ESSAYS ON APS CLASSIC PAPERS

The exercise dose response: key lessons from the past

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This essay looks at the historical significance of an APS classic paper that is freely available online:


Over the past few decades, investigations into the physiological responses to single bouts of exercise, and the consequent adaptations during extended periods of exercise training, have largely shifted from an integrated systems approach to understanding the underlying cellular and molecular biology. Today the most insightful exercise-based research projects translate cellular/molecular alterations to in vivo functional outcomes. This “systems-to-cells-to-systems” progression is improving our ability to conduct mechanistic dose-response studies with the overarching goal of designing efficacious exercise prescriptions targeted to achieve disease-specific or performance-specific benefits. However, prescription optimization research remains in a relatively early growth phase, which is why the dose-response study of Fitts et al. (1) over 30 years ago is a striking example of a pioneering, classic paper.

Impairments in skeletal muscle mitochondrial function and lipid oxidation are thought to play a role in metabolic derangements such as insulin resistance, obesity, and type 2 diabetes (6). It is now well-understood that endurance exercise training of sufficient intensity and duration robustly increases skeletal muscle mitochondrial oxidative capacity, which is an important means of enhancing lipid oxidation and insulin sensitivity. The powerful physiological effects of vigorous endurance exercise training on skeletal muscle mitochondrial function (5) as well as content and structure (2) were first realized in the classic original works by Holloszy (5) and Gollnick and King (2), respectively. In both studies, rats underwent endurance training (running) in a controlled manner, and gastrocnemius muscles were analyzed. These were indeed novel studies that demonstrated, for the first time, increases in mitochondrial respiratory function, oxidative enzyme activities, and mitochondrial protein content following 13–18 wk of vigorous treadmill running (up to 120 min at 31 m/min up an 8° incline, interspersed with 12 × 30-s sprints, 5 days/wk) (5), and an increased number and size of mitochondria following 10 wk of forced wheel running at 1.0–1.4 mph for up to 60 min every-day (2). Holloszy’s work published in 1967 (5) is arguably the first ever dose-response study of endurance training’s effects on skeletal muscle mitochondrial function, as he reported no improvements in a second group of animals exercise trained at a mild dose (10 min/day, up to 31 m/min, 5 days/wk). Based on the results of these studies and others implementing relatively mild swimming protocols (3, 4), Holloszy and Gollnick both concluded that the exercise stimulus must be of sufficient intensity and duration to modulate mitochondrial function and/or size and number; however, the minimum exercise stimulus needed (in the rat) remained elusive until the novel work of Fitts et al. in 1975 (1).

Fitts (Fig. 1) was the first to titrate multiple doses of exercise to fully characterize training-mediated changes in skeletal muscle mitochondrial function as well as physical performance capacity in a dose-dependent manner. In this project involving controlled treadmill running in rats for 13 wk, intensity (1.2 mph, 15% grade) and frequency (5 days/wk) were held constant while daily running duration varied across four groups of animals (10, 30, 60, or 120 min per session). Overall, the authors found that a minimum of 30 min/day was required to induce favorable changes in gastrocnemius muscle oxidative capacity. While no gains were noted in the 10 min/day training group, the authors found incremental improvements in several markers of muscle oxidative capacity across the 30, 60, and 120 min/day training protocols. Compared with sedentary control, muscle respiratory capacity (malate pyruvate oxidation) was elevated more than twofold in the 120 min/day training group, which was significantly higher than all other training groups. Additionally, the elevation after training 60 min/day was 28% higher than the gain found in the 30 min/day group. Increments in citrate synthase activity and cytochrome c oxidase concentration followed similar, dose-dependent trends. Run performance (time to exhaustion) followed suit as it was significantly lower in the 10 min/day group compared with all other training groups, and higher in the 120 min/day group than all others, with a fivefold difference between animals that trained 10 min/day vs. 120 min/day. The investigators also showed that muscle oxidative capacity correlated positively with run time to exhaustion.

An additional aim of this novel work was to determine the dose-response effects of the four exercise training prescriptions on muscle and liver glycogen depletion during a standardized 30 min bout of graded treadmill running conducted post train-
ing. Interestingly, all four training protocols led to enhanced muscle (but not liver) glycogen storage at rest with no differences among training groups. Exercise duration during training did, however, influence the magnitude of liver glycogen sparing during the standardized 30-min exercise test in a stepwise manner, whereby liver glycogen levels were unchanged following the 30-min run in the 120 min/day group but were 70% depleted in the 10 min/day group. Furthermore, glycogen levels remaining in the liver and muscle after 30 min of running were positively related to muscle respiratory capacity, indicating the dependence on carbohydrate utilization during exercise was inversely related to muscle mitochondrial content/function.

This seminal work of Fitts et al. was instrumental in shaping much of our current thinking regarding exercise training-mediated changes in muscle oxidative capacity and its relationship to fuel utilization. The paper also was among the first to demonstrate dose-response effects that have subsequently helped to define the minimum exercise dose required to achieve enhanced muscle oxidative function. As a testament to its significance, this work has been cited 162 times over the past 32 years.

In the time since the 1975 publication, each of the authors has continued to make important and lasting contributions to the study of muscle biology/metabolism and exercise adaptation. In fact, the three contributing authors who were trainees in Dr. John Holloszy’s laboratory at the time now read like a “who’s who” among current international leaders in muscle biology: Drs. Robert Fitts, Frank Booth, and William Winder. Fitts is a well-established expert in single myofiber physiology and the effects of unloading on both rodent and human skeletal muscle. According to the Web of Science database, Fitts has published 143 articles and numerous book chapters and reviews. Of note, 7 of Fitts’s original papers and reviews have been cited over 100 times. Booth’s work has laid the foundation for much of our understanding regarding molecular processes regulating muscle mass. He is a world-renowned leader in the field with 208 publications (including 6 cited over 100 times) and an impressive record of research training, having mentored numerous students and postdoctoral fellows who continue to make important scientific contributions as independent scientists in their individual niches in muscle/exercise physiology. Booth has also led the charge in recent years to increase awareness among politicians, funding agencies, and the general public alike regarding the impact of physical inactivity on myriad risks of disease and the powerful benefits of exercise training on the same. Winder, another prominent international figure, has remained true to his muscle metabolism roots, having conducted numerous elegant studies of muscle oxidative metabolism and glucose transport signaling with particularly notable contributions toward molecular approaches to type 2 diabetes prevention and treatment. He has published more than 125 papers, 11 of which have been cited 100+ times (and 5 papers cited over 200 times). Finally, their mentor, Dr. Holloszy, has a record of meaningful scientific productivity and research training that is simply unparalleled. Notably, Drs. Ronald Terjung and Ken Baldwin, two more celebrated pioneers in the field, were also active trainees in the Holloszy laboratory in the early 1970s. Together, these pioneers have published hundreds of papers in the APS family of journals. The classic 1975 paper by Fitts et al. is one of many classics generated by this team, and it is difficult to imagine a more important formative time in the advancement of muscle/exercise physiology. These are the scientists many of us emulate today, and I for one would have relished the opportunity to witness the exchange of ideas during a typical Holloszy lab meeting in 1973.

REFERENCES