Review Article

Lactic acid – The innocent culprit of muscle fatigue

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Abstract:
What causes muscle fatigue? Is lactic acid considered to be a major culprit in the underlying mechanisms of muscle fatigue? These are very important questions and the answers are difficult and sophisticated. For decades, lactic acid was the major culprit of muscle fatigue. This review reveals that muscle fatigue would occur more badly if lactic acid was not produced in anaerobic cellular conditions to regenerate NAD^+ required for continuation of glycolysis, the major pathway for generation of energy needed for muscle performance.

Key words: Lactic acid, Fatigue, Lactic acidosis, Troponin C

When a muscle contracts in an anaerobic condition, glycogen disappears and lactate appears as the principal end product[1].

Pyruvate is the end product of glycolysis in cells with mitochondria and an adequate supply of oxygen. The series of reactions by which glucose is transformed into pyruvate is called **aerobic glycolysis.** This because oxygen is required to reoxidize the NADH formed during the oxidation of glyceraldehyde 3-phosphate. Aerobic glycolysis sets the stage for the oxidative decarboxylation of pyruvate to acetyl CoA, a major fuel of the citric acid cycle. Alternatively, glucose can be converted to pyruvate, which is reduced by NADH to form lactate. This conversion of glucose to lactate is called **anaerobic glycolysis** because it can occur without the participation of oxygen. Anaerobic glycolysis allows the continued production of ATP in tissues that lack mitochondria (like red blood cells) or in cells deprived of sufficient oxygen[2].

The lactate concentration in blood can rise from its normal value of 1 – 2 mM to as much as 22 mM after very severe exercise such as sprinting, but it gradually returns to normal, requiring up to 6–8 h, less if mild exercise is continued.

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However, continuously high lactic acid levels are observed when enzymes of the gluconeogenic pathway are deficient or when oxidation of pyruvate is partially blocked[3].

Thus, lactic acid was always seen as a by-product of metabolizing glucose for energy and a waste product that caused a burning sensation in the muscles. Now it is seen as another important fuel source in the body. Lactic acid is formed from glucose, and used by working muscles for energy. Now it is thought that muscle cells convert glucose or glycogen to lactic acid. Then lactic acid is absorbed converted to a fuel by mitochondria in muscle cells.

Biochemistry of exercise-induced metabolic acidosis**:**

The development of acidosis during intense exercise has traditionally been explained by the increased production of lactic acid, causing the release of a proton and the formation of the acid salt sodium lactate. These biochemical events have been termed lactic acidosis. The lactic acidosis of exercise has been a classic explanation of the biochemistry of acidosis for a long time. Robergs et.al (2004) presented clear evidence that there is no biochemical support for lactate production causing acidosis. Similarly, there is a wealth of research evidence to show that acidosis is caused by reactions other than lactate production. Every time ATP is broken down to ADP and Pi, a proton is released. When the ATP demand of muscle contraction is met by mitochondrial respiration, there is no proton accumulation in the cell, as protons

are used by the mitochondria for oxidative phosphorylation and to maintain the proton gradient in the inter-membranous space. It is only when the exercise intensity increases beyond steady state that there is a need for greater reliance on ATP regeneration from glycolysis and the phosphagen system. The ATP that is supplied from these non-mitochondrial sources and is eventually used to fuel muscle contraction, increases proton release and causes the acidosis of intense exercise. Lactate production increases under these cellular conditions to prevent pyruvate accumulation and supply the NAD+ needed for the step catalyzed by glyceraldehyde 3-phosphate dehydrogenase in glycolysis. Thus increased lactate production coincides with cellular acidosis and remains a good indirect marker for cell metabolic conditions that induce metabolic acidosis. If muscle did not produce lactate, acidosis and muscle fatigue would occur more quickly and exercise performance would be severely impaired[4,5].

Muscle fatigue (decrease in force generation) is a reduction of simultaneously attached cross-bridges in the force generating state. This is caused by a combination of reduced maximum force-generating capacity, reduced myofibrillar Ca^{2+} sensitivity and reduced Ca^{2+} release[5,6].

Impaired calcium release from the sarcoplasmic reticulum (SR) has been identified as a contributor to fatigue in isolated skeletal muscle fibers. A number of possible mechanisms for impaired calcium release have been proposed. These include reduction in the amplitude of the action potential, potentially caused by extracellular K^+ accumulation, which may reduce voltage sensor activation but is counteracted by a number of mechanisms in intact animals. Reduced effectiveness of SR Ca^{2+} channel opening is caused by the fall in intracellular ATP and the rise in Mg^{2+} concentrations that occur during fatigue. Reduced Ca^{2+}available for release within the SR can occur if inorganic phosphate enters the SR and precipitates with Ca^{2+}. Further progress requires the development of methods that can identify impaired SR Ca^{2+} release in intact, blood-perfused muscles and that can distinguish between the various mechanisms proposed[7].

