It’s all in the genes, so pick your parents wisely

Aerobic exercise capacity is a complex phenotype influenced by a myriad of environmental and genetic factors. At one end of the continuum, elite endurance athletes represent a rare union of genetic potential that, given appropriate environmental stimulus (e.g., training, nutrition) can culminate in superior performance capabilities. At the other end of the spectrum, genetic predisposition and environmental factors (including, most notably, a lack of physical activity) conspire to ultimately determine one susceptibility to a number of chronic metabolic disease states such as coronary heart disease, insulin resistance, Type 2 diabetes, and obesity (see Ref. 1). While a high maximum oxygen uptake is a prerequisite for successful endurance performance (10), low aerobic power (4) and coordinated deficits in oxidative metabolism (7, 9) have been linked to the pathogenesis of several metabolic disorders. As such, it would appear that the ability of an organism to utilize oxygen during exercise represents a point of divergence for health-disease outcomes.

Over a decade ago, researchers Steven Britton and Lauren Koch recognized the importance of aerobic capacity for health and disease and began a breeding project to create rat genetic models of intrinsic aerobic endurance running capacity (see Ref. 2). In a feasibility study using outbred Sprague-Dawley rats, they found that three generations of two-way selective breeding produced lines that differed in endurance treadmill running capacity by 70% (6). This was followed by initiation of large-scale selective breeding to produce divergent strains of low-capacity runners (LCR) and high-capacity runners (HCR) using the genetically heterogeneous N:NIH rats as the founding population (5). After 11 generations of selective breeding, intrinsic endurance capacity had diverged by a massive 347% (12). Of note was that artificial selection for low or high aerobic exercise capacity simultaneously generated a differential load of metabolic and cardiovascular risk factors: LCR animals expressed low amounts of key proteins in skeletal muscle required for mitochondrial function and presented with cardiovascular risk factors that constitute the metabolic syndrome such as hypertension, hyperlipidemia, and insulin resistance (12).

The link between mitochondrial function and aerobic metabolism is explored further in the study of Walsh and colleagues (11) in this issue of the Journal of Applied Physiology. Using animals selected from generation 15 of the Koch and Britton colony (5), these researchers tested the hypothesis that some of the qualitative properties of skeletal muscle mitochondrial function (i.e., an enhanced sensitivity to metabolites of ATP breakdown) may be due to genetic (i.e., inherent) rather than environmental (i.e., training induced) factors and that these characteristics, in part, may explain the superior endurance capacity observed in the HCR animals. Accordingly, Walsh and coworkers measured mitochondrial respiratory rate (i.e., oxygen consumption) in oxidative skeletal muscle fibers in the absence of ADP; 2) in the presence of a submaximal concentration of ADP, with and without creatine; and 3) in the presence of a maximally stimulating concentration of ADP. During exercise, mitochondria become more sensitive to a given cytosolic ADP concentration by virtue of the decrease in the ratio of phosphocreatine to creatine. Indeed, an early adaptation to endurance training is increased respiratory sensitivity to creatine (8). Hence, a novel finding from Walsh et al. (11) was the 33% ($P < 0.05$) higher rate of respiration with submaximal concentrations of ADP in the presence of creatine in muscle from HCR vs. LCR animals. Although speculative, it might be predicted that mitochondria in muscle from HCR rats becomes progressively more sensitive to ADP with an increase in exercise intensity/duration, thus minimizing the normal increases in ADP and P_i concentrations. If this were the case, then increased mitochondrial sensitivity to creatine may be one mechanism to help explain the enhanced running capacity of the HCR animals, independent of any qualitative alterations in local muscle oxidative capacity (i.e., mitochondrial density).

Whether endurance training in LCR animals would compensate for the lower innate muscle respiratory sensitivity warrants further work. Regardless, a growing body of evidence suggests that, compared with HCR rats, animals from the LCR line have compromised mitochondrial function (3, 11, 12). In this regard, it is tempting to liken the “exercise-deficient” phenotype produced in these animals to the rising incidence of inactivity creeping (or should that be sprinting?) into modern Western societies. The case for a causal link between the rise in physical inactivity during the past century and the increase in a cluster of prevalent metabolic disease states is compelling (1). Because of the multifactorial nature of many diseases, animal models of complex phenotypes such as that developed by Koch and Britton (5), in which both genetic and environmental factors approach minimums, are of substantial value for determining the underlying mechanisms causative of variation in specific outcome variables (i.e., disease risk factors). Future investigations using this unique animal model should be aimed at increasing our understanding of the cellular, biochemical, and molecular basis of gene-exercise interactions. The results from such studies should provide both clinicians and sports physiologists with essential information in the quest to improve human health and athletic performance.

REFERENCES


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