Mammalian skeletal muscle can convert lactate to glycogen

To the Editor: I wish to congratulate Dr. Ken Baldwin (2) on an insightful and stimulating essay regarding the classical 1933 oxygen debt paper by Margaria, Edwards, and Dill (11). However, I would like to offer one suggestion for a correction in the paper. Dr. Baldwin states that “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.”

I propose a different scenario [see Gladden (8) and Pascoe and Gladden (16) for more details]. Meyerhof first reported the conversion of lactate to glycogen in frog muscle in 1920 (13) and again in 1925 (14). However, over the next 40 years, conclusive support for Meyerhof’s results failed to appear. There were some reports of lactate conversion to glycogen in muscle, but none of the studies clearly demonstrated the phenomenon during net glycogen synthesis, and some of the results were probably obtained during net glycogen breakdown. These results were reinforced by biochemical studies that failed to find some or all of the necessary enzymes for glycolytic reversal in skeletal muscle. However, in 1965, Krebs and Woodford (10) found fructose-1,6-bisphosphatase (F-1,6-bisPase) in the muscles of several animals including humans. Since then, others have confirmed this finding. F-1,6-bisPase provides a bypass around the nonequilibrium phosphofructokinase reaction. Similarly, more recent evidence suggests that the pyruvate kinase reaction can be quantitatively reversed in skeletal muscle (see Ref. 7), a postulate previously held to be unlikely if not impossible.

More directly to the point, beginning with the report of Bendall and Taylor in 1970 (4) and continuing through the work of McLane and Holloszy in 1979 (12), there have been a host of studies showing lactate conversion to glycogen in isolated skeletal muscles (e.g., Ref. 5), perfused skeletal muscles (e.g., Ref. 15), skeletal muscles within intact animals of various species (e.g., Ref. 9), and skeletal muscles in humans (e.g., Ref. 1, 3). So, skeletal muscle, including that of both amphibians and mammals, can reconvert lactate back into glycogen.

A careful review of the literature suggests that mammalian skeletal muscle glycogen synthesis from lactate is unlikely to exceed 50% of the total lactate removal even under optimal conditions; i.e., sustained high muscle [lactate] after short-term high-intensity exercise (8), and it is most prevalent in fast twitch, glycolytic muscles (15). In most situations, as summarized by Brooks et al. (6) and noted by Dr. Baldwin (2), oxidation will be the dominant lactate removal process in mammals, with its contribution becoming even greater during active recovery.

REFERENCES


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REPLY

To the Editor: The article by Dr. Gladden pertained to the paper concerning Comments on Classical Papers (1), in which I provided a historical perspective on the scientific impact of the classical 1933 paper by Margaria, Edwards, and Dill (3), which dealt with mechanisms of contracting and paying the oxygen debt that occurs during muscular activity in the context of kinetic analyses of lactic acid disappearance in blood.

In that brief review I provided background on the origin of oxygen debt theory based on the classical work of Hill and Meyerhoff, which placed a primary focus on the role of skeletal muscle (1). Subsequently in the article, I alluded to a general prevailing consensus in the early 1960s that mammalian skeletal muscle was different from amphibian in that the former did not appear to have the enzymatic capacity to stoichiometrically reconvert the quantity of lactic acid that was produced via contractile activity directly back into glycogen to account for the extra oxygen consumed during the recovery period (e.g., the oxygen debt). Thus researchers in that time frame turned to dissecting the role of the liver and in particular manipulating the Cori cycle (1), which proposes that lactate in the blood is removed by the liver and subsequently converted back into glucose, a process that is energy consuming. (In fact, discovery of the Cori cycle resulted in the Nobel Prize being awarded to Carl and Gerti Cori in 1947).

As pointed out by Dr. Gladden, more recent studies clearly demonstrate that mammalian muscle does indeed have the enzyme system to convert significant amounts lactate to glucose/glycogen in isolated skeletal muscle (see references cited
in his paper). In my myopia of focusing on the historical perspective that drove the research in the 1960s as summarized in the essay paper, I inadvertently ignored the interesting findings outlined by Dr. Gladden. Certainly I appreciate his setting the record straight.

Nevertheless, as summarized by Dr. Gladden in his article, the key point to emphasize in the context of this historical perspective is that in the intact organism the majority of lactic acid that is formed by muscle contraction is not converted to glycogen in the skeletal muscles, but oxidized by a variety of tissues including skeletal muscle, heart muscle, and possibly other vital organs, thereby serving as the primary substrate to pay off the oxygen debt rather than being the primary culprit of causing it (2).

REFERENCES


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