Lactic Acid Still Remains the Real Cause of Exercise-Induced Metabolic Acidosis

To the Editor: We appreciate the article of Robergs et al. (5), which gives a complete overview of the biochemistry of metabolic acidosis originating from intense muscular exercise. However, with the intention to clarify the causes of the pH decrease, the authors try to prove that lactic acid plays no role in this process and thus declare that generations of exercise physiologists have been using a false concept. We feel that this attempt results in confusion. A number of statements cannot be accepted:

Source of Increasing Pi in Exercising Muscles

“...the origin of accumulating intramuscular Pi is ATP hydrolysis, not creatine phosphate breakdown, which is still mistakenly interpreted by many physiologists.” (p. R509)

As known from numerous studies, creatine phosphate (CrP) concentration in hard-working muscle is massively reduced while changes in [ATP] are only small. Binding of Pi to the latter is a transitory step only. Consequently, CrP breakdown is the real and the most important source of accumulating Pi.

Amount of Proton Release During Glycolysis

Most problematic is the calculation of the balance of proton release provided by Robergs et al. (5). Equations 1 and 2 ending with pyruvate show that glycolysis produces 2 H⁺ or 1 H⁺ starting with glucose or glycogen, respectively:

\[ \text{glucose} + 2 \text{ADP} + 2 \text{Pi} + 2 \text{NAD}^+ \rightarrow 2 \text{pyruvate} + 2 \text{ATP} + 2 \text{NADH} + 2 \text{H}_2\text{O} + 2 \text{H}^+ \]  

and

\[ \text{glycogen} + 3 \text{ADP} + 3 \text{Pi} + 2 \text{NAD}^+ \rightarrow 2 \text{pyruvate} + 3 \text{ATP} + \text{glycogen}_{n-1} + 2 \text{NAD}^+ + 2 \text{H}_2\text{O} + 1 \text{H}^+ \]  

To produce lactate, 2 H from NADH and 2 H⁺ are added to pyruvate. Therefore, if glycolysis starts with glucose, Eq. 1 must be continued as follows:

\[ 2 \text{pyruvate} + 2 \text{ATP} + 2 \text{NADH} + 2\text{H}^+ \rightarrow 2 \text{lactate} + 2 \text{ATP} + 2 \text{NAD}^+ \]  

According to Eq. 1a, there is no acidois at all. If glycolysis starts with glycogen, we obtain:

\[ 2 \text{pyruvate} + 3 \text{ATP} + 2 \text{NADH} + 1 \text{H}^+ \rightarrow 2 \text{lactate} + 3 \text{ATP} + 2 \text{NAD}^+ - 1 \text{H}^+ \]  

According to Eq. 2a, there is actually a net consumption of one proton, that is, alkalization occurs. Equations 3 and 4 in Robergs' article (5) express this result in a simplified manner as well; consequently, the authors come to the same conclusion at this step of the glycolysis.

However, ATP is not stored but immediately hydrolyzed to 1 ADP, 1 Pi, and 1 H⁺ per ATP (Fig. 10 in 5). Because three ATP are obtained when starting with glycogen but only two ATP when starting with glucose, the result is two negatively charged lactate and 2 H⁺ in both cases. Irrespective of this, Robergs et al. (5) present the incorrect summary Eq. 6 (including ATP hydrolysis): glycogen \[\rightarrow 2 \text{lactate} + \text{1 H}^+\]  

The summary equation has to be corrected as follows:

\[ \text{glycogen} \rightarrow 2 \text{lactate} + 2 \text{H}^+ \]

Consequently, the amount of H⁺ obtained is equal for either glucose or glycogen as the initial source. The resulting metabolite is lactic acid in spite of the last step for proton release being ATP hydrolysis.

This acid, as well as its effects on acid-base equilibrium is completely indistinguishable from the lactic acid that you may add from outside to the cell. Assuming exchange of lactate by an anion of a weak acid with pK above 7, which would bind most produced H⁺, clearly demonstrates that lactate is essential for metabolic acidosis.

Exercise-Induced Metabolic Acidosis Without Production of Lactic Acid?

“...if muscle did not produce lactate, acidois ... would occur more quickly ...” (p. R502)

In subjects being unable to produce lactate (McArdle’s disease and subjects with phosphofructokinase-deficiency), Vissing et al. (8) have shown that even under exhaustive exercise, muscle pH did not decrease but instead increased.

Lactate and Proton Release From Muscle to Blood

Robergs et al. (5) present calculations of Juel et al. (4) on lactate and proton release into the blood during exercise as further evidence against a close interrelationship between lactate production and metabolic acidosis, and state:

“Clearly, muscle proton release was greater than lactate release ... with an almost twofold greater proton-to-lactate release at exhaustion.” (p. R512)

However, the calculations of proton release by Juel et al. (4) are questionable. They are based on differences in actual base excess between arterial and venous blood, but this quantity is additionally influenced by movement of bicarbonate to the interstitial fluid when buffering acids (e.g. 1) and by delayed movement of lactate (compared to protons) into the red blood cells (2). Calculations based on extracellular nonbicarbonate buffer capacity yield an approximate 1-to-1 release of lactate ions and H⁺ from the muscle cells (3).

Muscular Buffers

“The published data reveal that the muscle buffer capacity (structural and metabolic) is almost double that of lactate production” (p. R512)

To prove the latter, Robergs et al. (5) compare “the theoretical proton release from lactate production” corresponding to 32 mmol lactate/kg wet weight to a suggested consumption of 65 mmol/kg wet weight by titratable buffers, creatine phosphate splitting, and Pi accumulation based on three references (Fig. 16). Astonishingly, the references contain different data. Sahlin (6) calculates 68 slykes for the sum of structural and metabolic buffering, resulting in a proton consumption of 41 mmol/l muscle water for a pH decrease from 7.0 to 6.4. Spriet et al. (7) obtain 77.5 slykes, which yield 43 mmol/l muscle water for a slightly smaller pH decrease to 6.45. The remaining difference is at least partly caused by CO₂ from aerobic metabolism and other acids like pyruvic acid. These results heavily contradict the statement of Robergs et al. (5).
Calculation of Nonmitochondrial ATP Production

There is a false multiplication in Eq. 7. The corrected version is

\[
\text{ATP-NM} = (\Delta \text{CrP} + \Delta \text{ATP}) + (1.5\cdot\Delta \text{La})
\]

In spite of our criticism, we are grateful for the stimulation of such discussion regarding the role of lactic acid in the process of metabolic acidosis, originating from intense muscular exercise. Indeed, too often, lactic acid is only regarded in a very simplistic manner in sports medicine, and furthermore, the meaning of lactic acid and lactate is not always discerned. However, there is no need to rewrite the whole story.

REFERENCES


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