e-SPEN, the European e-Journal of Clinical Nutrition and Metabolism 6 (2011) e158–e164

Contents lists available at ScienceDirect

e-SPEN, the European e-Journal of Clinical Nutrition and Metabolism

journal homepage: http://www.elsevier.com/locate/clnu

Educational Paper

Clinical Nutrition University: Muscle physiology and bioenergetics

Rocco Barazzoni*

Dept. of Medical, Technological and Translational Sciences, University of Trieste, Ospedale di Cattinara, Strada di Fiume 447, 34100 Trieste, Italy

ARTICLE INFO

Article history:
Received 4 October 2010
Accepted 7 February 2011

Keywords:
Skeletal muscle
Mitochondria
ATP

SUMMARY

Skeletal muscle relies on a constant, adequate ATP supply to sustain contractile activity and preserve tissue mass and protein content. Skeletal muscle mitochondrial oxidative phosphorylation provides adequate amounts of ATP under physiological conditions, contributing to preserve muscle protein mass and playing a major role in glucose and lipid substrate utilization. Inflammation, oxidative stress and insulin resistance are emerging contributors to skeletal muscle mitochondrial dysfunction occurring under several disease conditions including insulin resistant states and obesity. Skeletal muscle mitochondrial dysfunction may lead to loss of muscle mass and strength as well as to altered glucose and fatty acid utilization, and these effects are associated with poor clinical outcome. Exercise training enhances skeletal muscle mitochondrial biogenesis and whole-body oxygen consumption (aerobic capacity), and these effects are likely to represent relevant mediators of the positive clinical impact of controlled exercise programs.

1. Muscle substrate metabolism and mitochondria

Skeletal muscle is an obvious, essential component of the locomotive apparatus, and its locomotive function requires maintenance and renewal of tissue contractile proteins as well as an adequate energy supply in the form of adenosine tri-phosphate (ATP). ATP cannot be stored in tissues, implying the need for continuous ATP production in the contracting muscle. ATP is provided by anaerobic glycolysis in relatively small amounts under resting conditions, and by oxidative phosphorylation in tissue mitochondria (as described below).

The concept that mitochondrial function and ability to produce ATP is crucial for muscle contraction is supported by the observation that physiological differences in mitochondrial density in different muscle groups are closely related to their ability to sustain contractile work and are inversely related to muscle fatigability. High mitochondrial density characterizes type I or "slow" fibers and is associated with prolonged aerobic contractile activity and resistance to fatigue[1] Skeletal muscles with low mitochondrial density and a majority of type II fibers in turn rely strongly on anaerobic glycolysis for energy supply and are adapted to short sets of contraction due to early fatigue. Most human muscle groups are considered to have a mixed fiber content, but prevalence of either type may have an important impact on muscle characteristics in terms of function and substrate utilization, with potential clinical implications.

From a metabolic standpoint, skeletal muscle represents a major protein reservoir. Muscle protein balance is regulated by nutritional, endocrine and cytokine-mediated signalling pathways to maintain body protein homeostasis and inter-organ amino acid exchange, in turn regulating protein metabolism in different organs and tissues.[2–5] Under fasting conditions, net amino acid release from skeletal muscle due to net excess of protein breakdown over synthesis represents a major source of precursors for hepatic gluconeogenesis. On the other hand, dietary protein and energy intake reverse net muscle protein catabolism through anabolic signalling involving insulin and amino acid elevation, leading to net muscle amino acid uptake and protein deposition.[2–5] Adequate ATP availability is necessary for muscle contraction during exercise. ATP is however also required to sustain muscle protein turnover (i.e. the continuing processes of protein renewal through breakdown and synthesis) which also represents a relevant component of tissue energy requirements. Glucose and lipid substrates are the major sources utilized for by skeletal muscle for ATP production both at rest and during exercise. Utilization at the skeletal muscle level is conversely an important component of both glucose and lipid whole-body metabolism and disposal.

1.1. Mitochondrial glucose and fatty acid oxidation and oxidative phosphorylation

Mitochondria are the key site of tissue oxygen consumption for energy production[6] A detailed description and review of glucose

* Tel.: +39 040 399 4416; fax: +39 0 40 399 4593.
E-mail address: barazzon@units.it.

1751-4991/$36.00
doi:10.1016/j.eclnm.2011.02.002

and fatty acid metabolism and of mitochondrial biochemical reactions is beyond the scope of this work. Catabolism of exogenous substrates, mostly fatty acids and glucose, leads to the formation of acetyl-coenzyme A (CoA) which enters the mitochondrial tricarboxylic acid cycle. Glucose is initially catabolised through the major metabolic pathway of glycolysis, that converts glucose into pyruvate under anaerobic conditions with concomitant production of relatively limited amounts of ATP. Glucose-derived pyruvate can be then converted to acetylCoA before transport into the mitochondria, through decarboxylation and combination with coenzyme A by pyruvate dehydrogenase (PDH) that links anaerobic and aerobic glucose metabolism (Fig. 1). Long-chain free fatty acids are entirely catabolised in the mitochondria, where they are transported through the rate-limiting enzyme carnitine palmitoyl transferase – I (CPT-I) 7. Acetyl-CoA also represents the product of mitochondrial fatty acid beta-oxidation, and therefore a major common step of substrate oxidative utilization.