There exists a long history of studies on the effects of increased lactate/H^+ concentrations in muscle or plasma on contractile performance of skeletal muscle. Evidence suggesting that lactate/H^+ is a culprit has been based on correlation-type studies, which reveal close temporal relationships between intramuscular lactate or H^+ accumulation and the decline of force during fatiguing stimulation in frog, rodent or human muscle. In addition, an induced acidosis can impair muscle contractility in non-fatigued humans or in isolated muscle preparations and several mechanisms to explain such effects have been provided. However, a number of recent high-profile papers have seriously challenged the `lactic acid hypothesis'. In the 1990s, these findings mainly involved diminished negative effects of an induced acidosis in skinned or intact muscle fibers, at higher more physiological experimental temperatures. In the early 2000s, it was conclusively shown that lactate has little detrimental effect on mechanically skinned fibres activated by artificial stimulation[8].

In a study carried out by Bellinger et al. at Columbia University Medical Center, it was found that muscle fatigue experienced by athletes after long and intense exercise may be caused by a problem with calcium flow inside muscle cells. According to Dr. Andrew Marks, who lead the study, fatigue occurs due to tiny leaks of calcium inside the muscles. One of the functions of calcium is to help control muscle contractions. This research found that after extended high-intensity exercise, small channels in the muscle cells begin to leak calcium, which leads to weakened muscle contractions. This leaked calcium also stimulates an enzyme that attacks muscle fibers and also leads to fatigue. The study had experienced cyclists riding stationary bikes for three hours a day, for three consecutive days at a high intensity. Muscle cell samples at the end of the third ride showed calcium channel leaks. After a few days of rest, these leaks were repaired.

Although this theory of calcium being involved in muscle fatigue has been around for several years, but this is the first time anyone has been able to identify a specific reason for muscle fatigue[9].

Pedresen et al. showed that intracellular acidification of skeletal muscles is commonly thought to contribute to muscle fatigue. However, intracellular acidosis also acts to preserve muscle excitability when muscles become depolarized, which occurs with working muscles. This process may be mediated by decreased chloride permeability, which enables action potentials to still be propagated along the internal network of tubules in a muscle fiber (the T system) despite muscle depolarization. Their results implicated chloride ion channels in muscle function and emphasized that intracellular acidosis of muscle has protective effects during muscle fatigue[10].

Muscle fatigue has been associated with disturbances in Na^+–K^+ balance, changes in intracellular pH, accumulation of inorganic phosphate, impaired energy metabolism, accumulation of free radical species, and impaired intracellular Ca^{2+} handling and sensitivity. The debate about muscle fatigue has intensified recently. For instance, there has been a controversy about the role of intracellular H^+ accumulation[11, 12]. Thus, the disturbance in Na^+ and K^+ gradients during muscle activity that impairs excitability is the well-known fatigue factor. The underlying mechanism is the inability of the Na^+,K^+ pump to restore ionic gradients completely during intense exercise. Therefore, the activity of the pump is central to the development of fatigue. To meet its requirements the pump is activated acutely during and after muscle activity by changes in ion affinity, by hormones and by translocation of pump subunits. Although this up-regulation of the pump is expected to improve both the Na^+ and K^+ homeostasis during muscle activity, changes in concentrations of these ions occur during muscle activity[13].

Importantly, decreasing intracellular pH to ~ 6.7 actually counters the inhibitory effect of raised extracellular [K^+]. This is because intracellular acidity blocks the Cl^- channels in the surface and T-system membranes and hence reduces the normal high leakiness to Cl^-, thereby making it possible for action potentials to still propagate into the T-system despite the raised [K^+] having caused substantial inactivation of the Na^+ channels. Extracellular [K^+] does rise to critical levels during normal exercise, so it seems very likely that the decrease in intracellular pH has substantial beneficial effects in exercising humans by delaying the onset of fatigue due to action potential failure. This is further supported by findings in humans deficient in myophosphorylase activity (McArdle's disease) who are unable to break down glycogen or accumulate lactic acid. These subjects display faster onset of fatigue, which is associated with failure of muscle excitation. These findings are fully consistent with muscle acidity normally playing a crucial role in helping keep action potentials propagating despite the large rise in extracellular [K^+] occurring with strenuous activity[14].

