PERSPECTIVES

Is there an intracellular lactate shuttle in skeletal muscle?

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As detailed in my review in this journal (Gladden, 2004), a fundamental change in the overall view of the role of La^- in metabolism occurred with the introduction of the lactate shuttle hypothesis (now called the cell-to-cell lactate shuttle) by George Brooks in the mid-1980s (Brooks, 1985). Since then, evidence for the cell-to-cell lactate shuttle has been essentially unanimous. It is now clear that O_2 limitation is not a requirement for net La^- formation, and that La^- is an important intermediary in numerous metabolic processes, a mobile fuel for aerobic metabolism, and perhaps a mediator of redox state among various compartments both within and between cells. Skeletal muscle, once considered to be simply the major site of La^- production, is now known to be a ready consumer of La^- in many circumstances, including steady state exercise.

Since 1998, Brooks and colleagues (e.g. Brooks *et al.* 1999) have also promulgated the idea of an intracellular lactate shuttle in skeletal muscle, cardiac muscle and liver. If verified, this shuttle would require a revision of biochemistry textbooks. The basic idea is that cytosolic activity of the enzyme lactate dehydrogenase (LDH) is so high that pyruvate-to La^--conversion is prevalent, making La^- the primary endproduct of glycolysis even under aerobic conditions. La^- would then diffuse to mitochondria and into the mitochondrial matrix via facilitated diffusion across the inner membrane with the assistance of a monocarboxylate transporter (MCT). In the matrix, La^- would be converted back to pyruvate in a reaction catalysed by intramitochondrial LDH. Such a shuttle would bring reducing equivalents into the mitochondria, and at least to some extent, replicate or replace the role of the malate–aspartate and glycerol phosphate shuttles. This shuttle would also be a major pathway for pyruvate transfer from the cytosol to the mitochondrial matrix. Although there is some disagreement about the exact isoform of the MCT, there is accord on the premise that MCTs are present in mitochondria, apparently on the inner membrane. The catch is that LDH must be present in the mitochondrial matrix, and there is strong disagreement on this point.

In this issue of *The Journal of Physiology*, Bonen and coworkers (Yoshida *et al.* 2007) offer strong evidence against the presence of LDH in mitochondria and against the ability of mitochondria to directly oxidize La^- without prior extramitochondrial conversion of La^- to pyruvate. They (Yoshida *et al.* 2007) isolated both subsarcolemmal and intermyofibrillar mitochondria from both oxidative and glycolytic rat skeletal muscle and report these key findings: (1) in agreement with previous work, MCTs are present on both types of mitochondria; (2) $[La^-]$ has to be 57–139 times higher than [pyruvate] to achieve the same mitochondrial oxidation rate; (3) addition of LDH increases the rate of La^- oxidation, but not pyruvate oxidation; (4) excess pyruvate inhibits the oxidation of palmitate and La^- whereas excess La^- does not inhibit either palmitate or pyruvate oxidation; (5) AICAR (a cell-permeant adenosine analogue) increases pyruvate but not La^- oxidation; and (6) LDH activity in either type of mitochondria is only about 0.4–0.5% of that in whole muscle. *In toto*, these results along with previous congruous reports by other investigators may lay to rest the idea of intramitochondrial oxidation of La^-.

However, correctly in my opinion, Bonen and colleagues (Yoshida *et al.* 2007) retain the idea of an intracellular lactate shuttle that does not involve the mitochondrial matrix. This is a concept originally proposed by Stainsby & Brooks (1990) and it is compatible with recent observations of Brooks and colleagues (Hashimoto *et al.* 2006) suggesting the presence of a lactate oxidation complex (an association of MCT, CD147, LDH and cytochrome oxidase) within the inner mitochondrial membrane. In this model, La^- would still be the primary endproduct of glycolysis in the cytosol. Uptake of pyruvate and subsequent intramitochondrial oxidation would create a sink for pyruvate in areas adjacent to mitochondria, perhaps in the mitochondrial intermembrane space. A low [pyruvate] near the mitochondria would in turn create a sink for La^- via reversal of the LDH reaction, creating a $[La^-]$ gradient from cytosolic sites of La^- production to mitochondrial sites of La^- removal. Due to the higher concentration of La^- relative to pyruvate, this $[La^-]$ gradient would be much larger than the [pyruvate] gradient making La^- the primary diffusive species.

Such a model is compatible with the compartmentation of metabolism. Is it possible that La^- derived from glycolysis compartmentalized with sarcolemmal Na^+–K^+-ATPase activity is shuttled towards subsarcolemmal mitochondria whereas La^- derived from glycolysis associated with sarcoplasmic Ca^{2+} pumping is shuttled towards intermyofibrillar mitochondria? Next comes the arguably more difficult task of detecting, quantifying and explaining an intracellular lactate shuttle that does not require a mitochondrial matrix component.

References

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