Regulation of glucose and fatty acid utilization for skeletal muscle energy production is a key metabolic process involving both substrate availability (through exogenous dietary intake or endogenous supply) and hormonal regulation. In particular, it has been reported that enhanced glucose availability and PDH activation result in higher glucose utilization with relative suppression of fat oxidation[8] Insulin is a major regulator of this process by stimulating PDH via activation of PDK[8] resulting in net stimulation of muscle oxidative glucose disposal under hyperinsulinemic conditions as observed in the post-prandial state. Lower glucose availability or excess fatty acid supply (such as observed following a fatty meal) may in turn result in PDH suppression[7] Fatty acid elevation has been in turn reported to induce resistance to insulin's effect on PDK activation[8] with potential net shift towards fat oxidation.

Acetyl-CoA is combined with oxaloacetate to produce citrate, the first substrate of the tricarboxylic acid (TCA) cycle in the mitochondrial matrix. TCA cycle reactions provide reduced FAD (flavin adenine dinucleotide) and NAD (nicotinamide adenine dinucleotide) in the form of $FADH_2$ and $NADH_2$, which support electron flux through the respiratory chain. Respiratory chain enzymes (from NADH reductase to cytochrome c oxidase: complexes I to IV) are located in the inner mitochondrial membrane where they transport electrons to oxygen as final acceptor, while creating an electrochemical transmembrane proton gradient. The gradient is utilized by ATP synthase (complex V of the respiratory chain) to synthesize ATP from ADP and phosphate, thereby providing chemical energy in the from of high-energy bonds. Modulation of mitochondrial biogenesis and mitochondrial gene expression and oxidative capacity are key processes for maintenance of skeletal muscle homeostasis. It is important to point out that mitochondria contain DNA molecules encoding for a small but essential fraction of mitochondrial proteins. The above characteristic implies that mitochondrial biogenesis and modulation of mitochondrial gene expression requires the coordinated expression of both nuclear and mitochondrial genomes.

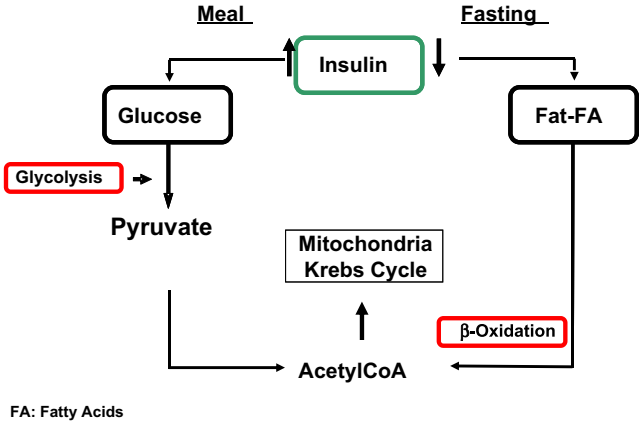

Fig. 1. Scheme of substrate interaction for utilization for mitochondrial-energy production; insulin may favor glucose utilization under post-prandial conditions by enhancing pyruvate conversion to acetylCoA.

2. Altered muscle mitochondrial function in disease states

Mitochondrial respiration is regulated by tissue and cell energy needs (Fig. 2). Cell energy status is typically sensed as the absolute and relative abundance of adenosine phosphates (ATP, ADP, AMP with AMP excess as a major signal of low energy availability and need for ATP production: this aspect will be described in detail as a mediator of exercise-stimulated mitochondrial changes). Changes in muscle mitochondrial biogenesis (i.e. the process by which mitochondria are formed in the cell) and oxidative capacity are further modulated by complex nutritional and endocrine factors as well as cytokine networks. Several important and common disease-associated alterations have been described to negatively affect both muscle protein balance and mass and muscle energy metabolism, with particular regard to impaired mitochondrial gene expression, mitochondrial protein synthesis, enzyme activities and ATP production. The following section will focus on inflammation, oxidative stress and insulin resistance (Fig. 3), although it should be kept in mind that additional factors may also contribute to muscle mitochondrial changes, including changes in muscle blood supply and neuromuscular signalling alterations.

2.1. Inflammation

Both local and systemic inflammation result from imbalanced production of proinflammatory and anti-inflammatory cytokines. While acute inflammation at both local and systemic levels may represent an adaptive mechanism contributing to limit and reverse a specific infectious or traumatic insult, a sustained activation of systemic inflammatory responses is associated with a major negative metabolic and nutritional impact.[9–12] Several chronic disease conditions lead to sustained low-grade activation of chronic systemic inflammation,[9–12] and regardless of the underlying mechanism, the onset and maintenance of a chronic elevation of the pro- to anti-inflammatory cytokine balance represents a common pathogenetic mechanism underlying wasting and cachexia.[9–12] Skeletal muscle protein catabolism by stimulation of protein degradation and inhibition of synthesis is specifically enhanced by proinflammatory TNF-alpha whose effect involves nuclear translocation of transcriptional factor NF-kB,[13–15] in turn

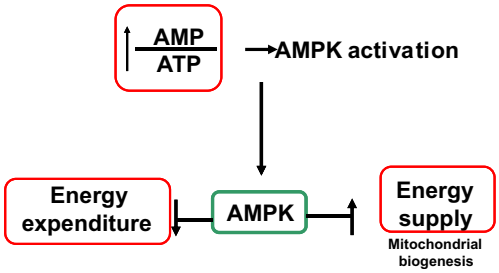

Fig. 2. AMP-activated protein kinase is a key sensor of cellular energy status favoring mitochondrial biogenesis after activation in the presence of lower energy availability.

