

# The Regulation of Catabolism\*

## I. The Concept of Regulation

A. Introduction to these notes: here, we will tie together much of what we have learned in the past and add one new wrinkle. Your success will depend very much on well you have learned the previous material on metabolism. In these notes, you should glimpse how all organisms manage to pull off a feat that is not found in the inorganic world -- they regulate their internal conditions over a vast range of conditions. The variable we will look at is the regulation of the [ATP]; we have already learned why it crucial that this level not be allowed to drop too far.

### B. The concept of homeostasis:

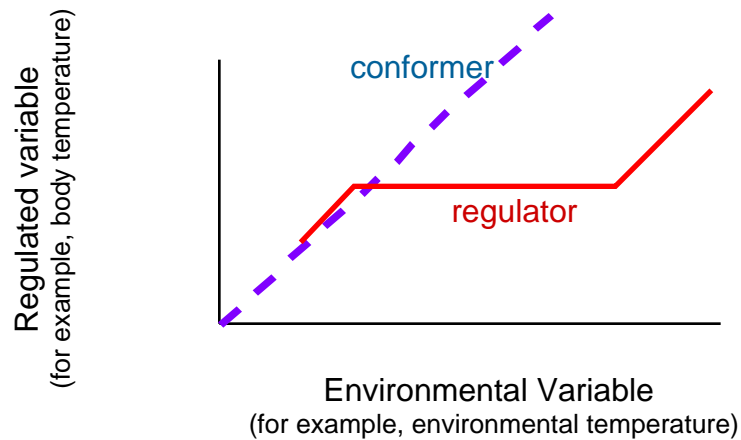
1. You have certainly encountered this term on your previous studies of biology. The term itself refers to constant internal conditions. The physiologist Walter Cannon coined the term in about 1920 and what he had in mind was the ability of animals to, in some cases, precisely control their internal environments in the face of factors that should cause large changes. ***In fact, no organism is absolutely homeostatic in regards to any important variable but in some cases organisms are quite exacting in their ability to regulate important factors.***

**Regulators and Conformers:** Although we will not discuss it in this course, in many cases organisms simply do not possess the ability to regulate a particular physiological variable. A good example is temperature -- organisms are sometimes classified as "cold blooded" (ectotherms) or "warm blooded" (endotherms). So-called cold blooded animals are conformers because their temperature varies directly with the environmental temperature whereas warm blooded animals are "homeotherms" because they regulate their temperature at a constant value over a wide range of temperatures. Graphically:

Animals don't regulate either because they don't need to, because it is expensive metabolically, or because it might actually be better for them not to regulate. So when we consider different species and different physiological factors, we find a continuum from **conformers** who don't regulate at all through all degrees of precision of **regulation** to something that approaches homeostasis. There are advantages to each level of regulation or lack thereof and it is a mistake to always regard homeostasis as the best possible state. A graph showing a typical regulator and conformer is shown on the top of the next page.

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*Note that the conformer's internal value always equals the external value. By contrast, in the regulator, there is a certain range of environmental values (the flat portion of the line) over which the internal values remain constant even though the external values are changing.*

2. We will see that regulation is achieved using a variety of mechanisms. Chief among these are:

(a) buffers (this may or may not have to do with pH -- there are all kinds of buffers). We have already seen one example -- C~P as a buffer for the [ATP]

(b) regulation of metabolic pathways -- in these cases, the **ability of certain proteins to catalyze crucial reactions is increased or decreased**. In these notes, we will focus on this mechanism.

