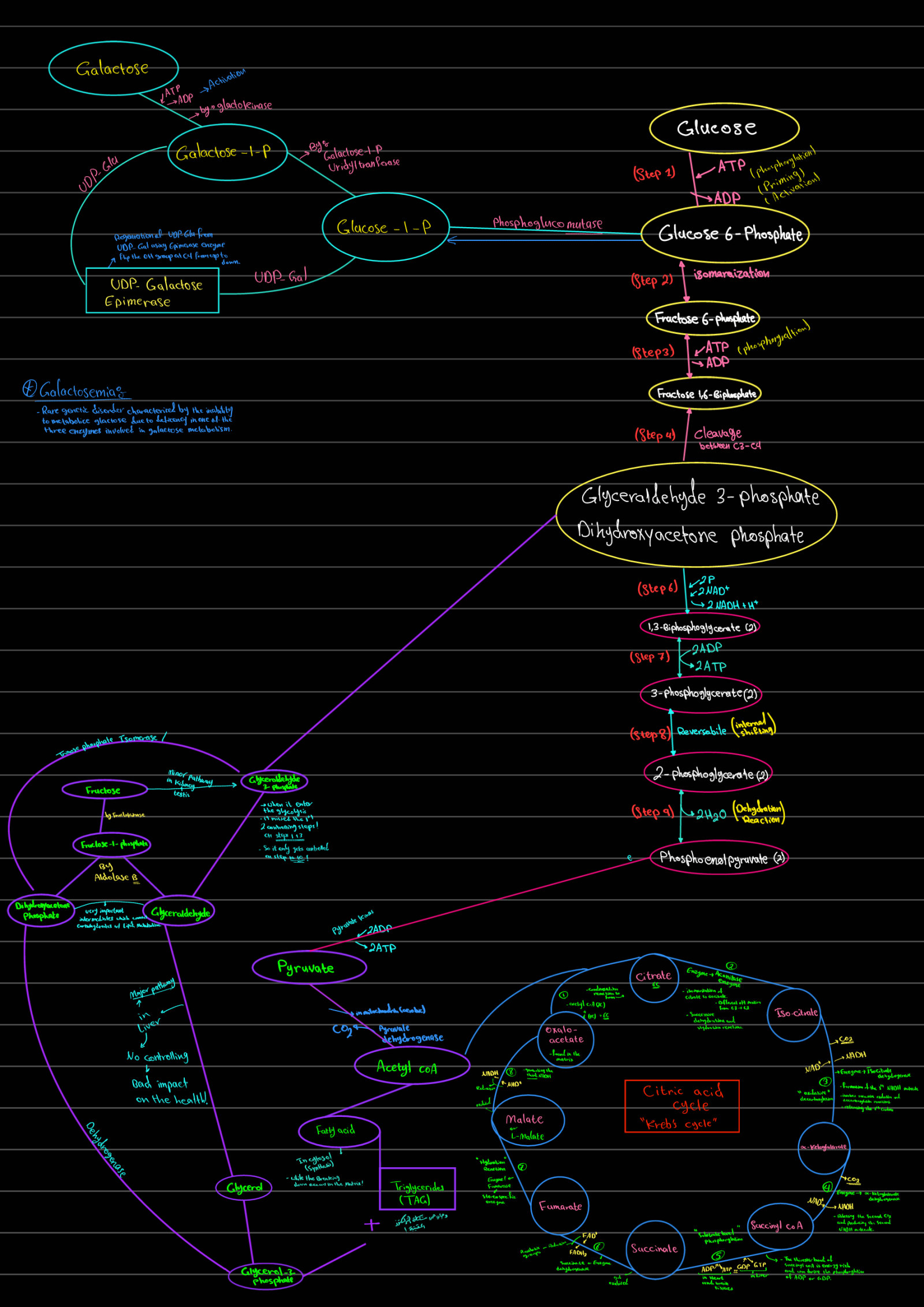
⑧ IV infusion of fructose would make the liver so busy by trapping the Pi and phosphorylation of fructose by fructokinase 1 and it's lipogenic.

