Sources of ~P During Exercise•

I. Transitions in Exercise and Energy Sources

A. **<u>Transitions</u>** are periods when one changes from one exercise level to another -- for example, from rest to exercise, from one intensity level to another, or from exercise back to rest. There is a normal sequence of changes in energy sources during transitions. This set of notes deals with the order in which these sources are used.

B. **<u>ATP</u>**: Keep in mind that the most immediate source of energy for muscle contractions is <u>always</u> ATP. It is the only fuel that myosin and the Ca^{++} pump use.

1. **We have seen that there is only a small amount of ATP in muscle cells**.

2. If one could deplete all of it, it would fuel exercise in any activated muscle for at most 2 s. However, in reality, <u>the small store of ATP would work for less than two s.</u> because the muscles start becoming tetanic well before [ATP] reaches zero. This has to do with the **<u>affinity</u>** of myosin and the Ca^{++} ATPase for myosin; *affinity will be discussed in a few days*.

C. <u>It takes some time to increase the rate of glycolysis and aerobic metabolism</u>.

A Review from the last notes:

To <u>increase the rate of glycolysis</u>, recall that:

(a) the levels of AMP and ADP must increase -- this will happen as a direct result of the exercise and the fact that production of ATP is presently too low!

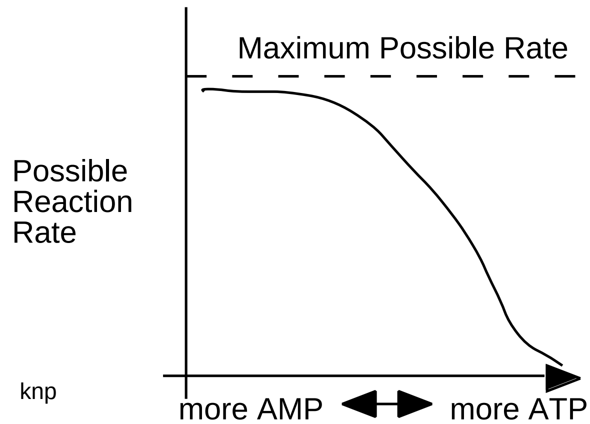
(b) the AMP must bind to PFK and other enzymes such as glycogen phosphorylase and the enzyme that controls the rate of reaction in the Krebs cycle,

(c) the enzymes must become activated and fuel needs to start to flow into the pathway.

(i) The way to think about this is to view the process of activating (or inhibiting) these critical "rate-controlling enzymes" as the equivalent of **<u>increasing or decreasing the amount of fully functional enzyme molecule</u>**.

(ii) Each time particular PFK molecule binds an AMP, it becomes more activated. The more PFK molecules that are affected, the more "activated" the overall PFK reaction becomes. The reason for this is simply that more and more PFK molecules have undergone an allosteric change that makes them excellent (instead of mediocre) catalysts.

Notice what is being said here. You already know that there are thousands and thousands of enzymes of each type (for example, PFK) in each cell. At any moment in time, the overall rate of the reaction pathway is dependent on the proportion of these molecules that are in the allosteric form that makes them excellent catalysts. This in turn depends on the relative concentrations of AMP and ATP as compared to their "set point" values.



Notice also that for any reaction that there is a maximum possible rate. ***<u>This would be achieved only when all PFK molecules are fully activated very (low [ATP] & very high [ADP])</u>*** **and** ***<u>when there is plenty of substrate and little product</u>***. This maximum rate is a measure of the number of enzyme molecules present in the cell and is called the **<u>ENZYME ACTIVITY</u>**.

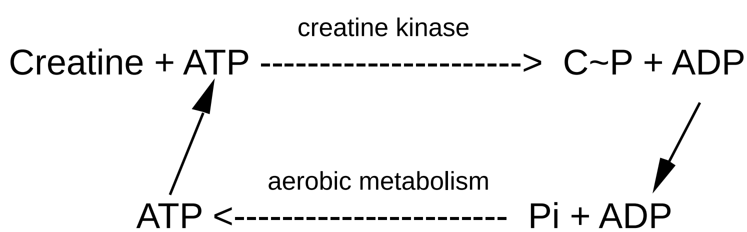
II. Immediate Sources of Stability: ~P Buffering

A. As was just mentioned, when demand for ~P suddenly increases, it takes a moment for glycolytic and mitochondrial metabolism to be turned up.

