Commentaries on Viewpoint: Fatigue mechanisms determining exercise performance: Integrative physiology is systems physiology

TO THE EDITOR: The importance of considering the complex interaction of various biological responses to exercise in the process of explaining the limitation to human performance has previously been re-emphasized (5). In his timely Viewpoint, Hargreaves (4) now specifically highlights the possible link, or interaction, between feedback from fatiguing locomotor muscles, the “psyche,” and the degree of neuromuscular activation of the working limbs, i.e., central motor command (CMC), the ultimate determinant of exercise performance. Although inhibitory somatosensory feedback from the working/fatiguing limbs to the CNS is certainly only one of various factors influencing the ultimate determination of the magnitude of CMC during systemic endurance exercise, its negative impact on CMC—and consequently athletic performance—has been shown previously (1–3, 6). The authors of these papers have demonstrated the role of peripheral locomotor muscle fatigue as a significant determinant of exercise performance via its negative feedback effects on the CNS and consequently on the magnitude of CMC. In this context, it is very important to note that the inhibitory influence from the working/fatiguing limbs to the CNS is not the ultimate determinant of the magnitude of CMC and that it can voluntarily be “overridden,” although only for a very brief moment (1). However, research investigating the interaction between (fatiguing) locomotor muscles and CMC during whole body exercise is still in its infancy and has so far only scratched the surface. Therefore, additional experimental approaches, including the pharmacological modulation of the cortical projection of ascending sensory pathways originating in the locomotor muscles, are necessary to outline a more comprehensive model linking locomotor muscle fatigue and athletic performance.

REFERENCES

Markus Amann
University of Zürich, Institute of Physiology and ETH Zürich, Exercise Physiology, Switzerland

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Samuele M. Marcora
School of Sport, Health and Exercise Sciences, Bangor University, Wales, United Kingdom

TO THE EDITOR: When physiologists study fatigue they often search for the ultimate factor that results in exhaustion. But fatigue is complex and exercise performance will to my opinion always involve both peripheral and central aspects (2, 3, 5).
Letters To The Editor

1544

There may be conditions where central fatigue dominates and perturbations of the muscle function only play a minor role, e.g., exercise performed at a relatively low intensity, but with a very large environmental heat stress (4), while peripheral fatigue may be the main factor determining exercise performance during brief very intense exercise where disturbances of muscle homeostasis become prominent (3). In contrast to Hargreaves, I have spent my professional life trying to provide evidence for a significant role of central fatigue during prolonged exercise and prove that such fatigue involves physiological changes within the central nervous system (5). However, the importance of psychological factors, which eventually also involve neurobiological changes, and all the various aspects of skeletal muscle metabolism, must certainly not be neglected. I fully agree with Hargreaves (1) that advances in our understanding of fatigue and limitations to exercise will require experiments that investigate the interaction between skeletal muscle metabolism, alterations within the central nervous system, and motor activation. In this process, the “muscle metabolism physiologists” and researchers with a neurobiological background should cooperate to explore how factors interact rather than disputing whether it is central or peripheral factors that are of utmost importance to fatigue.

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Lars Nybo
Institute of Exercise and Sport Sciences, University of Copenhagen, Denmark

TO THE EDITOR: Physiologists are increasingly utilizing an integrative systems biology approach, rather than reductionism. This movement has gained momentum as large amounts of data have been accumulated describing the regulation of a variety of biological processes in specific tissues, without adequately explaining how these distinct processes interact to influence biological functions across multiple organ systems. The viewpoint presented by Hargreaves (5) recognizes this paradigm shift and identifies the value of applying an integrative biology approach to examine the causes of fatigue. Indeed, Hargreaves skillfully makes his case by focusing his discussion on the peripheral (i.e., muscle) and central (i.e., neurobiological) processes that impair exercise performance during states of reduced carbohydrate availability. Like Hargreaves, our research program seeks to characterize the peripheral causes of fatigue by determining if carbohydrate metabolism regulates excitation and contraction processes in human skeletal muscle (3, 4). Although these contributions have added to the body of evidence describing the peripheral causes of fatigue, they have not yet considered how these peripheral factors interact with central processes to influence the development of fatigue during states of altered carbohydrate availability (2) or reduced central motor command (1). Consequently, it is evident that our contributions, like many published studies in the literature, would have benefited from employing an integrative biology perspective. Therefore, it is imperative that exercise physiologists consider creating transdisciplinary research teams, which possess sufficient expertise to employ an integrative biology approach to characterize peripheral as well as central fatigue processes. Indeed, integrative and transdisciplinary research teams will be positioned at a point where they can significantly advance our knowledge of the limitations to human performance.