Fructose Absorption:
Lumen —GLUT5→ Enterocytes —GLUT2→ Blood
Insulin Independent

Galactose:
Lumen —SGLT1→ Enterocyte —GLUT2→ Blood
Insulin Independent

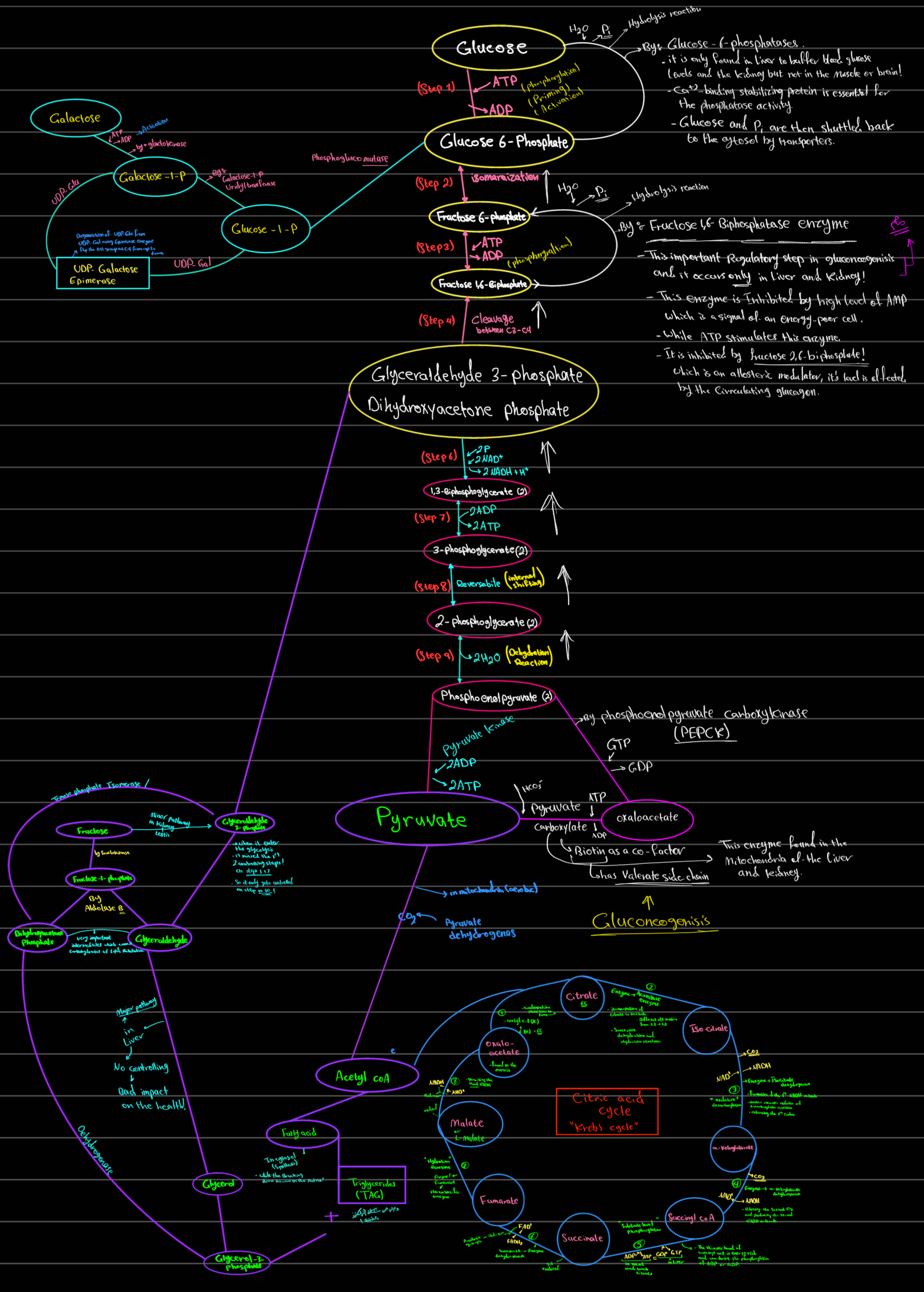






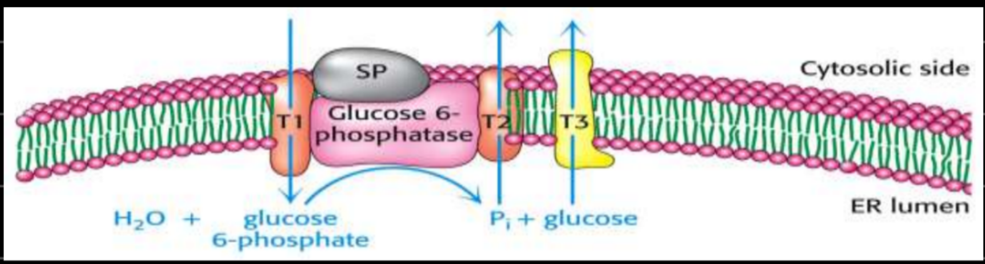
Galactosemia

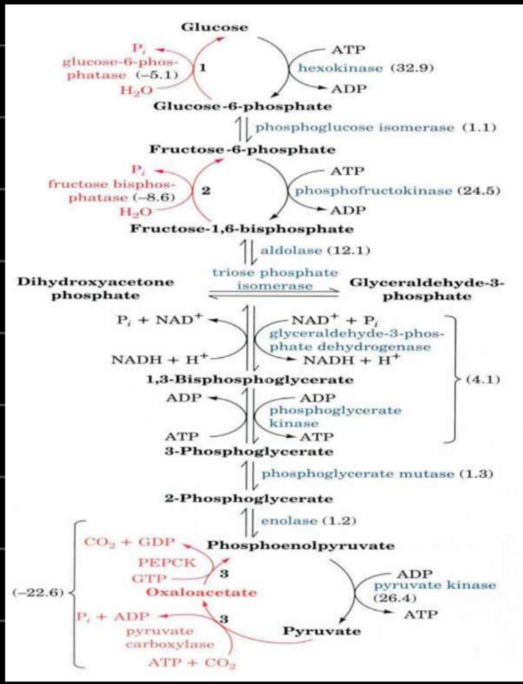
- Rare genetic disorder characterized by the inability to metabolize glactose due to deficiency in one of the three enzymes involved in galactose metabolism.



Glucose
H2O
Pi
Hydrolysis reaction
By: Glucose-6-phosphatases.
- it is only found in liver to buffer blood glucose levels and the kidney but not in the muscle or brain!
- Ca+2-binding stabilizing protein is essential for the phosphatase activity.
- Glucose and Pi are then shuttled back to the cytosol by transporters.
(Step 1)
ATP
ADP
(phosphorylation)
(Priming)
(Activation)
Glucose 6-Phosphate
Phosphoglucomutase
Galactose
ATP
ADP
Activation
by: galactokinase
Galactose-1-P
By: Galactose-1-P Uridyltransferase
UDP-Glu
Glucose-1-P
UDP-Gal
UDP-Galactose Epimerase
(Step 2)
isomerization
Fructose 6-phosphate
H2O
Pi
Hydrolysis reaction
By: Fructose 1,6-Biphosphatase enzyme
- This important Regulatory step in gluconeogenisis and it occurs only in liver and kidney!
- This enzyme is Inhibited by high level of AMP which is a signal of an energy-poor cell.
- While ATP stimulates this enzyme.
- It is inhibited by fructose 2,6-biphosphate! which is an allosteric modulator, it's level is affected by the circulating glucagon.
(Step 3)
ATP
ADP
(phosphorylation)
Fructose 1,6-Biphosphate
(Step 4)
Cleavage between C3-C4
Glyceraldehyde 3-phosphate
Dihydroxyacetone phosphate
(Step 6)
2P
2NAD+
2NADH+H+
1,3-Biphosphoglycerate (2)
(Step 7)
2ADP
2ATP
3-phosphoglycerate (2)
(Step 8)
Reversabile
(internal shifting)
2-phosphoglycerate (2)
(Step 9)
2H2O
(Dehydration Reaction)
Phosphoenolpyruvate (2)
By phosphoenolpyruvate carboxykinase (PEPCK)
GTP
GDP
Pyruvate kinase
2ADP
2ATP
Pyruvate
HCO3-
Pyruvate Carboxylate
ATP
ADP
oxaloacetate
Biotin as a co-factor
has Valerate side chain
This enzyme found in the Mitochondria of the liver and kidney.
Gluconeogenisis
in mitochondria (aerobic)
CO2
Pyruvate dehydrogenas
Triose phosphate Isomerase
Fructose
Minor pathway in kidney testis
Glyceraldehyde 3-phosphate
by fructokinase
Fructose-1-phosphate
By Aldolase B
Dihydroxyacetone Phosphate
Glyceraldehyde
Major pathway
in Liver
No controlling
Bad impact on the health!
Dehydrogenase
Glycerol
Glycerol-3-phosphate
Acetyl coA
Fatty acid
Triglycerides (TAG)
Citrate
Iso-citrate
CO2
NADH
NAD+
Citric acid cycle
"Krebs cycle"
α-Ketoglutarate
Succinyl coA
Succinate
Fumarate
Malate
L-malate
Oxalo-acetate
FAD
FADH2
GDP
GTP
ADP
ATP

Generation of glucose from glucose-6-phosphate:





Glucose
P_i
glucose-6-phosphatase (−5.1)
H_2O
1
ATP
hexokinase (32.9)
ADP
Glucose-6-phosphate
phosphoglucose isomerase (1.1)
Fructose-6-phosphate
P_i
fructose bisphosphatase (−8.6)
H_2O
2
ATP
phosphofructokinase (24.5)
ADP
Fructose-1,6-bisphosphate
aldolase (12.1)
Dihydroxyacetone phosphate
triose phosphate isomerase
Glyceraldehyde-3-phosphate
P_i + NAD^+
NAD^+ + P_i
glyceraldehyde-3-phosphate dehydrogenase
NADH + H^+
NADH + H^+
1,3-Bisphosphoglycerate
(4.1)
ADP
ADP
phosphoglycerate kinase
ATP
ATP
3-Phosphoglycerate
phosphoglycerate mutase (1.3)
2-Phosphoglycerate
enolase (1.2)
CO_2 + GDP
PEPCK
GTP
Phosphoenolpyruvate
3
Oxaloacetate
(−22.6)
P_i + ADP
pyruvate carboxylase
ATP + CO_2
3
ADP
pyruvate kinase (26.4)
ATP
Pyruvate

Protein involved: SP-Ca binding proteins

T_1 ⇒ transports G-6-P into the lumen of ER. } T_2 ⇒ transport P_i into the cytosol
T_3 ⇒ 〃 Glucose 〃 〃 〃 .