1. The problem is that this all takes a bit of time and the body needs the ATP NOW! ATP-requiring processes simply do not work without the ATP.

2. Recall that the body also has a creatine phosphate reserve or "~P buffer". In cells such as muscles that can use a lot of ATP in a very short time, there are typically much more C~P than ATP.

(a) remember that creatine phosphate is formed in <u>resting muscles</u> when ATP transfers its outer-most high energy phosphate to the compound creatine. The enzyme required to do this is **<u>creatine kinase</u>**:



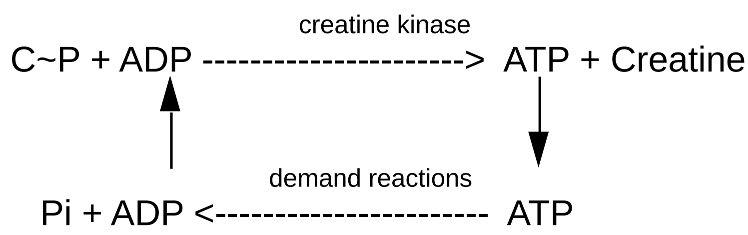
Notice that this reaction only occurs when the muscle is resting -- that is, when its demand for ATP is low. In such as resting cell, as soon as this reaction is complete, the ADP will be phosphorylated by the ETS glycolysis or Krebs cycles. If there is still extra creatine present, it will tend to react with ATP until most creating is converted to CP. Eventually, a typical resting muscle cell in a human will end up approximately the following ratios of compounds:

1 ADP: 10 ATP: 50 C~P

(b) This "charging" process will continue until nearly all of the creatine in the cell is converted to C~P, at which point it stops.

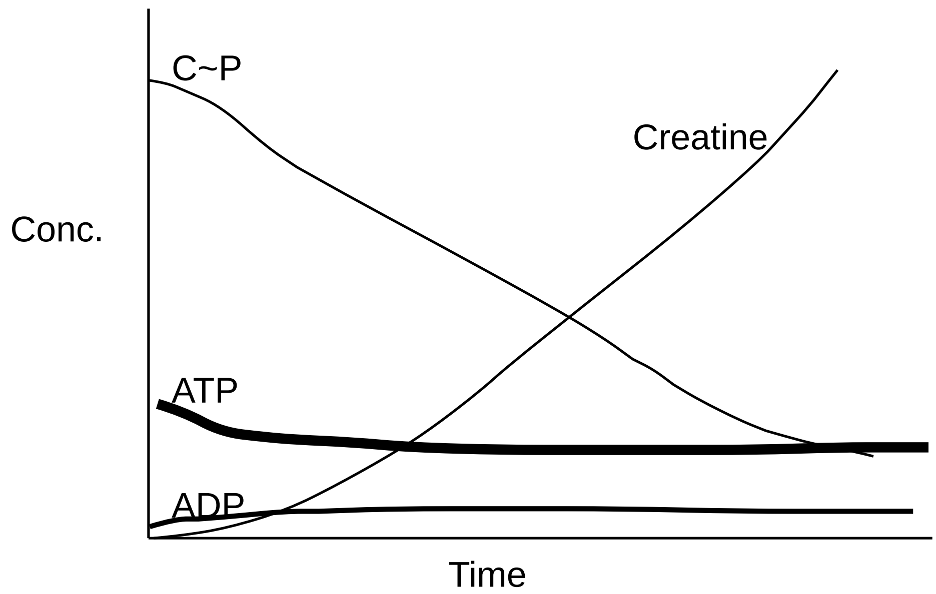
(c) The C~P just sits around and waits for periods of heavy use. Unlike the cell's ATP pool which is always being used and resynthesizes, C~P is only used during periods of exceptionally high demand for ATP. Thus, many cells which never experience such high demands do not have high levels of C~P. Think of C~P as money in the bank. The reaction just shown (last page) is the process of filling the bank account with money.