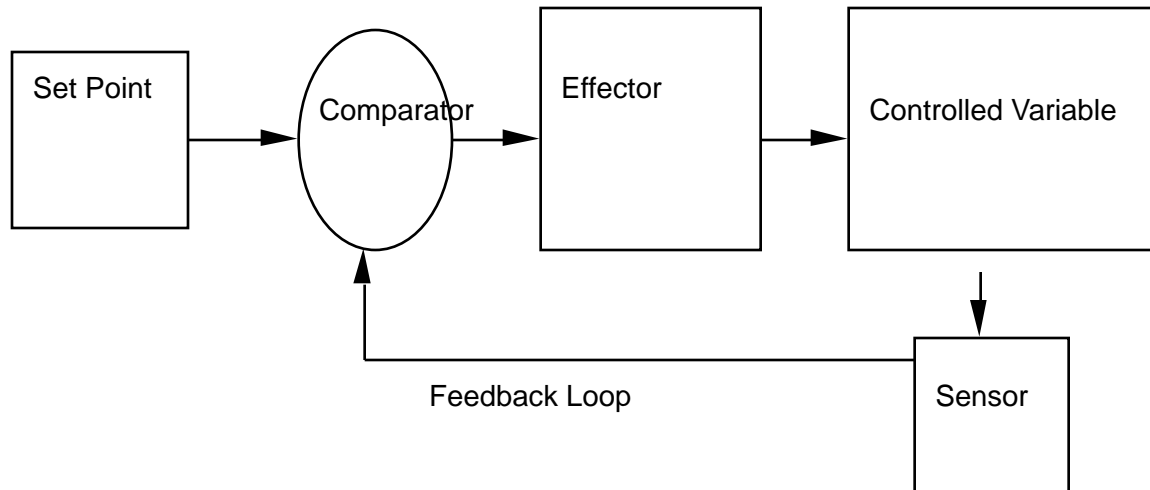
## II. Regulation and Negative Feedback:

A. Definition: A negative feedback control process is one that **tends to maintain some regulated variable at a more or less preset constant value**.

1. The preset value or range is inherited -- biologists said it was set by natural selection.

2. Anytime a disturbance occurs to the value, a negative feedback system takes action to return the value to the set point.

3. Recall our consideration of the mechanical elements of a muscle. At the time we stated that physiologists and other scientists often find it useful to make conceptual models of complex processes. The components of these models each represent separate functions that the process must perform. Here is a schematic of the mechanisms we believe are required in a negative feedback control system:



This diagram is quite useful. Let's understand what each of the boxes does:

- **Set Point:** this simply the ideal value for the controlled variable. Its actual value depends on conditions and so it is possible for it change. For example, during exercise we regulate our body temperature at a higher point then when we rest and so the set point changes. But for the purposes of discussion, let's assume that set points are constant. This is pretty much the case for [ATP].
- **Controlled variable:** This is whatever it is that we are regulating. So, in these notes it will be the [ATP] but it could be something like body temperature or blood glucose concentration or a hormone's concentration. Anything that might be regulated.
- **Sensor:** something that senses the present value of the controlled variable. For [ATP], we will see shortly that the sensor is a protein. In fact, and it should not be too surprising to you, proteins are generally either the sensors of entire cells that contain complex s of certain proteins act as sensors.
- **Feedback loop:** a pathway to transmit the output of the sensor to the comparator (see next). In our example with ATP, this will all be inside of a single protein but it may be more complex. For example, with body temperature, it is a series of neural pathways in the brain and for many systems involving hormones, the loop involves the blood.
- **Comparator:** something that detects any difference between the set point and the sensed value of the controlled variable. It is the essential computational step in the chain. **If there is a difference, an error signal is produced.** This error signal operates the next step in the chain:
- **Effector:** The processes or whatever that change the present value of the controlled variable back towards the set point value. In our example this will be an enzyme which speeds up or slows down all of glycolysis or the Krebs cycle. In the case of core body temperature, the effectors include skeletal muscles for shivering, smooth muscles to regulate blood flow, sweat glands, etc.

**A familiar example: the thermostat.** Here the regulated variable is the room temperature, the set point is the desired value, the sensor is a thermometer in the thermostat, the comparator is a simple device that compares the set point and present temperature and produces an error signal if necessary. The effector would be the furnace or air conditioner.

