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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

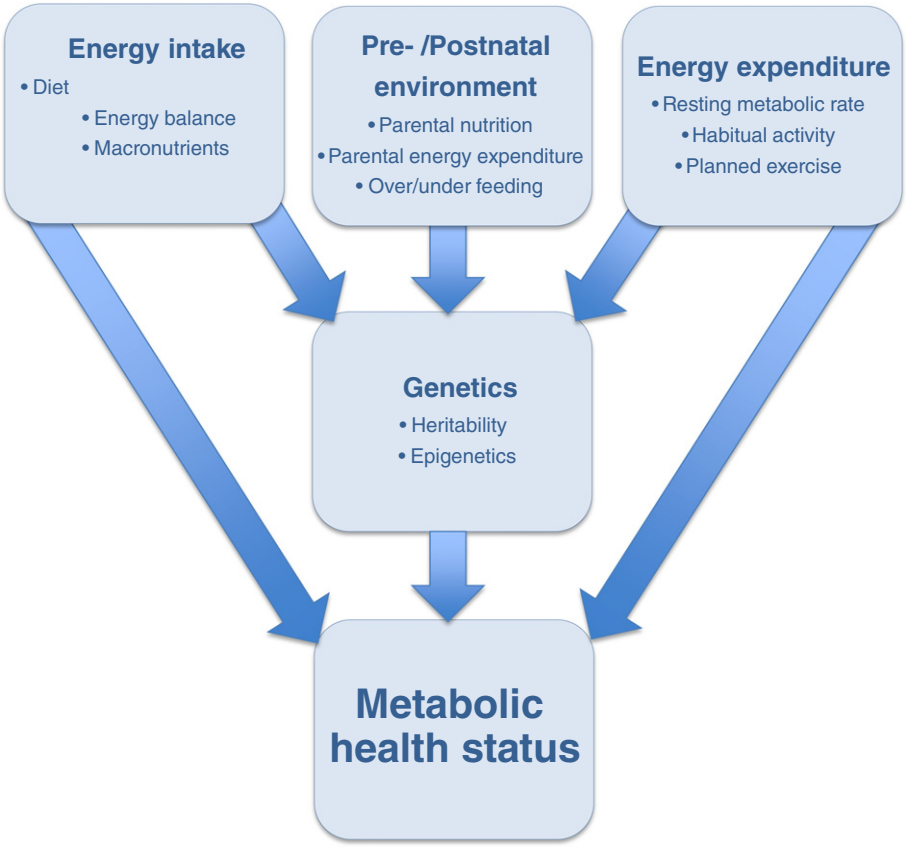

Fig. 1. Metabolic health status is determined through complex interactions between inherent factors (i.e., genes) and the environment. Modulation of factors linked to energy intake (i.e., the macronutrient composition of the diet) and/or energy expenditure (i.e., level of habitual physical activity),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

transformation in peripheral tissues, especially in skeletal muscle, is also of major importance [34]. Indeed, while the capacity for mitochondrial energy transformation is not likely to be rate-limiting for the attainment of VO_{2max} [33], it is a fundamental requirement for the tolerance of sustained submaximal physical activity typical of everyday tasks encountered in daily living [36–38]. Therefore, skeletal muscle mitochondrial function indirectly influences whole-body aerobic capacity by determining the economy of exercise at different workloads [39] and, subsequently, the extent to which the cardiovascular system is challenged and whether or not adaptations occur in the O_2 delivery systems [35,40,41]. Moreover, this positive correlation between VO_{2max} and the aerobic capacity of skeletal muscle [42] strongly suggests that any factor with the potential to enhance skeletal muscle mitochondrial content and/or function will positively affect VO_{2max} (and possibly its correlated traits). Thus, understanding how physical activity induces favorable adaptations to the skeletal muscle mitochondrial network is essential to our understanding of metabolic disease.