(d) when vigorous exercise starts, we reverse the process shown at the top of the page:



(e) Notice again that the C~P **buffers** the stores of ATP -- **it prevents them from changing as rapidly as they would if the C~P stores had not been there.**

(f) By way of review, here is a graph that summarizes what happens to ATP, ADP, C~P and C during the first couple of seconds of an activity transition (this one is for going from rest to exericse):



Although the [ATP] does drop and the [ADP] does increases a comparable amount, the changes are very small. What really changes is the [C~P] and [C]. The decrease in C~P is what prevents large changes in [ATP] and [ADP].

Important Note: Remember -- some change in [ATP] and [ADP] is good. We have seen in the last set of notes that a small change is required to signal to the cell that something has happened and therefore that the reaction rate of glycolysis or the Krebs cycle needs to be increased or decreased.

III. <u>Anaerobic Metabolism -- Generation of ~P When There is Insufficient Oxygen</u>

A. In less than a second, the increase in [ADP] and decrease in [ATP] cause PFK and glycogen phosphorylase to start to be activated.

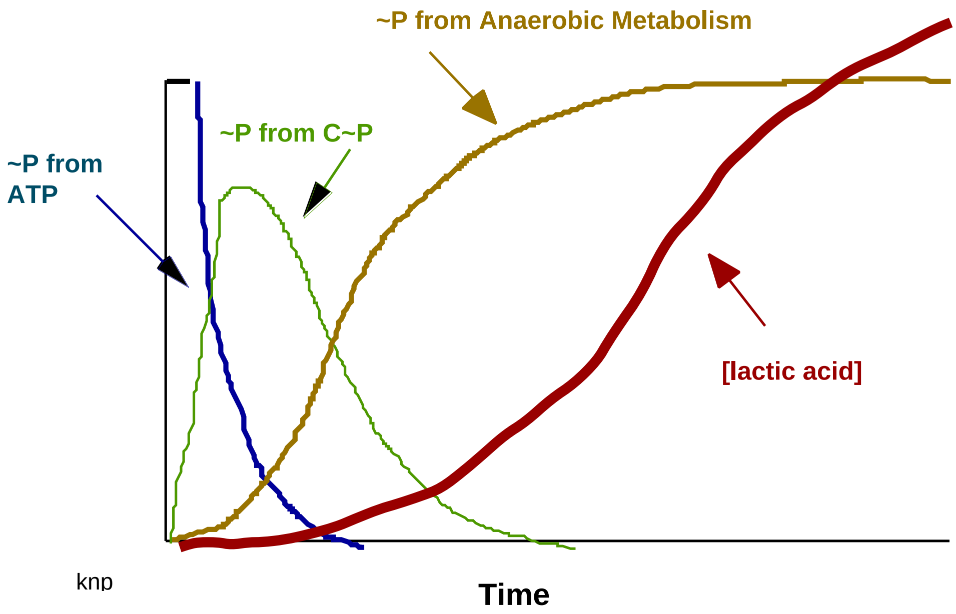
B. The rate of glycolysis starts to increase. However, it may take a a second or two to fully activate glycolysis. <u>The degree of activation depends on how much [ADP] increases</u> -- <u>within the capacity of the system (determined by the [rate limiting enzymes]) the higher the [ADP], the more activation</u>.

C. Nevertheless, during the time when activation occurs, the body continues to rely on C~P stores and to some degree it also further depletes ATP (this of course makes more ADP and further activates the process, within the limit of the system's capacity).

D. On the top of the next page is a graph akin to the last one, except this time <u>instead of showing the concentrations of various substances,</u> it shows:

a. the **relative amount of ~P used by the demand processes that comes from ATP, C~P and anaerobic metabolism**, and,

b. the **lactic acid concentration in the muscle**:



Notice:

- Initially all the ~P comes from ATP -- but for reasons we have stated many times, this could not persist for long
- C~P quickly becomes the most important source of ~P -- some ATP is still being used but not nearly as much.
- Anaerobic metabolism is initially OFF. However, as [ADP] increases and [ATP] declines, it becomes activated. The amount of ~P from anaerobic metabolism increases steadily until it becomes the only source. In the process, [lactic acid] increases steadily.