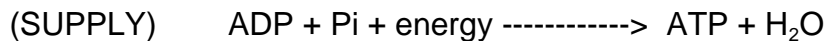
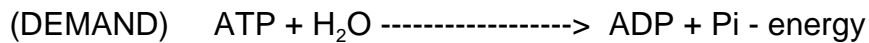
**B. Negative Feedback and the Regulation of Metabolism:**

1. Recall from what you have learned previously that the purpose of the "**Supply**" reactions was to **keep adequate supplies of ATP present regardless of demand.**

a. Recall that we said that there was very little ATP actually present in cells and that in some cells, especially muscles, the demand process could easily use up all of the ATP in less than 2 s. (in humans for instance).

b. In order to achieve a nearly constant level of ATP, **if demand increases, then the supply reactions would also need to increase.**

c. As long as the rate of these two types of processes were equal, the [ATP] would remain constant:



2. **We'll use anaerobic glycolysis as an example**, but everything I will say also applies to aerobic metabolism.

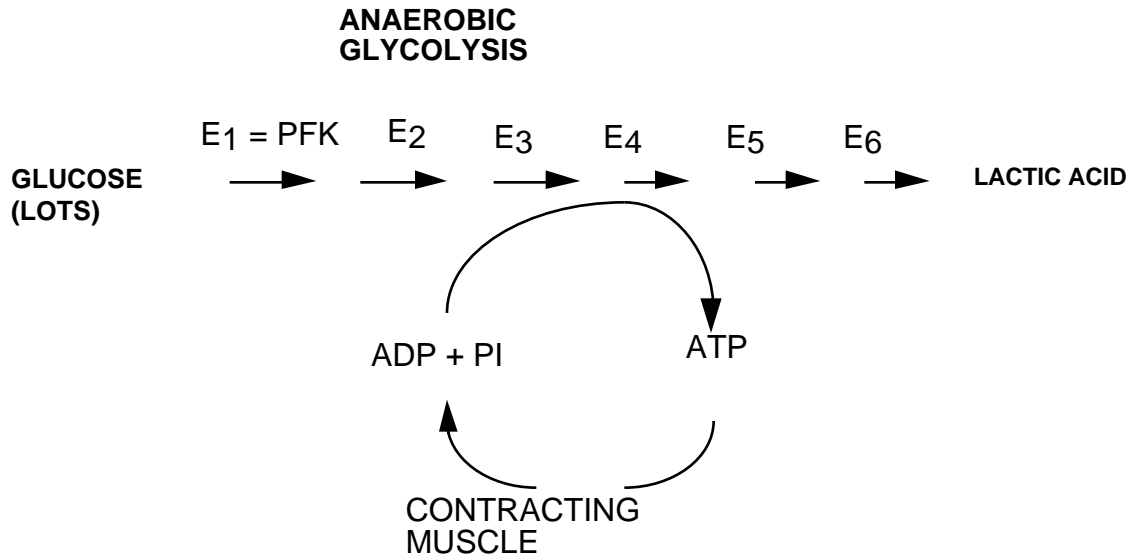
a. Recall that anaerobic glycolysis is an example of a biochemical pathway.

i. A series of enzymes (about 10 different kinds) perform a step-by-step disassembly of the glucose molecule.

ii. Remember that each enzyme performs a specific reaction.

iii. Think of this pathway as an orderly disassembly line where each enzyme is a worker who performs a specific task and then passes the results on to the next worker.

iv. Thus the product of one enzymes reaction is the reactant for the next. The cartoon on the next page gives a general overview of the glycolytic pathway -- there is an input, waste, a useful output (ATP) and the process itself is a series of steps. The **E** above each rx is the enzyme that controls it:



b. Enough of each enzyme is present in sufficient concentration so that its reaction and the overall speed of the entire process (pathway) can -- under certain circumstances -- be very high.

c. **So, given that there are lots of enzyme molecules and there is usually plenty of substrate (glucose) one would expect the reaction rate to always be very high. But it isn't.**

(i) The **body is economical** and reaction rates are only high when needed.

