

Removal of Lactic Acid -- Oxidation and Gluconeogenesis*

I. Let's review what happens in glycolysis -- what is used, gained, and what the waste products are (skip this first section if you remember all of this)

Here we go -- per **6C**:

A. **Net Gain of ~P:**

1. 2 if starting with glucose (4 made - 2 cost)
2. 3 if starting with glycogen (4 made - 1 cost)

B. **Waste Products: 2 molecules of lactic acid and heat.**

1. This tends to **lower the pH** and if enough is added, the pH goes down far enough to affect the tertiary structure of every enzyme in the cell, decreasing their function. This causes a loss of performance that we call **fatigue**. **Notice that the ratio of lactic acids to ATP is close to or equal to 1:1.**

2. There are also potentially osmotic effects. The increase in lactate, which has trouble getting out of the cell, means that for every 6C added, 2 or more particles are created and the concentration of dissolved substances in the cell increases. **Water will tend to enter the cell and the cell will swell.**

II. How does lactic acid get out of cells and what happens if it doesn't?

A. Lactic acid can only leave a cell by a process called **facilitated diffusion**. This means that the lactic acid can only leave after it first attaches to **specific lactic acid transport proteins in the sarcolemma**. When lots of lactic acid is produced, the removal is slow since the transport proteins are overwhelmed and lactic acid cannot get out as fast as it is made. You can think of this like a line of cars trying to leave a parking lot onto a small road at the end of a sporting event or concert.

B. So, when lactic acid concentration gets high, the cell has trouble getting rid of it. This not only serves to keep the pH low for a long period, but it can also have other effects.

C. The result is that water tends to diffuse from where it is more concentrated (outside of the cell -- there is less stuff dissolved in it there) to where it is less concentrated (inside the cell since there is more junk dissolved in it there).

D. As water enters the cell, the cell will begin to swell. The movement we just described is called **osmosis**. In severe exercise that results in the production of a lot of lactic acid or in cases where blood flow is reduced to a muscle, this process will cause muscle cells to swell.

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E. The swelling itself makes it difficult for the circulation to adequately serve the tissues -- swollen cells around the blood vessels reduce blood flow.

III. What happens to the lactic acid?

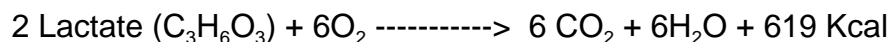
A. Muscle can't deal with it. It is trouble, and the more of it that is present, the more trouble. So, muscles do the equivalent of humans putting wastes in the river - they let it escape into the circulation which takes it away. That takes care of the problem from the muscle's point of view. The rate at which the muscle can get rid of the lactate is determined:

1. Mainly by number and proximity of blood vessels (more about this in a week or so) and the flow of blood within these vessels.

2. Secondly by the number of transport molecules in the sarcolemma - remember that lactate must first attach to protein to get through the cell membrane.

B. **What happens to lactate once it is in the blood?**

1. First, we need to realize that the only reason that lactate is a waste as far as muscles are concerned is that they are not able to use it. But other parts of the body can use the lactate. It is important to realize that **lactate is a compound that is very rich in energy**. It contains more energy than pyruvate, the nominal end product to glycolysis. To give you an idea of the energy stored in lactate, if we burn lactic acid in a bomb calorimeter:



Notice that this is only slightly different from burning glucose (686 Kcal -- the difference (67 Kcal) was the energy that was used to make the 4 molecules of ATP). So, again, lactate is very rich in energy.

2. The body finds two ways to utilize this energy:

(a) **Oxidize the lactate** -- *i.e.*, use it as a metabolic fuel --

we'll look at the process a bit later but suffice it to say that the heart loves to use this as a fuel.

(1) the **heart** normally has an excellent supply of oxygen.

(2) the heart is highly aerobic (see below) -- it normally only uses aerobic processes to generate the ATP it needs for contractions.

(3) the heart's demand for fuel increases during activity since obviously the demand for blood in muscles and to the skin (for cooling) increases.

