UNIT-2-Carbohydrate metabolism.

The Glycolytic Pathway Is Tightly Controlled/Regulation of Glycolysis

The flux of glucose through the glycolytic pathway is regulated to maintain nearly constant ATP levels (as well as adequate supplies of glycolytic intermediates that serve biosynthetic roles). The rate of conversion of glucose into pyruvate is regulated to meet two major cellular needs: (1) the production of ATP, generated by the degradation of glucose, and (2) the provision of building blocks for synthetic reactions, such as the formation of fatty acids. *In metabolic pathways, enzymes catalyzing essentially irreversible reactions are potential sites of control*. The required adjustment in the rate of glycolysis, is achieved by a complex interplay among ATP consumption, NADH regeneration, and allosteric regulation of several glycolytic enzymes-hexokinase, phosphofructokinase, and pyruvate kinase _ by second to second fluctuations in the concentrations of key metabolites that reflect the cellular balance between ATP production and consumption. These enzymes act as regulatory as well as catalytic roles and serves as a control site. Their activities are regulated by the reversible binding of allosteric effectors or by covalent modification.

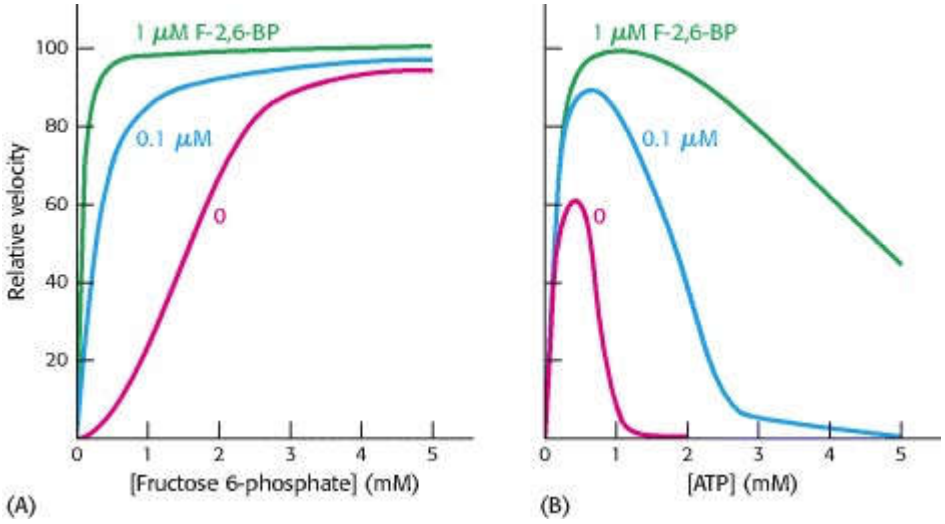
On slightly longer time scale, **glycolysis is regulated by the hormones glucagon,epinephrine and insulin, and by changes in the expression of the genes for several glycolytic enzymes.** An interesting case of abnormal regulation of glycolysis is seen in cancer. Warburg frist observed in 1928 that tumors of nearly all types carry out glycolysis at a much higher rate than normal tissue, even when oxygen is available. This Warburg effect is the basis of detection and treatment of cancer.

Phosphofructokinase is the most prominent regulatory enzyme in glycolysis, .High levels of ATP allosterically inhibit the enzyme in the liver (a 340-kd tetramer), thus lowering its affinity for fructose 6-phosphate. A high concentration of ATP converts the hyperbolic binding curve of fructose 6-phosphate into a sigmoidal one (Figure 1). ATP elicits this effect by binding to a specific regulatory site that is distinct from the catalytic site. AMP reverses the inhibitory action of ATP, and so *the activity of the enzyme increases when the ATP/AMP ratio is lowered*.

Hexokinase, the enzyme catalyzing the first step of glycolysis, is inhibited by its product, glucose 6-phosphate. High concentrations of this molecule signal that the cell no longer requires glucose for energy, for storage in the form of glycogen, or as a source of biosynthetic precursors, and the glucose will be left in the blood.

Glucokinase phosphorylates glucose only when it is abundant because it has about a 50-fold affinity for glucose than does hexokinase.Glucose 6-phosphate can also be converted into glycogen or it can be oxidized by the pentose phosphate pathway to form NADPH. The first irreversible reaction unique to the glycolytic pathway, the *committed step*, is the phosphorylation of fructose 6-phosphate to fructose 1,6-bisphosphate. Thus, it is highly appropriate for phosphofructokinase to be the primary control site in glycolysis. In general, *the enzyme catalyzing the committed step in a metabolic sequence is the most important control element in the pathway*.

Pyruvate kinase, the enzyme catalyzing the third irreversible step in glycolysis, controls the outflow from this pathway. This final step yields ATP and pyruvate, a central metabolic intermediate that can be oxidized further or used as a building block.



Allosteric Regulation of Phosphofructokinase. A high level of ATP inhibits the enzyme by decreasing its affinity for fructose 6-phosphate. AMP diminishes and citrate enhances the inhibitory effect of ATP.

Source-Lehninger. Principles of Biochemistry.