(ii) Glycolysis only runs at higher speeds when more ATP is needed – we don't waste glucose and energy by running the process at full speed when not needed anymore than we normally floor the accelerator on car when it is out of gear waiting at a traffic light. Such a procedure is highly wasteful. **How do we turn the glycolysis pathway up and down? We use a negative feedback process that senses the level of ATP, ADP, AMP and Pi.**

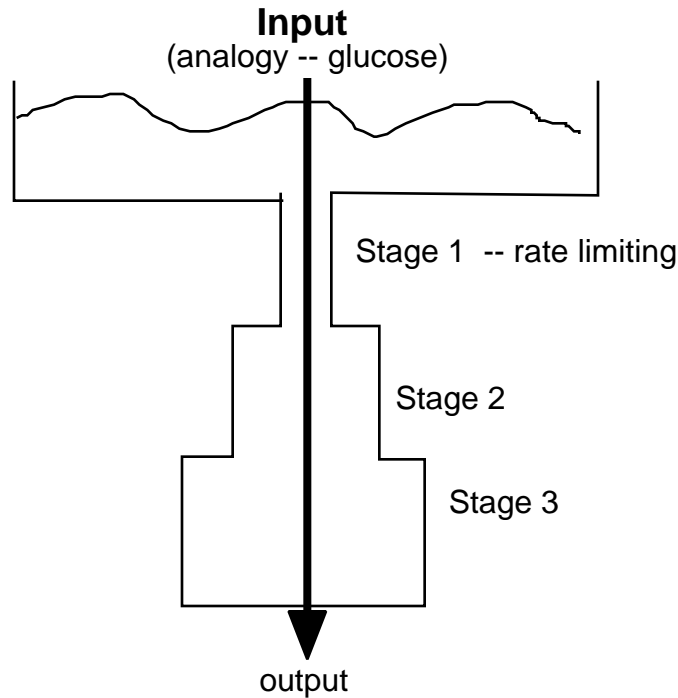
d. The highest rate that a biochemical pathway, such as glycolysis, can run (in other words, the maximum amount of 6C it can accept per time) is sometimes called its **capacity**. What sets the maximum rate *i.e.*, the capacity, of aerobic and anaerobic metabolism?

(i) By far the most important factor is **the concentration of enzymes used in the pathway**. In the case of aerobic processes this is reflected in the number of mitochondria and cristae within the mitochondria (since each mitochondrion is essentially a bag of Krebs cycle (matrix) and ETS enzymes (cristae)).

(ii) In fact, not all enzymes are equally important in setting capacity. All need to be present, but it is the enzymes that are least concentrated that set the rate for the overall process. We call these particular enzymes **rate-limiting enzymes**.

(iii) A good way to envision the relationship between a rate-limiting process and capacity is to imagine the flow of water through a pipe that is wide in some places and narrow in others. **The narrowest section limits the flow through**

**all other sections.** Thus, this is the rate-limiting section; it determines the flow through all of the other parts of the system. The obvious analogy is that **the width of the pipe is akin to the concentration of enzymes used in a particular step -- narrow, rate-limiting sections are the equivalent of steps where there are fewer enzymes molecules and therefore where fewer reactions can take place per time.**



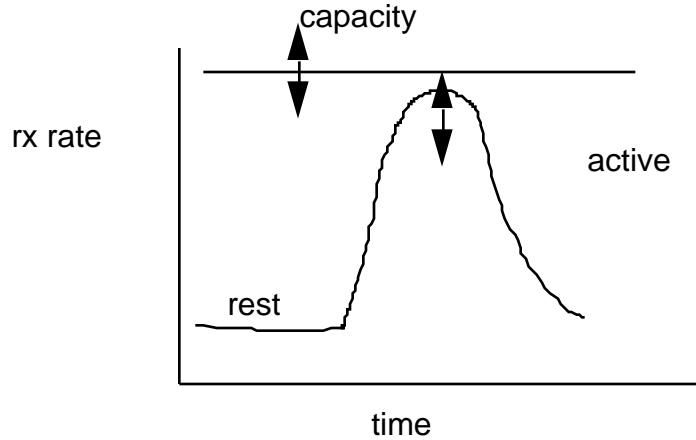
(iv) **Adaptations in Capacity:** The capacity can change over time if there is a change in the number of protein molecules for given steps -- increases will increase the capacity of the system and decreases will decrease the capacity. We often call these changes **PHYSIOLOGICAL ADAPTATIONS**. (Please do not confuse physiological adaptation, which is short term response within an individual) with evolutionary adaptation which is a long-term (many generations) change in characteristics of individuals in a population.

