Ankita Mam.
B.Sc. S. year

★ Glycogenesis ★

All living cell require energy to carry out various cell cellular activites. This energy is in the chemical bonds of organic molecules (carbohydrate, fat proteins) that we eat as food. These organic molecules are broken down by enzymatic reaction in the cell to generate energy in the form of adenosine triphosphate (ATP).

The ATP generated by these pathway in cells is used to drive fundamental cellular processes. The food we consume is mainly composed of protein, carbohydrates & fat. These are first broken down into smaller units; protein into amino acid, polysaccharides into sugar and fat into fatty acid and glycerol. The amino acid, simple sugars and fatty acid then enters the cell and undergo oxidation by glycolysis (in the cytosol) & the citric acid cycle (in the mitochondria).

Defination of Glycolysis :- [EMBDEN-MEYERHOF PATHWAY]

In glycolysis pathway glucose is converted to pyruvate (aerobic condition) or lactate (anaerobic condition), along with production of small quantity of energy.

Glycogenesis Defination :-

Glycogenesis is the biosynthesis of glycogen, the major storage form of carbohydrate in animals similar to starch.

★ What is Glycogen :-

Glycogen is a homopolymer made up of repeated units of α D glucose and each molecule is linked to each other by 1 → 4 glycosidic bond which is a link connecting

the first C-atom of the active glucose residue to the 6^{th} C-atom of the approaching glucose molecule.
Once there is a chain consisting of 8 to 10 glycosidic residues in the glycogen fragment, branching begins by $1 \rightarrow 6$ linkages. Liver glycogen is synthesized in well fed states. Muscle glycogen is synthesized when the muscle glucose get depleted in intense physical exercise.

★ Glycogensis Pathway :→

Glycogensis pathway is made up series of steps resulting in the formation of Complex glycogen molecule from αD glucose in the cytoplam of liver and muscle Cell.

★ Importance of glycolysis Pathway :→

- It is the only pathway that is taking place in all the cell of the body.
- Glycolysis is only source of energy in erythrocytes.
- In strenuous, when muscle tissue lacks enough oxygen, anerobic, glycolysis from the major source of energy for muscles.
- The glycolytic pathway may be considered as the preliminary step before Complete oxidation.
- The glycolytic pathway provides Carbon skeletons for synthesis of non essential amino acid as well as glycerol part of fat.
- Most of the reactions are reversible.

* Step of pathway :→

Glucose (6C)
Hexokinase ↓ ATP add → ADP out — Locks glucose in cell
Glucose 6- phosphate (6C)
Phosphoglucose isomerase ↕ Frees up Carbon 1
Fructose -6-phosphate (6C)
Phospho-fructokinase ↓ ATP add → ADP out — Adds phosphate to prepare for cleavage
Fructose -1-6-phosphate (6C)
Aldolase ↑ Cleavage

(3C) DHAP — Dihydroxyacetone phosphate
Glyceraldehyde -3phosphate (3)
Triose phosphate isomerase makes single product
ip — H_3PO_4
(ip) dehydrogenase ↓ → 2H (NAD + pick up → $NADH_2 + H^+$]
2 molecule 1-3- Biphosphoglycerate
Fist ATP of glycolysis
phosphoglycerate kinase ↓ ADP add x2 → ATP outer x2
2 molecule 3-phosphoglycerate acid.
Mutaase ↓ ADP → ATP — move phosphate
2 - phosphoglycerate acid (3C)
Endase ↓ → H_2O out
2molecule (3C) phosphoenolpyruvate PEP
↓ ADP Add x2 → ATP out 2
2 molecule x Pyruvate acid 3

① Glucose is phosphorylated to glucose-6-phosphate. The enzyme is hexokinase, which split ATP into ADP and pi (inorganic phosphate) is added on to the glucose. The energy released by hydrolysis of ATP is utilised for the ~~for~~ the forward reaction. Hexokinase is the key glycolytic enzyme and the reaction is irreversible.

② Glucose-6-phosphate is isomerised to fructose-6-phosphate by phosphohexose isomerase.

