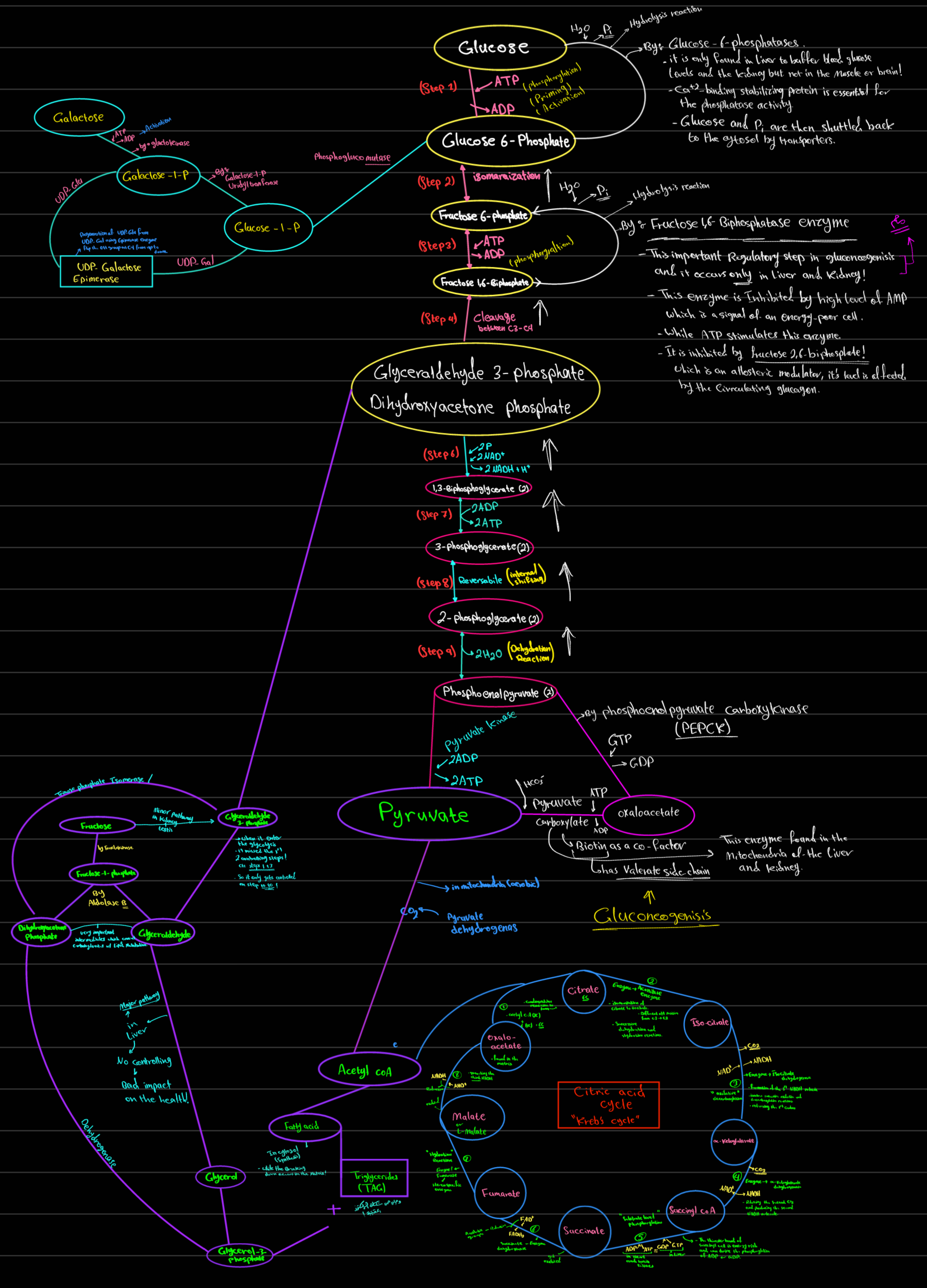
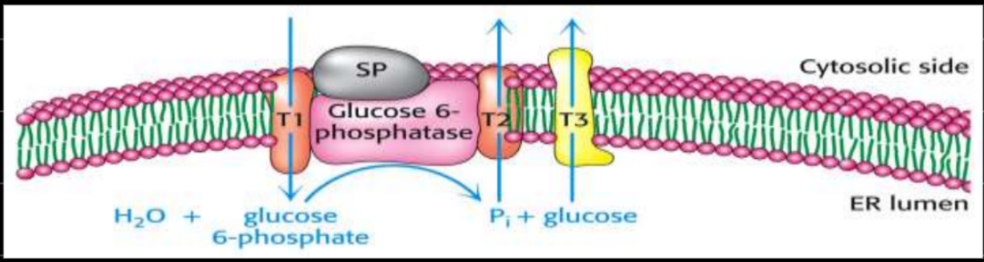
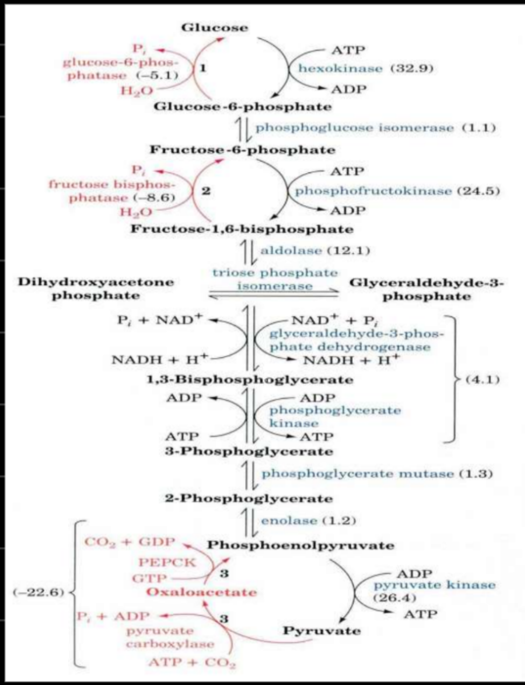


