

Welcome to module number 22, which deals with the Regulation of Glycolysis, for the Unit 3 of Carbohydrate Metabolism from the paper Biochemistry and Metabolic Processes.

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Glycolysis describes the breakdown of a 6-carbon Glucose to two molecules of 3-carbon Pyruvic acid. Glycolysis produces high energy at high rate in short durations. And therefore glucose, which are easily available to the cell is in constant supply most of the time. The process of glycolysis is also continuous. And therefore there is a need of regulatory processes to control it as and when it is been not required. Because the outcome of glycolysis is to produce pyruvate molecule and which enters into the Krebs cycle for the ATP generation. As soon as there is a large amount of ATP already generated, there is no more requirement of glucose, to be broken down further, and therefore the regulatory mechanism plays a major role to control the process of glycolysis.

The regulation of glycolysis occurs at the three equilibrium reactions. This is the glycolytic pathway. The first one is the preparatory phase of glycolysis. Which shows the glucose been catabolized into glyceraldehyde-3-phosphate and dihydroxyacetone phosphate. Glucose to glucose 6 phosphate by Hexokinase, glucose 6 phosphate to fructose 6 phosphate catalyzed by phosphohexose isomerase, fructose 6 phosphate to fructose 1,6 Biphosphate catalyzed by phosphofructokinase 1. Fructose-1,6-biphosphate to glyceraldehyde three phosphate, is with the help of aldolase. And the glyceraldehyde-3-phosphate to dihydroxyacetone phosphate, and vice versa, with the help of triose phosphate isomerase. And this we have learnt with its sequence in detail in the previous modules.

But more emphasis has to be given in the present module, as far as hexose kinase and phosphofructokinase 1 is concerned in the preparatory phase of glycolysis because these are the one who catalyzes an irreversible reaction. And they are the point of regulation for glycolysis.

Similarly, in the payoff phase of glycolysis, the glyceraldehyde-3-phosphate converts into 1,3-biPhosphoglycerate with the help of a glyceraldehyde-3-phosphate dehydrogenase enzyme. And further, this molecule of 1,3 biphosphoglycerate is being converted to 3-phosphoglycerate by phosphoglycerate kinase and 3-phosphoglycerate to two phosphoglycerate by phosphoglycerate mutase, and finally two phosphoglycerate to phosphoenolpyruvate and later into pyruvate with the help of enolase and then pyruvate kinase. And that is how a glucose a single 6 carbon compound is being converted to two carbon pyruvic acid and pyruvate kinase plays a very important role when it comes to the regulation of glycolysis in payoff phase of glycolysis.

So let us see at the enzyme hexose kinase reaction, how a glucose breakdown is being regulated.

The first regulation is at glucose 6 phosphate formation, which is the starting point of glycolysis, the enzyme who catalyzes this reaction is the hexokinase by feedback inhibition by a glucose 6 phosphate. It is sequestered in the nucleus of the hepatocyte, but released when the cytosol, a glucose concentration, rises.

Let us try to understand using this chart. The glucose is converted into glucose 6 phosphate, which is the starting point of a glycolysis process, and this has been catalyzed with the help of an enzyme hexokinase. The moment there is enough amount of glucose 6 phosphate and enough amount of glucose, glucose 6 phosphate itself will have a feedback inhibition on enzyme hexokinase. And allosterically it will block the hexokinase from further converting the glucose into a glucose 6 phosphate. So, this is the first checkpoint where the glycolysis process is been regulated.

Second is regulation during the conversion of fructose 6 phosphate to fructose 16 phosphate. So, one of the most important regulatory steps in the process of glycolysis is the reaction by phosphohexose isomerase wherein ATP and citrate inhibits the PFK phosphofructokinase activity. AMP and fructose-2,6-biphosphate activates this enzyme.

Let us try to understand using this chart again of a preparatory phase of glycolysis. In this, the glucose 6 phosphate is converted to fructose 6 phosphate and the fructose 6 phosphate is further phosphorylated with the help of an enzyme phosphofructokinase one. PFK-1 to convert it into fructose 1,6 biphosphate. ATP, as well as sometimes citrate, inhibits this enzyme allosterically. Therefore, there won't be further conversion of fructose 6 phosphate to fructose 16 biphosphate. At the same time, it is also been activated by the AMP. If suppose the amount of ATP drops down, then the AMP and the fructose-2,6- biphosphate will activate the phosphofructokinase enzyme so that it will convert fructose 6 phosphate to fructose 1,6 biphosphate molecule. This is one of the important steps of regulation of glycolysis.

The 3rd and most important is the regulation during the formation of pyruvate from phosphoenolpyruvate. So, third big step during which, regulation occurs is the pyruvate kinase reaction. Wherein ATP, acetyl coenzyme A and fatty acids inhibits pyruvate kinase enzyme activity allosterically. So, using this chart, let us try to understand in payoff phase of glycolysis. Glyceraldehyde-3-phosphate is converted into pyruvate molecule wherein there are five steps involved in this process and the 10th step which is the conversion of phosphoenolpyruvate. Two pyruvate is being formed with the help of enzyme pyruvate kinase. And enzyme pyruvate kinase is allosterically inhibited by ATP or acetyl Co A or long chain fatty acids. It's only because, if there is a large amount of pyruvate already existing which enters into the Krebs cycle, which gets converted into Acetyl Co A and later ATP is being generated. Then there is no more pyruvate required to be formed, and this ATP, acetyl Co A and fatty acids will act as negative inhibitor for the enzyme pyruvate kinase, thus regulating the glycolysis process.

To conclude with this module. There are three important glycolytic enzymes subject to allosteric regulation, controls the glycolysis process that is hexokinase, phosphofructokinase 1, and pyruvate kinase, and thus these regulatory mechanisms maintain a constant level of this key metabolites and the key metabolites are the ATP and NADH in the cells.

This module was prepared using the following references, thank you.