**\*\* ONLY TEXT AND IMAGES APPEARING INSIDE THE RED BOXES WILL BE GRADED\*\***

Protein function is modulated/regulated by

* protein synthesis and degradation,
* sequestration (association with ligands or other proteins),
* covalent modification (there are 500 known protein modifications, including phosphorylation, acetylation, glycosylation, myristoylation..),
* proteolytic activation (example, proteolytic activation of the protrypsin zymogen or preproinsulin to insulin)
* allosterism; the binding of a ligand to one site can affect the binding of anther ligand at a different binding site on the same protein. What is a ligand? A ligand is a smallish molecule that binds by non-covalent interactions. O2 is an allosteric ligand (i.e., allosteric effector) of hemoglobin and is a non-allosteric ligand of myoglobin [page 454, Lehninger, 7th Edition].

Diagram

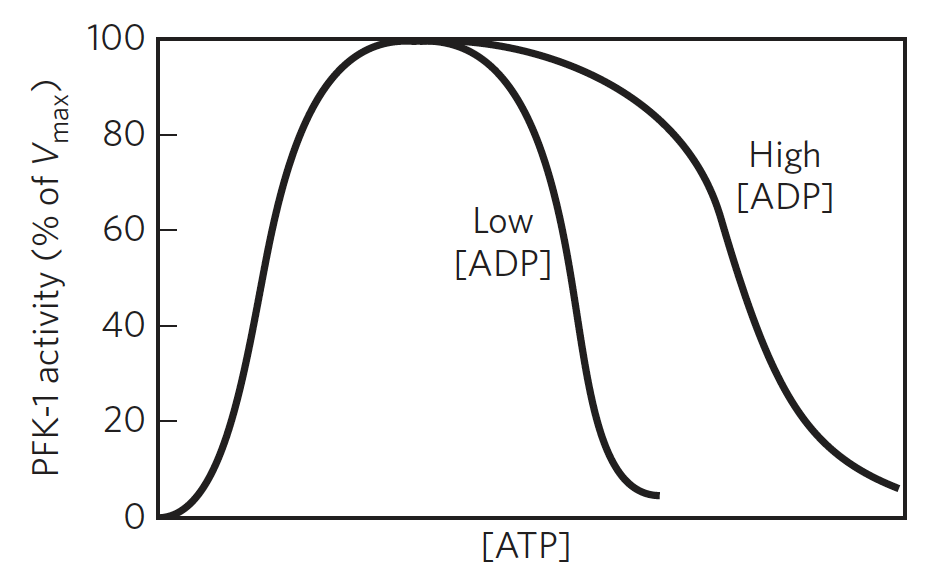
Description automatically generatedFIGURE 6-33 [page 609, Lehninger 7th Edition] An allosterically regulated enzyme showing the effects of an allosteric effector. In many allosteric enzymes, the substrate-binding site and the modulator-binding site(s) are on different subunits (polypeptide chains) called the catalytic (C) and regulatory (R) subunits. Binding of the allosteric effector (M) to its specific site on the regulatory subunit is communicated to the catalytic site through a conformational change of both proteins. This conformational change renders the catalytic subunit more active (i.e., kcat/KM goes up).

Diagram

Description automatically generatedPhosphofructokinase-1 (PFK-1) catalyzes the conversion of fructose 6-phosphate and ATP to fructose 1,6-bisphosphate and ADP, which is the committed step of glycolysis (big -DGRXN). PFK-1 is the primary regulatory enzyme of glycolysis and is controlled by many activators and inhibitors. [page 1528, Lehninger, 7th Edition]

ATP is both a substrate for PFK-1 and an allosteric inhibitor (and is an end-product of the glycolytic pathway). High cellular [ATP] indicates that ATP is being produced faster than it is being consumed. ATP inhibits PFK-1 by binding to an allosteric site and lowering the affinity of the enzyme for fructose 6-phosphate (Fig. 15-16, 7th Edition). Low cellular [ATP] means high [ADP] and [AMP], which act allosterically to relieve this inhibition by ATP. These effects combine to produce higher enzyme activity when ADP or AMP accumulates and lower activity when ATP accumulates.

Citrate (the ionized form of citric acid), a key intermediate in the aerobic oxidation of pyruvate, fatty acids, and amino acids, is also an allosteric regulator of PFK-1; high citrate concentration increases the inhibitory effect of ATP, further reducing the flow of glucose through glycolysis. In this case, as in several other cases encountered later, citrate serves as an intracellular signal that the cell is meeting its current needs for energy-yielding metabolism by the oxidation of fats and proteins.



The effect of [ATP] on the activity of PFK-1 is shown here. For a fixed concentration of fructose 5-phosphate, at low [ATP], PFK-1 activity increases with increasing [ATP]. However, at high [ATP], PFK-1 activity decreases with increasing [ATP].

1. Briefly (one sentence), what is an ‘allosteric’ enzyme?

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1. Briefly (one sentence) explain how ATP can be both a substrate and an inhibitor of PFK-1.

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1. In what ways is glycolysis regulated by [ATP] (one sentence)?

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1. The inhibition of PFK-1 by ATP is diminished when [ADP] is high, as shown in the illustration. Briefly, explain this observation?

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Table

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1. The intracellular concentrations of the substrates and products of the PFK-1 reaction in isolated rat heart tissue are given in the table.
   1. Calculate the reaction quotient Q [fructose 1,6-bisphosphate][ADP]/[fructose 6-phosphate][ATP], for the PFK-1 reaction under physiological conditions (as in the table).

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* 1. Given that DGo for the PFK-1 reaction equals -14.2 kJ/mol, calculate the equilibrium constant for this reaction (RT at 25 °C = 2.48 kJ/mol).

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* 1. Compare the values of *Q* and *K*eq. Is the physiological state near or far from equilibrium?

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