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Todd A. Duhamel
Institute of Cardiovascular Sciences, University of Manitoba, Winnipeg, Manitoba, Canada

TO THE EDITOR: Dr. Hargreaves’ masterly review (2) reminds us that exercise is a behavior. Behaviors are regulated by the brain to protect the “milieu interieur” (3). In actual competition, humans chose a pace they can sustain for the expected exercise duration while still allowing an “endspurt” (5). This “endspurt” indicates the absence of “fatigue” conventionally defined as the inability to sustain the required power output. This definition is derived, in part, from in vitro models such as the isolated skeletal muscle preparation (1) in which muscle stimulated to contract tetanically without neural control, develops progressive mechanical failure within minutes. But progressive mechanical failure does not appear to occur in the best athletes in real world, out-of-laboratory athletic competitions.

Cardiologists once believed that heart failure could be explained by the “descending limb” of the Frank-Starling curve studied in isolated perfused working hearts. But heart failure is a multi-organ disease, the complexity of which cannot be uncovered by studying a single organ. Exercise-related fatigue is no different.

Hargreaves (2) is correct to acknowledge his life-long bias that fatigue is due to the failure of a single organ. But the complex nature of “fatigue” will only be understood when the behavioral component of exercise is properly acknowledged; in particular the manner in which exercise is regulated “in anticipation” (4) specifically to ensure that the “milieu interieur” is
protected and “limiting” biological conditions, identified in isolated systems studied in the absence of neural control (1), are seldom if ever reached, at least in health (3).

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Timothy David Noakes
Discovery Health Chair of Exercise & Sport Science Director

TO THE EDITOR: In his excellent article, Dr. Hargreaves (4) described mechanisms of fatigue or performance limitation and finally suggested that the maintenance of oxygen and of overall glucose supply to the central nervous system might play one of the most important roles of fatigue in exercise physiology. As underlined, fatigue in vivo can either be central or peripheral, i.e., due to a decreased ability of nervous system to activate muscle cells, or due to impairment in the function of muscle cells themselves (2). Finally fatigue results from the inadequacy between demand and supply of either energetic substrate or of the oxygen required for substrate degradation. Amazingly, although the cardiovascular system (cardiac output) has largely been studied as a potential limiting factor of metabolic supply, the idea that peripheral vessel and peripheral vascular resistance might play a central role in exercise limitation has scarcely been discussed and studied. There might clearly be a limit to the ability of peripheral vasodilatation to decrease vascular resistance and facilitate flow to exercising muscles. Indeed, even mild to moderate vessel stenoses can impair exercise performance in male athletes (1). There is a complex interaction between exercise and vascular reactivity (3, 5). Unexplored domains of physiology can be part of the so-called “psyche.” Peripheral circulation is one of these domains. Current knowledge of vessel limitation during exercise in athletes is weak, not only in “the weaker vessel.” NB: “The weaker vessel”; female gender, p. 976 in Harrap’s shorter.

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Vincent Jaquinandi
Jean Louis Saumet
Pierre Abraham
University Hospital of Angers

