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Mitochondrial function in metabolic health: A genetic and environmental tug of war☆

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ABSTRACT

Background: The increased prevalence of obesity and its co-morbidities and their strong association with inactivity have produced an 'exercise-deficient phenotype' in which individuals with a particular combination of disease-susceptible genes collide with environmental influences to cross a biological 'threshold' that ultimately manifests as overt clinical conditions (i.e., risk-factors for disease states). These risk-factors have been linked to impairments in skeletal muscle mitochondrial function.
Scope of review: The question of whether 'inborn' mitochondrial deficiencies and/or defective mitochondrial metabolism contribute to metabolic disease, or if environmental factors are the major determinant, will be examined.
Major conclusions: We contend that impaired whole-body insulin resistance along with impaired skeletal muscle handling of carbohydrate and lipid fuels (i.e., metabolic inflexibility) is associated with a reduced skeletal muscle mitochondrial content which, in large part, is a maladaptive response to an 'inactivity cycle' which predisposes to a reduced level of habitual physical activity. While genetic components play a role in the pathogenesis of metabolic disease, exercise is a powerful environmental stimulus capable of restoring the metabolic flexibility of fuel selection and reduces risk-factors for metabolic disease in genetically-susceptible individuals.
General significance: Given the apathy towards voluntary physical activity in most Western societies, it is clear that there is an urgent need for innovative, clinically-effective exercise strategies, coupled with changes in current attitudes and methods of delivering exercise prescription and dietary advice, in order to improve metabolic health and reduce metabolic disease risk at the population level. This article is part of a Special Issue entitled Frontiers of Mitochondrial Research.

1. Introduction and overview

Skeletal muscle comprises about 55% of individual body mass in sedentary humans and plays important roles in locomotion, heat production during periods of cold stress, and whole-body metabolism [1]. There is a remarkable capacity for skeletal muscle to adapt to a variety of external stimuli including habitual level of contractile activity, substrate availability, and the prevailing environmental conditions [2,3]. This phenomenon of plasticity, common to all vertebrates [4], explains, in part, the marked differences observed in physical performance (such as feats of endurance or strength) between individuals, and also underpins the vastly divergent health profiles observed within a population. In this regard, skeletal muscle plays a major role in determining whole-body energy homeostasis because in healthy individuals it is the predominant site for post-prandial glucose disposal [5–7]. However, in inactivity-related conditions such as obesity, insulin resistance and type 2 diabetes, a reduction in insulin-stimulated glucose uptake into muscle is often observed, and this reduction has been associated with impairments in skeletal muscle mitochondrial content and/or function [8,9]. The extent to which impaired skeletal muscle mitochondrial function play a causal or coincidental role in metabolic disease progression and whether these changes are secondary to lifestyle factors is a matter of current debate. Here we provide a synopsis of studies that have examined the relationship between skeletal muscle mitochondrial energy production, whole-body aerobic capacity (maximal aerobic capacity; VO_{2max}) and metabolic disease risk, with a focus on some of the intrinsic (genetic/epigenetic) and environmental factors that are strongly associated with metabolic health status.

Abbreviations: VO_{2max}, maximal aerobic capacity; TCA cycle, tricarboxylic acid cycle; NAD^+, nicotinamide adenine dinucleotide; FAD, flavin adenine dinucleotide; FFAs, free-fatty acids; ATP, adenosine triphosphate; ADP, adenosine diphosphate; PGC-1α, peroxisome proliferator activated receptor (PPAR)-γ co-activator-1α; LCR, low-capacity runner; HCR, high-capacity runner

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1.1. Physical inactivity and metabolic disease states: a metabolic cross-road

The recent proliferation in the rate of diagnosis of many lifestyle-related diseases stems from the readiness of industrialized nations to adopt a sedentary lifestyle in the face of excess energy intake [10]. Accordingly, during the past 50 years there has been an explosion in the prevalence of a number of chronic metabolic disorders including obesity, type 2 diabetes and cardiovascular disease. The etiological basis of these disorders is polygenic and highly dependent on the environment (i.e., existing genes interact with environmental factors to result in phenotypic expression (Fig. 1) [11,12]). Although complex interactions between intrinsic and environmental stimuli underpin an individual's ability to respond to transient perturbations in energy availability, very few new major human gene mutations have occurred in the latter half of the 20th century to cause the greater frequency of chronic metabolic disease; therefore, the increased incidence must principally be due to alterations in environmental conditions. Thus, modulation of factors linked to energy intake (i.e., the macronutrient composition of the diet) and/or energy expenditure (i.e., level of habitual physical activity), have the potential to enhance, or conversely, impair overall metabolic health [13,14].