-The overall reactions of gluconeogenesis are:

2 Pyruvate +2 NAD + 4 H+ + 4 ATP + 2 GTP + 6 H2O

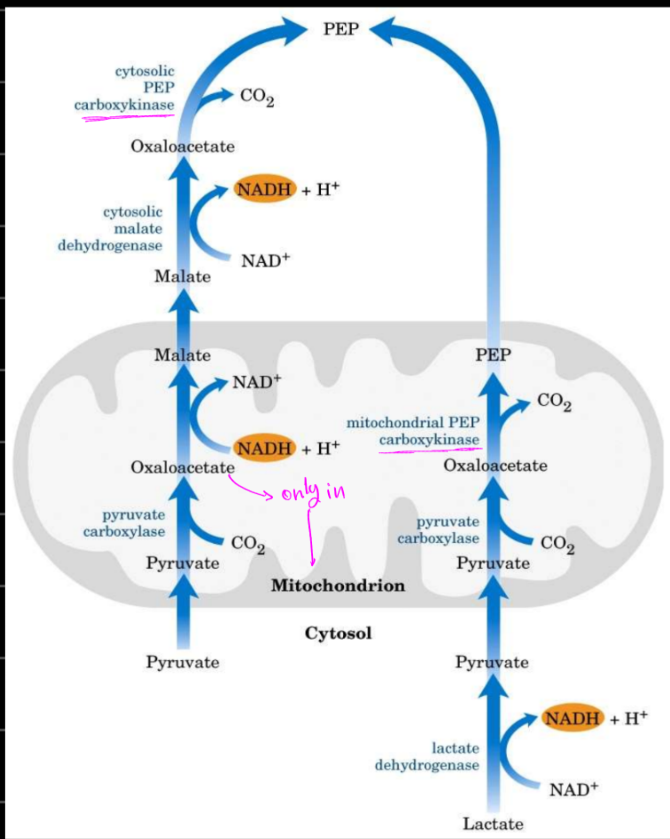
⇓

Glucose + 2 NAD+ + 4 ADP + 2 GDP + 4 Pi

Reciprocal Regulation by ATP/AMP:

- AMP inhibits fructose 1,6-Biphosphate but activates PFK-1
- ATP and citrate inhibits PFK-1 but activates fructose 1,6-Biphosphate.
- High levels of ATP and Alanine, which signals that the energy charge is high and the building blocks are abundant, inhibits pyruvate kinase
- Pyruvate carboxylase is activated by acetyl-coA.
- ADP inhibits PEP carboxykinase and pyruvate carboxylase.

⊛ Gluconeogenisis is favored when the cell is rich in biosynthetic precursors and ATP.



PEP
cytosolic PEP carboxykinase
CO_2
Oxaloacetate
NADH + H^+
cytosolic malate dehydrogenase
NAD^+
Malate
Malate
NAD^+
NADH + H^+
Oxaloacetate
only in
pyruvate carboxylase
CO_2
Pyruvate
Mitochondrion
PEP
CO_2
mitochondrial PEP carboxykinase
Oxaloacetate
pyruvate carboxylase
CO_2
Pyruvate
Cytosol
Pyruvate
Pyruvate
NADH + H^+
lactate dehydrogenase
NAD^+
Lactate

⊛ Reciprocal Regulation by fructose-2,6-Biphosphate:

- Fructose 2,6-Biphosphate stimulate glycolysis by activating PFK-1 and Inhibiting gluconeogenisis through the inhibition of fructose 1,6-Biphosphatase.
- During starvation, gluconeogenisis predominates because the level of Fructose-2,6-Biphosphate is low! ([illegible])

Insulin: - Activates glycolysis (by activating PFK-1) and inhibits gluconeogenisis (By suppressing Fructose 1,6-Biphosphatase).

Glucagon: - Activates gluconeogenisis (By activating F-2,6-BP) and Inhibits glycolysis (By suppressing PFK-1).

Acetyl-CoA regulates pyruvate carboxylase:

-The increase in Oxaloacetate Concent.↑the activity of TCA cycle.

- Acetyl coA is an allosteric activator of pyruvate Carboxylase (Gluconeogenisis).

- ATP and NADH concetrations are increased --> Oxaloacetate goes into TCA cycle.

Allosteric activation by acetyl CoA

- During starvation → excessive lipolysis → excessive oxidation of fatty acid into acetyl CoA → accumulation of acetyl CoA → activation of pyruvate carboxylase → activation of gluconeogenesis.

Substrate availability:

- The availability of gluconeogenic precursors like glucogenic amino acids → ↑ the hepatic gluconeogenesis.
- ↓ Insulin / glucagon ratio favor the mobilization of amino acids from muscle protein to provide their skeletons for gluconeogenesis.

Substrates for gluconeogenesis:

- Include all intermediates of glycolysis and TCA cycle, glycerol, lactate and the α-keto acids obtained from deamination of glucogenic A.A.s.
- **Glycerol**: obtained from the hydrolysis of the triglycerides in adipose tissue, travels to liver which is phosphorylated and metabolized.
- DHAP is converted into glyceraldehyde 3-P by triose isomerase.

-Lactate: released from the RBC and exercising muscle, carried to the liver by the blood and converted to glucose and released again to blood through Cori cycle.

- Odd chain fatty acids: upon oxidation → propionyl CoA to be converted into succinyl CoA to join TCA cycle.

α-keto acids: like pyruvate and α-ketoglutarate derived from amino acids alanine and glutamate. These substances enter TCA cycle to provide the oxaloacetate.

- All amino acids can feed into gluconeogenesis except leucine and lysine.