2.1. Mitochondrial function in health

To understand disease progression it is important to understand what constitutes a 'healthy muscle'. In individuals without metabolic disease, skeletal muscle has the capacity to oxidize both carbohydrate- and lipid-based fuels and to transition between these substrates in response to hormones (predominantly insulin), substrate signals (such as elevated fatty acid flux) and the contractile status of the muscle (rest versus contraction) [43]. This 'metabolic flexibility' underpins the major role that skeletal muscle has in whole-body energy homeostasis, and highlights the importance of well-coordinated mitochondrial function in maintaining metabolic control [44]. Thus, functional defects in the energy transforming systems of skeletal muscle mitochondria are likely to have profound systemic effects on overall metabolic health.

The main energy-transforming process in skeletal muscle (and most mammalian cells) is oxidative phosphorylation. Under fully aerobic conditions, pyruvate (the end product of glycolysis) is converted to acetyl coenzyme A (CoA) in the mitochondrial matrix, where it enters the TCA cycle and undergoes a series of reactions that reduce the coenzymes nicatinamide adenine dinucleotide (NAD^+) and flavin adenine dinucleotide (FAD; Fig. 2A) [45]. Similarly, the oxidation of free fatty acids (FFAs) occurs in the mitochondrial matrix and involves the reduction of NAD^+ and FAD with the end product also being acetyl CoA (Fig. 2A) [46]. These reduced coenzymes (from the TCA cycle and β-oxidation pathway) then pass electrons to the electron transfer system, a series of oxido-reductase enzymes located on the inner mitochondrial membrane where the transfer of electrons between enzyme complexes ultimately reduces oxygen to water in a process that is coupled to the production of adenosine triphosphate (ATP; Fig. 2B) [47]. Essentially, the skeletal muscle mitochondrial reticulum acts as a 'sink' for incoming energy substrates and uses them for the transformation of cellular energy, switching between the oxidation of lipid and carbohydrate substrates according to rates of supply and demand [48]. Therefore, rates of substrate uptake and the capacity for oxidation once inside the mitochondria are crucial points of metabolic regulation for not only skeletal muscle, but also whole-body metabolism.

2.1.1. Moving muscles make more mitochondria

The role and importance of mitochondrial function in endurance training adaptation have long been recognized [49–53]. Classic work undertaken by John Holloszy almost 50 years ago demonstrated the potent role that exercise training plays in the biosynthesis of mitochondrial proteins [49]. For example, the capacity of the mitochondrial fraction from trained muscle to oxidize pyruvate doubled in rats subjected to a strenuous program of treadmill running. Mitochondria from muscle of trained animals also exhibited a higher level of respiratory control and tightly coupled oxidative phosphorylation. Thus, the increase in electron transport capacity was associated with a concomitant rise in the capacity to produce ATP. This training-induced adaptation in mitochondrial function accounts for the increase in aerobic work capacity that occurs with regularly performed, prolonged exercise. Of importance when examining the role of exercise training in promoting mitochondrial biogenesis is that a single bout of endurance exercise triggers a cascade of molecular signaling events that ultimately lead to mitochondrial proliferation (Fig. 3A) [54–61] and other adaptations that favor the transport and oxidation of carbohydrate and lipid substrates [56,62,63]. Notably, a rapid but transient elevation in PGC-1α mRNA is observed following each acute bout of exercise [64], and this is accompanied by a steady increase in PGC-1α protein, as well as an increase in the activity of several oxidative enzymes (i.e., citrate synthase) over a period of training (Fig. 3B [64]). Thus, the cumulative benefits of each (acute) bout of exercise result in chronic adaptations in skeletal muscle (i.e., increased mitochondrial content) that favor improvements in fuel uptake and utilization, exercise economy and, ultimately, whole-body aerobic capacity.

