The following is the abstract of the article discussed in the subsequent letter:

Baldwin J, Snow RJ, Gibala MJ, Garnham A, Howarth K, and Febbraio MA. Glycogen availability does not affect the TCA cycle or TAN pools during prolonged, fatiguing exercise. J Appl Physiol 94: 2181–2187, 2003.—The hypothesis that fatigue during prolonged exercise arises from insufficient intramuscular glycogen, which limits tricarboxylic acid cycle (TCA) activity due to reduced TCA cycle intermediates (TCAI), was tested in this experiment. Seven endurance-trained men cycled at ~70% of peak O2 uptake (VO2peak) until exhaustion with low (LG) or high (HG) preexercise intramuscular glycogen content. Muscle glycogen content was lower (P < 0.05) at fatigue than at rest in both trials. However, the increase in the sum of was similar after 103 min of exercise was not different between trials, and TCAI content during prolonged exercise to fatigue. Therefore, our data do not support the concept that a decrease in muscle TCAI during prolonged exercise arises from insufficient intramuscular glycogen, which limits tricarboxylic acid cycle (TCA) activity due to reduced TCA cycle intermediates (TCAI), as shown by a number of other studies to which the authors refer. Left unanswered is the possibility that the rate of increase in RPE may reflect the rate at which crucial fuel reserves are being depleted and hence the duration of the exercise bout that can still be sustained at that particular exercise intensity without threatening homeostasis.

To evaluate this possibility, I plotted the data for RPE reported by Baldwin et al. (1) against 1) the duration of exercise in the two different conditions (Fig. 1A) and 2) the percentage of time that had been completed, again in both exercise conditions (Fig. 1B). The hypothesis is that, if the terminal RPE is the same, then perhaps the rate at which the RPE rises may provide information of how close to the end of exercise the athlete is at any time during the exercise bout. Because manipulation of the size of the starting body carbohydrate stores produced a 34% difference in exercise duration, it seemed probable that a sufficient range of data would be available to evaluate this hypothesis when all data were expressed relative to the percentage of the total exercise bout that had been completed (or remained).

Accordingly, Fig. 1A shows that there is a linear relationship between the RPE and the duration of exercise in carbohydrate-depleted and carbohydrate-replete conditions. Hence, the rate at which the RPE increases could indeed serve as a marker of the time left to exhaustion during exercise at a constant workload.

Figure 1B confirms this possibility by showing that the linear relationship between RPE and the duration of exercise overlaps for both conditions when the exercise duration is expressed as a percentage of the total exercise time.

To the Editor: Perhaps the study of Baldwin et al. (1) finally establishes that muscle glycogen depletion does not cause fatigue within the muscle by reducing the available energy below a critical amount. This study also proves the logical error in the statement of Conlee (2): “When glycogen runs out . . . the muscle fails from lack of aerobic adenosine triphosphate (ATP) production. However, plausible and attractive this theory is, it is unproven. . . . What is clear is that, in glycogen-depleted muscle, ATP is being used up faster than it can be manufactured, and so force output is diminished.” If this logic were correct, then muscle glycogen depletion would lead not to fatigue but to muscle rigor. That is, if the rate of ATP production falls below the rate of ATP use, then there must be a progressive reduction in muscle ATP concentrations leading to skeletal muscle rigor if no other safety mechanism exists.

This logical error, in what has been termed the “energy depletion model of exercise fatigue,” has been emphasized previously (5). The essential contribution of Baldwin et al. (1) is to show that some other control mechanism must be present to ensure ATP and total adenine nucleotide pool (TAN) homeostasis during prolonged exercise, as shown by a number of other studies to which the authors refer. Left unanswered is the nature of that control process. However, the authors’ data do provide an enticing, novel hint of what that control might be.

Baldwin et al. (1) included data for ratings of perceived exertion (RPE) reported by the subjects during two exercise bouts in which subjects began in either the carbohydrate-replete or carbohydrate-depleted state. The authors do not fully discuss why they chose either to measure or to report these data; they only note that the RPE values at fatigue were identical, despite the exercise lasting for 34% longer (52 min) in the carbohydrate-replete state. It should be noted that, if fatigue is regulated purely by a peripheral control mechanism in the exercising muscles, regardless of its chemical or other nature, it makes no sense for the brain to be informed and hence to perceive that the exercise is becoming progressively more difficult (8). The brain is singularly unable to influence the outcome because it cannot, according to the usual model, overcome the effects of these peripherally acting metabolic events (8).