In a **type IIb fiber**, this is all that would happen. Lactic acid would continue to build up as long as the exercise continued. C~P would decline to near zero. Fatigue would increasingly be evident as the [lactic acid] climbed as the cell produced the stuff faster than it could eliminte it.

IV. <u>Aerobic Metabolism</u>:

A. In a type I fiber, aerobic processes also become activated.

B. Within the fiber this activation starts nearly at the same time as glycolysis is activated. However, it is a little bit behind since the ADP that activates the first Kreb Cycle enzyme must get from the sarcoplasm to the mitochondrial matrix.

C. But what really slows the full activation of aerobic metabolism is the availability of oxygen.

1. Recall that there is some oxygen already stored in the muscle on the myoglobin proteins that are found in type I fibers. However, this is a very small amount.

2. Moreover, in a muscle that was recently resting, there was very little blood flow to that muscle. Once again, this is an example of the body conserving energy -- pumping blood is expensive metabolically, so why should much blood flow into muscles when they are resting and have very little demand for oxygen or waste removal? So, little does.

3. As exercise starts, a combination of metabolites (CO_2, lactic acid), hormones, and neurotransmitters (this time from the other part of the peripheral nervous system -- the autonomic nervous system -- review it) cause blood vessels in the muscle to open up and the heart to pump more blood. So more oxygen is delivered to the fibers.

4. Up until the time that more O_2 is delivered to the muscles, most of the NADH made in glycolysis was used to make lactic acid (see above). Recall that this step regenerated NAD^+ and allows glycolysis to continue. The limited amount of oxygen already in the cell is used to run aerobic metabolism at a low rate.

5. However, as more oxygen arrives at the fiber, the ETS suddenly has lots of oxygen and can accept lots of electrons from NADH made in glycolysis and the Krebs cycle. The result is:

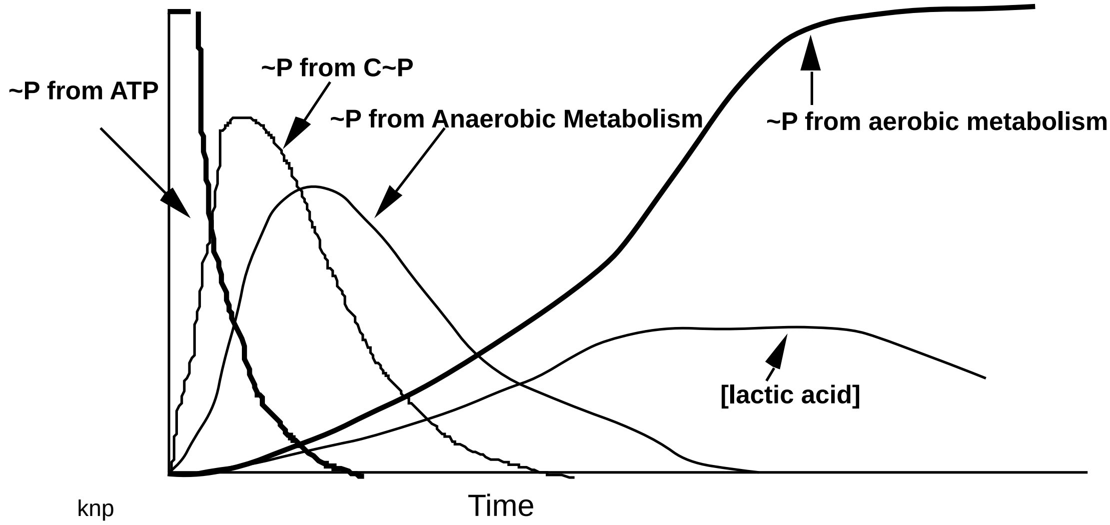
(a) glycolysis becomes aerobic as very little of the NADH made there is used to make lactic acid -- instead it all goes to the ETS and makes ATP.

(b) the Krebs cycle can now go "faster" since the NADH it makes can also be taken by the ETS; this of course both makes ATP and also regnerates NAD^+ needed for Krebs cycle reactions.

6. The extra circulation also removes the CO_2 produced by metabolism.

Note: realize that in all exercise except that which lasts for a long time or that which occurs in starved individuals, the fuel needed for the exercise is already largely present in the muscle cells -- delivery by the blood is not usually a main factor in limiting exercise.

