

Acute and Chronic Regulation of Mitochondrial Function and Cardiometabolic Disease Risk

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Obesity and type 2 diabetes (T2D) comprise a growing global burden on healthcare and financial resources, particularly as a function of the Westernization of diets and reduced activity levels across the world. The mitochondria within our cells are the end users of products of the metabolism of nutrients that we consume in order to meet our energetic demands and thus may represent a viable target for the prevention and treatment of these and other cardiometabolic diseases. In addition to their role as energy producers, mitochondria are also a potent source of reactive oxygen species (ROS), an unavoidable byproduct of aerobic metabolism. Chronic exposure to excessive ROS in amounts that overwhelm the antioxidant capacity may result in the oxidation of nearby lipids, proteins, and nucleic acids, damaging these cellular components in the mitochondria and surrounding tissues [1]. Accumulation of this oxidative stress has been linked to obesity, insulin resistance (IR), and T2D [2]. In order to meet the demands of both chronic and acute metabolic challenges and to prevent excessive ROS production, a number of adaptations to mitochondrial physiology and morphology can occur [3].

Acute metabolic challenges such as elevated insulin and overnutrition create conditions that can promote the production of excessive ROS [4,5]. Hyperglycemia (due to IR/glucose intolerance) also promotes excessive ROS production [6]. ROS produced may play a critical signaling role in adaptations to mitochondrial structure and function to respond to metabolic stress [7,8] and limit excessive ROS production. The uncoupling of mitochondrial oxygen consumption from ATP production induced by ROS is thought to be one mechanism that can decrease ROS production in the presence of an elevated substrate load [9-12]. Studies in rodent models have indicated mitochondrial respiratory kinetics favor more uncoupled respiration in response to ROS produced following an acute high-dose iron exposure, likely in an effort to prevent or limit oxidative damage [13]. Additionally, we have recently shown that following a hyperinsulinemic-euglycemic clamp, ROS production is elevated and mitochondrial coupling is decreased in human skeletal muscle mitochondria measured in permeabilized myofibers from healthy premenopausal women [14]. While uncoupled respiration is thought to reduce ROS production, it should be noted that if mitochondrial respiration is chronically uncoupled, this will severely restrict ATP availability when inevitably presented with a new energetic demand. This appears to require that mitochondria exhibit some level of flexibility to shift between a coupled and uncoupled state in order to adapt to the present metabolic environment.

A number of mitochondrial adaptations are known to occur following more chronic metabolic stimuli. The “chronic” metabolic condition of obesity is often associated with mitochondrial dysfunction and oxidative stress [15], perhaps reflecting a detrimental adaptation or a loss of plasticity. Many studies in obese persons report a lower mitochondrial

oxidative capacity [16,17] and impairment in the flexibility to adapt to a given substrate [18]. In contrast, a number of *in vivo* methods for assessing mitochondrial function have indicated an enhanced capacity for fatty acid (FA) oxidation in obese persons [19-21]. In support of these findings, we have recently published work that describes a positive relationship between FA oxidative capacity at the level of the skeletal muscle mitochondria and body fat in a cohort of lean to obese women [22]. These data suggest that the increased FA oxidation observed in obese persons using *in vivo* methods reflects an adaptation at the mitochondrial level to utilize excess FA substrate, though this phenotype has been shown to become impaired once body mass index (BMI) surpasses 40 kg/m² [23]. Additionally, we found that mitochondrial coupling was positively associated with body fat, a phenotype that may promote continued fat accumulation in the context of chronically elevated FA substrate due to obesity. Numerous studies have also described the beneficial adaptations to an exercise program. Exercise promotes the expression of peroxisome proliferator-activated receptor- γ coactivator-1 α (PGC1 α) [24], a key protein involved in mitochondrial biogenesis [25], function [26], and dynamics [25,27], thus regulating mitochondrial quality. In an aging population, twelve weeks of moderate intensity aerobic training was sufficient to enhance electron transport and mitochondrial content [28]. Various chronic metabolic stressors can also have tissue-specific effects. Rodent models suggest liver mitochondria adapt to chronic alcohol consumption [29] and chronic hypoxia induced decreases in mitochondrial respiration in cardiac muscle [30].

Skeletal muscle mitochondrial dysfunction and ROS production are thought to be important mediators in the onset and exacerbation of IR and T2D and other chronic diseases. Others have previously hypothesized that sufficient mitochondrial plasticity to respond both rapidly and adequately to meet a metabolic demand may be a mechanism to regulate ROS production [31] and thus disease onset and progression. We speculate that if individuals with obesity and T2D do not display the necessary mitochondrial plasticity to prevent excessive ROS production promoted by a metabolic insult, it may lead to oxidative damage, disease progression, and further complications. Given the role of mitochondria in both the production of energy and ROS and the hypotheses linking ROS and oxidative damage to IR, we suspect that maintaining or restoring mitochondrial plasticity to meet acute and chronic metabolic demands warrant further investigation as a potential target for the treatment and prevention of obesity, T2D, and other chronic diseases linked to mitochondria dysfunction and oxidative stress.

Future studies should seek to evaluate acute mitochondrial plasticity in the context of various metabolic conditions in human, animal, and cellular models to determine if a loss of plasticity contributes to the onset of disease. For instance, characterizing acute changes in mitochondrial function in

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patients with T2D in response to a meal challenge or determining whether an exercise intervention can restore acute mitochondrial plasticity would provide insight into the acute responses of the mitochondria in the population but also determine whether these acute response can be altered by exercise training. These types of studies will move forward from simply looking at overall changes in mitochondrial oxidative capacity and lend insight into changes in efficiency, ROS emission, and mitophagy. Additionally, novel uncoupling agents are currently under investigation for use in the prevention and treatment of cardiometabolic diseases [32]. However, given that ROS production has been shown to be associated with insulin secretion and insulin signaling [33], it will be important to determine if these agents will present with deleterious side effects. We believe that future studies need to be conducted that characterize mitochondrial responses to metabolic stressors in order to better understand how mitochondria adapt under different situations. These endeavors will not be without challenges as both samples and direct methods for obtaining measures of oxidative phosphorylation capacity and efficiency require considerable resources and time.

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