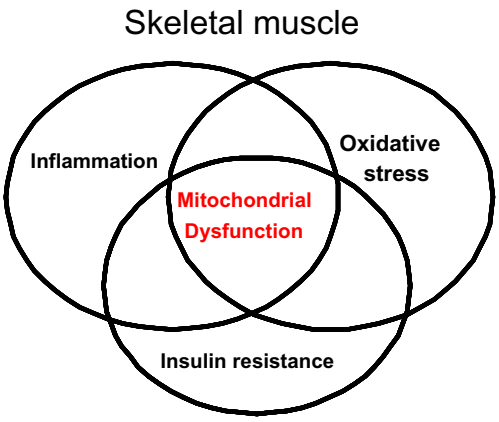

Fig. 3. Inflammation, oxidative stress and insulin resistance are common and interrelated potential emerging mechanisms contributing to skeletal muscle mitochondrial dysfunction and its negative clinical consequences in several chronic diseases including obesity, type 2 diabetes and chronic wasting diseases.

activating tissue cytokine expression to further enhance inflammation. Interestingly, recent studies in experimental models have indicated that muscle proinflammatory cytokines may inhibit tissue mitochondrial enzyme activities such as the key tricarboxylic acid cycle regulator citrate synthase,[16] thereby providing an additional, potentially synergistic mechanism for inflammation-associated muscle catabolism through reduced tissue energy production.[16]

2.2. Oxidative stress

Production of reactive oxygen species (ROS) from incompletely reduced oxygen molecules is inevitably associated with oxidative substrate metabolism.[17] Antioxidant defence systems eliminate ROS and maintain their tissue concentrations within physiological levels. Excess production of ROS may however overcome antioxidant capacity, thereby leading to oxidative damage to cell and tissue molecules and potential disease. Similar to inflammation, several factors may lead to oxidative stress in chronic disease and aging.[17–20] Importantly, oxidative stress may amplify inflammatory alterations[20] by enhancing proinflammatory cytokine production in polymorphonucleates[21] and by activating NF-kB nuclear translocation in peripheral tissues including skeletal muscle.[20]

As noted above, NF-kB activation leads to muscle protein catabolism with muscle protein degradation exceeding synthesis, thereby directly implicating oxidative stress in loss of muscle protein and mass associated with wasting diseases. Mitochondria are the site of ROS generation and are therefore exposed to high risk of oxidative stress. Sustained oxidative stress has been indeed postulated to lead to mitochondrial damage through cumulative alterations including DNA mutations, that have been proposed as a key mechanism underlying the aging process also in skeletal muscle.[19,22] Importantly, oxidative stress has also been recently recognized as a negative modulator of mitochondrial function in skeletal muscle in non-chronic disease models.[23]

2.3. Insulin resistance

Since both inflammation and oxidative stress are causes of skeletal muscle insulin resistance, it is not surprising that insulin resistance is a common feature of several chronic disease conditions. Insulin is an anabolic hormone also with regard to skeletal muscle mass maintenance due to its ability to inhibit protein breakdown and favor net amino acid deposition.[2–5] In addition and importantly, acute insulin elevation to peak post-prandial levels was shown to stimulate skeletal muscle mitochondrial gene expression, oxidative capacity and ATP production in healthy humans.[24] In addition to its previously-described effects to stimulate glucose oxidation through PDH activation[8] insulin-induced enhancement of mitochondrial oxidative capacity could therefore be involved in insulin effects to stimulate muscle glucose utilization, both in the post-prandial state and under different conditions involving a stimulation of skeletal muscle insulin action (Fig. 4). Insulin effects on muscle mitochondria did however not occur in insulin-resistant type 2 diabetic human skeletal muscle.[10]

The onset of insulin resistance has therefore the potential to activate a vicious cycle of muscle catabolism and mitochondrial dysfunction, leading to impaired muscle function and worsening morbidity and mortality.

3. Nutrients and nutritional status

Regulation of mitochondrial function by macronutrients and nutritional state has been studied most extensively for fat (which is oxidized only in the mitochondria).

3.1. High-fat diet and free fatty acids

High-fat feeding with saturated fat has been a well-established model for studies of nutritional regulation of mitochondrial function, since a fat-calorie rich diet is common in western societies and is associated with high risk of metabolic and cardiovascular disease. The effects of chronic high-fat feeding per se on skeletal muscle mitochondrial function remain at least in part controversial in experimental models, and it should be kept in mind that changes in duration of dietary treatment, percent of dietary fat and animal strain could all affect its metabolic impact. Some studies have reported a negative mitochondrial impact of excess dietary fat, with lower mitochondrial enzyme activities and oxygen consumption.[25,26] Other studies have reported a stimulatory effect,[27,28] with enhanced muscle mitochondrial protein levels and oxidative capacity following sustained consumption of a high-fat diet.

