Enzyme Control and Metabolic Design

Imagine if your cells did not have enzymes. How would this impact your physiology? In short, it would be devastating. So many processes of the body are dependent on enzymes, and life would not exist if it wasn't for the ability of enzymes to rapidly convert molecules from one structure to another, and as you will read, to have this done in a very regulated manner. You would not be able to respond rapidly to change, to have muscles contract in a rapid and controlled pattern to ensure correct movement. You would not be able to have control over blood carbon dioxide content through transport from cells and elimination during exhalation in the lung. You would not be able to regulate blood glucose, or eliminate amine groups from cells or the body. You would not be able to synthesize important molecules to support cell structure and function, and you would not be able to digest complex food compounds into smaller compounds your body can use. One could argue that enzymes were probably some of the first proteins every formed, for no life could exist without them.

Now, let's see if you have been following along with the bioenergetic and enzyme content thus far. If a chemical reaction inside a cell does not occur fast enough without an enzyme, then the presence of the enzyme allows the reaction to occur at a meaningful rate of product formation. For an **allosteric enzyme**, or a **Michaelis-Menten** enzyme that can be inhibited, regulation of the enzyme will determine the rate of catalysis for the reaction. If the **regulated reactions** of metabolism occur in strategic places within **pathways** (Figure 1), then entire pathways can be turned on and off simply by controlling a few, rather than all, of the enzymes of the pathway. As previously explained, it is interesting that most allosteric enzymes are located near the beginning and end of pathways. As such, <u>the control of enzymes allows for the control of metabolism</u>.

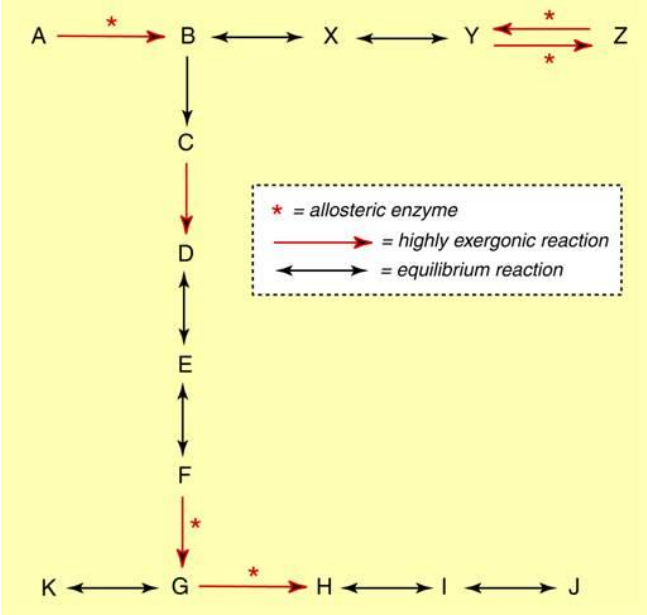

Figure 1. A simplistic example of how allosteric enzymes located near the beginning and end of metabolic pathways can essentially control the activity of the entire pathway.

Another feature of allosterically regulated enzyme catalyzed reactions is that many also occur where there is a large use or release of free energy. In this context, this is also understandable. For enzymes that couple ATP breakdown to the need for free energy to transfer a functional group, or for where sufficient free energy is released to form

ATP, many of these reactions are allosterically controlled. Again this makes sense, for it would be disadvantageous for a cell to waste free energy release when there is no need for added ATP. This would result in increased heat release, and a decreased effectiveness of energy transfer in metabolism.

The control of metabolism can therefore be viewed as the controlled flux of substrates through pathways, which in turn involves the controlled activation of reactions that use and regenerate ATP. As you now know, both aspects of this metabolic control are based on the control of enzymes in a manner sensitive to the energy needs of a cell, while always obeying the second law of thermodynamics.

Despite the importance of allosteric enzymes, do not think that only regulated enzymes are of importance to energy metabolism, or are in some way "superior" to their unregulated counterparts. It is not a negative trait of nature to reveal that most reactions of metabolism are catalyzed by unregulated Michaelis-Menten enzymes. Why is this so? Well, if only 1 or 2 reactions of a pathway were needed to be regulated, then why increase the complexity of metabolism by having a myriad of other enzyme activator and/or inhibitor molecules?

