WEEK FIVE

GLUCONEOGENESIS

This is defined as the bio-synthesis of CH_2O from 3 carbon and 4 carbon precursors generally non-carbohydrate in nature (production of carbohydrate from non-carbohydrate precurssors). Principal substrates for gluconeogenesis are lactate produced from glycolysis, amino acid and glycerol. Gluconeogeneisis occurs primarily in the cytosome. Although some precursors are generalized in mitochondria which must be transported to the cytosome.

The major gluconeogenic organ in animals is the liver with kidney cortex contributing in a minor way. The major fate of glucose formed in gluconeogenesis are catabolised by nervous tissues and utilization by skeletal muscle.

Note: Those points that you have energy been used on the pathway or gluconeogenetic chart is called critical points and they are irreversible. They are called control point. Gluconeogenesis (starting from protein, glycerol, lactate until you get to glucose) is a direct reversal of glycolysis.

Question

Explain in details how an animal can regain its exhausted glucose.

Glycogen is many glucose joined together by α 1-6 and α 1-4 reaction.

Gluconeogenesis simply resemble glycolysis and run in reverse, there are important steps which allow it to run in the direction of glucose synthesis. The reduction from glucose to pyruvate is strongly Exergonic. Conversion of pyruvate to glucose is made possible by the fact that 3 reaction of glycolytic pathway are strongly exergonic and are irreversible. They are catalysed by the following enzymes;

1. Hexokinase
2. Phospho-fructoskinase.
3. Pyruvate kinase.

In gluconeogenesis, different enzymes are used at each of these steps, these 3 irreversible reactions of glycolysis are by-passed by enzymes specific to gluconeogenesis at energy cost. The remaining reactions of gluconeogenesis are catalysed by glycolytic enzymes. The focus of glyuconeogenesis is on the 3 reactions that by-pass the irreversible reactions of glycolysis.

The process of gluconeogenesis is needed in the body because it provides the animal with glucose when it is not supplied in the diet in sufficient quantity. There are certain tissues which require a continuous supply of glucose at all times e.g brain, nervous system, red blood cell (erythrocytes) and the placenta. Apart from these needs, glucose helps to maintain the levels of intermediates participating in the TCA cycle. Glucose is the only source of fuel that will supply energy to skeletal muscle under anaerobic condition. This is required in the placenta because it is actively taken up by the foetus. Glucose which is the precursor of lactase is also useful in the production of milk in the mammary gland.

Gluconeogenesis therefore effects the conversion of non-carbohydrate precursors to glucose. And by virtue of this gluconeogenesis act as a clearing agent or house for the end products of metabolism of other tissues from the blood. Some of these metabolites can be injurious to the body if allowed to accumulate. The site of gluconeogenesis is chiefly liver and secondly the kidney.

Energy barriers in the glycolytic pathway obstruct the direct reversal of the pathway.

1. From pyruvic acid(enol) to 2-phospho-enol pyruvic acid.
2. From fructose-1-6 biphosphate to fructose-6-phosphate.
3. Conversion of glucose-6-phosphate to glucose.

In the first point1-2 things happen in the reaction.

a. The conversion of pyruvic to oxalo-acetic catalysed by enzyme pyruvate carboxylase in the presence of ATP, biotin and CO_2.

Pyruvate + HCO_3^- + ATP $\longrightarrow$ Oxalo-acetate + ADP + Pi

Pyruvate + HCO_3^- + ATP $\longrightarrow$ Oxalo-acetate + ADP + Pi (inorganic) + H^+

Question: Is biotin a dependent reaction ? Biotin helps to transport CO_2

b. Oxalo acetic is converted to phospho-enol pyruvate by the enzyme phospho-enol pyruvate carboxy kinase.