Elevation of circulating free fatty acids and higher tissue free fatty acid availability is a relevant consequence of fat ingestion, and the direct impact of free fatty acids on muscle mitochondria can be studied in vitro in myocytes. In muscle cell preparations incubated with saturated fatty acids (commonly palmitate) reduced mitochondrial parameters such as DNA copy number and fat oxidation were reported,[29,30] which was associated in one study with a paradoxical increase of AMPK activation.[30] A potential palmitate-induced AMPK activation may in turn provide a possible

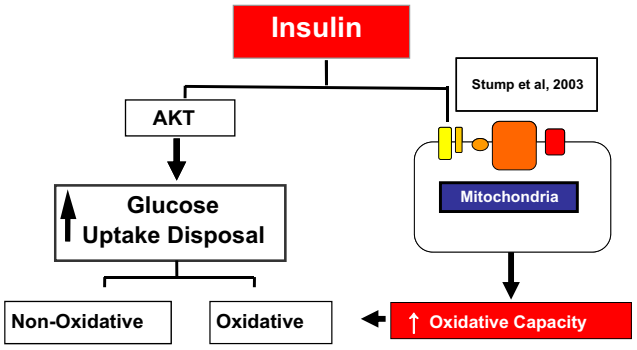

Fig. 4. Scheme of potential interactions between classical insulin-mediated activation of the insulin signalling cascade with a key role of AKT phosphorylation and the emerging impact of insulin on mitochondrial gene expression and functions.

explanation for the in vivo reports of mitochondrial stimulation following high-fat feeding, although a link between free fatty acids and muscle AMPK activation in vivo needs to be directly investigated. Available in vivo studies of the impact of free fatty acid elevation per se (i.e. independently of high-fat feeding) on muscle mitochondria are indeed scarce. Consistent with most in vitro reports, one human study however reported the suppression of mitochondrial-energy transcripts with concomitant elevation of inflammatory gene transcript levels following sustained free fatty acid intravenous infusion.[31] Acute free fatty acid elevation also induces oxidative stress in healthy humans.[32] Overall, the above reports suggest that free fatty acids may exert a negative impact on skeletal muscle mitochondrial oxidative capacity, but this hypothesis needs to be directly tested in vivo. It should be pointed out that concomitant changes in inflammation, oxidative stress and insulin resistance could differentially modulate the impact of fatty acids and high-fat feeding on muscle mitochondrial oxidative capacity under different experimental conditions, and could contribute to explain the existing discrepancies.

3.2. Caloric restriction

Low caloric intake [in the absence of starvation or undernutrition[33]] induces major health benefits and is associated with prolonged lifespan in several animal species, with recent reports supporting this effect also in non-human primates.[34] Although a long-term caloric restriction study in non-obese humans with survival as endpoint may be impossible to perform, data from selected groups of healthy individuals voluntarily undergoing long-term strict hypocaloric dietary regimens have confirmed its substantial positive impact on several cardiometabolic risk factors.[35] From a metabolic standpoint, fasting is associated with a shift towards preferential fatty acid oxidative utilization in skeletal muscle[7] which is in part mediated by reduced PDH activity and may be associated with initial increments of fatty acid supply from enhanced adipose tissue lipolysis. Studies have also demonstrated that caloric restriction may enhance muscle mitochondrial oxidative capacity in experimental models under physiological conditions[36,37] and in aging rodents, particularly in the presence of selective dietary protein supplementation.[38] Indeed, enhanced mitochondrial function through prevention of oxidative damage has been also suggested as a key mediator of the life-prolonging effects of caloric restriction in non-obese animals.[19,22] Importantly, the positive effects of caloric restriction on markers of inflammation and insulin action, demonstrated in non-obese healthy humans,[35] may contribute to improve skeletal muscle mitochondrial function. In recent years, sirtuins including SIRT1 have rapidly emerged as key mediators of life-prolonging effects of caloric restriction in rodents.[39] These deacetylating enzymes are overexpressed in long-term calorie-restricted animals and their targets include the pivotal mitochondrial biogenesis stimulator PPAR-gamma coactivator-1 alpha (PGC-1alpha).[40,41] SIRT1 overexpression is accordingly associated with enhanced muscle mitochondrial oxidative capacity and lower muscle lipid content, with improved metabolic profile also in the presence of high fat-calorie intake.[41] These findings indicate that changes in muscle energy metabolism are pivotal components of the metabolic response to moderate caloric restriction, and likely major contributors to its beneficial effects on health.

