Lactate Production

We are now ready to discuss the most misunderstood reaction in all of chemistry – well at least within the exercise sciences! The historical development of muscle biochemistry and exercise physiology viewed intense exercise (muscle contractions) to cause the production of lactic acid, which in turn released a proton (H^+) to cause metabolic acidosis. However, such a belief was totally incorrect. Rather, and as you will learn, lactate production occurs in a non-acidic form, and actually consumes, not releases a H^+. Yes, lactate production retards, not causes, acidosis!

Lactate is produced by the **lactate dehydrogenase** reaction, as shown in Figure 1. For this reaction, the substrates are pyruvate, NADH and a proton (H^+), with the products being lactate and NAD^+. Note that pyruvate, like lactate, is also a **weak acid**, and is present mostly in the form of an acid salt, such as sodium or potassium pyruvate. Thus, not only does evidence of the dissociation constant (Kd) of lactic acid reveal that more than 98% of lactate is present in the acid salt form, the fact that pyruvate is also predominantly in the acid salt form means that there is no H^+ on the carboxylic acid group to be released during lactate production. In fact, based on your prior study of glycolysis, this is also true for all the glycolytic carboxylic acid intermediates. As will be discussed in more detail in the Topic on Metabolic Acidosis, this means that the protons that are released from glycolysis do not come from the production of **metabolic acids**.

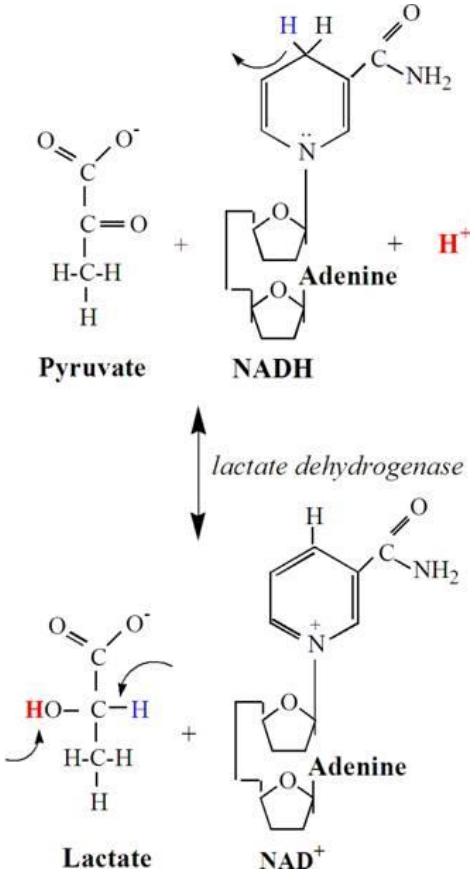

Figure 1. The substrates and products of the lactate dehydrogenase reaction.

Wow, this is interesting isn't it? Lactate is not the harmful molecule that we may have all once been taught. In fact, it gets a little more interesting. Look at the lactate dehydrogenase reaction of Figure 1 again. Note that instead of producing a proton, what lactate production really does is consume a proton. As such, lactate production is a major component of what is called **metabolic proton buffering**, thereby retarding not contributing to acidosis.

Now let's look at lactate production from a NAD^+ perspective. Remember that the 2 electrons and 2 protons from the 2 NADH + 2 H^+ produced from glycolysis need to get into the mitochondria to allow for NAD^+ regeneration. During intense exercise, the stimulation of glycogenolysis and glycolysis is so great that there is a dramatic increase in the rate of substrate flux through glycolysis (Figure 2). Depending on the proportion of slow vs. fast twitch motor units, and the endurance training status of these motor units, the capacity for converting pyruvate to acetyl CoA, and having the glycerol-3-

phosphate shuttle functioning at similar rates, depends on the mitochondrial mass (density) within the working muscle. The more endurance trained the muscle, and the higher the proportion of slow twitch motor units, the greater the capacity of the contracting muscle fibers to use mitochondrial respiration to supply most of the ATP and regenerate most of the NAD^+. However, for a specific individual at specific exercise intensities, there comes an intensity and rate of ATP demand that exceeds the capacity of the recruited muscle fibers to sustain the cellular ATP demand from mitochondrial respiration.