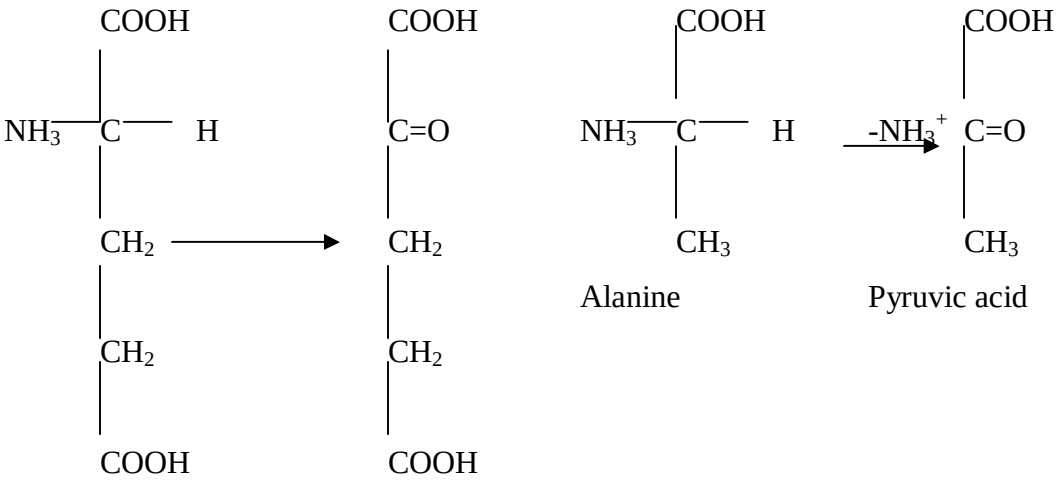
Second point phospho-enol pyruvate is converted to fructose-1-6-biphosphate or biphosphate by glycolytic enzyme acting in reverse, since the phoshphofructokinase reaction of glycolysis is essentially irreversible and also by pass in gluconeogenesis by a simple irreversible hydrolytic removal of 1-phosphate group.

Third point Fructose-6-phosphate undergoes isomerization in the presence of phospho-glucoisomerase to glucose-6-phosphate. This is converted to glucose by reversible action of hexokinase or glucokinase. Another enzyme specific to gluconeogenesis, glucose-6-phosphate come into play instead this by-pass reaction involves a simple hydrolysis in the presence of magnesium ion.

Glucose-6-phosphate + H_2O ⟶ Glucose + Pi

All the enzymes that are specific for these by-pass reactions are referred to as key ENZYMES OF GLUCONEOGENESIS. Their counterpart in glycolysis is called KEY ENZYEMS OF GLYCOLYSIS.

For amino-acid, 1st deamination occurs and after this, the amino acid form pyruvic acid or other intermediates of TCA.



Glutamic acid α-Ketoglutamic acid Alanine Pyruvic acid

In the case of ruminant, propionic acid plays a major role and is converted to succinylCoA and enters the TCA.

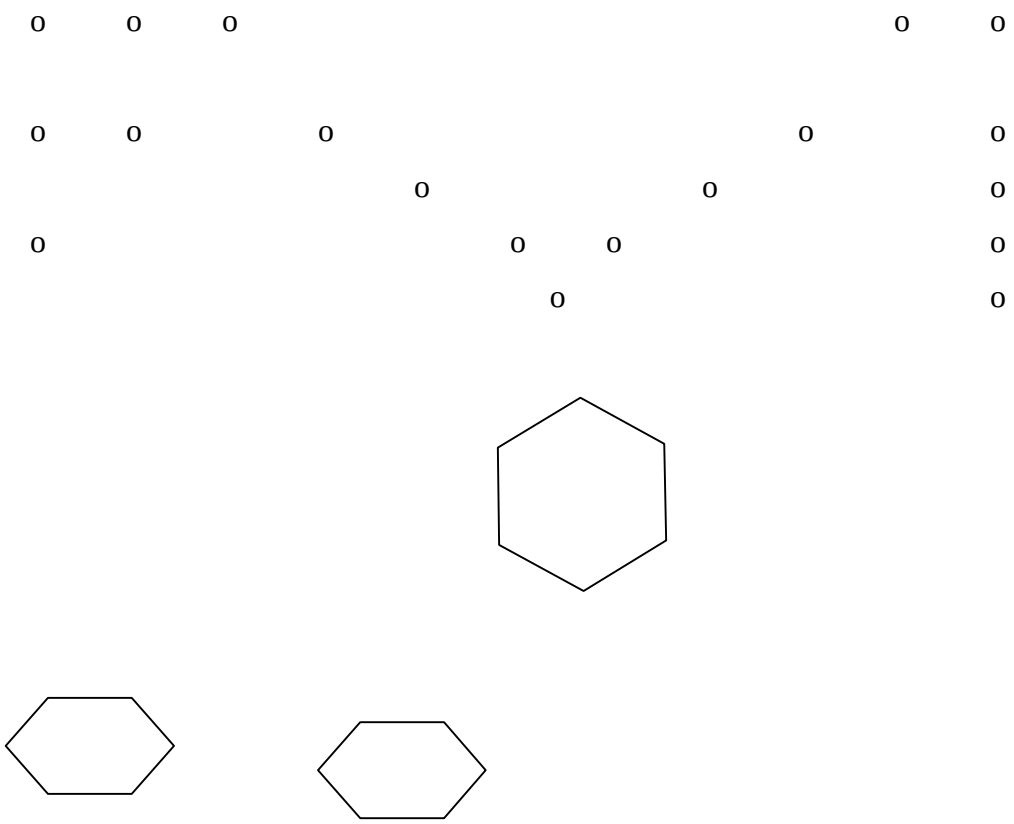
GLYCOGENESIS (FORMATION OF GLYCOGEN)