There is another benefit of non-regulated enzymes. Think back to bioenergetics. Reactions that have the least free energy transfer are equilibrium reactions. Based on the second law of thermodynamics, equilibrium reactions will change free energy release, or change direction, depending on the change in substrate and product concentrations. Such reactions are incredibly sensitive to conditions inside a cell, and as such, if the substrates and products of these reactions are important to a pathway, or to overall free energy transfer, then maybe they do not need additional regulation at all. Simply changing substrate and product conditions inside the cell are enough to change the energetics of these reactions.

A classic equilibrium reaction is the creatine kinase (CK) reaction (Figure 2, Equations 1 and 2). As discussed previously, this reaction is a coupled reaction combining ATP formation and creatine phosphate (CrP) breakdown. During intense muscle contraction, when ATP is broken down to ADP plus inorganic phosphate (Pi) and a free proton (H+) at rates that exceed the capacity of the mitochondria, the sudden small increase in ADP and H+, and small decrease in ATP changes the kinetics of the CK reaction in the direction of CrP breakdown and ATP regeneration. As you know from prior study, CrP is important for allowing rapid rates of ATP regeneration during intense muscle contraction, thereby preventing a meaningful decline (more explanation of this soon!) in cellular ATP and to some extent, consuming a H^+ and retarding metabolic acidosis (Equation 1).

$$\begin{array}{l} Exercise: CrP + ADP + H^+ \rightarrow Cr + ATP \\ \qquad\qquad\quad \downarrow \quad \uparrow \quad \uparrow \quad\quad \uparrow \quad \downarrow \end{array}$$

Equation 1

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$$\text{Recovery: } CrP + ADP + H^+ \leftarrow Cr + ATP$$
$$\uparrow \quad \downarrow \quad \downarrow \quad \downarrow \quad \uparrow$$

Equation 2

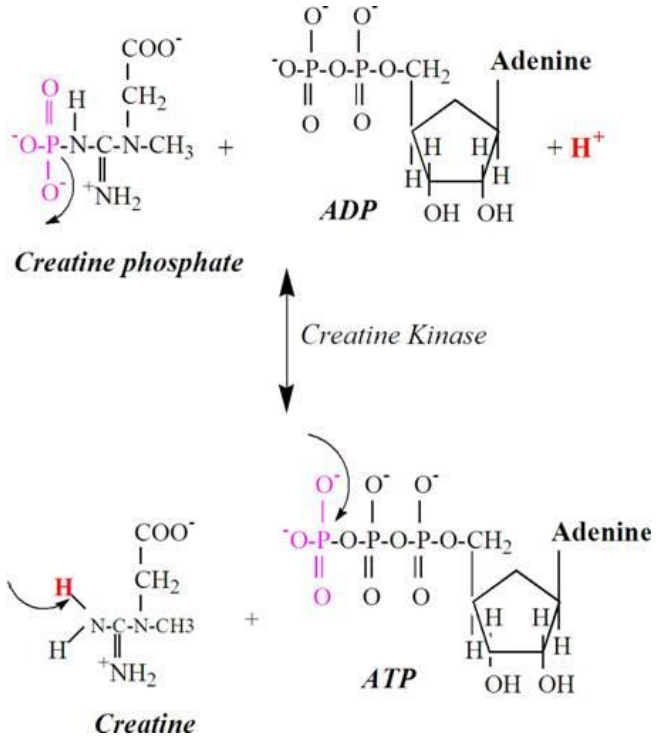

Figure 2. The creatine kinase reaction.

During recovery from intense exercise, there is a large free creatine concentration, low CrP, and higher than normal ADP. Muscle ATP stores rapidly return to normal thanks to mitochondrial respiration, and all this favors the reversal of the CK reaction to CrP formation (Equation 2). The only cellular events that would slow CrP recovery would be a lack of oxygen that compromises mitochondrial function, and/or extreme acidosis. Acidosis delays CrP recovery because a H^+ is now a product of this reaction.

Glossary Words

allosteric enzyme is an enzyme that has its catalytic effectiveness either improved through the binding of an activator molecule, or decreased by the binding of an inhibitor molecule.

Michaelis-Menten enzymes have a monexponential hyperbola activity:substrate activity curve.

regulated reactions are those that have an enzyme that can be influenced by one or both of activator and inhibitor molecules.

pathways are a sequence of enzyme catalyzed reactions that provide products which in turn are substrates for another reaction, and so on for the x number of sequential reactions that form the pathway.