2.2. Mitochondrial (dys)function in metabolic disease

Skeletal muscle energetics has long been implicated in the pathogenesis of obesity and other lifestyle-related metabolic disorders in both humans [8,65–67] and animals [68–72]. However, the extent of mitochondrial involvement in metabolic disease progression, and whether changes observed in mitochondria are secondary to lifestyle factors (such as inactivity and/or diet) is a matter of much debate [73–75]. One of the hallmark features of advancing metabolic disease is insulin resistance in peripheral tissues such as skeletal muscle [5]. Insulin-resistant muscle demonstrates an impaired ability to transition between carbohydrate and lipid fuels and, as such, is often described as having 'metabolic inflexibility' [76]. For example, in both obesity and type-two diabetes, the rate of skeletal muscle lipid oxidation does not suppress effectively in response to a meal (i.e., with insulin stimulation), whereas during the postprandial state, the rate of lipid oxidation is incapable of increasing sufficiently [77,78]. This leads to the accretion of triglyceride within both adipose and non-adipose tissues, the latter being a pathology strongly associated with both the insulin resistant state [79] and altered mitochondrial metabolism [80]. As such, patients with type 2 diabetes [77], direct relatives (i.e., parents, siblings or offspring) of patients with type 2 diabetes [81,82] and obese individuals [78,83,84] display an overt reduction in the capacity for lipid oxidation and an impaired ability to transition between fuel sources when subjected to changes in substrate availability [85,86].

Given that the mitochondria are almost entirely responsible for the β-oxidation of FFAs, it is perhaps not surprising that mitochondrial 'deficiencies' have been observed in the skeletal muscle of obese rodents [68,87,88] and humans [8,89,90]. These findings have led to the notion that abnormalities in skeletal muscle lipid metabolism may play a causative role in the pathogenesis of obesity and insulin resistance [8,9,68,69,91–93]. However, the issue of whether mitochondrial deficiency and/or defective mitochondrial metabolism contributes to insulin resistance has been questioned in light of two lines of evidence. First, Boushel et al. [94] reported that when O_2 flux (as measured using high-resolution respirometry) was normalized for markers of mitochondrial content (such as mitochondrial DNA content or citrate synthase activity), adenosine diphosphate (ADP)-stimulated electron flux through complex I of the respiratory chain, alone, and in parallel with complex II; as well as the maximal capacity of the electron transfer system, was not different in muscle extracts obtained from patients with type 2 diabetes when compared to muscle from age-matched, healthy control subjects. In other words, they found no evidence for a decrease in the quality of the mitochondria in skeletal muscle from type 2 diabetic patients. A key feature of the data presented by Boushel et al. [94] was that ADP-stimulated respiration was indeed lower in the muscle of patients with type 2 diabetes than in the healthy control group, but that this was due to a reduction in muscle oxidative capacity