On the top of the next page is the summary graph for a type I fiber:



<u>Summary:</u>

- Most parts of this graph are the same as the previous graph; however, this one covers a longer time period.
- Note the relatively slow activation of aerobic metabolism. The reasons for this are partially biochemical (activation of enzymes, just as with glycolysis) but they mainly have to do with the time it takes to increase the delivery of O_2 to muscle cells. Thus, as will soon see, the delay mostly has to do with changes in the circulation.
- <u>Note that lactic acid levels off and then declines</u>. This is because the fiber manages to dump it into the blood. So after a short bit of exercise, even what will become aerobic exercise, there is a brief spike of lactic acid. The lactic acid will be removed from the blood primarily by the heart and secondarily by the liver (during exercise). \
- Exercise can now continue for a very long time with 100% of the ATP used being generated aerobically.

V. <u>Type 1 Fibers and Mixes of Aerobic and Anaerobic Metabolism</u>:

A. At intense levels of exercise, type I fibers often show both aerobic and anaerobic metabolism at the same time. This sort of exercise, if continued, will result in fatigue in the type I fibers. Also, since this type of exercise inevitably occurs when type IIb fibers are also active, large amounts of lactic acid will enter the blood. More about this aspect at a later date.

B. How can a fiber be both aerobic and anaerobic at the same time? Easy -- we have just seen it happen in the transition from rest to exercise (go back and review the last graph).

1. If demand for ATP increases to a high enough level, even with maximum delivery of oxygen to the mitochondria, the aerobic processes will not be able to meet demand. Aerobic capacity is not unlimited.

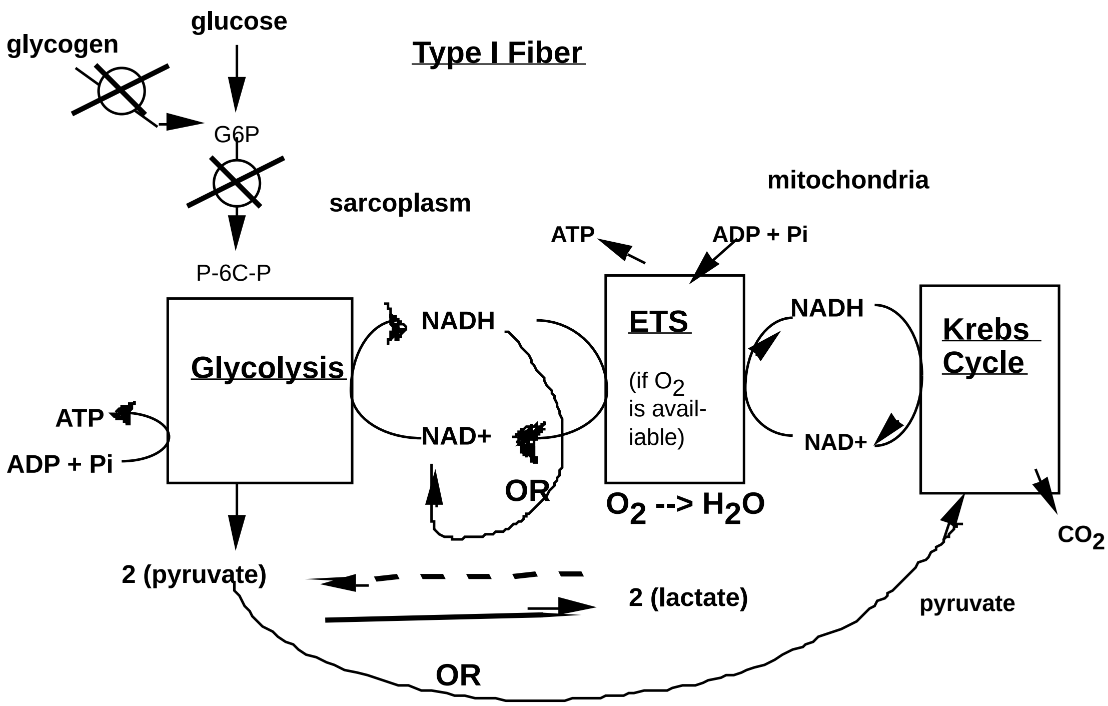
2. The result is that [ADP] will start to increase (since demand does not meet supply).