(4) lactate (along with 6C) are the preferred fuels of the heart. When lactate levels increase in exercise, the heart takes up the lactate and burns it to CO₂ and H₂O.

(5) After exercise, heart still takes up lactate but less so (since it gradually needs to pump less during recovery and therefore uses less and less energy). At this point another process becomes more important in the removal of lactate from blood:

Note: In the heart, when lactic acid is removed from the blood, all that happens is that:

(a) it is converted back to pyruvic acid by reversing the reaction that occurred in the muscle:

lactic acid + NAD⁺ -----> pyruvic acid + NADH

(b) the pyruvic acid now goes through the Krebs cycle as above

(c) the NADH gives it s electrons to the ETS. It is reborn as NAD⁺ and is ready to oxidize more lactic acid.

It is as if aerobic glycolysis started in the muscle and finished in the heart.

(b) **Gluconeogenesis**: the production of glucose from simpler molecules. These simpler molecules include lactic acid (the case we are presently studying), the products of the breakdown of some amino acids, and fragments obtained by breaking down fats. For the moment, let's stick with lactic acid.

(1) Gluconeogenesis is mostly confined to the **liver** although there is abundant evidence that it can also occur in type 1 muscles during recovery

(2) It occurs throughout exercise but it is a slow process and so, during exercise and early recovery when the heart is beating rapidly, oxidation of lactate by the heart is a far more important process. However, late in recovery from heavy exercise, there will still be plenty of lactate around and the heart will not be using it at a high rate. Gluconeogenesis becomes the main process for dealing with the lactate.

(3) Basically what that happens is that **the liver takes two molecules of lactic acid, adds energy (more than was released when the original 6C molecule was broken down -- remember what the second law of thermodynamics requires that we can't get something for nothing and for all real situations, we can't ever really get back all that we put in to a process -- something is always lost) and we get glucose**

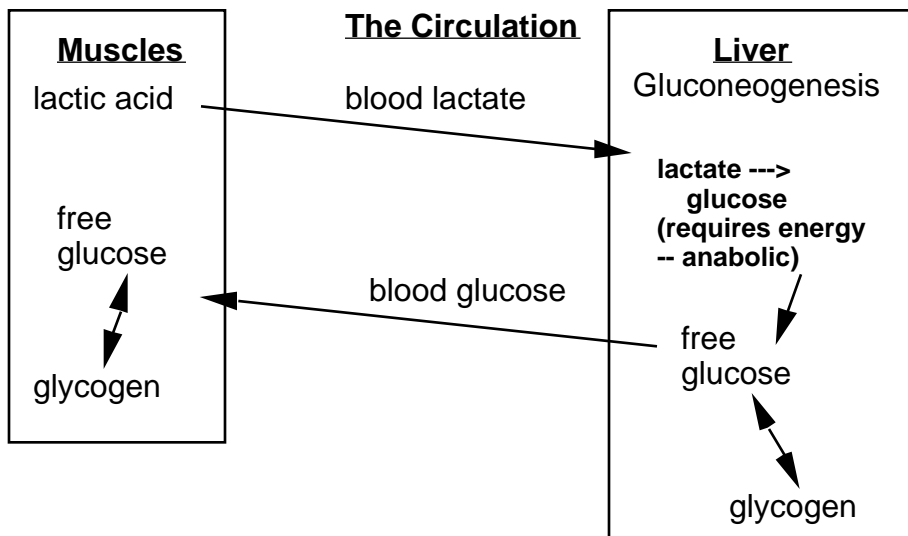
2 lactate (C₃H₆O₃) + energy (from 16 ATP) ---> glucose (C₆H₁₂O₆)

(4) Once the liver makes glucose, it either:

(i) stores it as glycogen (remember, if it wants to store carbohydrate, it is best to do so as a starch to avoid osmotic effects) or

(ii) releases it to the blood where cells that need it (muscles and the brain) **take it up and either burn it (brain) or store it**. The cycle whereby 6C is broken into lactate, transported to the liver, turned back into glucose, and then transported back to the muscles is called the **Cori Cycle**.

The Cori Cycle



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