ESSAYS ON APS CLASSIC PAPERS

Comments on Classical Papers

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This essay looks at the historical significance of one APS classic paper that is freely available online: Margaria R, Edwards HT, and Dill DB. The possible mechanisms of contracting and paying the oxygen debt and the role of lactic acid in muscular contraction. Am J Physiol 106: 689–715, 1933 (http://ajplegacy.physiology.org/cgi/reprint/106/3/689).

WHAT IS THE ROLE OF LACTIC ACID in muscle contraction and at the whole body level? Since the beginning of the 20th century physiologists have known that when an isolated, unperfused frog muscle was stimulated to contract, lactic acid was produced as part of the contractile response and that oxygen was necessary during recovery to metabolize the lactic acid to eliminate its presence. These phenomena formed the Hill-Meyerhof “O2 debt” theory, which proposed that during recovery, one-fifth of the lactate was oxidized to provide energy for converting four-fifths of the produced lactate back to glycogen (7–9). The findings, in part, resulted in the Nobel Prize being awarded to A. V. Hill and Otto Meyerhof in 1922.

Subsequently, in 1933, Margaria, Edwards, and Dill at the Harvard Fatigue Laboratory, published their seminal paper, which attempted to elaborate on the oxygen debt theory by studying the oxygen consumption and blood lactate kinetics in human subjects during and after short-duration treadmill exercise of high intensities (4–10 min). Their key findings were that 1) recovery oxygen consumption rapidly declined initially and then slowly tailed off toward resting values, a process that took approximately 1 h, and 2) the high level of lactic acid that was present in the blood at the end of exercise did not decline immediately and then it declined slowly with kinetics, approximating the observed pattern of the oxygen consumption response.

Therefore, Margaria and associates surmised that the first fast phase of the postexercise oxygen consumption curve was not temporally associated with a change in blood lactate. This phase was termed “alactacid,” meaning not associated with lactate metabolism. Also, they proposed that the second, slow postexercise O2 consumption curve, which temporally coincided with the decline in blood lactate, was due to the reconversion of lactate to glycogen. Thus this slow phase was termed the “lactacid” component of the oxygen debt. This paper was significant, not only for defining two phases of the oxygen debt response, but also for conceptually departing from the classical work of Meyerhof and Hill and coworkers.

As history would prove, they were largely correct concerning the alactacid component, inasmuch as collective observations suggest that the alactacid component is largely attributed to the oxidative replenishment of high-energy phosphagen stores that are rapidly broken down during the initial phases of the exercise response before oxygen consumption reaches a true metabolic steady state for covering the energy requirements. The subsequent replenishment of these compounds, which occurs very rapidly in the muscles after exercise, is indeed not linked to lactate metabolism. However, with regard to the lactacid component of the O2 debt, Margaria and associates were clearly incorrect concerning the contribution of lactate metabolism in accounting for the extra oxygen (e.g., the lactacid oxygen debt) consumed during recovery.

On the basis of their experimental design of using only short-duration exercise before the recovery protocols, these investigators could not have known that, in fact, lactate was rapidly entering and leaving the blood immediately after exercise and that oxidation was the major fate of lactate during both exercise and recovery. Nevertheless, the world came to know and accept the hypothesis of the lactic and alactacid oxygen debts. However, it took several decades to unravel further insightful research on this topic as spearheaded by the work of Margaria, Edwards, and Dill. A brief synopsis of the highlights of this subsequent work is summarized below.
One of the first challenges to the oxygen debt-lactic acid theory was by Ole Bang (1) in 1936. He showed by using exercises of varied intensities and durations that the results of Margaria, Edwards, and Dill were essentially fortuitous based on the duration that they chose to study. With prolonged exercise, Bang showed that blood lactate level reaches a maximum after about 10 min of exercise and then declines over time whether exercise is stopped or continuous for longer and longer durations. Some of his experiments also showed that resting levels of lactate concentration could be achieved during the exercise itself. However, after exercise, there was always an oxygen debt regardless of exercise duration, with predictable kinetics to be paid. Thus these results cannot be reconciled with the idea that lactic acid determines oxygen consumption during recovery from exercise.

During the early 1960s, it became apparent that mammalian skeletal muscle unlike amphibian (e.g., frog) skeletal muscle cannot directly reconvert lactic acid back into muscle glycogen. This is inconsistent to the early findings, which initially founded the basis of the oxygen debt theory of Hill and Meyerhof. Because such was not the case in mammalian muscle, the thinking on lactate metabolism needed significant revision, especially in the context that the Cori cycle (5; a process in which lactic acid production in skeletal muscle is released into the blood and brought to the liver and converted back into glucose/glycogen for subsequent delivery back to the muscle) had been discovered in the 1940s. That discovery resulted in the Nobel Prize for Physiology being awarded to Carl and Gerty Cori in 1947. Therefore new approaches were needed to dissect the role of lactate metabolism and O2 debt.

On the basis of the above information, a paper was published in 1970 by R. J. Barnard, M. L. Foss, and C. M. Tipton (4) in which they pharmacologically blocked gluconeogenesis in the liver (an endergonic energy-requiring process) to prevent lactate conversion to carbohydrate derivatives during and after treadmill exercise of varying intensity involving dogs. Their findings showed that both exercise and recovery oxygen consumption levels were reduced when the Cori cycle was inhibited. Their findings suggested that that the metabolic processes involving lactate removal by the liver could only account for ~40% of the extra oxygen used during recovery, thus suggesting that oxidative processes not involved in converting lactate to glycogen account for the majority of the oxygen debt that is occurring.

However, three key questions remain. 1) What is the primary fate of the lactic acid that is produced by skeletal muscle during exercise? 2) Does lactic acid contribute to the phenomena of the extra oxygen that is consumed during recovery. 3) What are the biological roles of lactic acid? In addressing the first question, G. Brooks and coworkers (2, 3) employed the ingenuity of using radioactive lactate infusion into rodents at the end of exercise and have traced the fate of the labeled lactate. Their findings suggest that the primary fate (~75%) of the lactate in recovery is CO2 (the major product of oxidative metabolism) along with a variety of other end points including liver glycogen, amino acids, and other metabolic intermediates. Their findings also suggest that lactate is the primary fuel source that pays for the oxygen debt rather than being the cause of the oxygen debt. If such is the case, then what are the causes of the oxygen debt or the extra oxygen that is used during recovery after exercise? These questions have been partially resolved (6), but many aspects persist as challenges facing physiologists in the 21st century. Hopefully it will not take an approximate 90-yr span to resolve the current issues on lactate metabolism and oxygen debt as it did in bringing us to the current stage based on the original findings of A. V. Hill.

REFERENCES