3.3. Obesity

Most studies in obese models agree on the negative impact of chronic positive energy balance on muscle mitochondrial oxidative capacity.[42,43] Similar to experimental conditions of high fat availability (Section 3.1), obesity is often associated with inflammation, oxidative stress and insulin resistance[44,45] which may indeed be due at least in part to excess dietary fat. As reported above, all of these alterations have the potential to independently exert a negative impact on muscle mitochondria. Mitochondrial dysfunction could in turn contribute to muscle insulin resistance by favoring tissue fat accumulation, since intramyocellular lipids are strongly associated with insulin resistance.[46] It is therefore plausible that a vicious cycle operates in obese, insulin resistant skeletal muscle whereby altered mitochondrial function (caused by a combination of inflammation, oxidative stress and possibly pre-existing insulin resistance) might further enhance insulin resistance through negative impact of lipid accumulation, with further negative effects on body fat accumulation and worsening of the obese phenotype.

Although adipose tissue adipokine production may negatively affect inflammation and metabolism also in wasting-associated chronic diseases, the additional negative metabolic impact of adipose tissue must be particularly taken into account in the setting of obesity.[47–50] It is well described in both human and animal models that excess adipose tissue is associated with unbalanced adipokine production which may favor the onset of systemic and skeletal muscle insulin resistance and inflammation,[47–50] thereby potentially exerting a negative impact on muscle mitochondrial function. Increased adipocyte and adipose tissue macrophage TNF-alpha and IL-6 expression and production are reported in human and animal obese individuals.[47–49] In addition, expression and circulating levels of adiponectin are low in adipocytes from obese patients.[50] Adiponectin exerts anti-inflammatory and insulin-sensitizing effects, and its positive metabolic impact in experimental models has been reported to be associated with activation of AMPK in skeletal muscle,[48] potentially resulting in stimulated mitochondrial biogenesis and function.

Modulation of inflammation, oxidant status and insulin action by nutrition is a highly desirable and promising approach and could result in improved muscle mitochondrial function, but it should be kept in mind that reducing total caloric intake is not feasible in cachexia-prone patients with chronic wasting diseases whose prognosis is worsened by losses of lean as well as fat body mass. Caloric restriction is instead an integral part of treatment in obese individuals. Few studies have however reported the effects of diet on muscle mitochondrial function in obese patients. Some reports demonstrated improved muscle mitochondrial parameters or lipid oxidation following integrated diet and exercise programs,[51,52] but in one study these effects where not confirmed for diet alone.[51] On the other hand, studies have reported increased aerobic performance (an indirect marker of muscle oxidative metabolism) following diet- and exercise-induced weight loss in obese individuals.[53,54] An important component of muscle metabolic responses to weight gain and loss is related to potential concomitant changes in muscle mass. It should be pointed out that, in spite of positive energy balance and excess body weight, recent studies have indicated that muscle protein anabolism may be impaired in obese humans particularly under acute insulin-stimulated conditions.[55] Weight gain may be in turn associated with absolute or relative decrease of muscle or lean mass leading to sarcopenic obesity in adult and elderly patients.[56] Mechanisms underlying resistance to the protein-anabolic effects of insulin and relative loss of muscle mass could involve several obesity-related alterations, including inflammation and oxidative stress. Balanced weight-reducing programs involving moderate caloric restriction are conversely not reported to be associated with loss of muscle strength.[53] More studies are needed to further assess these important issues.

4. Exercise and skeletal muscle mitochondria

Muscle contraction for physical activity (locomotion and work-related) represents its key function and requires an adequate energy supply. Energy is mostly produced in the form of ATP and since there are no significant amounts of tissue ATP stores, prolonged muscle contraction implies the ability to continuously produce sufficient ATP. Limiting factors to this regard are substrate availability and efficiency of the ATP-generating processes, namely glycolysis and mitochondrial oxidative phosphorylation. Anaerobic glycolysis is however only responsible for relatively limited amounts of ATP production, and the current work will focus on adaptive responses of mitochondrial biogenesis and function to physical exercise as well as their implications in disease states.

4.1. Muscle contraction and mitochondrial biogenesis

Muscle contraction stimulates mitochondrial biogenesis and oxidative capacity through different, integrated mechanisms.[57] Contractile activity activates multiple signalling pathways including energy sensing AMPK and calcium-dependent signalling following contraction-associated calcium release from the sarcoplasmic reticulum.[57] AMPK is a pivotal energy sensor activated by an increase of the AMP-to-ATP ratio.[58] Its metabolic effects modulate intermediate metabolism in several tissues and organs including liver, brain and skeletal muscle, to promote energy production and suppress energy-consuming metabolic pathways.[58] In skeletal muscle, activation of AMPK during contraction is associated with low substrate availability as demonstrated by studies with exercise protocols performed at different muscle glycogen levels.[59] In the above report AMPK was strongly activated in case of glycogen depletion, while exercise with adequate glycogen supply did not result in substantial AMPK activation.[59] AMPK activation results in enhanced glucose and fatty acid uptake, as well as in activated signalling leading to mitochondrial biogenesis and enhanced oxidative capacity.[58] Increased intracellular Ca availability also activate stimulators of mitochondrial biogenesis, involving protein kinase C and Ca-calmodulin-activated protein kinase.[60] Transcription factors involved in contraction-induced mitochondrial biogenesis include PGC-1alpha, playing a pivotal role in orchestrating coordinated nuclear and mitochondrial gene expression.[40,61]