③ Fructose-6-phosphate is further phosphorylated to fructose-1-6-bisphosphate. The enzyme is phosphofructo-kinase, it is an important key enzyme and the reaction is irreversible.

④ Fructose 1,6 bisphosphate is cleaved into two 3 carbon atom; one glyceraldehyde-3-phosphate and other molecule of dihydroxyacetone phosphate. The enzyme is aldolase. Dihydroxy acetone phosphate is isomerised to glyceraldehyde 3-phosphate by the enzyme phosphotriose. isomerase.

⑤ Glyceraldehyde-3-phosphate is dehydrogenated and simultaneously phosphorylated to 1,3-bis-phosphoglycerate with the help of NAD^+: The enzyme is glyceraldehyde-3-phosphate dehydrogenase.

⑥ 1,3-bis-phosphoglycerate is converted to 3-phosphoglycerate by the enzyme 1,3-bis-phosphoglycerate kinase. Here one molecule of ATP is formed and this reaction is an example for substrate level of phosphorylation.

(7) 3-phosphoglycerate is isomerised to 2-phosphoglycerate by shifting the phosphate group from 3rd to 2nd carbon atom. The enzyme is phosphoglucomutase.

~~(8) 2-phosphoglycerate is isomerised to 3-phosphoglycerate by shifting the phosphate group~~

(8) 2-phosphoglycerate is converted to phosphoenol pyruvate by the enzyme enolase. One water molecule is removed. A high energy phosphate bond is produced. This enzyme requires Mg^{++} and inhibited by fluoride.

(9) phosphoenol pyruvate is dephosphorylated to pyruvate kinase one molecule of ATP is generated. This step is irreversi

(10) In anaerobic condition pyruvate is reduce to lactate b lactate dehydrogenase. In aerobic condition pyruvate enters citric acid cycle for complete oxidation.

★ **Energy yield from glycolysis :-**

Aerobic condition :- Number of ATP gained per glucose molecule is 8ATPs.

Anaerobic condition :- Number of ATP gained per glucose molecule is 2 ATPs.

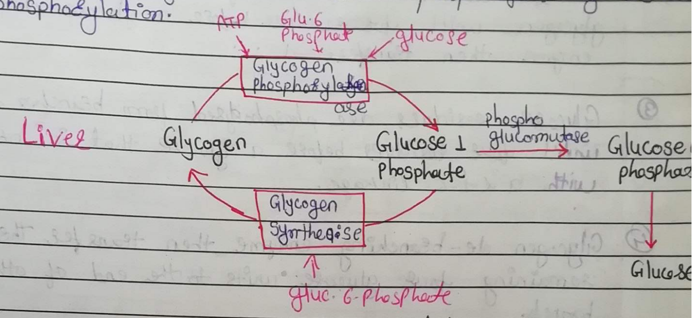
★ Glycogenolysis ★

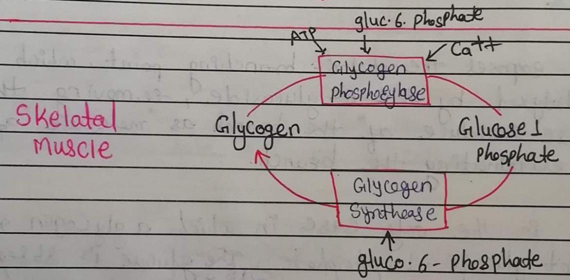
Glycogenolysis is the process of degradation of glycogen to glucose 1 phosphate and glucose in liver and muscle. When there is more supply of glucose to our body, immediately after meals, gets stored in the form of glycogen in liver and muscles. The stored Glycogen Comes to rescue when the blood glucose drops down, a Situation which prevails between our daily meals. This Cycle done for the balance between glycogen and glucose in our body. In our body we have two energetic state highly energetic state were highly excess amount of glucose right up eating something and second one is low energetic state were we have less amount of glucose that we desire.