The formation of glycogen occurs practically in every tissue of the body but chiefly in the liver and muscles. In humans, the liver may contain as much as 60% of its weight as glycogen when analysed shortly after a meal high in carbohydrate. After 12 to 18 hours of fasting, the liver becomes almost totally depleted of glycogen. Muscle glycogen is only rarely elevated to about 10% and its only depleted significantly after prolonged vigorous exercise.

Muscle glycogen is a readily available source of hexose units for glycolysis in the muscle. Liver glycogen is largely concerned with export of hexose units for maintenance of blood glucose practically between meals.

Glycogenesis involves 4 stages/steps:

1. Phosphorylation of glucose to give glucose-6-phosphate by enzyme glucokinnase.
2. Glucose-6-phosphate is converted to glucose-1- phosphate by the enzyme phosphoglucomutase.
3. Glucose-1-phosphate reacts with UTP (Uridine Triphosphate) to form UDPG (Uridine Diphosphate glucose) and the enzyme responsible for its pyrophosphorylase (PP).
4. As the UDPG brings glucose units one after another, the C_1 of the glucose join with the C_4 of the already existing molecule. This will continue until time for branching. The enzyme responsible for this joining is glycogen synthase or glycogen transferase. The body prefers to start with an oligosaccharide. This is called a Primer. The glycogen primer may in turn be from a protein backbone which may be similar to the synthesis of other glycoprotein when the chain length is up to 6 molecules, another enzyme come into play, it is called A BRANCHING ENZYME named AMYLO-1-4,1-6-TRANSGLUCOSIDASE which transfers part of 1-4 chain to a neighbouring chain to form an α-1-6chain. Thereby establishing a branched chain.



GLYCOGENOLYSIS

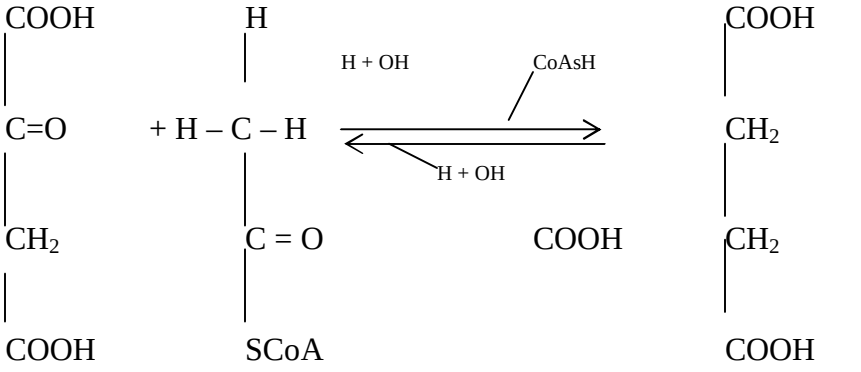
The importance of glycogenolysis and gluconeogenesis is to maintain a balance in the glucose content of the blood.