Glucose
H2O
Pi
Hydrolysis reaction
By: Glucose-6-phosphatases.
- it is only found in liver to buffer blood glucose levels and the kidney but not in the muscle or brain!
- Ca+2 binding stabilizing protein is essential for the phosphatase activity.
- Glucose and Pi are then shuttled back to the cytosol by transporters.
(Step 1)
ATP
ADP
(phosphorylation)
(Priming)
(Activation)
Glucose 6-Phosphate
Galactose
ATP
ADP
Activation
by: galactokinase
Galactose-1-P
By: Galactose-1-P Uridyltranferase
UDP-Glu
Glucose-1-P
Phosphogluco mutase
UDP-Galactose Epimerase
UDP-Gal
(Step 2)
isomerization
Fructose 6-phosphate
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.
in mitochondria (aerobic)
CO2
Pyruvate dehydrogenase
Gluconeogenisis
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
α-Ketoglutarate
Succinyl coA
Succinate
Fumarate
Malate
Oxalo-acetate
Citric acid cycle
"Krebs cycle"
CO2
NADH
NAD+
FAD
FADH2
GDP
GTP

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
$P_i + NAD^+$
$NADH + H^+$
$NAD^+ + P_i$
glyceraldehyde-3-phosphate dehydrogenase
$NADH + H^+$
1,3-Bisphosphoglycerate
ADP
ATP
ADP
phosphoglycerate kinase
ATP
(4.1)
3-Phosphoglycerate
phosphoglycerate mutase (1.3)
2-Phosphoglycerate
enolase (1.2)
CO_2 + GDP
PEPCK
GTP
3
Phosphoenolpyruvate
Oxaloacetate
(–22.6)
P_i + ADP
3
pyruvate carboxylase
ATP + CO_2
ADP
pyruvate kinase (26.4)
ATP
Pyruvate

Protein involved: SP-Ca binding protein:

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

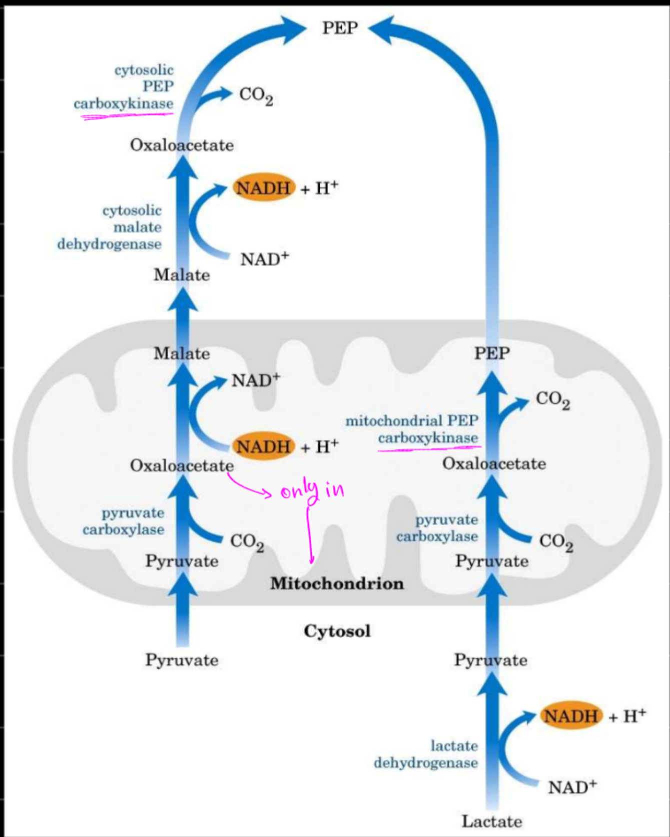
⇓

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