### 3. Regulation and Capacity.

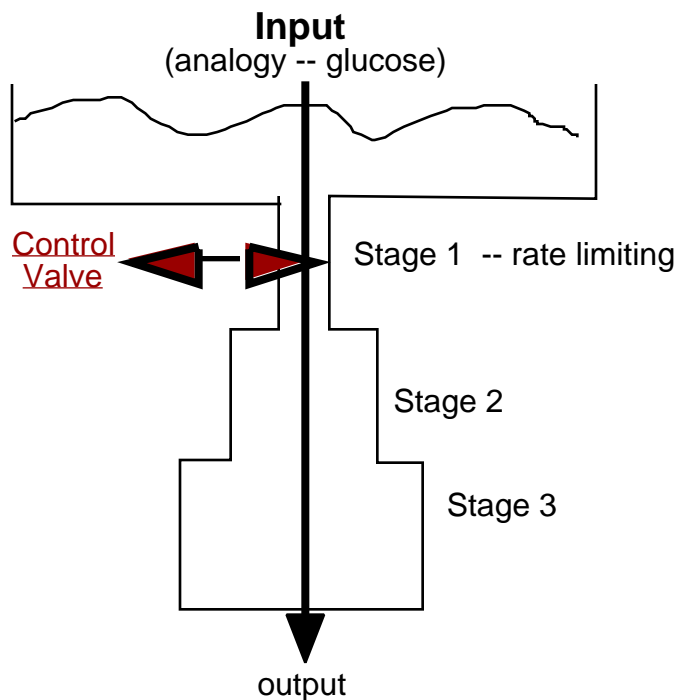
a. Full capacity (as is governed by the size of the smallest tube in the model above) is often not realized. For instance, when a muscle is at rest, very little of the metabolic capacity, aerobic and anaerobic, is realized<sup>1</sup>.

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<sup>1</sup> You can make the same argument about force -- at rest little or none of the force generating capacity of the sarcomeres is being used.



2. Turning an entire process up or down according to need is termed regulation. To review what we know about regulation, remember that the regulated enzymes is usually near the start of a pathway and it is generally rate-limiting. The regulated enzyme typically can have its catalytic ability enhanced (by substances called **activators**) or diminished by substances called **inhibitors**. The use of these substances on crucial enzymes is what accounts for the changes in the rate of entire processes such as glycolysis. We will have more to say about these below. In the meanwhile, let's modify our water pipe analogy and put a control valve on the narrow pipe. Valves are simply places where you can narrow or widen the path for water flow and thereby decrease or increase flow:



3. A few enzymes that are particularly important in determining capacity. We should know their names:

(a) Glycolysis:

(1) **PFK** -- overall rate (see below)

(2) **Glycogen Phosphorylase** -- availability of 6C input ("fuel" for glycolysis) from glycogen

(3) **LDH** -- although this enzyme is NOT REGULATED, I include it here because the extent to which it is present indicates the capacity for anaerobic metabolism.

(b) Aerobic Metabolism: primarily **the concentration of the ETS and Krebs Cycle enzymes** (especially the first Krebs Cycle enzyme and cytochrome - - don't worry about names). **As we learned when we considered fiber typing, aerobic capacity on the cellular level is indicated by the number and development (folding) of mitochondria**. The percentage of capacity that is used is determined by both the amount of ADP present (ADP activates the rate controlling Krebs cycle enzyme) and by the availability of oxygen.