Glycogenolysis is the opposite of glycogensis. The breakdown of glycogen that is glycogenolysis is activated by the enzyme phosphorylase which breaks the 1 – 4 linkages. Each time it breaks the linkages, it yields glucose-1-phosphate one at a time. Phosphorylase enters from the free end and available glycogen unit and start chopping off the molecule left on either side of the branch point i.e α—1-6-glycosidic bond are not susceptible to cleavage by phosphorylase but before this a transferase enzyme comes to play such that α-1-6 linkage is exposed. The transferase cleave the remaining 3 – 4 molecule to reach α-1-6 linkage thereby exposing it to another enzyme- debranching enzyme (amylo-1-6glucosidase) to break it down.

Glucose is transported in the blood as natural glucose not glucose-1-phosphate, so to convert this to glucose, first glucose-1-phosphate is converted to glucose-6-phosphate, the enzyme is phospho-glucomutase. The glucose-6-phosphate is converted to glucose by glucose-6-phosphatase.

TRICARBOXYLIC ACID CYCYLE (TCA)

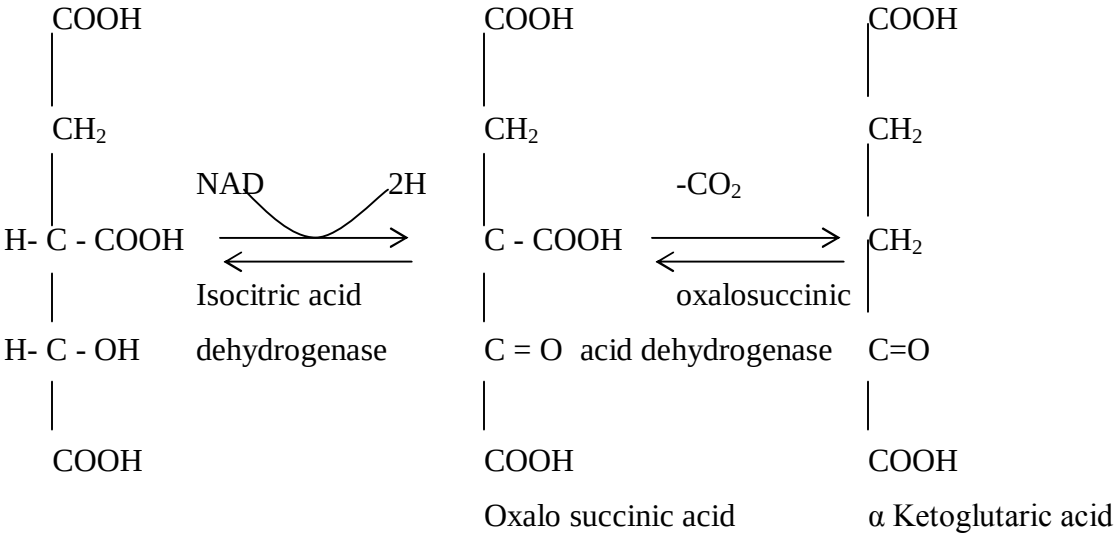
The TCA completes the oxidation of glucose to generate energy. The first thing that happens is the conversion of pyruvic acid to acetyl CoA. It is the CoA that enters the TCA cycle. The TCA is very important for plants because it is a way of metabolizing their organic acids. It is called the TCA because most of the compounds formed have 3 or more carboxylic groups, also called citric acid cycle because citric acid is the first tricarboxylic acid produced in the cycle. The acetyl CoA now condenses with oxaloacteic acid to yield citric acid.