4.2. Exercise training and mitochondrial biogenesis

Consistent with the effects of muscle contraction, bouts of exercise training and sustained exercise programs are associated with increments of muscle mitochondrial parameters.[57] Effects of aerobic training in vivo have also been thoroughly investigated, and the positive impact of aerobic training on aerobic capacity and mitochondrial enzyme activities has long been recognized[62,63] (Fig. 5). It must be pointed out that acute exercise, particularly strenuous bouts of activity, can induce oxidative stress and inflammation.[64] Under trained conditions, these negative effects are over-compensated by stimulation ofantioxidant capacity and anti-inflammatory effects, resulting in protection against oxidative stress and reduction of systemic and tissue inflammatory responses.[65–67] Aerobic training is also commonly associated with improved insulin sensitivity.[63,67,68] Based on previous discussion, this effect could be at least in part mediated by a pattern of beneficial changes involving its anti-inflammatory and antioxidant activities as well as its ability to stimulate mitochondrial substrate oxidation. Recent studies have shown that overexpression of muscle sirtuins, reported to mediate positive mitochondrial effects of caloric restriction, also occurs following aerobic exercise training in both young-adult and elderly humans,[68] suggesting a potential common pathway for the effects of caloric restriction and exercise. The effects of chronic resistance exercise and training on muscle mitochondria are less obvious and remain less investigated, although resistance training produces similar potential stimuli in terms of contractile activity, and has been reported to improve antioxidant status as well as inflammation in muscle.[69] Recent studies indeed directly reported a positive impact of resistance training on muscle mitochondrial parameters in chronic kidney disease patients.[70]

4.3. Exercise training as therapy

The above observations strongly support the potential for beneficial effects of exercise training to reduce functional and

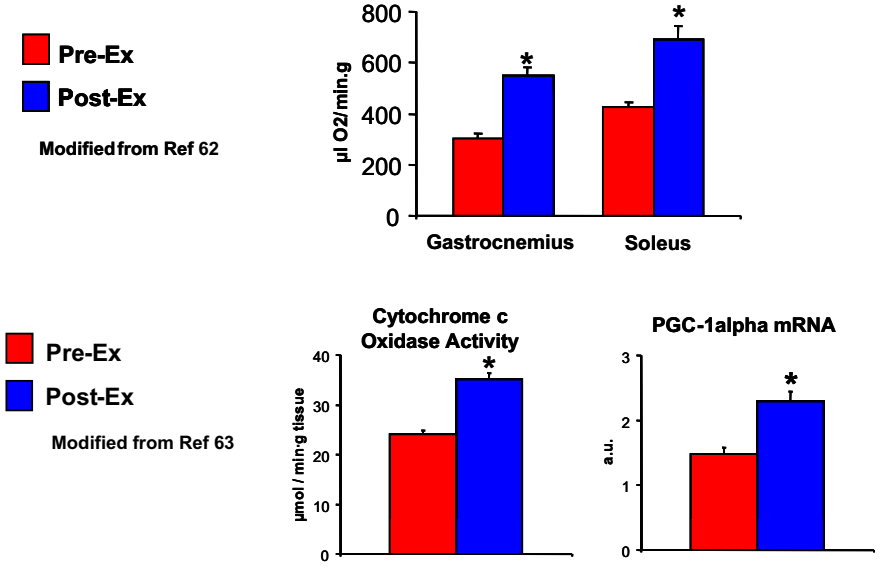

Fig. 5. Positive impact of aerobic exercise training on muscle (gastrocnemius and soleus) oxygen consumption in rodents (Ref 62) and on quadriceps muscle mitochondrial enzyme activities and PGC-1alkpha mRNA in humans (Ref 63).

metabolic complications in disease states with low muscle mitochondrial oxidative capacity. Several studies have indeed demonstrated that resistance and endurance exercise training may improve muscle strength and performance with potential strong positive impact on quality of life in patients with chronic diseases and in aging individuals.[61,70–75] Importantly, these changes likely involve stimulation of muscle protein anabolism, that has been reported also following aerobic exercise.[76] Muscle mitochondrial data is not directly available in most of the numerous studies investigating the clinical benefits of exercise in chronic disease states. However, available evidence supports the involvement of mitochondrial changes in aerobic exercise-induced beneficial effects, with less numerous studies also available for resistance exercise. Increased mitochondrial biogenesis has been indeed reported in muscle following aerobic or resistance exercise training in patients with end-stage renal disease,[70,71] COPD,[72] heart failure,[73,74] and many studies have confirmed these effects in elderly individuals.[63] Also based on available evidence, skeletal muscle mitochondrial effects were reported in studies employing eight to twenty-four weeks of training, based on two-three 20–60 min sessions per week with increasing intensity over time.[63,70–75]

Obese insulin resistant patients also benefit from exercise training, with reported higher muscle mitochondrial density and lipid oxidative capacity.[51,52] As stated above, some studies have reported a positive impact of exercise training, associated with dietary intervention, on fatigue and aerobic performance in diabetic patients.[53,54] It should also be pointed out that improvements in mitochondrial oxidative capacity are not invariably associated with higher insulin sensitivity,[51,63,77] and this observation is consistent with the notion that mitochondrial dysfunction is not the only cause-contributor to skeletal muscle insulin resistance. Duration of exercise program, its intensity and baseline patient characteristics with regard to inflammatory and metabolic status should also be taken into account and might modulate responses to exercise.