- Acetyl CoA cannot give rise to a net synthesis of glucose because of the irreversible nature of PDH that converts pyruvate to acetyl CoA.
- The Alanine cycle:

- The liver can also use the amino acid alanine similarly to lactate
- Following transamination to pyruvate, gluconeogenesis allows the liver to convert it to glucose for secretion into the blood

Glycogen metabolism:

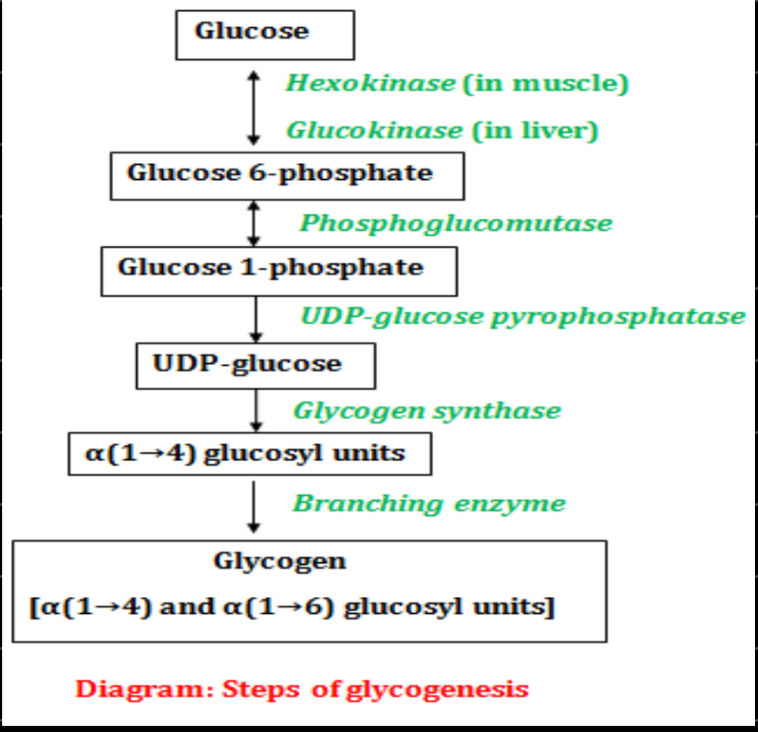
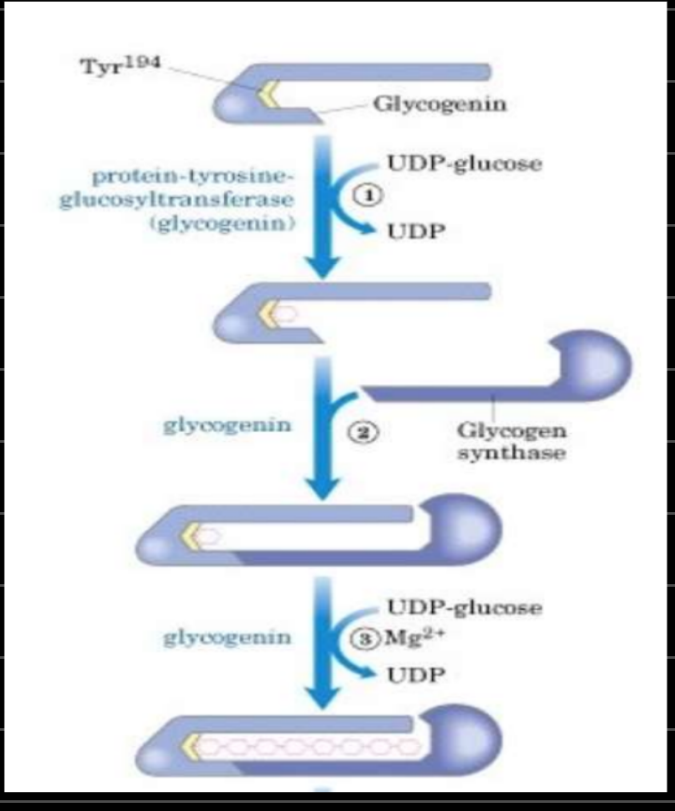


Diagram: Steps of glycogenesis

- Glycogen is mainly found in the skeletal muscle and the liver.
- Glycogen is senthesized when blood glucose level is high.

- GLUT4 is mainly found on adipose tissues, skeletal and cardiac muscles. it is insulin dependent!! so the insulin stimualate the synthesis of more GLUTs.
- ~~GLUT 3 in neurons.~~
- GLUT 2 is bidirectional transporter expressed mainly in the liver and pancreatic B cells. and goes with Fascilitated diffusion.

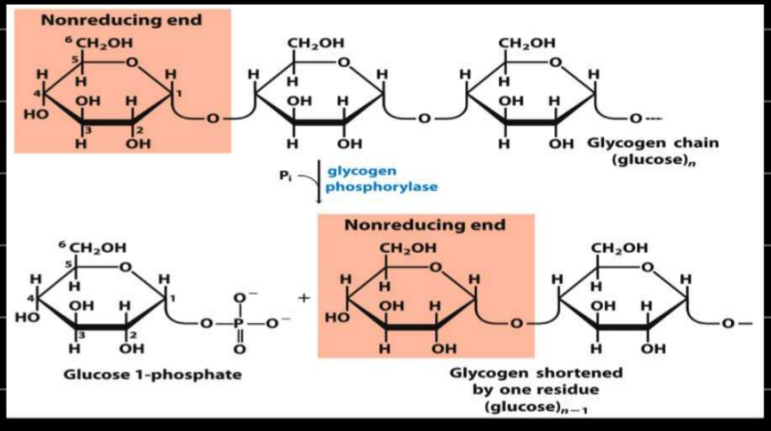
- The insulin hormone stimulate the Glycogenesis proccess