Glycogen is polymer of α-1-4 linkage glucose with α-1-6- branches Comes in ordered and these α-1-6 branches are visiable after every ten recedue reptly. ~~It mostly polymer are visiable after every~~

It mostly polymer made up of glucose link each other and the bond between the adjesant glucose or α-1-4 kind of linkages and the link that is present in the branch region α-1-6- linkage. Liver uses glycogens as a reserve for maintaing blood glucose level in our body, its very importance that their is Constant supply of glucose to our cell or body so that can utilize the glucose, glycogen is bulid from a starting single involving attachement of a first sugar to small protein Called glycogenin.

- Glycogenolysis take place in the cytoplasm of cell in muscle, liver and adipose tissue.
- Glycogen branches are catabolised by the sequential removal of glucose monomers via phosphorylysis by the en[illegible] phosphorylation.
-



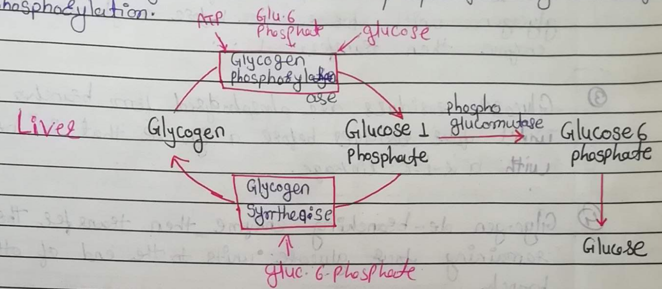


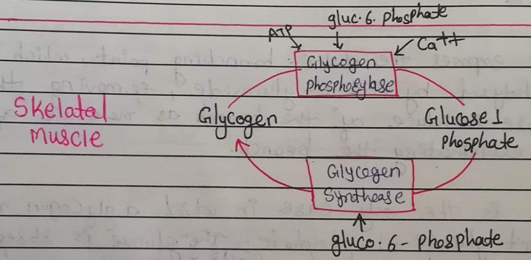
- Glucose-1-phosphate is released from the non-reduci end of glycogen chains.

Steps Envolved in this pathology :-

1) Glycogen phosphorylase cleaves the bond linking a termi glucose residue to a glycogen branch by substitution of a phosphoryl group for the α-1-4 linkage.

- Glycogenolysis take place in the cytoplasm of cell in muscle, liver and adipose tissue.
- Glycogen branches are catabolised by the sequential removal of glucose monomers via phosphorolysis by the enzyme phosphorylation.
-





- Glucose-1-phosphate is released from the non-reducing end of glycogen chains.

Steps Involved in this pathway :-

1) Glycogen phosphorylase cleaves the bond linking a terminal glucose residue to a glycogen branch by substitution of phosphoryl group for the α-1-4 linkage.

② Glucose - 1 - phosphate is converted to glucose - 6 - phosphate by the enzyme phosphoglucomutase.

~~Glucose residues are phosphorylsed from branches of glycogen until four residues before a glucose de-branching enzyme then transfers~~

③ Glucose residues are phosphorylsed from branches of glycogen until four residues before a glucose that is branched with a α-1-6- linkage.

④ Glycogen de-branching enzyme then transfer three of the remaining four glucose units to the end of other glycogen branch.

⑤ This exposes the α-1-6- branching point, which is hydrolyzed by α 1-6- glucoside, removing the final glucose residue of the branch as molecule of glucose and eliminating the branch.

⑥ This is the only case in which a glycogen metabolite is not glucose - 1 - phosphate. The glucose is subsequently phosphorylated to glucose-6-phosphate by hexokinase.

★ Enzymes :- Ⓐ Glycogen phosphorylase :→ Breakes α-1-4- linkage and de-branching enzyme breaks α-1-6 linkages to release single units of glucose 1-phosphate.

Ⓑ phosphoglucomutase :→ Converts glucose -1 -phosphate to glucose - 6 - phosphate, which is then shuttled into the glycolytic pathway.

Significance ↦

Glycogenolysis play an important role in the fight or flight response.