5. Conclusions

Muscle physiology relies strongly on a constant, adequate energy supply. Mitochondrial oxidative phosphorylation provides adequate amounts of ATP under physiological conditions, contributing to preserve muscle protein mass and playing a major role in glucose and lipid substrate utilization. Muscle mitochondrial dysfunction occurs in many chronic diseases associated with impaired muscle mass and strength as well as metabolic abnormalities. Inflammation, oxidative stress and insulin resistance likely contribute to disease-associated mitochondrial changes, and they can be induced and modulated by changes in nutrient intake and nutritional status. Exercise training represents a major stimulator of mitochondrial biogenesis and a powerful therapeutic tool for disease conditions involving mitochondrial-related alterations.

Conflict of interest

The author has no conflicts of interest to disclose.

References

1. Saunders PU, Pyne DB, Telford RD, Hawley JA. Factors affecting running economy in trained distance runners. *Sports Med* 2004;**34**:465–85.
2. Tessari P, Inchiostro S, Biolo G, Vincenti E, Sabadin L. Effects of acute systemic hyperinsulinemia on forearm muscle proteolysis in healthy man. *J Clin Invest* 1991;**88**:27–33.
3. Nair KS, Ford GC, Ekberg K, Fernqvist-Forbes E, Wahren J. Protein dynamics in whole body and in splanchnic and leg tissues in type I diabetic patients. *J Clin Invest* 1995;**95**:2926–37.
4. Biolo G, Declan Fleming RY, Wolfe RR. Physiologic hyperinsulinemia stimulates protein synthesis and enhances transport of selected amino acids in human skeletal muscle. *J Clin Invest* 1995;**95**:811–9.
5. Barrett EJ, Fryburg DA. Protein metabolism in healthy and diabetic humans. In: Draznin B, Rizza R, editors. *Clinical Research in diabetes and obesity, Part I: Methods, Assessment, and metabolic regulation*. Totowa, NJ: Humana Press, Inc; 1988. p. 321–6.
6. Duchen MR. Roles of mitochondria in health and disease. *Diabetes* 2004;**53**: S96–102.
7. Stephens FB, Constantin-Teodosiu D, Greenhaff PL. New insights concerning the role of carnitine in the regulation of fuel metabolism in skeletal muscle. *J Physiol* 2007;**581**:431–44.
8. Kim YI, Lee FN, Choi WS, Lee S, Youn JH. Insulin regulation of skeletal muscle PDK4 mRNA expression is impaired in acute insulin-resistant states. *Diabetes* 2006;**55**:2311–7.
9. Kalantar-Zadeh K, Stenvinkel P, Bross R, Khawar OS, Rammohan M, Colman S, et al. Kidney insufficiency and nutrient-based modulation of inflammation. *Curr Opin Clin Nutr Metab Care* 2005;**8**:388–96.
10. McMillan DC. Systemic inflammation, nutritional status and survival in patients with cancer. *Curr Opin Clin Nutr Metab Care* 2009;**12**:223–6.
11. Sandek A, Doehner W, Anker SD, von Haehling S. Nutrition in heart failure: an update. *Curr Opin Clin Nutr Metab Care* 2009;**12**:384–91.
12. Shoelson SE, Lee J, Goldfine AB. Inflammation and insulin resistance. *J Clin Invest* 2006;**116**:1793–801.
13. Li YP, Reid MB. NF-kappaB mediates the protein loss induced by TNF-alpha in differentiated skeletal muscle myotubes. *Am J Physiol Regul Integr Comp Physiol* 2000;**279**:R1165–70.
14. Tisdale MJ. Protein loss in cancer cachexia. *Science* 2000;**289**:2293–4.
15. Wei Y, Chen K, Whaley-Connell AT, Stump CS, Ibdah JA, Sowers JR. Skeletal muscle insulin resistance: role of inflammatory cytokines and reactive oxygen species. *Am J Physiol Regul Integr Comp Physiol* 2008;**294**:R673–80.
16. Valerio A, Cardile A, Cozzi V, Bracale R, Tedesco L, Pisconti A, et al. TNF-alpha downregulates eNOS expression and mitochondrial biogenesis in fat and muscle of obese rodents. *J Clin Invest* 2006;**116**:2791–8.
17. Laviano A, Meguid MM, Preziosa I, Rossi Fanelli F. Oxidative stress and wasting in cancer. *Curr Opin Clin Nutr Metab Care* 2007;**10**:449–56.
18. Ramos LF, Shintani A, Ikizler TA, Himmelfarb J. Oxidative stress and inflammation are associated with adiposity in moderate to severe CKD. *J Am Soc Nephrol* 2008;**19**:593–9.
19. Harman D. The aging process. *Proc Natl Acad Sci* 1981;**78**:7124–8.
20. Supinski GS, Callahan LA. Free radical-mediated skeletal muscle dysfunction in inflammatory conditions. *J Appl Physiol* 2007;**102**:2056–63.