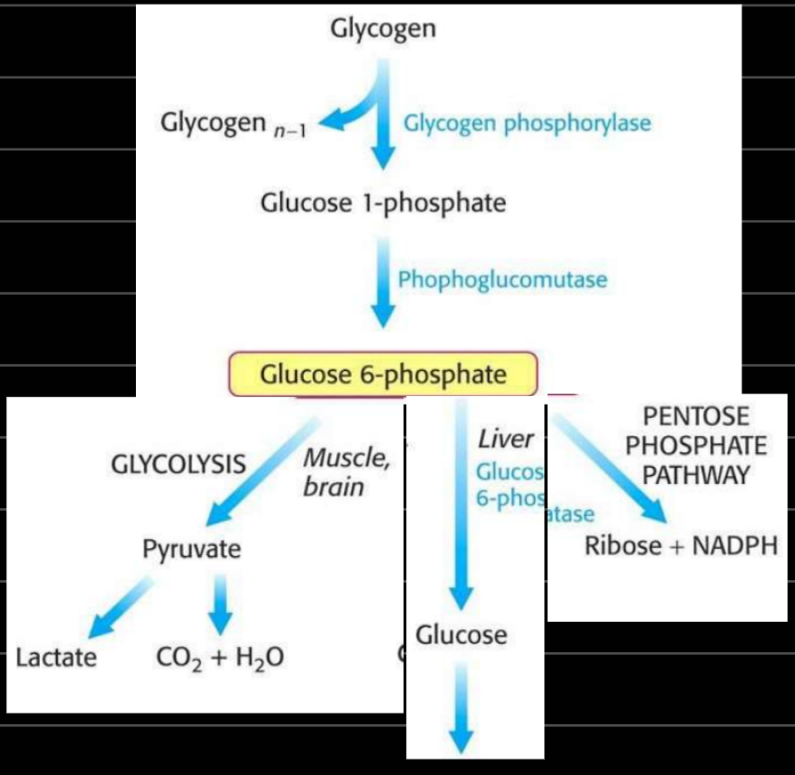


- Step 1: the first glucose is attached to tyrosine residue of a protein called glycogenin
- Step 2: glycogenin forms a tight complex with glycogen synthase
- Step 3: the chain is extended by sequential addition of up to 7 glucose residues autocatalyzed by glycogenin itself (α-1,4-glycosidic bond)
- Step 4: at this point, glycogen synthase dissociates and starts to extend the linear glycogen chain
- Step 5: the combined action of glycogen synthase and branching enzyme completes the glycogen particle
- Step 6: glycogen synthase dissociates from the newly synthesized glycogen molecule while the glycogenin remains covalently attached to reducing end

- Formation of branches:

the (α1→6) bonds found at the branch points of glycogen are formed by glycogen branching enzyme which catalyzes the transfer of small fragment (6-7 glucosyl residues) from the non-reducing end of a branch having at least eleven residues.





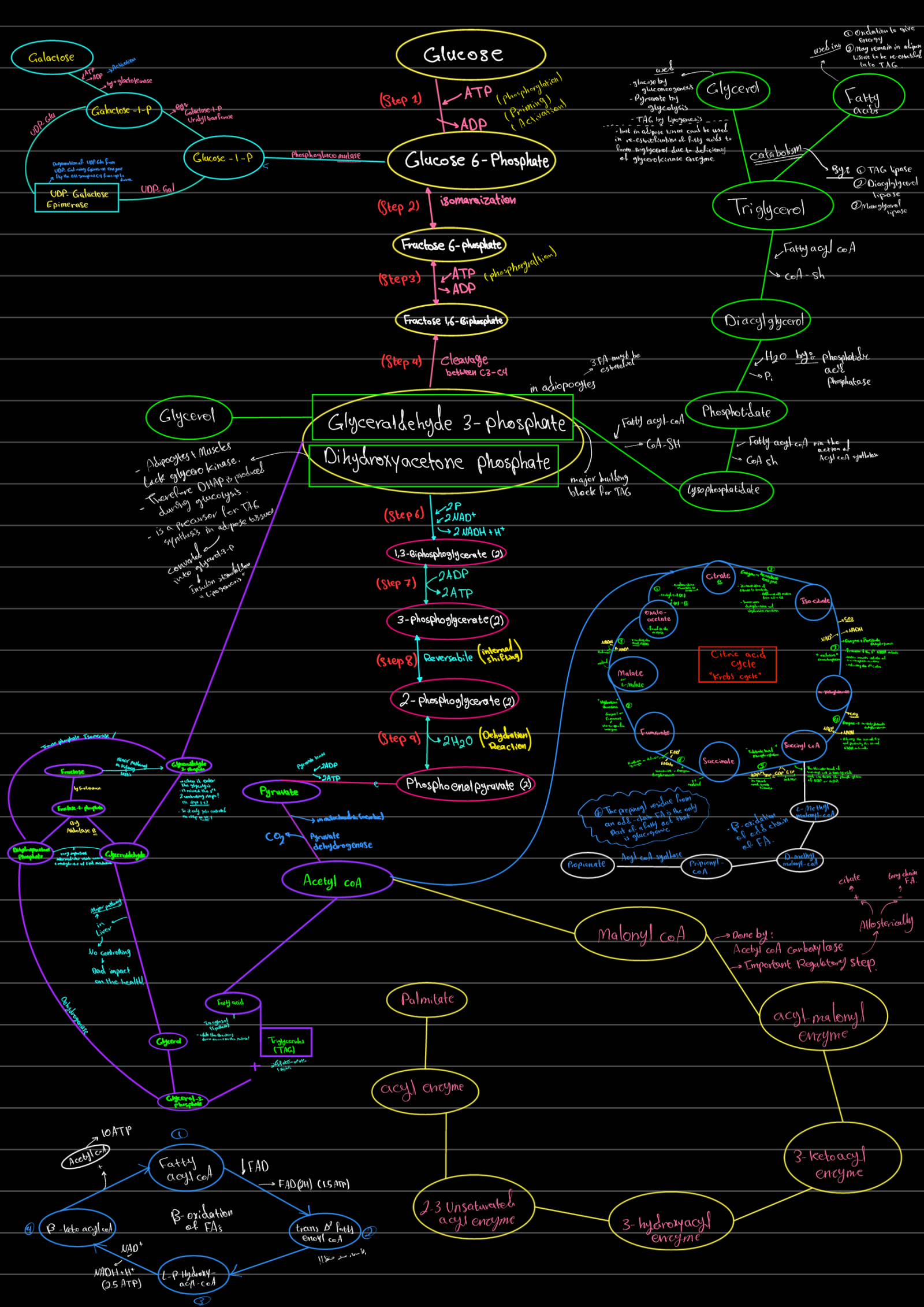
Glycolysis

- the first step is to make the phsphorylase enzyme catalyzes the phosphorolysis step " the cleavage of the bond by the addition of inorganic phosphate".
- another enzyme; Debrancher enzyme then causes:

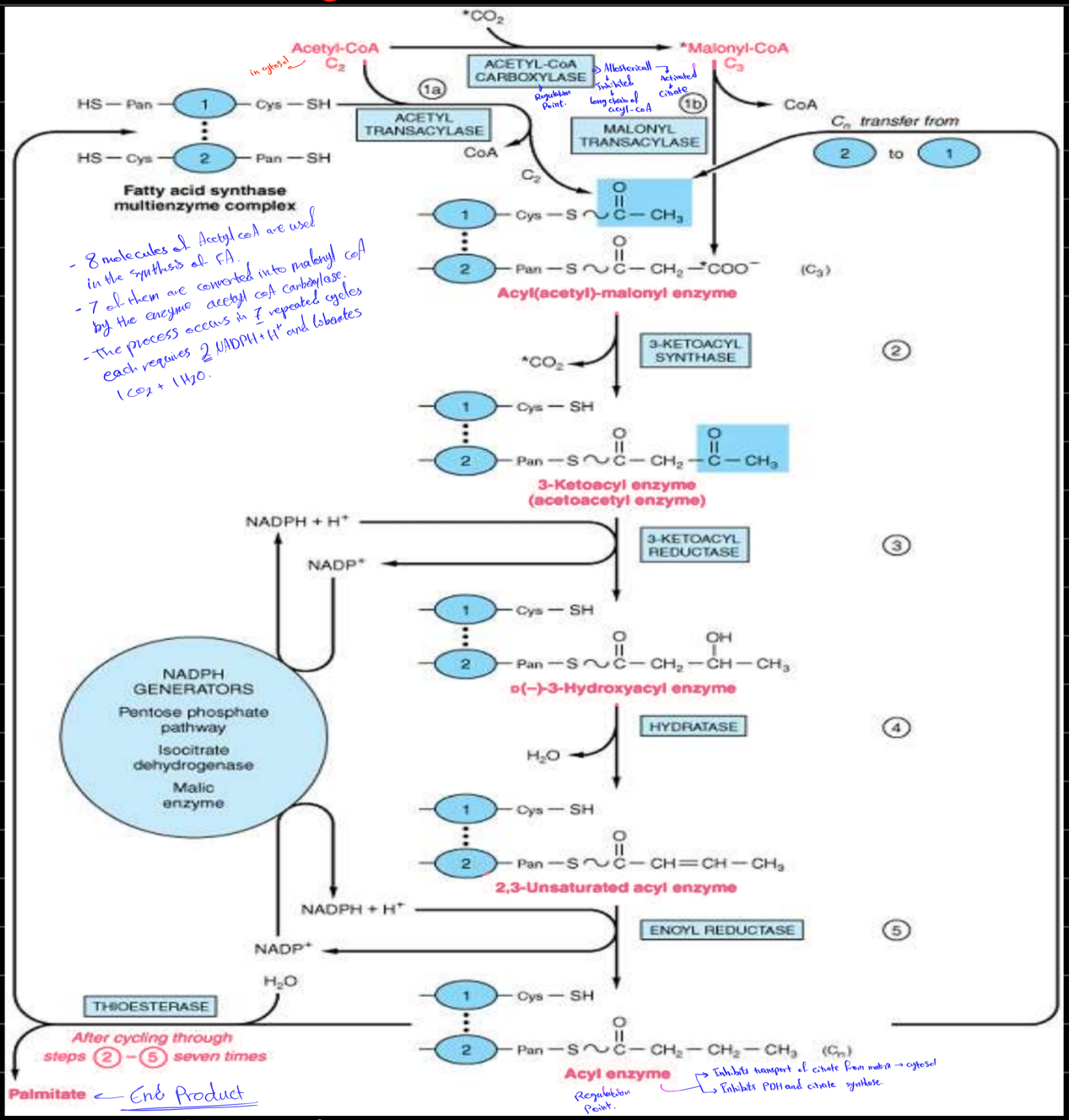
1) Transferase activity: removes intact trisaccharide moiety (3 Glucose units) and transfer it to the end of some other branch.

2) Second " the (α1→6) glucosidase activity": the enzyme removes the last glucose unit attached to the chain by (α1→6) glycosidic bond.

- The end result of this debranching process is the release of one glucose moiety each time.
- The end products of glycogenolysis are G1P (the major product) and glucose.


Glucose
(Step 1)
ATP
ADP
(phosphorylation)
(Priming)
(Activation)
Glucose 6-Phosphate
(Step 2)
isomarization
Fructose 6-phosphate
(Step3)
ATP
ADP
(phosphorylation)
Fructose 1,6-Biphosphate
(Step 4)
Cleavage
between C3-C4
Glyceraldehyde 3-phosphate
Dihydroxyacetone phosphate
(Step 6)
2P
2NAD+
2 NADH + H+
1,3-Biphosphoglycerate (2)
(Step 7)
2ADP
2ATP
3-phosphoglycerate (2)
(Step 8)
Reversabite
(internal shifting)
2-phosphoglycerate (2)
(Step 9)
2H2O
(Dehydration Reaction)
Phosphoenolpyruvate (2)
Pyruvate
2ADP
2ATP
Pyruvate dehydrogenase
Acetyl coA
Galactose
ATP
ADP
Activation
by α-galactokinase
Galactose-1-P
UDP-Glc
Glucose-1-P
Phosphoglucomutase
UDP-Galactose Epimerase
UDP-Gal
Glycerol
Fatty acids
used in
① Oxidation to give energy
② May remain in adipose tissue to be re-esterified into TAG
used
- glucose by gluconeogenesis
- Pyruvate by glycolysis
- TAG by lipogenesis
- but in adipose tissue can be used in re-esterification of fatty acids to form triglycerol due to deficiency of glycerokinase enzyme
catabolism
Triglycerol
By: ① TAG lipase ② Diacylglycerol lipase ③ Monoglycerol lipase
Fatty acyl coA
coA-sh
Diacylglycerol
H2O
Pi
by: phosphatidic acid phosphatase
Phosphotidate
Fatty acyl-coA
CoA sh
by the action of Acyl coA synthase
Lysophosphatidate
3FA must be esterified in adipocytes
major building block for TAG
Glycerol
- Adipocytes & Muscles lack glycerokinase.
- Therefore DHAP is produced during glycolysis.
- is a precursor for TAG synthesis in adipose tissues
converted into glycerol-3-P
Insulin stimulates ↑ Gluconeogenesis
Citrate
Iso-citrate
Oxalo-acetate
Malate
L-Malate
Citric acid cycle
"Krebs cycle"
Fumarate
Succinate
Succinyl coA
L-Methyl malonyl-coA
D-methyl malonyl-coA
Propionate
Acyl-coA-synthase
Propionyl-coA
② The propionyl residue from an odd-chain FA is the only part of a fatty acid that is glucogenic
β-oxidation of odd chain of FA.
Fructose
Fructose-1-phosphate
Aldolase B
Dihydroxyacetone phosphate
Glyceraldehyde
Glyceraldehyde 3-phosphate
Major pathway in Liver
No controlling
Bad impact on the health!
Dehydrogenase
Glycerol
Glycerol-3-phosphate
Fatty acid
Triglycerides (TAG)
Palmitate
acyl enzyme
acyl-malonyl enzyme
Malonyl coA
Done by: Acetyl coA carboxylase
Important Regulatory step.
Allosterically
citrate
long chain F.A.
Acetyl coA
10ATP
Fatty acyl coA
FAD
FAD(2H) (1.5 ATP)
β-keto acyl coA
β-oxidation of FAs
trans Δ Fatty Enoyl coA
NAD+
NADH+H+ (2.5 ATP)
L-β-Hydroxy-acyl-coA
2,3 Unsaturated acyl enzyme
3-hydroxyacyl enzyme
3-ketoacyl enzyme

Fatty acid Synthesis



- 8 molecules of Acetyl coA are used in the synthesis of FA.
- 7 of them are converted into malonyl coA by the enzyme acetyl coA carboxylase.
- The process occurs in 7 repeated cycles each requires 2 NADPH + H+ and liberates 1 CO_2 + 1 H_2O.