TO THE EDITOR: In the context of the neuro-muscular system in vivo (hyphenated for emphasis), it is an oversimplification to consider the development of fatigue as an either/or situation, and for this reason, the Hargreaves Viewpoint of fatigue as a question of integrative physiology (1) is topical and timely. There is a reason beyond simple convenience that textbook physiology is typically taught with first emphasis on the nervous system, in the appreciation of excitable tissue function. In this instance, muscle follows, and is usually considered as a specialized part of the excitable tissue, having the special end-organ characteristic of movement, unlike nerves. Thus it makes sense that the outputs of the neuro-muscular system, i.e., neural activation and muscle movement, respectively, can be suppressed or fatigued, resultant of events occurring within either the neural or muscular component, because they are so intimately associated as excitable tissue. An example that bears consideration is gymnastic training to perfect movements on the long floor routine, a combination of strength, endurance, and skill of neuro-muscular performance. In essence, the whole neuro-muscular system is trained simultaneously, from the brain, to neural outflow, to muscular movement, to neuro-muscular proprioceptive and performance feedback. Within this integrative activation, movement, and feedback loop, it is clear that events occurring at many points in the loop can predispose or result in fatigue, observed ultimately as a decrement or failure in muscular performance. Years of training this system allow it to resist fatigue and to perform at the extreme levels of power and control observed at the level of master gymnasts. Thus, following on Hargreaves’ suggestion (1), the integrative assessment of fatigue should be driven by the neuro-muscular system’s associative infrastructure, allowing us to better understand its elegance and complexity within the body.

REFERENCE


Bill T. Ameredes
Internal Medicine-Pulmonary and Critical Care,
University of Texas Medical Branch

TO THE EDITOR: The mechanisms of fatigue are undoubtedly complex (3), but we echo Lars Nybo in expressing the view that this complexity can be reduced through appropriate definition of exercise intensity. This definition is all too often vague or, worse, based on the utterly flawed notion that assigning work rate as a fraction of maximal oxygen uptake normalizes the stress (and likely fatigue mechanisms) of exercise. All hope of understanding fatigue is lost when experimental subjects are experiencing different types
of stress (and thus fatigue) at ostensibly the same “relative” work rate, a point that has been made repeatedly by Whipp and colleagues (e.g., 5).

We suggest that fatigue-related research would benefit from the adoption of the concept of “exercise intensity domains,” wherein the lactate threshold (LT), critical power (CP), and maximal oxygen uptake provide physiological landmarks demarcating moderate (<LT), heavy (between LT and CP), and severe (or “very heavy,” >CP) intensity domains (1, 2, 5). Adopting such a strategy is known to “normalize” the dynamics of the blood acid-base and pulmonary gas exchange responses to exercise. Moreover, it has recently been demonstrated using 31P-magnetic resonance spectroscopy that the muscle metabolic responses to exercise (including the dynamic behavior of muscle phosphocreatine and inorganic phosphate concentrations and pH) differ profoundly when exercise is performed just above, compared to just below, the CP (4).

In summary, a physiologically justifiable categorization of exercise intensity needs to be agreed upon before the necessary integration between exercise metabolism and neurobiology can begin to shed light on the nature of muscular fatigue.

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Mark Burnley
Andrew M. Jones
Department of Sport and Exercise Science, Aberystwyth University, United Kingdom

TO THE EDITOR: The “elegant” figure of Bigland-Ritchie (1) from the 1980 Ciba Symposium meeting on fatigue is used by Mark Hargreaves (4) to emphasize the multifaceted nature of human muscle fatigue. His view is that “muscles are ‘central’ to fatigue” while acknowledging that afferent feedback and factors within the central nervous system contribute. Motoneurons provide the critical output that makes muscles contract. Here, some developments since the simplifying figure of Bigland-Ritchie deserve comment (see also Ref. 3). First, as long suspected from animal studies, the “gain” of motoneurons decreases with continuous activity. This means that stronger excitatory drives are needed to sustain output from active motoneurons, a change that would increase the subjective command or effort required for the task. Evidence comes from studies such as those in which a motoneuron is maintained firing voluntarily at a constant rate during which the overall EMG and even force can increase (5) or studies in which a constant descending input evoked by a stimulus to the corticospinal tract evokes a smaller output from the motoneuron pool during fatiguing maximal contractions (2). Second, corticospinal synapses on motoneurons alter their efficacy with activity. Following even brief maximal efforts, they show depression, which can be reversed by an additional strong contraction. As revealed in matching tasks, this synaptic depression reduces voluntary motoneuronal output (6). Hence, there is a dynamic nonlinear relation between corticospinal output and motoneuronal output. No longer can we regard the motoneuron as a simple waystation between a commanded action and the force generated.

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Simon C. Gandevia
Jane E. Butler
Janet L. Taylor
Prince of Wales Medical Research Institute and University of New South Wales