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Commentary

Commentary on "The tortuous path of lactate shuttle discovery: From cinders and boards to the lab and ICU"

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It is a pleasure to provide a commentary on the outstanding review[1] by Dr. George Brooks that discusses both the discovery and importance of the lactate shuttle. Clearly, Professor Brooks is highly qualified to review this important topic. Indeed, Dr. Brooks and his colleagues pioneered the original research that defined the metabolic conditions that regulate lactate production in skeletal muscle as well as the fate of lactate following production. In the following paragraphs, I highlight several key concepts emerging from this important review.

Interest in how, when, and why lactate production in contracting skeletal muscle emerged from the early contributions of 2 luminaries in exercise physiology, Otto Meyerhof and A.V. Hill. Work by these investigators stimulated interest in this field that eventually led to the debate about the causation of the "anaerobic threshold". In fact, the question of whether lactate production in contracting skeletal muscle originated from a lack of oxygen or simply increased glycolytic flux has been hotly debated among exercise physiologists for several decades. Thankfully, this issue has now been resolved largely due to work by Dr. Brooks and others indicating that lactate can be produced in aerobic conditions in skeletal muscle fibers.

Guided by studies using radiotracers to investigate the metabolism of both glucose and lactate, Dr. Brooks proposed the lactate shuttle hypothesis in the early 1980s. In the simplest terms, the lactate shuttle describes the physiological process of lactate production in cells and the subsequent movement of lactate within and between cells throughout the body. Importantly, the lactate shuttle concept also describes the role that lactate plays as both fuel and a signaling molecule between cells, tissues, and multiple organ systems. As discussed by Dr. Brooks, the inspiration to formulate the lactate shuttle evolved from experimental findings in humans and other mammals indicating that lactate was exchanged between cells across the body and that most of this lactate was disposed via intramuscular oxidation. Subsequent experiments by Brooks and colleagues expanded the original lactate shuttle hypothesis to include the controversial idea that lactate can undergo within-cell oxidation in the mitochondrion. The controversy associated with this concept centers around the issue that some researchers have failed to produce *in vitro* mitochondrial preparations that oxidize lactate. Nonetheless, as debated by Dr. Brooks in his review, this controversy can likely be explained by the fact that isolated mitochondrial preparations disrupt the organization of the mitochondrial reticulum that exists in skeletal muscle fibers; indeed, isolation of muscle mitochondria can result in damage to mitochondrial constituents such as cytochrome C and L-lactate dehydrogenase. Hence, the failure of isolated mitochondria to oxidize lactate appears to be an experimental artifact resulting from damage to mitochondria during the isolation process.

Finally, it is important to appreciate that studies elucidating the basic science behind the lactate shuttle have led to discoveries that may have significant clinical implications. Indeed, as discussed in the review, Dr. Brooks points out that rising blood lactate levels is an important biomarker not only for sports practitioners but clinicians as well. Moreover, the infusion of exogenous L-lactate to patients is now being investigated as a treatment for heart failure, traumatic braining injury, pancreatitis, hepatitis, dengue fever, and sepsis. Further, investigations into the basic science behind the various lactate shuttles have contributed to our understanding of the exciting possibility that manipulation of lactate production and/or uptake in tumor cells may play a role in cancer therapy. Together, these advances in understanding the basic biology of lactate metabolism illustrate how exploring the basic science of exercise physiology has the potential to provide new therapies. Stay tuned-there is much more to be learned about the lactate shuttle and the clinical applications of lactate.

Competing interests

The author declares that he has no competing interests.

Reference

1. Brooks GA. The tortuous path of lactate shuttle discovery: from cinders and boards to the lab and ICU. *J Sport Health Sci* 2020;**9**:446–60.

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