One environmental factor to have changed dramatically in this time and strongly associated with a plethora of chronic metabolic disorders is a decline in physical activity [11]. A recent systematic review highlights that in healthy individuals, acute but persistent sedentary behavior (inactivity for 2–7 h/day) can impair whole-body insulin sensitivity and glucose tolerance [15]. Therefore, it is hardly surprising that an inactive lifestyle initiates a cascade of physiological events that are mechanistically linked to metabolic disease progression [16]. Indeed, the results of several cross-sectional and epidemiological studies provide direct evidence that a lack of physical activity is strongly associated with the prevalence of a number or risk-factors associated with chronic metabolic disease [17–22]. In line with this notion, the increased prevalence of obesity, insulin resistance and type 2 diabetes and their strong association with inactivity has produced an 'exercise-deficient phenotype' in which individuals with a particular combination of disease-susceptible genes (i.e., risk factors) interact with undefined environmental conditions (e.g., level of physical activity) and cross a threshold of biological significance that results in overt clinical conditions. Strong evidence in support of this premise comes from array studies which show multiple genes involved in oxidative phosphorylation (94 out of 106 genes [23]), the tricarboxylic acid (TCA) cycle and fatty acid oxidation [23], are coordinately down-regulated in skeletal muscle from individuals with impaired glucose tolerance and type 2 diabetes, a feature which has been linked to the pathogenesis of several metabolic disease states [23,24]. Thus, low cardio-metabolic fitness (i.e., VO_{2max}) is now recognized as a strong independent risk-factor for not only several cardiovascular conditions, but also all-cause mortality [25,26]. In line with this notion, it is now well accepted that regular physical exercise offers an effective therapeutic intervention to prevent, improve, or in some instances reverse, many of the hallmark features of metabolic disease [27,28]. Thus, an understanding of the mechanisms that control how different biochemical pathways respond to physical activity (or inactivity) is critical for establishing the biological basis of obesity and its interrelated co-morbidities.

2. Mitochondrial metabolism matters!

The relationship between VO_{2max} and metabolic health highlights the importance of the body's capacity to deliver and utilize O_2 in energy producing pathways [29–32]. VO_{2max} is primarily limited by O_2 delivery systems [33–35], although the capacity for mitochondrial energy

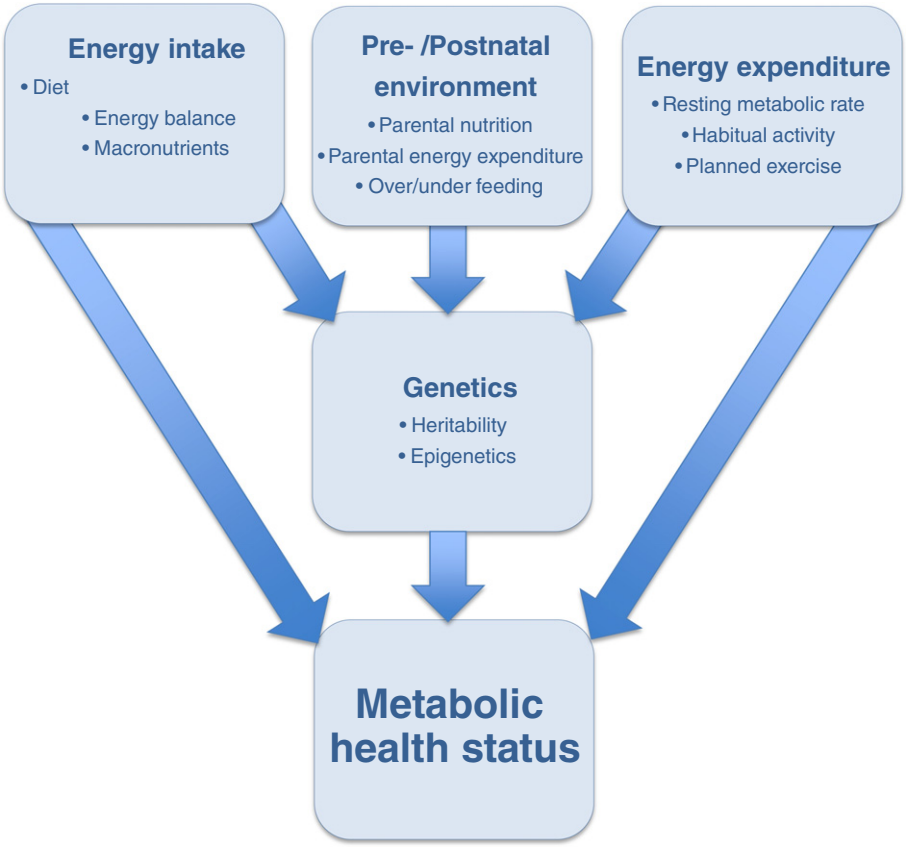

Fig. 1. Metabolic health status is determined through complex interactions between inherent factors (i.e., genes) and the environment. Modulation of factors linked to energy intake (i.e., the macronutrient composition of the diet) and/or energy expenditure (i.e., level of habitual physical activity), has the potential to enhance, or conversely, impair overall cardio-metabolic health.

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