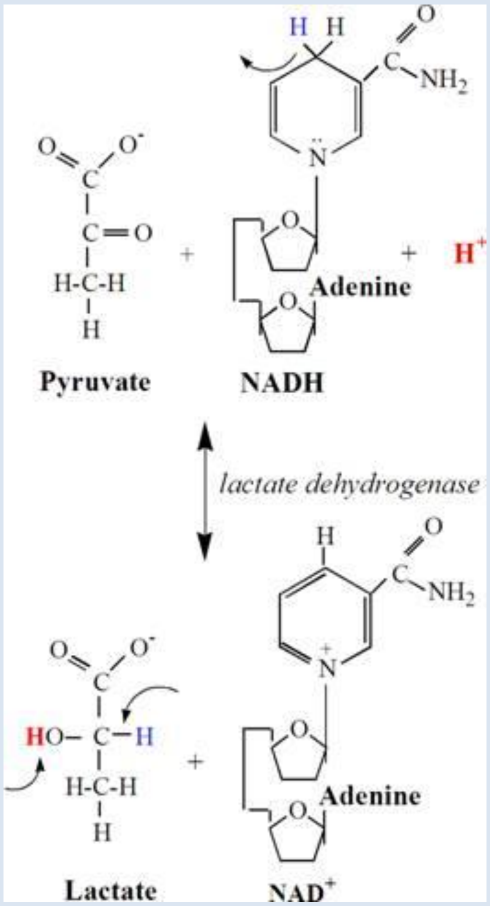
What is Lactate?



The continued perception by most sports enthusiasts, as well as the wider public, is that muscle produces lactic acid, and that lactic acid causes muscle to feel a "burn", impair contraction, and cause metabolic acidosis, or indeed a "lactic acidosis". Hopefully you are aware that this belief is just that, a belief and not a fact. This Section of the book will provide all the evidence you need to better understand the chemical difference between lactic acid and lactate, the biochemistry of the production of lactate, and the benefits of muscle lactate production during moderate to intense exercise. Added clarification of the biochemistry of metabolic acidosis will be provided in that Section. In fact, to really understand muscle lactate production you are going to have to apply what you have learned from the study of the three energy systems, muscle contraction, and differences in the metabolic capacity of the muscle fibers of different motor units in human skeletal muscle. Collectively, this knowledge will provide a thorough account of why proton release occurs from ATP hydrolysis and other metabolic reactions, and reinforce the essential role of lactate production during intense exercise.

The terms **lactic acid** and **lactate** have a long history in each of exercise physiology, muscle metabolic biochemistry and medicine. Unfortunately, this history has not been characterized by good scientific thought or application, and has led to incorrect educational content, research interpretations and clinical terminology and practice concerning the causes and implications of lactate production.

Before we can venture down this path to understand the implications of lactic acid vs. lactate, we must first know the difference between lactic acid and lactate.

Lactic Acid and Lactate

Lactic acid has the chemical name of **2-hydroxypropanoic acid**. It is a 3 carbon carboxylic acid, as shown in Figure 1a, where in its acid form has a proton bound to the single bond oxygen of the carboxylic acid functional group. Like all acids, the important feature of this acid functional group concerns the pH of the medium (cytosol of the muscle

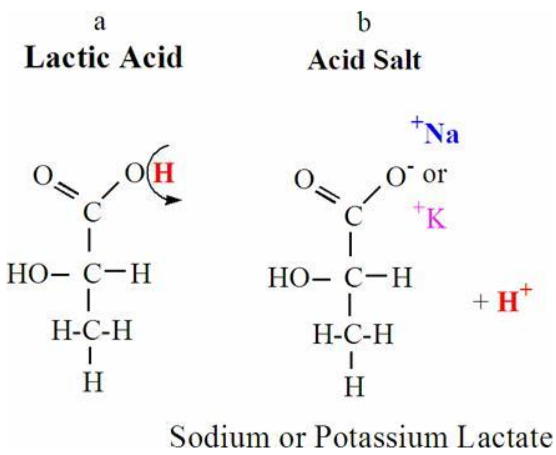


Figure 1. The chemical structures of a) lactic acid vs. b) lactate.

fiber) that corresponds to specific proportions of proton bound and unbound structures. When the proton has been removed from the structure, the molecule is called lactate. The remaining negative charge on the carboxylic acid functional group can be balanced by a cation, such as sodium or potassium, forming sodium or potassium lactate, respectively (Figure 1b).