- It contributes to the regulation of glucose level in the blood.
- The metabolism of glycogen polymers become important during fasting.
- In myocytes (muscle cell), glycogen degradation serve to provide an immediate source of glucose -6-phosphate for glycolysis to provide energy for muscle contraction.

Gluconeogenesis

It is the process of formation of new glucose molecule from carbohydrate or non-carbohydrate precursor. The importance of precursor are lactate, pyruvate, renal medulla as sole source of energy.

pathway ↦

Gluconeogenesis is pathway consisting of a series of eleven enzyme-catalyzed reaction. The pathway will being in either the liver, kidney, in the mitochondria or cytoplasm of these cell, this being dependent on the on the substrate being used. many of the reactions are the reverse of steps found in

(1) Glucogneogenesis process First, two pyruvate molecules are carboxylated to form oxaloacetate. one ATP molecule is needed for this.

② Oxaloacetate is reduced to malate by NADH so that can be transported out of the mitochondria.

③ Malate is oxidized back to oxaloacetate once it is out of the mitochondria.

④ Oxaloacetate forms phosphoenolpyruvate ~~once it is out of the mitochondria~~. using the enzyme PEPCK

⑤ phosphoenolpyruvate is changed to fructose 1-6-bisphosphate and then to fructose-6-phosphate. ATP also used during this process, which is essentially glycolysis in reverse.

⑥ Fructose-6-phosphate becomes glucose-6-phosphate with the enzyme phosphoglucoisomerase.

⑦ Glucose is formed from glucose-6-phosphate in the cells endoplasmic reticulum via, the enzyme glucose-6-phosphatase To form glucose, a phosphate group ~~is~~ is removed and glucose-6-phosphate and ATP becomes glucose and ADP.

Pathway of gluconeogenesis ⇒

pyruvate

② ATP → ② ADP ↓ PEP Caeboxykinase (~~oxaloacetate~~)

phosphoenolpyruvate

GTP → 2 GDP ↓ enolase

2-phosphoglycerate

↓ phosphoglycerate mutase

3-phosphoglycerate

ATP → ADP ↓ phosphoglycerate kenase

1·3-bisphosphoglycerate

↓ glyceraldehyde phosphate dehydrogenase

Glyceraldehyde-3-Phosphate

NADH+H⁺ ← → NAD⁺ ↓ triose Phosphate isomerase

Dihydoxyaceton Phosphate

↓ aldolase

Feuctose-1-6-bisphosphate

Pi ← ↓ Feuctose 1-6-phosphatase

Feuctose 6 phosphate

↓ phosphohexo isomerase

Glucose-6-phosphate

Pi ← ↓ phosphatase

Glucose.

Hormonal Regulation and Importance of Gluconeogenesis

- Glucagon and Glucocorticoids increase Neoglucogenesis.
- When glucagon levels rise, the cellular cAMP level also increase. The CAMP concentration inactivates the enzyme pyruvate dehydrogenase (PDH) by phosphorylation process.
- The gluconeogenesis and glycolysis have opposite directions, their reaction to regulatory signals may be opposite or they work against one of the futile cycle.

Importance :-

- A continual supply of glucose is necessary as a source of energy, especially for the Nervous system and the Erythrocytes.
- Gluconeogenesis mechanism is used to clear the products of the metabolism of other tissues from the blood eg: Lactate, produced by Muscle and erythrocyte and glycerol, which is continuously produced by adipose tissue.