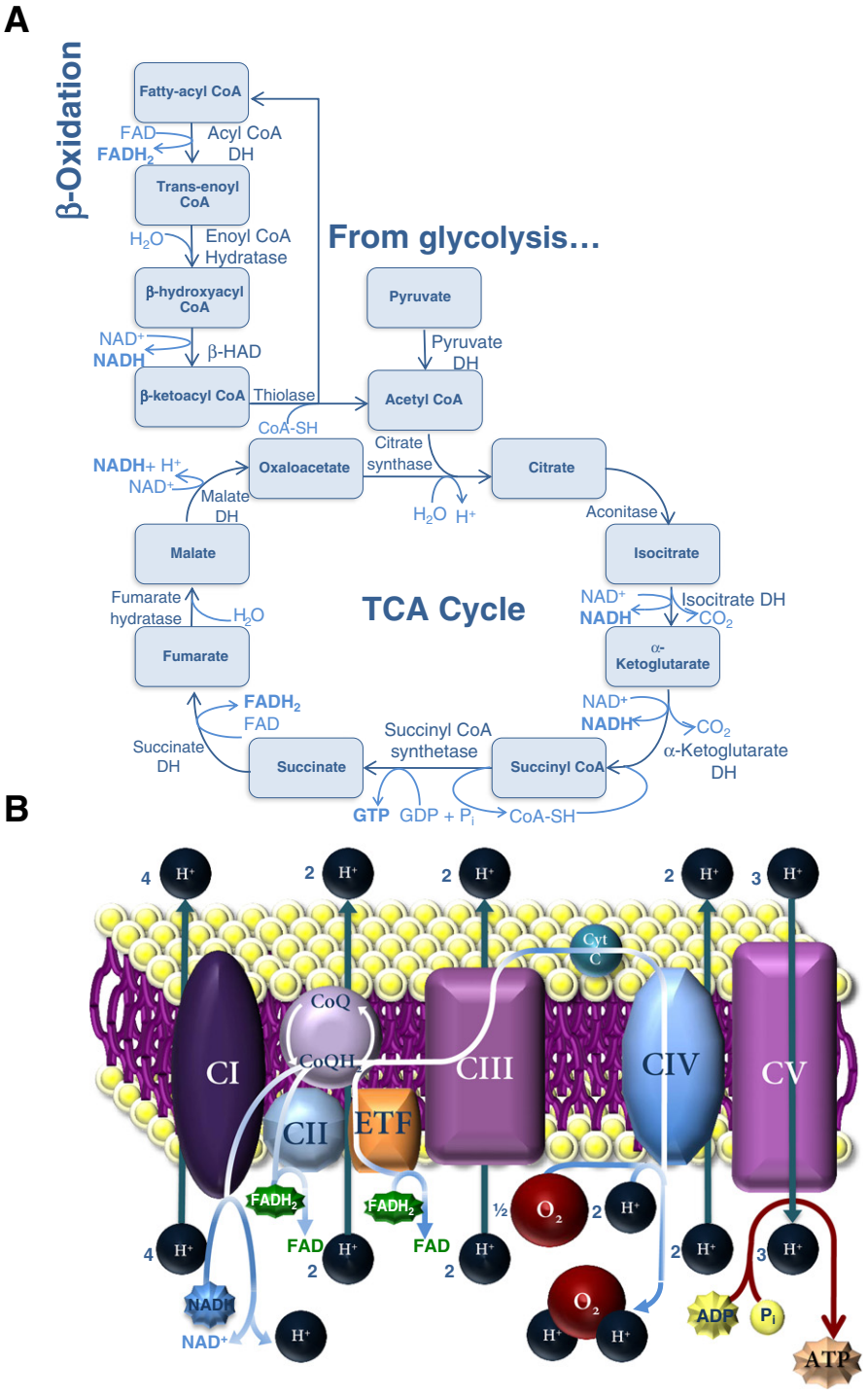

Fig. 2. Energy production pathways in the mitochondria. Reduced coenzymes from β-oxidation and the tricarboxylic acid cycle in the mitochondrial matrix (A) pass electrons to a series of oxido-reductase enzymes located on the inner mitochondrial membrane (B). The free energy released during the transfer of electrons between enzyme complexes generates an electrochemical proton gradient by pumping protons from the matrix into the intermembrane space. The flow of protons back into the matrix through CV drives the synthesis of ATP (oxidative phosphorylation) [45–47]. ADP, adenosine diphosphate; ATP, adenosine triphosphate; β-HAD, β-hydroxyacyl-CoA DH; CI, NADH DH; CII, succinate DH; CIII, cytochrome b–c_a complex; CIV, cytochrome C oxidase; CV, ATP synthase; CoA, coenzyme A; CoQ, coenzyme Q; Cyt C, cytochrome C; DH, dehydrogenase; ETF, electron transferring flavoprotein; FAD/$FADH_2$, falvin adenine dinucleotide (oxidized and reduced forms, respectively); GDP, guanosine diphosphate; GTP, guanosine triphosphate; NAD/NADH, nicotinamide adenine dinucleotide (oxidized and reduced forms, respectively); P_i, inorganic phosphate; SH, sulfhydryl.