Notes:

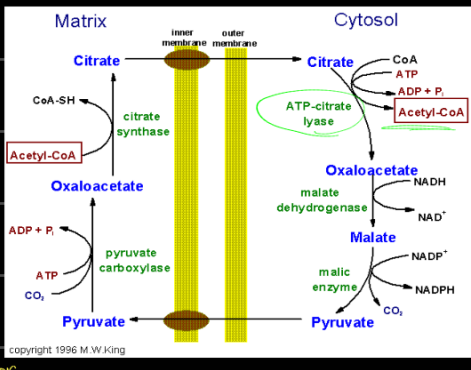
① Acetyl coA is always derived from glucose, never from FA. This is because Insulin after a meal drive lipogenesis not lipolysis from glucose.

② NADPH + H+ is provided by:
- Ⓐ Pentose phosphate pathway (Ribose-5-P)
- Ⓑ Action of cytoplasmic isocitrate dehydrogenase on Isocitrate.
- Ⓒ Action of malic enzyme on malate to produce pyruvate.

③ Every enzyme transfer CO_2 ⇒ requires Biotin as a co-factor.

④ Translocation of acetyl-coA from matrix into cytosol occurs by:
- combining it w/ oxaloacetate and exit from the matrix.

-Acetyl coA may also pass through mitochondorial membrane into the cytosol in the form of acetyl carnitine by carnitone acetyl transferase, and Biotin as a co-factor.



Fate of palmitate:
- ① Esterification: Palmitate esterified w/ glycerol to form acyl glycerols or w/ Cholesterol to form cholesterol esters
- ② chain elongation: Palmitate may be elongated to form longer FA.
- ③ Desaturation: synthesis of unsaturated FA. Palmitate may undergo desaturation to form palmitoleic acid.
- ④ Sphingosine formation: it is formed by condensation of palmity coA and the amino acid serine.

Microsomal pathway for FA synthesis & main site for elongation for existing long chain, more than 16C.

(A) The elongated molecules are derived from:
① Palmitate: cytoplasmic pathway. ② FA of diet.

(B) The microsomal pathway needs malonyl CoA as acetyl donor and $NADPH+H^+$ as coenzyme

(C) Function: This system becomes active during myelination of nerves in order to provide C22 and C24 FAs which are present in sphingolipids.

Synthesis Of Unsaturated Fatty Acids:

A. Nonessential unsaturat ed fatty acids:

1. These are fatty acids which contain one double bond e.g. palmitoleic acid (16: 1) and oleic acid (18:1).
2. Synthesis of oleic acid (oleyl CoA) : It is synthesized - in the microsomes - from stearyl CoA (active stearic acid)

B. Essential fatty acid:

These are unsaturated fatty acids which contain more than one double bond.

Examples: linoleic acid and linolenic and arachidonic acid.

Functions:

a- They are Important for normal growth.

b- Synthesis of phospholipids

c- Prevention of atherosclerosis: Essential fatty acids combine with cholesterol forming esters which are rapidly metabolized by the liver. This prevents precipitation of free cholesterol along the endothelium of blood vessels ~ prevents atherosclerosis.

d- Synthesis of eicosanoid.

Regulation of lipolysis:

The key enzyme controlling lipolysis is Hormone sensitive triacylglycerol lipase (HSL):

-This enzyme is activated when phosphorylated by 3' 5'-cyclic AMPdependent protein kinase.

- In the presence of high plasma level of insulin and glucose, HSL is dephosphorylated, and become inactive. So during fasting → stimulation of lipolysis.

- Coffee contains caffeine and tea contains theophylline. Both inhibit phosphodiesterase enzyme → stimulation of lipolysis.

- Causes of excessive lipolysis: where there is a need for energy; starvation, diabetes mellitus, low carbohydrate diet, and in certain infectious disease as in tuberculosis (due to high catabolic state).

Types of fatty acid oxidation

- Fatty acids can be oxidized by:

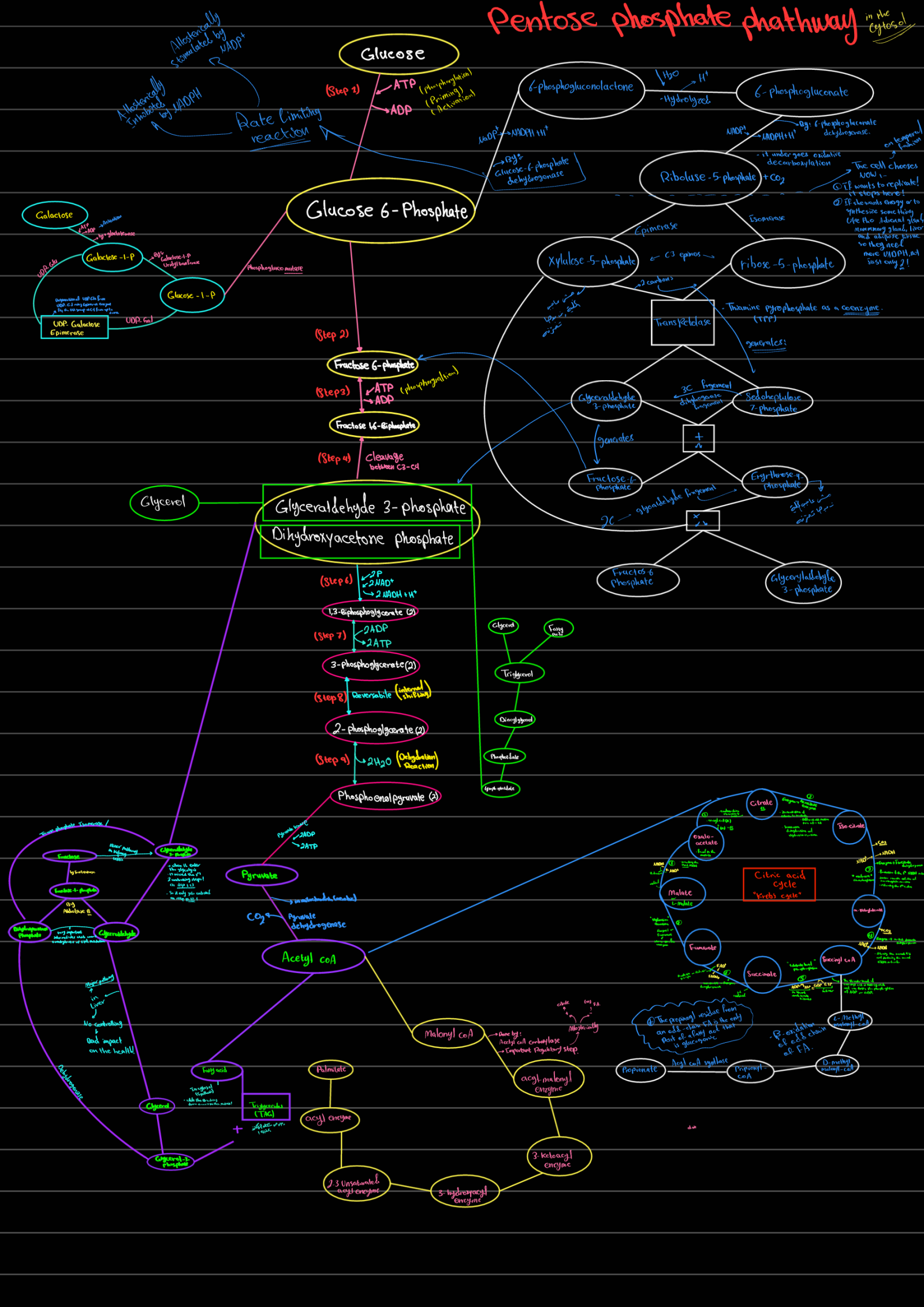
1- β- oxidation- major mechanism, occurs in the mitochondrial matrix. 2-C units are released as acetyl CoA per cycle.