### C. Negative Feedback and the Regulation of Glycolysis

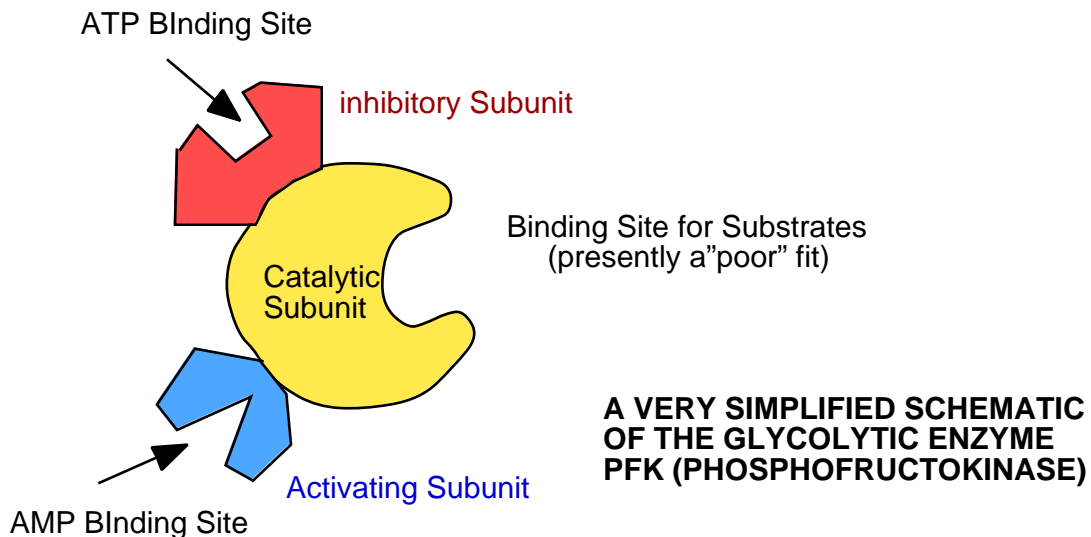
1. **The entire glycolytic process is regulated by an enzyme early in the process.**

(a) It should make good "economic" sense to you to regulate a step early in the pathway and not later on.

(b) In glycolysis the enzyme is near the beginning and is called **phosphofruktokinase** or **PFK** for short. Most of the other enzymes are not regulated in any significant manner and therefore they don't need regulatory sites in addition to their active sites.

Let's consider PFK in some detail.

- **PFK is a quaternary protein and has two allosteric regulatory sites and a catalytic site.**



- One of the regulatory sites is for an **activator site**.<sup>2</sup> In this case the **activator is AMP**. AMP is nothing more than ADP where one additional phosphate groups was removed.
- Why should AMP be an activator? For reasons we will not go into, the **[AMP] increases as the [ADP] goes up**<sup>3</sup>. Thus, it is an excellent activation signal. If the muscle starts using ATP and therefore needs more, the ADP will increase. So, if AMP concentration goes up enough (which will only happen when [ATP] goes down), it binds to PFK, induces an allosteric change, and makes the active site into a better fit for PFK's substrates. Let's reiterate -- AMP and ATP can never both be at high or low concentration at the same time.
- The **inhibitory site** is on a different polypeptide chain. The **inhibitor for PFK is a high concentration of ATP**. If too much ATP is made, it is best to slow or stop the glycolysis. High concentrations of ATP cause it to bind to PFKs inhibitor site and this in turn causes the active site to change to a shape that makes it a poorer catalyst.

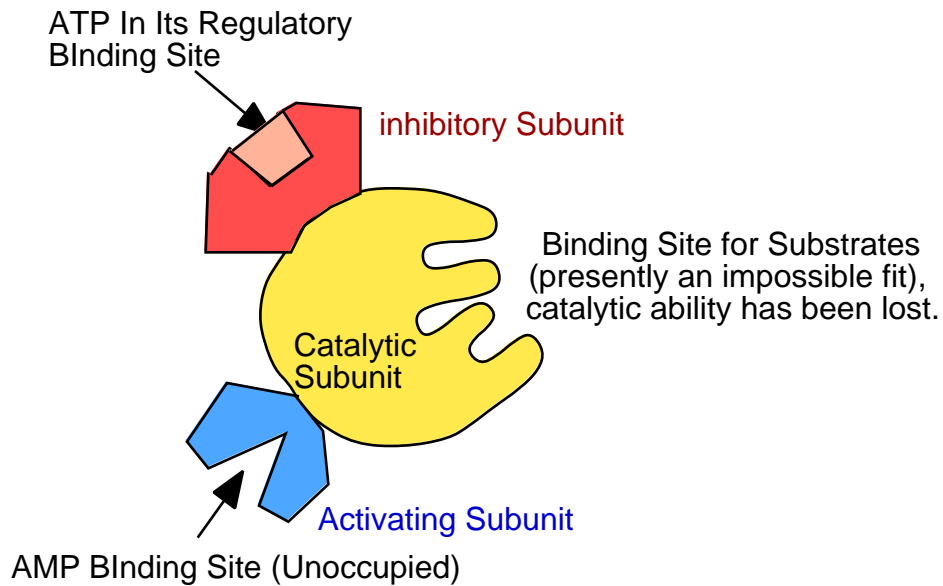
For those of you interested in fine details (that you will not be tested on!), there are actually two different binding sites for ATP on PFK -- one in the catalytic area where ATP acts as a substrate and the other on the inhibitory site.