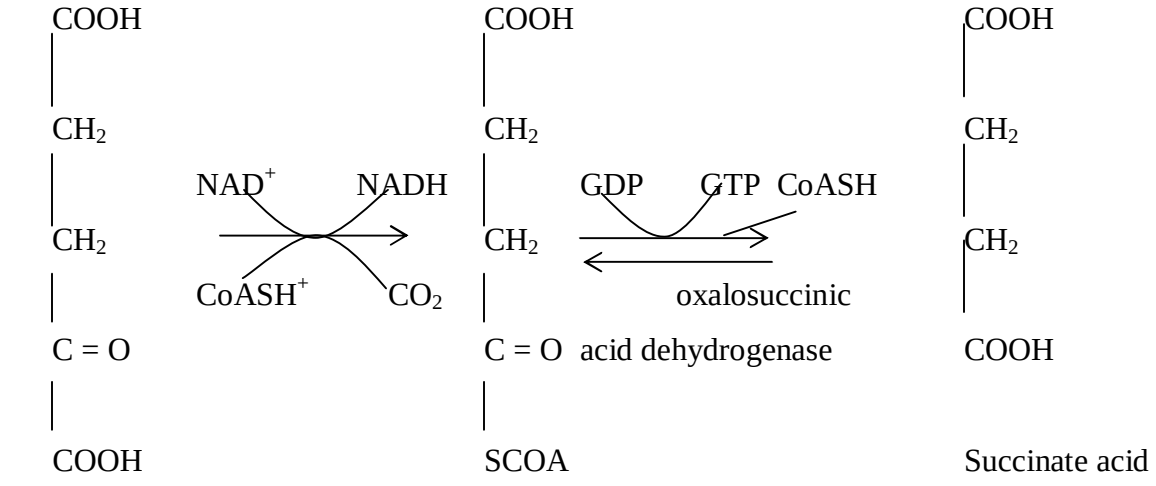
Assignment

Write a short note on the biosynthesis of a named amino acid in the glutamate family giving the structural formula amylation.

The citric acid losses water to form cis aconitic acid. The cis aconitic acid adds on water to form isocitric acid. The above two reactions are catalyzed by aconitase. Isocitric acid is dehydrogenated to yield oxalo succinic acid with the help of the enzyme isocitric dehydrogenase. At this point, 3 moles of ATP is generated.



Afterwards, oxalosuccinic acid is decarboxylated to form α-keto glutaric acid. This can be linked to protein metabolism i.e amino acids can be incorporated to give energy if need be. Also α-keto glutarate can be used to form backbone of some amino acid. The reaction is catalysed by oxalo-succinic acid decarboxylase. The α-keto glutaric acid adds on H_2O, decarboxylated and dehydrogenated to give succinic acid.

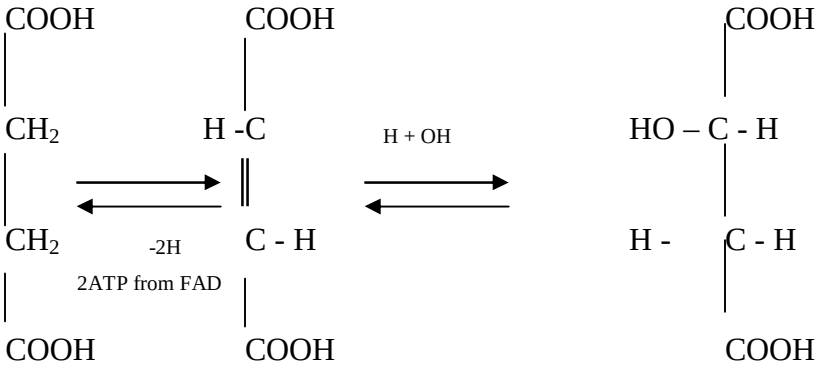


α-Ketoglutaric acid Succinyl CoA

GTP – Glutamine triphosphate

GDP – Glutamine Diphosphate

The reaction is catalysed by α Ketoglutaric acid dehydrogenase and produces 4 ATP molecules.



Succinic acid Fumaric acid Malate

Fumaric acid is formed by the dehydrogenation of succinic acid with the help of succinic dehydrogenase. 2 molecules of ATP by another kind of high energy compound FAD (Flavine Adenine Dinucleotide). Oxidation of energy is through respiration of FAD to produce 2 moles of ATP Fumaric acid add on H_2O to form L-malic acid. The enzyme responsible for this is fumarase.