The classical view for acidosis is that it will inhibit Ca^{2+} binding to troponin C via competition between H^+ and Ca^{2+}, but a reduced number of strongly bound cross-bridges may also contribute. Pi, on the other hand, does not change the Ca^{2+} binding to isolated troponin C, hence its depression of Ca^{2+} sensitivity is thought to occur via reduced co-operativity due to a reduced number of strongly attached cross-bridges. In fatigue there may also be factors that increase the Ca^{2+} sensitivity. With increased ADP. The mechanism described for Pi may work in the opposite direction. Thus, increased ADP will increase the number of strongly bound cross-bridges and, hence, the Ca^{2+} affinity of troponin C. In accordance with this, an increased Ca^{2+} sensitivity has been observed in skinned fibers exposed to 5 mM ADP[15].

Conclusion:

Muscle fatigue (decrease in force generation) is a reduction of simultaneously attached cross-bridges in the force generating state. This is caused by a combination of reduced maximum force-generating capacity, reduced

myofibrillar Ca^{2+} sensitivity and reduced Ca^{2+} release**.** The ATP that is supplied from these non-mitochondrial sources and is eventually used to fuel muscle contraction, increases proton release and causes the acidosis of intense exercise. Intracellular acidity blocks the Cl^- channels in the surface and T-system membranes and hence reduces the normal high leakiness to Cl^-, thereby making it possible for action potentials to still propagate into the T-system despite the raised $[K^+]$ having caused substantial inactivation of the Na^+ channels.

Lactic acid production increases under anaerobic cellular conditions to prevent pyruvate accumulation and supply the NAD^+ needed for the step catalyzed by glyceraldehyde 3-phosphate dehydrogenase in glycolysis. Thus increased lactic acid production coincides with cellular acidosis and remains a good indirect marker for cell metabolic conditions that induce metabolic acidosis. If muscle did not produce lactic acid, acidosis and muscle fatigue would take place more quickly and exercise performance would be severely impaired**.**

References:

1.Mayes PA. Glycolysis & the oxidation of pyruvate. In: Murray RK, Granner DK, Mayes PA, and Rodwell VW (eds). Harper's illustrated biochemistry. 26th edition. Lange Medical Books/McGraw-Hill. 2003; Ch. 17, pp136.

2. Champe PC, Harvey RA, and Ferrier DR. Lippincott's illustrated reviews-Biochemistry. 3rd edition. Lippncott Williams & Wilkins. 2005; Ch.8, pp 94.

3. Metzler DE and Metzler CM. Biochemistry - The chemical reactions of living cells. 2nd edition. Elsevier academic press. 2003; Ch 17, pp 1002.

4. Robergs R A, Ghiasvand F, and Parker D. Biochemistry of exercise-induced metabolic acidosis. Am J Physiol Regul Integr Comp Physiol 2004; 287: R502-R516.

5. Shalayel MHF, Elrobh MS & Ahmed SAM. Metabolic aspects of skeletal muscles. Sudan Medical Monitor. 2009; 4(3): 111-115.

6. Allen DG, Lannergren J, and Westerblad H. Muscle cell function during prolonged activity: Cellular mechanisms of fatigue. Experimental Physiology. 1995; 80: 497-527.

7. Allen DG, Lamb GD, and Westerblad H. Impaired calcium release during fatigue. J Appl Physiol. 2008; 104(1): 296-305.

8. Cairns Simeon P. Lactic Acid and Exercise Performance: Culprit or Friend?. Sports Medicine. 2006; 36 (4): 279-291.

9. Bellinger AM, Reiken S, Dura M et al. Remodeling of ryanodine receptor complex causes "leaky" channels: A molecular mechanism for decreased exercise capacity, The Proceedings of the National Academy of Sciences 2008; 5(6):2198- 2202 .

10. Pedersen TH, Nielsen OB, Lamb GD et al. Intracellular Acidosis Enhances the Excitability of Working Muscle. Science 2004; 305 (5687): 1144 – 1147.

11. Nielsen OB, de Paoli F, Overgaard K. Protective effects of lactic acid on force production in rat skeletal muscle. *J Physiol.* 2001;536:161–166.

12. Kristensen M, Albertsen J, Rentsch M et al. Lactate and force production in skeletal muscle. J Physiol. 2005;562:521–526.

13. Juel C. Muscle fatigue and reactive oxygen species. J Physiol. 2006; 576(P 1): 1.

14. Graham D L, Stephenson DG, s Bangsbo J et al. Point:Counterpoint: Lactic acid accumulation is an advantage/disadvantage during muscle activity. *J Appl Physiol.* 2006; 100: 1410–1414.

15. Allen DG, Lannergren J, and Westerblad H. Muscle cell function during prolonged activity: cellular mechanisms of fatigue. Experimental Physiology (1995), 80, 497-527.