(a) This will further activate glycolysis.

(b) As glycolysis is further turned up (remember, it has a very high capacity, this is required since it is so inefficient at producing ATP), more NADH will be produced and the amount of NAD^+ will decrease.

(c) Since the ETS can no longer accept all of this NADH, an alternative acceptor must be found. That acceptor is some of the pyruvic acid coming from glycolysis.

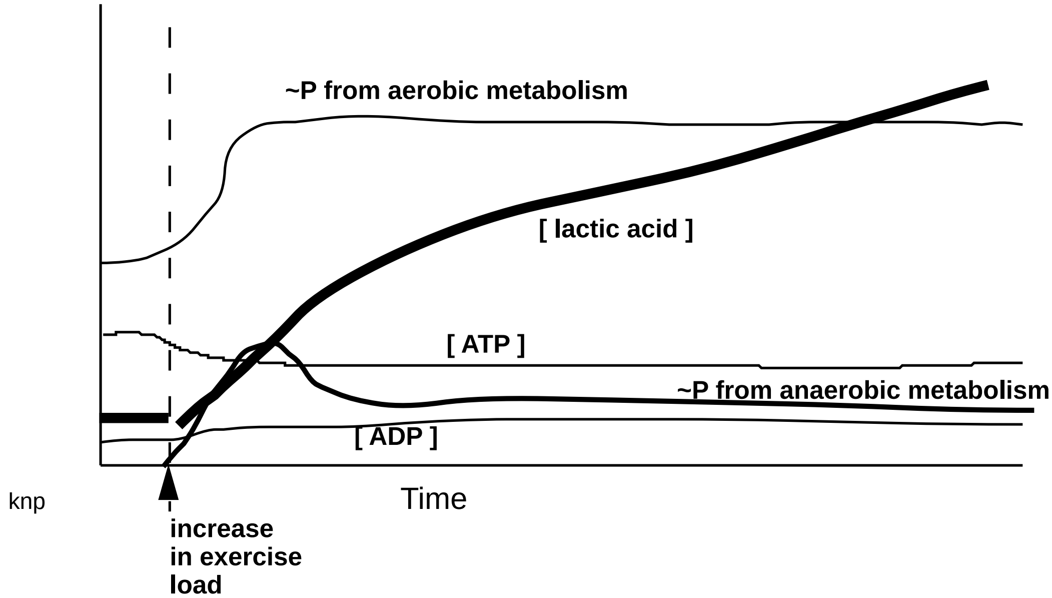
(d) The result is that although most pyruvic acid still goes to the Krebs cycle, increasing amounts are used to make lactic acid. This choice is summarized in the graph below:



3. Thus, the cell is engaging in both maximal aerobic metabolism and some anaerobic metabolism. The cell is both using oxygen and producing lactic acid at the same time. Once again, anaerobic metabolism has filled the "energy gap" that could not be covered by aerobic processes.

4. Accordingly, in heavy exercise the anaerobic metabolism in type I fibers that accompanies the aerobic metabolism is not due to a lack of oxygen, but instead a relative lack of oxygen -- there is a lot of oxygen but it is not enough for what the cell needs to do.

5 The top of the next page shows what would happen -- assume that the cell is already relying on aerobic metabolism when the demand for energy goes up:



Notice that:

- ATP demand changes instantaneouly with the new higher exercise load.
- The [ATP] decreases as soon as the load increases. This causes the [ADP] to increase.
- The increased ADP futher activates glycolysis and the Krebs cycle. We assume that some more oxygen is made available, but it is not enough to handle all of the metabolic needs.
- Anaerobic metabolism makes up the difference.
- Lactic acid begins a steady increase from a low initial level.

Again, be sure that you understand that **type I fibers are not anaerobic because there is no oxygen**. It is the r**<u>elative lack of oxygen</u>** -- they have less oxygen than the need to accept all of the electrons that are being produced in glycolysis that causes them to also use anaerobic metabolism.