In contrast, if performance during prolonged exercise is ultimately regulated centrally in the brain (3–9), specifically to ensure that muscle energy homeostasis is maintained and that a critical energy depletion does not occur (5), then the RPE may play some role in that homeostatic process. For example, the rate of increase in RPE may reflect the rate at which crucial fuel reserves are being depleted and hence the duration of the exercise bout that can still be sustained at that particular exercise intensity without threatening homeostasis.
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Baldwin et al. (1). [Data plotted from the relevant information in Table 1 of Baldwin et al. (1).]

without causing absolute whole body energy depletion. Anticipating the maximal RPE that it (or the individual) will tolerate, the brain center responsible for the generation of the RPE then increases that RPE as a function of the percentage of that total exercise time that has been completed (or the percentage of time that remains). Alternatively, some signaling energy substrate, increased by a high-carbohydrate diet, may decline as a linear function of exercise duration, resulting in a linear increase in RPE. The maximum RPE is then reached before complete depletion of that energy substrate.

Because similar RPE ratings at exhaustion occurred even though muscle glycogen contents were significantly different and were higher in the carbohydrate-replete trial, muscle glycogen content could not have been the exclusive determinant of the RPE in this study. Other sensory variables that also clearly did not contribute to this linear increase in RPE with increasing exercise duration were heart rate and oxygen consumption, which were little changed during exercise.

The pivotal importance of the study by Baldwin et al. (1) is that it allows us finally to close the chapter on the concept that a state of absolute energy depletion is ever reached during prolonged exercise, just as it also does not occur during any other form of voluntary exercise (5). The challenge now is to understand how the body anticipates the total duration of the exercise bout that is to be performed and how the increase in the perception of effort is regulated to ensure that skeletal muscle energy homeostasis is not sufficiently disturbed to produce local tissue damage, in particular, the development of skeletal muscle rigor.

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REFERENCES


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REPLY

To the Editor: Our paper (1) focused on the effect of muscle glycogen availability on skeletal muscle energy metabolism and fatigue. As Dr. Noakes indicated, our data do not support the theory that fatigue during prolonged cycling exercise at a constant work rate was caused by an energy crisis within the contracting muscle. However, it should be noted, which we also stated in the paper, that, “We were unable to determine the precise cause(s) of fatigue during prolonged exercise, but this
was not the aim of the study." In particular, our measurement of muscle ATP content only provides information on the average mixed-muscle ATP content but does not elucidate the ATP levels at critical cellular sites within the various fiber types that may be critical in the fatigue process (6). Indeed, in a previous study (4), our group also demonstrated no reduction in the total adenine nucleotide pool during prolonged fatiguing exercise but showed a strong correlation between exercise duration and glycogen use, albeit in a limited number of subjects. We argued, therefore, that the relationship between glycogen content and exercise duration suggested that the maintenance of contractile force is possibly dependent on glycogen availability. Studies in both animals (3, 7) and humans (2) have suggested a link between sarcoplasmic reticulum Ca\(^{2+}\) uptake and release and glycogen availability. In addition, topographical localization of glycogen within human skeletal muscle has been observed (5). Therefore, depletion of glycogen in the sarcoplasmic reticulum may possibly lead to a failure of contractile force, although further research in this area is warranted. Hence, based on our present knowledge and techniques, we cannot definitively eliminate the possibility that the fatigue during prolonged exercise is due to a muscle energy crisis, although we agree that this is unlikely. In support of Dr. Noakes’ theory on the cause of fatigue, we speculated that the fatigue may have a nervous system component, noting that fatigue was also associated with hypoglycemia. The theory that the onset of fatigue is associated with the perception of effort is extremely interesting and is entirely consistent with our experimental data, as reanalyzed by Dr. Noakes. We eagerly await further research designed to test this hypothesis.

REFERENCES


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