

## Lactic Acid: Fuel or Foe?

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### Background

For several decades, lactic acid has been thought of as an end-point of glycolysis that accumulates when muscles must use more anaerobic metabolism to meet high-energy demands during intense exercise.<sup>1</sup> In the body, lactic acid is almost entirely dissociated into lactate anions and protons, and it is this accumulation of protons that has been commonly named as the cause of muscle fatigue during exercise.<sup>2</sup> However, recent studies in the fields of exercise physiology and basic science have revealed that lactic acid is not an end-product, but is, in fact, shuttled to different cells and tissues, where it is taken up and oxidized as a fuel by skeletal muscle, myocardial and other tissues.<sup>1</sup> Furthermore, there is increasing evidence that the production of lactate anions may slow the progression of acidosis in the muscle, contrary to the popular belief that lactic acidosis is the cause of acidosis in the muscle, and hence of muscle fatigue.<sup>3,4</sup>

These recent studies have spurred an active debate about whether lactic acid is the cause of muscle fatigue, or whether it may actually have a role in retarding the onset of fatigue. One of the most recent forums for this debate appeared in the new "Point: Counterpoint" series of the *Journal of Applied Physiology*, where authors were invited to debate both sides of a statement, and opportunities were available for rebuttal in subsequent journals. The following are summaries of the main points for each side of the debate.

### Debate point: Fuel

While it is clear that lactic acid concentrations rise during exercise, and peak during muscle fatigue, this is not evidence that lactic acid is the cause of muscle fatigue. The only certainty is that lactic acid serves as a marker of muscle fatigue.<sup>5</sup> People with myophosphorylase deficiency (McArdle's disease) lack an enzyme important in the pathway of glycogen breakdown for energy; therefore, these patients produce no lactic acid. Yet they still develop muscle fatigue on exertion at a more rapid rate than people without the deficiency.<sup>5,6</sup> This is evidence that lactic acid, if it does contribute to fatigue, is not the sole cause. The cause of fatigue in patients with McArdle's disease appears to be the accumulation of metabolites in skeletal muscle, such as inorganic phosphates, ADP<sup>6</sup> and Mg<sup>2+</sup>, as well as the depletion of fuel substrates within the muscle fibres, such as ATP, glycogen, and creatine phosphate.<sup>7</sup> Another frequently cited cause of muscle fatigue is the buildup of K<sup>+</sup>, which depolarizes the muscle fibre, causing failure of action potential generation, and thus a decrease in force production by the muscle.<sup>7</sup> Any disruption in excitation-contraction coupling can lead to fatigue generation.

Contrary to causing muscle fatigue, lactic acid may facilitate muscle contraction by: 1) preventing the early inhibition of muscle fibre contraction, and 2) providing substrate for oxidation or glycogen production. The increase of intracellular acidity caused by the accumulation of lactic acid

decreases the normal leakiness of Cl<sup>-</sup> channels in the T-tubule membrane, allowing for action potentials to continue to be propagated despite the rise in K<sup>+</sup> concentration discussed earlier.<sup>7</sup> Acidosis in muscle fibres thus delays the fatiguing effects of K<sup>+</sup> buildup, preventing early onset of fatigue. In addition to delaying fatigue, lactate together with pyruvate serve as substrates for oxidative phosphorylation and ATP homeostasis.<sup>8</sup> Far from being a metabolic end-product, lactic acid is transported both intracellularly and extracellularly by several isoforms of monocarboxylate transporters (MCTs) in what is termed the lactate shuttle.<sup>9</sup> The majority of lactic acid, however, is oxidized to pyruvate,<sup>8</sup> which enters the tricarboxylic acid (TCA) cycle as a substrate of aerobic metabolism. This oxidation of lactic acid also provides the NAD<sup>+</sup> necessary for the TCA cycle.<sup>8</sup> The lactic acid that is released from muscle via the MCTs becomes a substrate in myocardial tissue or a substrate for gluconeogenesis.<sup>9</sup>