(i.e., mitochondrial content) rather than mitochondrial function per se. As we have previously noted [95], this finding highlights the importance of nomenclature when discussing aspects related to muscle mitochondrial function: a true mitochondrial 'dysfunction' implies an inherent abnormality within the mitochondrial machinery rather than a decline in mitochondrial number of density (mass per unit volume).

A second line of evidence that brings into question the issue of whether or not there is a mitochondrial 'dysfunction' in muscle of individuals with a range of chronic metabolic disease states are the recent reports clearly demonstrating high-fat diet-(HFD) induced increases in mitochondrial protein abundance and enhanced oxidative enzyme activities [96–102]. Indeed, HFDs cause elevated concentrations of

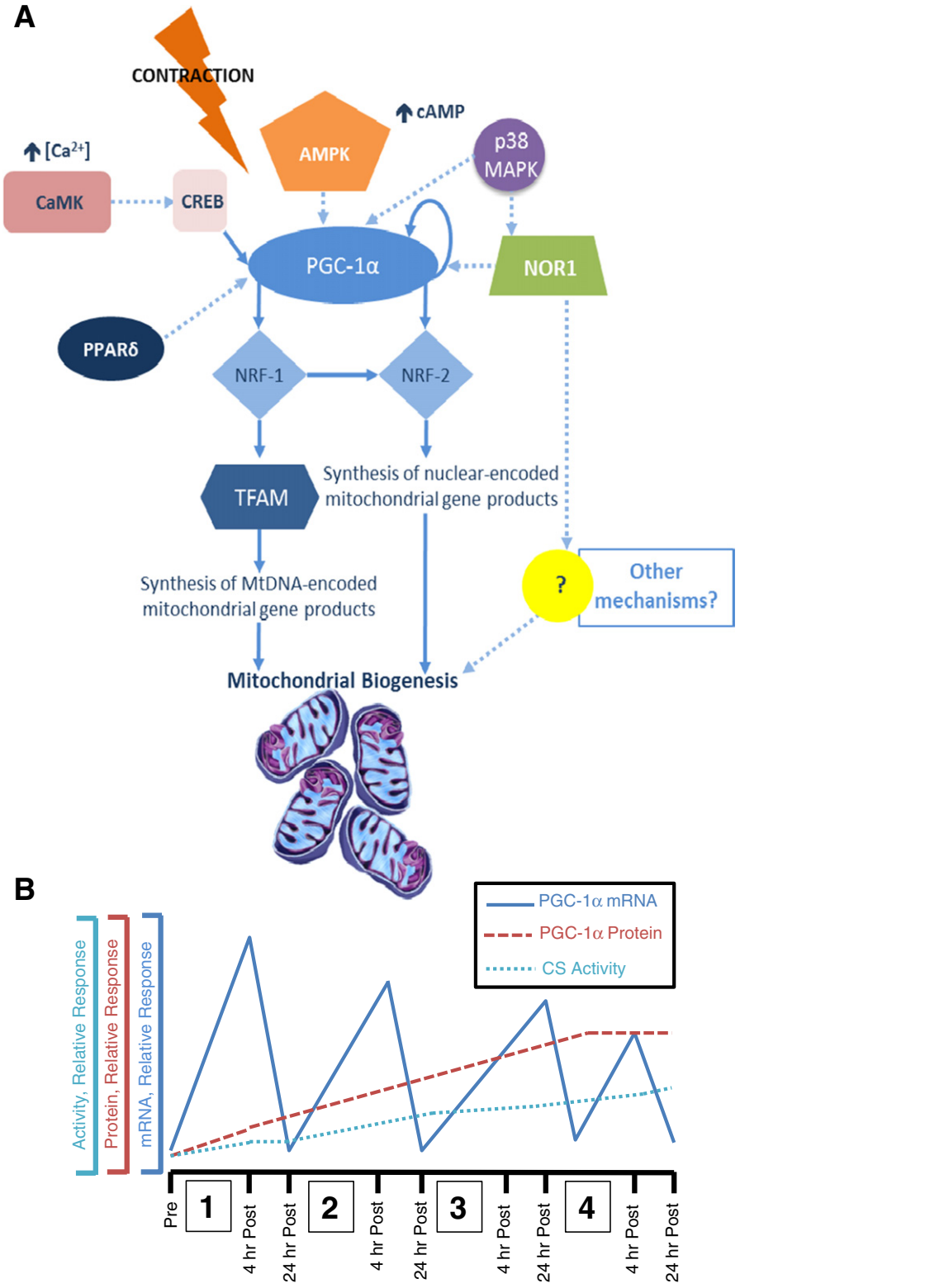

Fig. 3. Signaling to mitochondrial biogenesis. Contraction causes disturbances in the metabolic state of the muscle which leads to induction of PGC-1α (A). In response to successive exercise bouts, repeated, transient PGC-1α mRNA bursts precede increases in transcriptional- and mitochondrial-proteins (and their activities). Representative figure (B) adapted from Perry et al. [64]. AMPK, adenosine monophosphate (AMP)-activated protein kinase; CaMK, Ca^{2+}/calmodulin-dependent protein kinase; cAMP, cyclic AMP; CREB, cAMP response-element binding protein; NOR1, neuron-derived orphan receptor-1; NRF, nuclear respiratory factor; p38 MAPK, p38 mitogen-activated protein kinase; PGC-1α, PPARγ-coactivator-1α; PPARδ, peroxisome proliferator activated receptor-δ; TFAM, mitochondrial transcription factor A. CS, citrate synthase. PGC-1α, peroxisome proliferator activated receptor-γ coactivator-1α.