2. The signals to turn glycolysis up or down:
  - a. Increasing the rate of glycolysis:
    - (i) When **lots of ATP is used up and more is needed, [AMP] increases**.
    - (ii) The **PFK senses this when AMP binds to its activator site** and at the same time there is no ATP on the inhibitor site (since [ATP] has decreased).
    - (iii) The result is that the **PFK molecules undergo an allosteric change that enhances their catalytic ability**. As a result, the overall rate of the PFK reaction increases.

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<sup>2</sup> Strictly speaking, AMP is a de-inhibitor but activator captures the idea well enough for this course.

<sup>3</sup> (the brackets mean "the concentration of.." and so read [AMP] as "the concentration of AMP".



b. On the other hand, if the demand for ATP decreases but glycolysis is still moving along (such as at the end of exercise):

(i) the levels of ATP start to increase.

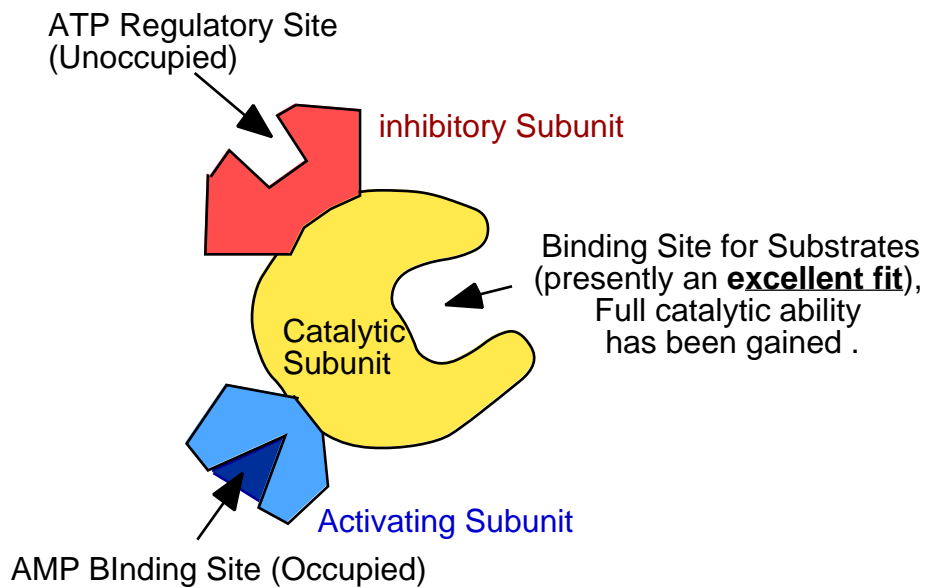
(ii) As ATP continues to increase, there is less and less AMP.

(iii) ATP begins to bind to the inhibitor site and meanwhile, there are very few PFK molecules with AMP on the activator site.

(iv) The PFK undergoes an allosteric change to decrease its catalytic ability and the velocity of the reaction decreases (see picture on the top of the next page)

(v) As a result the rate of the entire glycolytic pathway decreases and less ATP is made, in line with the lower demand.