These functions of lactic acid in muscle excitation and contraction seem to negate the hypothesis that it may be the cause of muscle fatigue. In fact, the infusion of lactate into muscles of rats was associated with increased endurance of contraction, as well as increased excitability of the muscle fibres.<sup>10</sup> In humans, performing a bout of heavy exercise before exhaustive aerobic exercise increased the blood lactate concentration prior to the second bout of exercise, and this lactate accumulation was associated with longer exercise times.<sup>11</sup> This evidence suggests that, instead of fatiguing the muscles, lactic acid primes the muscle to perform better and for longer periods of time before fatigue. Perhaps, as suggested by Allen and Westerblad in "Perspectives" in *Science*, lactic acid may one day be regarded as a performance-enhancing drug.<sup>12</sup>

### Debate point: Foe

Investigations into the role of lactic acid in exercising muscle began in the late 1800s. Early in the 1900s, it was shown that lactic acid metabolism occurs even in the absence of oxygen.<sup>2</sup> The year before Banting and Macleod won the Nobel Prize in Medicine for the discovery of insulin in 1923, Meyerhof and Hill became laureates for their work on carbohydrate metabolism in muscle, which gave rise to the "oxygen debt model" that has become the predominant explanation for the accumulation of lactic acid during exhausting exercise.<sup>2</sup> The belief that lactic acid is strictly an end-product of anaerobic metabolism is one that has persisted, and lactic acid has become known as the main cause of muscle fatigue in the lay exercise community.

Current arguments for lactic acid being the cause of muscle fatigue are based on the findings that increased lactic acid concentrations and decreased muscle pH are associated with a worsening of muscle performance after long or intense bouts of exercise.<sup>13</sup> Furthermore, alkalosis (i.e. via infusion or consumption of sodium citrate or bicarbonate) slows the

accumulation of  $K^+$ , reduces acidosis, and subsequently improves muscle performance.<sup>13,14</sup>

Studies performed in animals or in isolated muscle tissue, which have demonstrated that lactic acid may not cause muscle fatigue or that it may enhance performance, have been received with caution.<sup>15-18</sup> Critics acknowledge that performing studies in isolated and skinned muscle fibres at rest provide insight into the cellular mechanisms that are taking place. However, these findings cannot be generalized to intact muscle,<sup>16</sup> as lactic acid may exert its effect on the membrane surrounding the muscle fibres and not on the fibres themselves. Muscle twitch force was reduced in isolated animal muscles incubated in lactic acid, but twitch force was not impaired in skinned muscle fibres also incubated in lactic acid.<sup>13</sup>

Similarly, while lactic acid may be beneficial in optimizing contractions in isolated muscle fibres, this may not be the case in whole body movements. Acidosis prolongs the relaxation time between each contraction by preventing the accumulated  $K^+$  from constantly depolarizing the fibres. This may not be beneficial, however, in whole body movements, where the coordination and timing of muscle group contraction is critical to the movement of large segments.<sup>17,19</sup>

Furthermore, both in situ and in vivo evidence has shown that acidosis and lactate accumulation may contribute to fatigue by the effects of the lowered pH. The accumulation of protons within contracting muscle tissue may lead to the downregulation of some pH-sensitive enzyme systems, which can hinder processes in mechanical contraction as well as energy production.<sup>16</sup>

### Interpretation & Conclusions

Clearly, the debate over the role of lactic acid has not yet been resolved, although it has brought to light many fascinating facts about muscle metabolism. Recent studies involving isolated muscle fibres and improved techniques in exercise physiology have provided the means of obtaining new evidence for both sides of the debate. One thing is for certain: the answer to this burning question will have exciting appli-

cations in many fields, ranging from the training of elite athletes, to the possible therapeutic benefits of lactic acid administration to patients with muscle myopathies or rapid-onset muscle fatigue.

### References

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