The analytical chemistry quantification of the pH dependency of proton, or other competing cation, binding to a metabolite is quantified by the **dissociation constant (K_d)**, as shown in Equation 1.

$$K_d = \frac{[A]\times[H^+]}{[AH]}$$ Equation 1

For acids that readily release their proton into solution, and hence are termed strong acids, the Kd can be very large. This is because the sum of the separate products of the unbound components is much larger than the bound metabolite. The Kd of lactic acid is computed in Equation 2, where the Kd of lactic acid is 4,677.3514. To avoid using large numbers, the $\log_{10}$ of the Kd is computed, which for lactic acid is 3.67.

$$K_d\ (lactic\ acid) = \frac{[La^-]\times[H^+]}{[LaH]} = 4677.3514\,;\ where\ \log_{10} 4677.3514 = 3.67$$
$$\log_{10} K_d\ (lactic\ acid) = 3.67$$
Equation 2

So what does the $\log_{10}$Kd mean? Thanks to quality empirical and theoretical work by acid-base physiologists that date back to the 1940's, we know that the $\log_{10}$Kd also corresponds to the pH at which there are equal proportions of proton bound and unbound forms of the metabolite. Such derivations are presented in the Henderson-Hasselbalch equation (Equations 3 and 4). However, there is inconsistency in abbreviations in acid-base physiology. Rather than use the Kd abbreviation to describe the Kd applied to an acid, the abbreviation pKa is used. This is an inconsistency because the abbreviation pKa refers to the negative log of the association constant (Ka). However, just realize that for acids, the pKa really means the log Kd.

$$pH = pKa + \log 10 \frac{[A^-]}{[AH]}\,;\ where\ pKa = pH - \log 10 \frac{[A^-]}{[AH]}$$ Equation 3

$$when\ [A^-] = [AH];\ \log 10 \frac{[A^-]}{[AH]} = 0$$
$$then\ pH = pKa + 0\ or\ pKa = pH$$
Equation 4

Thus, for lactic acid, 50% of the metabolite is in the form of lactic acid, and 50% is in the form of lactate when the solution pH is 3.67. This is a very acid solution, given that the range of muscle cellular pH is approximately 6.1 to 7.05. For this cell pH range and the molecule lactic acid, the proportion of the unbound or proton dissociated form (lactate) varies from 99.06 to 99.38%! For these reasons, any physiologist or biochemist would state that there is a trivial amount of lactic acid inside the body. For details of added discussion and computations of the proton release characteristics and stoichiometry of lactate production, as well as other reactions that influence proton balance, see the Topic on Metabolic Acidosis.

Lactic Acid: The "Voldemort" of Exercise Physiology

OK, now that you know the difference between lactic acid and lactate, I hope you never talk about lactic acid again in an exercise physiology class!!! For my students, I work hard to develop an atmosphere of immediate repudiation if any one of them mutters such a term that should never be spoken. Yes, I tell my students that they should be like the students at Hogwarts School of Magic, where the word lactic acid is the "Voldemort" of exercise physiology!

Such a distinction between lactate and lactic acid is very important. The belief of lactic acid production causes acidosis, promoted and prolonged for more than 60 years, is completely unfounded. Unfortunately, such incorrect branding of lactate as lactic acid, has developed a view that lactate production is detrimental. This could not be more untrue. Lactate production is essential for contracting muscle to function during times of intense muscle contraction and associated high rates of ATP turnover. As you will soon learn, lactate production is a rapid and effective means for the muscle cytosol to better maintain NAD^+ supply, as well as **buffer** proton release from glycolysis.

So why have basic and applied scientists and medical clinicians got this lactic acid vs. lactate concept wrong for so long?

History Of Lactic Acid and Exercise Physiology

Explanation needs to be given for the use of terms in the paragraphs to follow. "Lactic acid" is used when the period of time in history used this term and did know the difference between lactic acid and lactate. As such, do not get confused that lactic acid does exist in human physiology. Based on the content above, it clearly does not.

Lactic acid was first discovered in samples of sour milk in 1780. It was the milk source of lactic acid discovery that led to the acceptance of the "lactic" name ("lactic" – of or relating to milk). By 1810 chemists had verified the presence of lactic acid in other organic tissues such as ox meat and blood. However, the muscle tissue relevance, or role, of lactic acid in energy metabolism was not initially researched. Instead, the production of lactic acid in the process of fermentation, and therefore relevance to the food and alcohol industries, was the main direction of early scientific inquiry. Such applications and topics of inquiry implanted a connection between lactic acid production and anaerobic conditions that was keenly adopted by muscle and exercise physiologists. For example, cell cultures placed in an **anoxic** (oxygen deprived) condition produce lactic acid (well, in actual fact they produce lactate, but once again, at this early phase of scientific history the researchers did not understand acid-base chemistry!). Therefore, an extension of this observation was that muscle that produces lactic acid must be deprived of oxygen. The next extension of this reasoning was that the acidosis accompanying anoxic conditions must therefore be caused by lactic acid production. Note that these extensions of observations to other applications are hypothetical inferences. Normally, the process of science works to make sure that such inferences are tested through experimental research. However, be aware that back in the 1920's there were no computers, no electronic measurement instruments, and no means to quantify the proton dissociation from specific metabolites in solution and specific pH values.