circulating FFAs which, acting as ligands to peroxisome proliferator activated receptors (PPARs), can induce mitochondrial biogenesis through PPARγ-coactivator-1α (PGC-1α) [99,103–105], while concomitantly causing rapid gains in whole-body adiposity, impaired glucose tolerance and peripheral insulin resistance [99,102,106]. Moreover, recent studies indicate that increases in mitochondrial content are

likely to *precede* insulin resistance in both rodents [107,108] and humans [109]. However, this increase is a transient phenomenon [107–109] that disappears as the insulin resistance becomes more severe [107,108]. This indicates that a reduction in the mitochondrial content of skeletal muscle is not likely to be a causative factor in the pathogenesis of insulin resistance and rather, that it is severely impaired insulin action which disrupts mitochondrial biogenesis. In line with this notion, the rate of insulin-stimulated mitochondrial protein synthesis is blunted in obese, insulin resistant individuals when compared to their lean counterparts [90]. Furthermore, in rodent models of diet-induced obesity, attenuation of mitochondrial lipid metabolism appears to *improve* insulin action and glucose tolerance [110–114]. Therefore, although diet undoubtedly plays a major role in the pathogenesis of obesity and insulin resistance, it is unlikely that 'dysfunctional' mitochondrial energy metabolism (and in particular, a reduced rate of lipid oxidation) is a direct cause [74].