2- α- oxidation- predominantly takes place in brain and liver, one carbon is lost in the form of CO_2 per cycle.

3- ω- oxidation- minor mechanism, but becomes important in conditions of impaired β-oxidation

4- Peroxisomal oxidation- mainly for the trimming of very long chain fatty acids.

The remaining of the Lecture are the Oxidations (some few details) and the last few slides.


Pentose phosphate pathway in the Cytosol
Allosterically stimulated by NADP+
Allosterically inhibited by NADPH
Rate limiting reaction
Glucose
(Step 1)
ATP
ADP
(phosphorylation)
(Priming)
(Activation)
6-phosphogluconolactone
H2O
H+
-Hydrolyzed
6-phosphogluconate
NADP+ → NADPH+H+
By: 6-phosphogluconate dehydrogenase.
- it undergoes oxidative decarboxylation
Ribulose-5-phosphate + CO2
The cell chooses NOW :-
① If wants to replicate! it stops here!
② If she wants energy or to synthesize something like the Adrenal gland, mammary gland, liver and adipose tissue so they need more NADPH, not just only 2!
NADP+ → NADPH+H+
By: Glucose-6-phosphate dehydrogenase
Glucose 6-Phosphate
Galactose
ATP
ADP
Activation
By: glycokinase
Galactose-1-P
By: Galactose-1-P Uridyl transferase
UDP-Glc
Glucose-1-P
Phosphoglucomutase
UDP-Gal
UDP: Galactose Epimerase
Epimerase
Isomerase
Xylulose-5-phosphate
C3 epimer
Ribose-5-phosphate
2 carbons
Transketolase
Thiamine pyrophosphate as a coenzyme. (TPP)
generates:
(Step 2)
Fructose 6-phosphate
(Step 3)
ATP
ADP
(phosphorylation)
Fructose 1,6-Biphosphate
Glyceraldehyde 3-phosphate
3C fragment
Sedoheptulose 7-phosphate
generates
Fructose-6-Phosphate
Erythrose-4-phosphate
2C
Glyceraldehyde fragment
Fructos 6 Phosphate
Glyceraldehyde 3-phosphate
(Step 4)
Cleavage between C3-C4
Glycerol
Glyceraldehyde 3-phosphate
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(Step 6)
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2 NADH + H+
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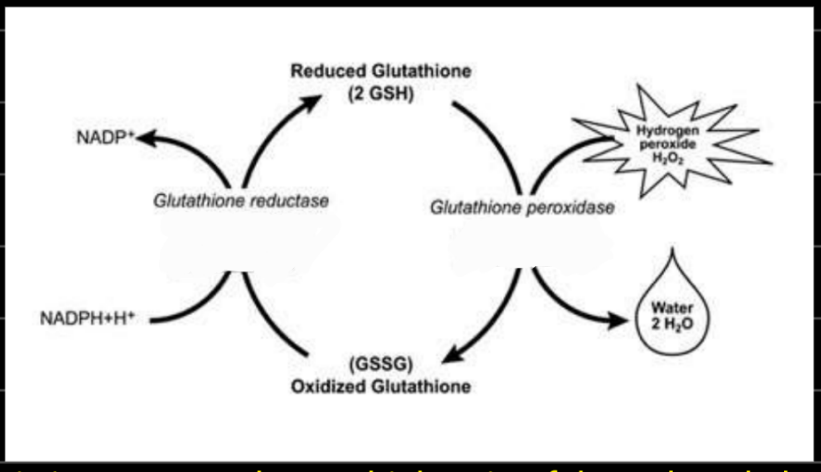
(Step 9)
2H2O
(Dehydration Reaction)
Phosphoenolpyruvate (2)
Glycerol
Fatty acid
Triglycerol
Diacylglycerol
Phosphatidate
Lipid droplet
Triose phosphate Isomerase
Fructose
Fructose-1-phosphate
By: Aldolase B
Dihydroxyacetone Phosphate
Glyceraldehyde
Glyceraldehyde-3-phosphate
Pyruvate kinase
2ADP
2ATP
Pyruvate
Pyruvate dehydrogenase
CO2
Acetyl coA
Citrate
Iso-citrate
oxalo-acetate
Citric acid cycle
"Krebs cycle"
Malate
L-Malate
Fumarate
Succinate
Succinyl coA
Major pathway in Liver
No controlling
Bad impact on the health!
Dehydrogenase
Fatty acid
Triglycerides (TAG)
Glycerol
Glycerol-3-phosphate
Malonyl coA
Acetyl coA carboxylase
Important Regulatory step.
Allosterically
citrate
(long) F.A.
Palmitate
acyl-malonyl enzyme
acyl enzyme
3-ketoacyl enzyme
2,3 Unsaturated acyl enzyme
3-hydroxyacyl enzyme
① The propionyl residue from an odd-chain FA is the only part of a fatty acid that is glucogenic
β-oxidation of odd chain of FA.
Propionate
Acyl coA synthase
Propionyl-coA
L-Methyl malonyl-coA
D-methyl malonyl-coA

G6P Dehydrogenase Deficiency:

- Also known as FAVISM
- it is X - Linked recessive genetic condition
- Inborn Error
- Congenital
- Inherited Disorder
- results in reduced intracellular NADPH level which participates in the glutathione cycle to protect cells against hydrogen peroxide.



- NADPH in RBCs is important to keep a high ratio of the reduced glutathione which is vital to protect cells from damaging effect of ROS (detoxification process)
- G6PD enzyme prevents oxidative damage
- G6PD deficiency is characterized by hemolytic anemia, especially in state of oxidative stress such as exposure to infection, some medications and certain foods (e.g. broad or fava beans).

- Oxidative stress is due to imbalance between the generation of ROS or free radicals (e.g. H2O2, .OH,…) and the removal by specific cellular enzymes (antioxidants) like glutathione peroxidase (enzyme abundant in cells).

- Oxidative stress depletes the reduced form of glutathione (GSH) and G6P dehydrogenase deficiency disorder can not supply enough NADPH to regenerate GSH from the oxidized one (GSSG) .

- Damaged RBCs are recycled to the spleen. The hemoglobin is metabolized to bilirubin causing jaundice in high concentration .

THE END

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Wateen 2020.