Clinical Significance :-

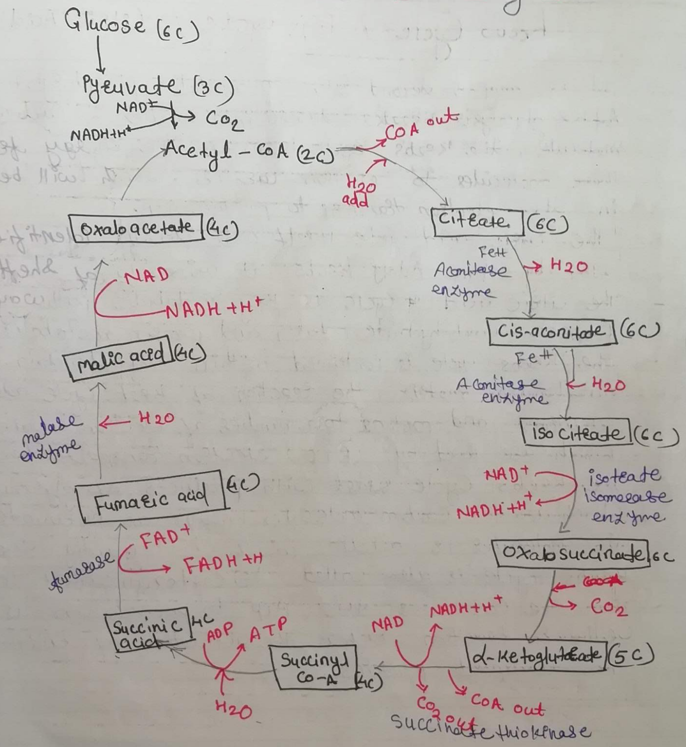
- The enzyme pyruvate carboxylase, a deficiency is seen as inborn error of metabolism, where mental retardation is manifested.
- It's incidence is one in 25,000 births.
- pyruvate carboxylase gene is located in human Chromosome No-11.
- In type II diabetes mellitus condition, the risen gluconeogenesis is responsible for the production of excessive Glucose after an overnight fast.

Unit III Ankita madam, ①
Zoology
B.sc. S.Y.

Krebs Cycle / TCA Cycle / Citric Acid

- It is major second step in oxidative phosphorylation.
- After glycolysis breaks glucose into smaller 3-Carbon molecule, the Krebs cycle transfers the energy from these molecules to electron carriers, which will be used in the electron transport to produce ATP.
- The citric acid cycle itself was finally identified in 1937 by Hans Adolf Krebs at university of Sheffield.
- The citric acid cycle is key metabolic pathway that connects carbohydrate, fat, and protein metabolism.
- The Krebs cycle is contained within mitochondria. Within mitochondrial matrix, the reaction of Krebs cycle adds electrons and protons to a number of electron carriers which are used by (ETC) electron transport chain - ATP.
- The Krebs cycle start with products of glycolysis which are two carbon molecules known as pyruvate.
- This molecules is acidic, which is why the Krebs cycle is also called tricarboxylic acid (TCA).
- Then, the cell uses this ATP to power various cellular reaction, such as the activation of enzyme or transport proteins.

C.C.I.O.K. Send Some Fast Money Order.



3 NADH+H = 9 ATP
1 FADH+H = 2 ATP
Direct = 1 ATP

12 ATP

When the Connecting link NADH+H+ add in the whole Net gain ATP i.e 15.

Steps in TCA or Kreb's Cycle :-

In order for pyruvate from glycolysis to enter the kreb's cycle it must be converted into acetyl-CoA by the pyruvate dehydrogenase complex which an oxidative process where in NADH and CO_2 are formed. Another source of acetyl-CoA is beta oxidation of fatty acid.

1) Condensation :-

Acetyl CoA enters the kreb cycle when it is joined or react with the oxaloacetate by citrate synthase to produce citrate. This process requires the input of water. Oxaloacetate is the final metabolite of the krebs cycle and it the enzyme citrate synthetase catalyse the reaction.

$$\underset{(4C)}{OAA} + \underset{(2\text{-}C)}{Acetyl\text{-}CoA} + H_2O \xrightarrow[\text{Synthetase}]{\text{Citrate}} \underset{(6C)}{Citrate} + CoA$$

Co-A thus relieved and is recycled for acetylation of another molecule of pyruvate. Citrate undergoes the biochemical reactions and finally the oxaloacetate gets regenerated. Its repeat the cycle.