Instead, it may well be that impaired lipid metabolism and reduced skeletal muscle mitochondrial function is, in part, an adaptive response to an 'inactivity cycle', driven by diet-induced gains in adiposity coupled with other environmental influences which predispose to a reduced level of habitual physical activity. In support of this hypothesis, the respiratory capacity of skeletal muscle from the lower limb (*m. vastus lateralis*) is reduced in obese individuals and patients with type 2 diabetes, whereas the muscle from the upper limb (*m. deltoideus*) shows 'normal' mitochondrial function [115,116]. Furthermore, despite differences in mitochondrial function in the leg musculature and a lower whole-body VO_{2max}, obese persons and patients with type 2 diabetes have a normal capacity for fat oxidation during exercise [86,115], suggesting that the reduced mitochondrial content observed in the leg musculature of these metabolically challenged individuals is likely a result of reduced habitual locomotor activity, rather than an intrinsic deficit per se. Indeed, exercise training increases the oxidative capacity of lower limb musculature in both otherwise healthy, lean individuals and obese, insulin resistant individuals [117–120]. Moreover, despite improving insulin action, non-exercise weight loss does not appear to improve mitochondrial content/function [118,119]. Thus, it seems entirely possible that the low skeletal muscle oxidative capacities observed muscle from obese or insulin resistant individuals reflect a lower level of habitual physical activity (and therefore a reduced rate of ATP turnover in the locomotor musculature) [121]. This line of reasoning is directly supported by findings from our laboratory in which we determined whole-body insulin sensitivity, long-chain fatty acyl CoA content, skeletal muscle triglyceride concentration, fatty acid transporter protein content, and oxidative enzyme activity in patients with type 2 diabetes and healthy control subjects matched for age, body mass index, percentage of body fat and VO_{2max} [122]. We found that despite markedly elevated skeletal muscle lipid content in type 2 diabetic patients and different levels of whole-body glucose disposal, the best predictor of insulin sensitivity was skeletal muscle oxidative capacity rather than more 'traditional' markers of insulin resistance, such as lipid status or body composition.

We, and others [74], contend that the missing link connecting muscle mitochondrial function with metabolic disease risk factors is the level of habitual contractile activity. Chronic inactivity (or disuse) results in a decrease in mitochondrial number [123], aberrant lipid handling [79] and an impaired metabolic health profile [14]. In contrast, chronic activity (exercise training) results in marked mitochondrial biogenesis [123], increased lipid oxidation and turnover [124] and an improved overall health status. It therefore follows that interventions that result in either a decrease or increase in mitochondrial content should cause reciprocal changes in health/disease outcomes [14].

3. Do the genes fit?

We have proposed that an 'inactivity cycle' leads to a reduction in mitochondrial content in skeletal muscle of individuals during the progression of several metabolic disease states. However, it must be acknowledged that a growing body of evidence is suggestive of a genetic component underlying the complexity of metabolic disease [23,24,125]. In the last decade a number of studies have demonstrated that cultured myotubes isolated from the skeletal muscle of obese individuals retain the metabolic program of the donor tissue [84,126–128], even though most of the adaptive factors have been removed (e.g., hormone and substrate fluctuations, neural input, contraction). Therefore, the remaining characteristics are primarily inherent, rather than due to environmental influences. This important finding suggests that several key features of metabolic inflexibility (such as impaired insulin action [126,129–131] and a reduced capacity for lipid oxidation [84,85,126,128]) may, in part, have a genetic or epigenetic origin [132]. In line with this notion, the heritability of endurance exercise capacity is estimated to be 40% or higher [133,134] and has been linked to skeletal muscle mitochondrial gene expression [133]. However, familial environmental influence may also be important [135], with the heritability of exercise participation estimated to be as high as 70% [136]. Thus, while it is clear that a genetic component may underlie many of the features of metabolic disease, it is difficult to identify and attribute specific features to disease progression in living humans because of the profound environmental influence.

Given the polygenic nature of complex disease, another approach to study this problem has been to control for genetics in the hope of teasing out which facets of metabolic disease are primarily environmental and which are inherent. Whereas studies in monozygotic twins that have been reared apart suggest a high degree of heritability for a number of cardio-metabolic risk-factors [137], studies in discordant monozygotic or same-sex dizygotic twins (where interpair differences are almost entirely environmental) have indicated that independent of genetic factors, acquired obesity and/or low aerobic capacity are associated with insulin resistance and a reduced expression of mitochondrial genes essential to lipid oxidation and oxidative phosphorylation in both muscle [138] and adipose tissue [138,139]. Additionally, these reports have highlighted physical activity as a potent environmental modulator of body mass and other heritable traits linked to metabolic health [138–140]. However, the information obtained through these investigations is hampered by the same limitations as other human studies in that individuals are studied in a free-living environment making factors such as diet and lifestyle difficult to control. While these studies attempt to control genetics in order to investigate environmental factors, they provide little insight into the underlying genetic underpinning of metabolic health/disease.