The prior interpretations of lactic acid production, anoxia, and acidosis were further reinforced by expanding research of muscle metabolism and exercise physiology. Two early pioneers of this research were Otto Meyerhof and Archibald V. Hill (Figure 2) who in 1922 both received a Nobel prize for their work on the energetics of carbohydrate catabolism in skeletal muscle, which once again showed a relationship between lactic acid production, energy catabolism without oxygen, and acidosis.

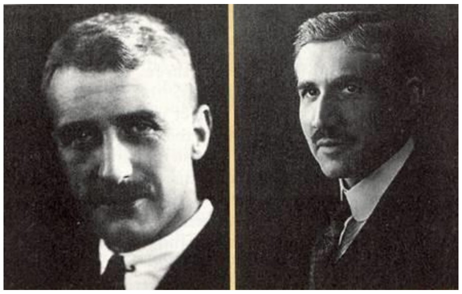


Figure 2. Photographs of Archibald V. Hill (left) and Otto Meyerhoff (right), recipients of the 1922 Nobel Prize in Medicine for their work on muscle glycolytic biochemistry and energetics.

The work of Hill and Meyerhoff reinforced the connection between lactic acid production and acidosis into the mind-set of biochemists and physiologists of that era. The Nobel prize status of this research and interpretations added scientific credibility, even though many of these interpretations remained hypothetical and unproven. For example, the connection between lactic acid and acidosis was based on observed relationships, and true cause-effect responses were never investigated for reasons of instrument and research method constraints, as well as deficient understanding at that time of acid-base physiology and computations of proton bound and un-bound metabolite complexes. Note that the Henderson-Hasselbalch equation was not developed until the mid-1940's!

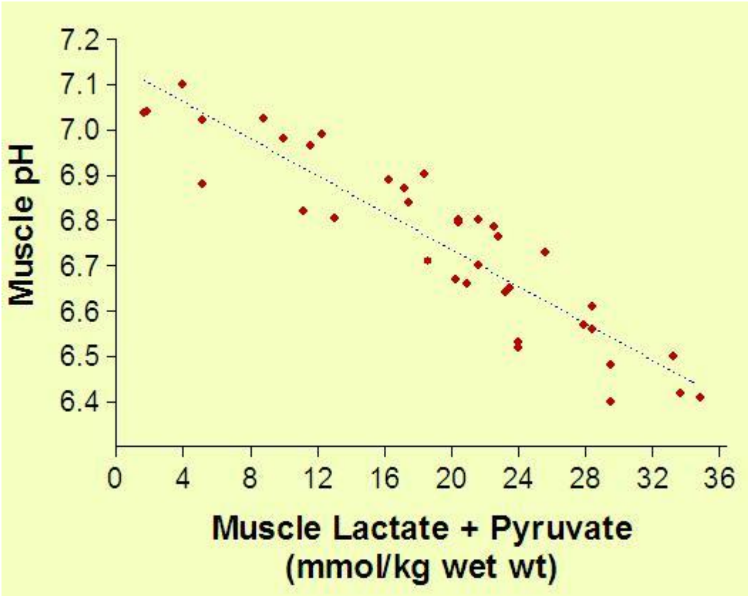


Figure 3. Negative linear relationship between muscle pH and the sum of lactate + pyruvate. ***Adapted from Sahlin K, Harris RC, Nylind B, and Hultman E. Lactate content and pH in muscle samples obtained after dynamic exercise. Pflugers Archives 367:143-149, 1976.***

What is Lactate?

The unquestioned acceptance of a cause-effect connection between lactic acid and acidosis led to the term, “lactic acidosis”, and has been a hallmark of almost all of the basic and applied science research of muscle metabolism since the 1920’s. More recent research has also been interpreted to support a lactic acidosis. For example, researchers have measured muscle pH, lactate and pyruvate during exercise and recovery. When muscle lactate and pyruvate are added and related to muscle pH, a remarkable linear relationship results, as shown in Figure 3. Once again though, as students you are often taught and reminded that correlation should not be interpreted as cause and effect. This concern applies here, as all the data of Figure 3 really show is a similar time onset of acidosis and the accumulation of lactate + pyruvate. The cause of the acidosis is not revealed by this data.

Added details of the true biochemical cause of metabolic acidosis is presented in the Topic on Metabolic Acidosis.

Glossary Words

lactic acid is a three carbon carboxylic acid, with the chemical name of 2-hydroxypropanoic acid.

lactate is the name for the proton dissociated form of lactic acid, usually present in the form of an acid salt, sodium- or potassium lactate.

2-hydroxypropanoic acid is the chemical name of lactic acid.

dissociation constant (K_d) is the ratio between the product of the unbound concentrations of a cation and metabolite, to the concentration of the bound metabolite-cation complex.

buffer is a molecule that can bind a proton (remove a proton from solution) within a specific pH range.

anoxic means without oxygen.