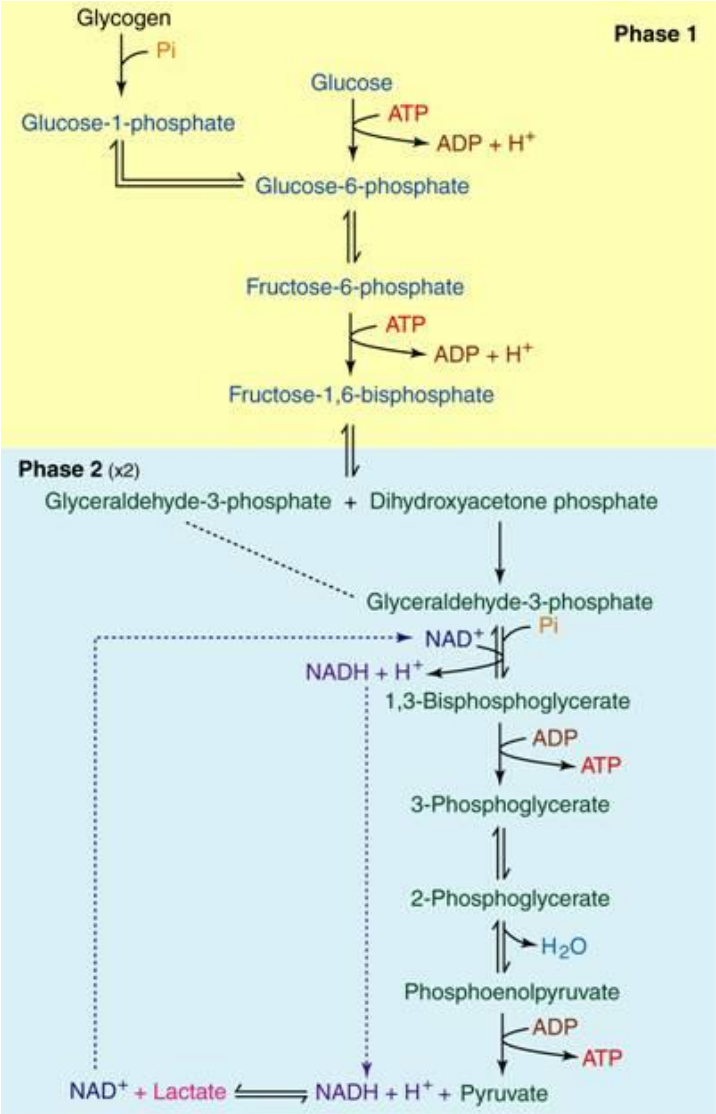

Figure 2. Schematic of the role of lactate production in maintaining cytosolic NAD^+ and the redox potential.

At these increasing exercise intensities, the contracting muscle fibers must now rely more and more on the lactate dehydrogenase reaction to regenerate NAD^+. Thus, increased lactate production, although not caused by a lack of oxygen or being the cause of acidosis, remains a good marker for a change in metabolism indicating an increasing role of glycolytic and phosphate system ATP regeneration in supporting the energetics of the repeated muscle contraction.

Now, think what would happen if muscle could not produce lactate. As soon as exercise became more intense there would be no way to rely on added ATP from glycolysis, as there would be no means for reactions in the cytosol to regenerate NAD^+ from the NADH from glycolysis. This would result in a falling NAD^+/NADH ratio, called the **redox potential**. The main consequence of this would be a decrease in the rate of the glyceraldehyde-3-phosphate dehydrogenase reaction causing a near shut down of the glycolytic pathway.

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The Lactate Threshold

The exercise intensity that coincides with an abrupt increase in muscle or blood lactate accumulation is called the **lactate threshold**. Figure 3 provides blood lactate data that clearly shows a sudden increase in blood lactate accumulation as exercise intensity transitions from moderate to more intense. A similar threshold response occurs inside contracting skeletal muscle. However, this simplified presentation of changing muscle and blood lactate is complicated by the size principle of motor unit recruitment, and therefore the contribution of an increasing fast twitch motor unit recruitment profile to total muscle metabolism.

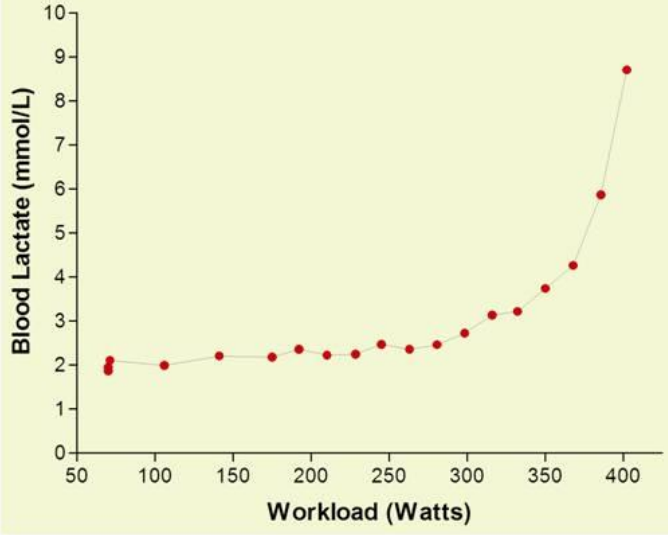

Figure 3. The increase in blood lactate during incremental exercise to fatigue. The data is from a test to VO2max on a cycle ergometer by a well-trained, competitive cyclist.

Glossary Words

lactate dehydogenase is the enzyme that catalyzes the conversion of pyruvate and NADH to lactate and NAD^+.

weak acid is an acid that has a high pK (close to 7.0), meaning that it is more likely to remain protonated, or have a higher proportion remain protonated, within the physiological pH range.

metabolic acids occurs when increased cellular energy demand causes an increased release of protons (H^+) and a subsequent decrease in cellular and system blood pH.

metabolic proton buffering refers to the removal of protons from solution during metabolism.

lactate threshold is the threshold increase in muscle and blood lactate during increasing exercise intensities.