Due to the heterogeneous nature of human populations and the countless environmental variables, many factors confounds our ability to distinguish between inherent features and environmental adaptations. This makes it difficult to study specific gene/environmental interactions in relation to health outcomes in humans, an effort which is of utmost importance if we are to understand the mechanistic role played by physical activity in determining metabolic health [141]. Therefore, animal models that select for the phenotypic expression of polygenic traits provide valuable insight into the gene/environmental interactions that determine metabolic health. In 1996, Koch and Britton began a selective breeding program in a population of genetically heterogeneous rats, artificially selecting for high- and low-endurance running capacity in the absence of exercise training [142]. Selection of opposing phenotypic extremes has concentrated contrasting allelic variation for running capacity from one generation to the next, leading to two extreme divergent phenotypes. Remarkably, co-selecting for high- and low-running capacity also yielded divergent models of metabolic disease risk, with low capacity runners (LCR) displaying many characteristics common to metabolic disease phenotypes (such as increased body mass and adiposity, hyperinsulinemia, impaired glucose tolerance and cardiovascular abnormalities) whereas high capacity runners (HCR) present with superior metabolic health, characterized by resistance to weight gain in the face of a HFD and an increased capacity for the uptake and utilization of both glucose and fatty acids [143–148]. Importantly, many of these opposing features appear to be linked to the metabolic

characteristics of the skeletal muscle and, in particular, the mitochondrial content and capacity for substrate uptake and oxidation [144,146,149]. Moreover, this feature is, in part, explained by differing levels of habitual activity between LCR and HCR phenotypes [102,145,150], a notion which is supported by the finding that many of the metabolic impairments specific to LCR animals can be reversed with exercise training [147,151]. Taken collectively, these findings suggest that there may be a genetic predisposition towards participation in physical activity and that the degree of habitual activity is linked to the capacity of the skeletal muscle to take up and oxidize carbohydrate and lipid fuels. However, whether differences in habitual activity are a cause or a consequence of differing skeletal muscle oxidative capacities is a question that remains unanswered.

4. Concluding remarks

There has been a recent explosion in the diagnosis of a host of chronic metabolic diseases whose origins can be traced to the adoption of a sedentary lifestyle in the face of excess food availability and energy intake. Indeed, the increased prevalence of conditions such as 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 collide with environmental influences to cross a biological 'threshold' that ultimately manifests in overt clinical conditions (i.e., risk factors for disease states). Evidence to support this premise comes from studies that reveal that subsets of genes with roles in oxidative phosphorylation are coordinately down-regulated in individuals with obesity and associated conditions, and are linked to the pathogenesis of these disorders. While a genetic predisposition undoubtedly plays a role in the pathology of chronic metabolic disease, the issue of whether 'inborn' mitochondrial deficiencies and/or defective mitochondrial metabolism contributes to obesity and/or insulin resistance is, in our opinion, questionable. Rather, we contend that impaired whole-body insulin resistance along with impaired skeletal muscle handling of carbohydrate and lipid fuels (i.e., metabolic inflexibility) is largely a result of reduced skeletal muscle mitochondrial function which, in large part, is a maladaptive response to an 'inactivity cycle', driven by diet-induced gains in adiposity and other environmental influences which predispose to a reduced level of habitual physical activity. The missing link connecting muscle mitochondrial function with metabolic disease risk factors is merely the level of habitual contractile activity! Given the apathy towards voluntary physical activity in the majority of 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 the risk of type 2 diabetes at the population level.

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