Fatigue mechanisms determining exercise performance: integrative physiology is systems biology

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For more than a century, applied physiologists have investigated the complex nature of fatigue and its implications for exercise performance. Long before the term “systems biology” entered the biomedical lexicon, physiologists appreciated the need to understand fatigue at various levels of integration and across multiple organ systems, a point eloquently highlighted in a recent editorial (13). In his early 20th century text Physiology of Muscular Exercise, Bainbridge (1a) noted the following:

It has long been recognized that the main seat of fatigue after muscular exercise is in the central nervous system. Mosso long ago stated that “nervous fatigue is the preponderating phenomenon and muscular fatigue is also at the bottom of the nervous system”. There appear, however, to be two types of fatigue, one arising entirely within the central nervous system, the other in which fatigue of the muscles themselves is superadded to that of the nervous system.

In the intervening years, physiologists have employed a vast array of experimental procedures and protocols to understand the fundamental mechanisms of fatigue and potential limitations to exercise performance. The key sites in neuromuscular activation that have been central to understanding fatigue mechanisms are summarized in the elegant figure from Brenda Bigland-Ritchie (2; Fig. 1). Of course, one cannot forget the crucial role of those systems responsible for oxygen delivery to vital organs and for fuel, metabolite, fluid, ionic, and temperature homeostasis. Indeed, the recent series of articles in the Highlighted Topic on fatigue mechanisms (15) provides an outstanding and timely review of the current state of knowledge across these multiple physiological systems.

It has been interesting to reflect on the integrative physiology of fatigue within my own area of research interest, namely carbohydrate metabolism. It is readily apparent from the early field studies on runners in the Boston marathon that reduced carbohydrate availability impaired whole body function and that carbohydrate supplementation improved performance (10). The application of the percutaneous needle biopsy to studies of muscle glycogen metabolism during exercise in the 1960s (12) focused attention on the link between muscle glycogen availability, muscle energy metabolism, and fatigue (18). The maintenance of skeletal muscle carbohydrate oxidation was proposed as a major mechanism by which carbohydrate supplementation improved endurance exercise performance (6, 7, 14, 19). However, equally important was the maintenance of glucose supply to the central nervous system (17) and the modification of cerebral energy metabolism and/or brain levels of key neurotransmitters (8), with concomitant effects on the fatigue (3) and central motor drive to muscle (16). Returning to the muscle, glycogen availability influences sarcoplasmic reticulum (SR) Ca²⁺ release and excitation-contraction coupling (5), an effect that may not be mediated entirely by ATP availability (21). Blood glucose availability appears to be less critical for SR function during prolonged, strenuous exercise (9). However, the activity of the Na⁺-K⁺ ATPase (11) is increased, and membrane excitability protected (22), by glucose supplementation during prolonged exercise. Finally, it has been suggested that the simple presence of carbohydrate in the oral cavity may interact with the central nervous system to enhance performance (4), echoing the observation of one of the 1925 Boston marathon runners who remarked “Every time I ate a piece of candy I felt fresh” (10). Clearly, carbohydrate availability can impact on multiple steps within the pathway of neuromuscular activation (Fig. 1), each providing viable mechanisms for the ergogenic effects of carbohydrate ingestion.

Fig. 1. Potential sites of fatigue: a, excitatory input to the motor cortex; b, excitatory drive to lower motoneuron; c, motoneuron excitability; d, neuromuscular transmission; e, sarcolemmal excitability; f, excitation-contraction coupling; g, contractile mechanism; h, metabolic energy supply. Reproduced from Ref. 2 with permission.

There can be little doubt that the regulation of central nervous output is crucial in determining exercise performance. The great Finnish runner Paavo Nurmi stated “Mind is everything, muscle pieces of rubber. All that I am, I am because of my mind.” The strong motivation for success, coupled with the fatigue resistance obtained through years of intense training, no doubt contributes to the outstanding athletic feats so often observed in the sporting arena. But there can be a fine line...
between glory and catastrophe, with this same motivation sometimes pushing athletes beyond the limits that fatigue might have ordinarily imposed. Understanding the complex links between the “psyche” and neuromuscular activation is a challenge for the future. It is teleologically appealing to have central motor output regulated to prevent excessive neuromuscular activation and there is empirical evidence that conditions such as hypoglycemia, hypoxia, and hyperthermia can modify central motor drive to skeletal muscle. Some have proposed complex “feedforward” regulation (20) that interacts with various feedback signals to regulate neuromuscular recruitment. The active skeletal muscles are not simply “pieces of rubber,” but provide crucial feedback to markedly affect central motor drive (1). Metabolic changes within active skeletal muscles appear to influence multiple supraspinal sites involved in motor control (24). Having spent my professional life studying various aspects of skeletal muscle metabolism, my bias remains with the skeletal muscles as being “central” to fatigue and exercise limitation. That said, impaired exercise performance under hot environmental conditions, in the absence of significant changes in peripheral biomarkers of fatigue (23), requires me to consider a more complex regulatory process. Thus advances in our understanding of fatigue and exercise limitation in humans require complex experiments that probe the fundamental neurobiology underlying the interactions between central motor drive and skeletal muscle. The simultaneous application of various investigative techniques such as functional magnetic resonance imaging, cortical spectroscopy, magnetic and electrical stimulation, and pharmacological blockade during varying exercise perturbations is needed. Systems biology perhaps, but integrative physiology at its finest! Given the complex redundancy in most biological systems, it is unlikely that a single locus or mechanism will explain fatigue and exercise limitation under all conditions. Later this year, we will no doubt enjoy the quadrennial Olympic festival of sports and marvel at the athletic achievements on display. They will provide great entertainment and enjoyment, but perhaps also stimulate our physiological curiosity in trying to understand just how they were achieved.

REFERENCES