2) Isomerisation :-

Citrate is converted into isocitrate by the enzyme aconitase and Fe^{++}. This is accomplished by the removal and addition of water to yeild an isomer.

$$\underset{(6\text{-}C)}{Citrate} \xrightarrow[Fe^{++}]{\text{Aconitase}} \underset{(6C)}{cis\text{-}aconitate} + H_2O$$

cis-aconitase combines with the water molecule to form iso-citrate, an isomer of citrate.

$$\text{Cis-aconitate} + H_2O \xrightarrow[Fe^{++}]{\text{aconitase}} \text{Iso-citrate}$$

③ Oxidation (Dehydrogenation - I) :-

Iso-citrate is oxidized to form oxalo-succinate. Two hydrogen atom released at this step are taken up by the coenzyme NAD and NADH + H^+ is formed. The enzyme iso-citrate dehydrogenase and Mn^{++} are necessary for this reaction.

$$\text{iso-citrate} + NAD \xrightarrow[Mn^{++}]{\text{iso-citrate dehydrogenase}} \text{oxalosuccinate} + NADH + H^+$$

④ Decarboxylation :-

oxalo-succinate undergoes decarboxylation in the presence of enzyme decarboxylase and α-keto-glutarate is formed. CO_2 gases out of the mitochondria.

$$\text{oxalosuccinate} \xrightarrow[\text{dehydroxylase}]{\text{oxalo succinate}} \alpha\text{-ketoglutarate} + CO_2$$

⑤ Oxidative-decarboxylation :-

α-ketoglutarate is converted into ~~succinate~~ by succynl-CoA synthetase which yields one ATP

α-ketoglutarate is converted into succynl-CoA by α-ketoglutarate dehydrogenase. NAD and CO_2 are once again produced. During reaction CO_2 goes out of mitochondria and one hydrogen removed from substrate is received by the Co-enzyme NAD + NADH + H.

α-ketoglutarate + NAD + CoA $\xrightarrow[\text{dehydrogenase}]{\alpha\text{-ketoglutarate}}$ Succinyl CoA + $NADH_2$ + CO_2

⑥ Hydration and phosphorylation :-
Succinyl CoA is converted into succinate by Succinyl CoA synthetase which yield one ATP per succinyl-Co-A. Energy liberated during this reaction is used in the formation of GTP from GDP (Guanosine Diphosphate) and in the reaction takes place in presence of enzyme Succinate thiokinase.

$$\text{Succinyl-Co-A} + H_2O \xrightarrow{GDP \rightarrow GTP} \text{Succinate} + \text{CoA}$$

$$GTP + ADP \longrightarrow ATP + GDP$$

⑦ Oxidation (Dehydrogenation III) :-
Succinate is oxidized by dehydrogenation into fumarate and the hydrogen removed in this reaction reduce the coenzyme FAD (Flavin Adenine Dinucleotide) to $FADH + H^+$ which is a prosthetic group of succinate dehydrogenase. Succinate dehydrogenase is a directly part of the ETC. It is also known as electron carrier II.

$$\text{Succinate} + FAD \xrightarrow[\text{Dehydrogenase}]{\text{Succinate}} \text{Fumarate} + FADH + H^+$$

⑧ Hydration :-
Fumarate accepts a water molecule to produce malate, by hydration with the use of fumarase enzyme.

$$\text{Fumarate} + H_2O \xrightarrow{\text{Fumarase}} \text{Malate}$$

(9) Oxidation (Dehydrogenation):→

malate is oxidized by removal of hydrogen removed and oxalo-acetate get regenerated. The hydrogen removed in this reaction is taken up the coenzyme NAD to from NADH+ H^+. The enzyme used as malate dehydrogenase.

$$\text{Malate} + NAD \xrightarrow[\text{dehydrogenase}]{\text{Malate}} \text{Oxaloacetate} + NADH + H^+$$

Therefore Krebs cycle is repeated twice for a every glucose molecule oxidized aerobically. Thus two turns of Krebs cycle produce, 6 molecules of NADH+H^+, two molecules of FADH+H^+ and two molecule of ATP. During each turns Krebs cycle three molecule of water are used up & two molecules of CO_2 are released.

Significance of TCA Cycle :→

The major significance of the citric acid cycle is to act as the final common pathway