(please see the top of the next page)

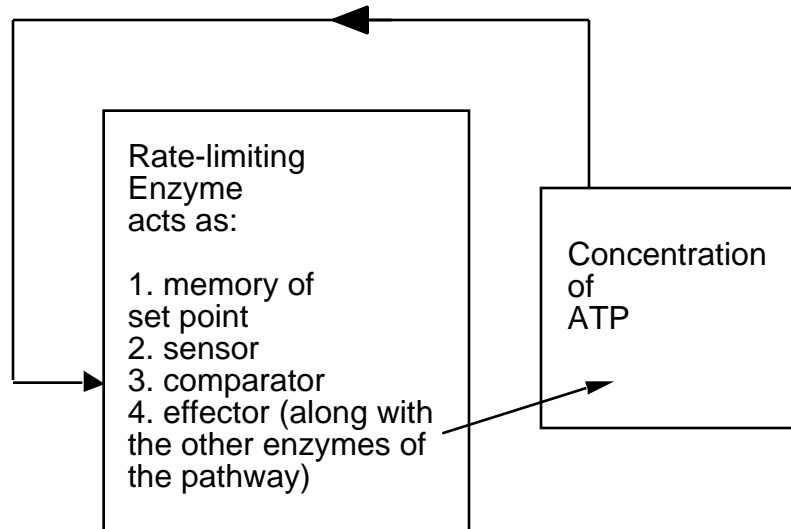


3. Thus, glycolysis is turned up or down according to the need to regenerate ATP from ADP and  $P_i$ . The PFK example is actually two examples of negative feedback.

a. One process, controlled by AMP (activation) increases production when ATP drops and

b. the other, inhibition, controlled by ATP itself, decreases production when  $[ATP]$  is high. But in both cases the result is a relatively steady  $[ATP]$ .

4. Here is a diagram that looks at the regulation scheme for ATP using anaerobic glycolysis but that uses the terminology of feedback control:



A similar process occurs with the Krebs cycle and in the activation of glycogen phosphorylase. Once again, it is the first couple of enzymes that are most crucial for control and ATP and ADP (in this case) are the most important regulators. ? Why is it important to activate the enzyme that breaks down glycogen at the same time that glycolysis is activated? Is this more important in some muscle types than others? Explain.

### III. The Roles of Fuels and Oxygen in Controlling Metabolism

A. Aerobic metabolism and **especially the balance of aerobic and anaerobic metabolism** is partially determined by the availability of  $O_2$ . Note that *the availability of fuel molecules is usually not a problem unless the organism is starving or has not engaged in vigorous exercise for an extended period of time (ask about marathons, for instance).*

#### B. **About $O_2$ Availability in Cells:**

1. *The amount of  $O_2$  that is in an aerobic cell is always measured relative to the cells need to generate  $\sim P$ .*
2. As long as sufficient  $O_2$  is present so that all  $\sim P$  is generated aerobically there is, by definition, plenty of  $O_2$ .
3. The quantity of  $O_2$  present under resting conditions will not be able to accept all the electrons made by glycolysis and the Krebs cycle during periods of high demand for  $\sim P$ .
4. **So, aerobic metabolism will be limited by the amount of  $O_2$  being delivered to the muscles.**
  - (a) As with the demand and supply sides of metabolism; the supply of  $O_2$  follows the demand.
  - (b) Systems that operate at levels in the biological hierarchy above those of the cell (circulatory and respiratory) are required to deliver additional  $O_2$  and make it possible for the ETS to speed up.
  - (c) In the meanwhile, the cell must find alternative ways to obtain the  $\sim P$  needed by contraction.
6. Notice that in cells with the ability to engage in both anaerobic and aerobic metabolism (*i.e.*, cells with enzymes such as lactic dehydrogenase and with lots of mitochondria -- for example, type I muscle fibers) that it is quite possible and common for anaerobic and aerobic pathways to be operating at the same time and for the relative amount of energy generated from each to vary according to the exact conditions and exercise. **This sort of dual metabolism is most likely to happen when an individual pushes themselves near to or beyond their maximum aerobic ability to generate  $\sim P$ .** They will generate as much  $\sim P$  as they can aerobically but will try to get additional  $\sim P$  by also running anaerobic metabolism at the same time. More about this as the course continues!