21. Witko-Sarsat V, Friedlander M, Nguyen Khoa T, Capeillère-Blandin C, Nguyen AT, Canteloup S, et al. Advanced oxidation protein products as novel mediators of inflammation and monocyte activation in chronic renal failure. *J Immunol* 1998;**161**:2524–32.
22. Barazzoni R, Short KR, Nair KS. Effects of aging on mitochondrial DNA copy number and cytochrome c oxidase gene expression in rat skeletal muscle, liver, and heart. *J Biol Chem* 2000;**275**:3343–7.
23. Bonnard C, Durand A, Peyrol S, Chanseaume E, Chauvin MA, Morio B, et al. Mitochondrial dysfunction results from oxidative stress in the skeletal muscle of diet-induced insulin-resistant mice. *J Clin Invest* 2008;**118**:789–800.
24. Stump CS, Short KR, Bigelow ML, Schimke JM, Nair KS. Effect of insulin on human skeletal muscle mitochondrial ATP production, protein synthesis, and mRNA transcripts. *Proc Natl Acad Sci U S A* 2004;**100**:7996–8001.
25. Iossa S, Lionetti L, Mollica MP, Crescenzo R, Botta M, Barletta A, et al. Effect of high-fat feeding on metabolic efficiency and mitochondrial oxidative capacity in adult rats. *Br J Nutr* 2003;**90**:953–60.
26. Sparks LM, Xie H, Koza RA, Mynatt R, Hulver MW, Bray GA, et al. A high-fat diet coordinately downregulates genes required for mitochondrial oxidative phosphorylation in skeletal muscle. *Diabetes* 2005;**54**:1926–33.
27. Turner N, Bruce CR, Beale SM, Hoehn KL, So T, Rolph MS, et al. Excess lipid availability increases mitochondrial fatty acid oxidative capacity in muscle: evidence against a role for reduced fatty acid oxidation in lipid-induced insulin resistance in rodents. *Diabetes* 2007;**56**:2085–92.
28. Garcia-Roves P, Huss JM, Han DH, Hancock CR, Iglesias-Gutierrez E, Chen M, et al. Raising plasma fatty acid concentration induces increased biogenesis of mitochondria in skeletal muscle. *Proc Natl Acad Sci U S A* 2007;**104**:10709–13.
29. Rachek LI, Musiyenko SI, LeDoux SP, Wilson GL. Palmitate induced mitochondrial deoxyribonucleic acid damage and apoptosis in l6 rat skeletal muscle cells. *Endocrinology* 2007;**148**:293–9.
30. Pimenta AS, Gaidhu MP, Habib S, So M, Fediuc S, Mirpourian M, et al. Prolonged exposure to palmitate impairs fatty acid oxidation despite activation of AMP-activated protein kinase in skeletal muscle cells. *J Cell Physiol* 2008;**217**:478–85.
31. Richardson DK, Kashyap S, Bajaj M, Cusi K, Mandarino SJ, Finlayson J, et al. Lipid infusion decreases the expression of nuclear encoded mitochondrial genes and increases the expression of extracellular matrix genes in human skeletal muscle. *J Biol Chem* 2005;**280**:10290–7.
32. Paolisso G, Gambardella A, Tagliamonte MR, Saccomanno F, Salvatore T, Gualdiero P, et al. Does free fatty acid infusion impair insulin action also through an increase in oxidative stress? *J Clin Endocrinol Metab* 1996;**81**:4244–8.
33. Awad S, Constantin-Teodosiu D, Macdonald IA, Lobo DN. Short-term starvation and mitochondrial dysfunction - A possible mechanism leading to post-operative insulin resistance. *Clin Nutr* 2009;**28**:497–509.

34. Colman RJ, Anderson RM, Johnson SC, Kastman EK, Kosmatka KJ, Beasley TM, et al. Caloric restriction delays disease onset and mortality in rhesus monkeys. *Science* 2009;**10**(325):201–4.
35. Fontana L, Meyer TE, Klein S, Holloszy JO. Long-term calorie restriction is highly effective in reducing the risk for atherosclerosis in humans. *Proc Natl Acad Sci U S A* 2004;**101**:6659–63.
36. Barazzoni R, Zanetti M, Bosutti A, Biolo G, Vitali-Serdoz L, Stebel M, et al. Moderate caloric restriction, but not physiological hyperleptinemia per se, enhances mitochondrial oxidative capacity in rat liver and skeletal muscle–tissue-specific impact on tissue triglyceride content and AKT activation. *Endocrinology* 2005;**146**:2098–106.
37. Nisoli E, Tonello C, Cardile A, Cozzi V, Bracale R, Tedesco L, et al. Calorie restriction promotes mitochondrial biogenesis by inducing the expression of eNOS. *Science* 2005;**310**:314–7.
38. Zangarelli A, Chanseaume E, Morio B, Brugère C, Mosoni L, Rousset P, et al. Synergistic effects of caloric restriction with maintained protein intake on skeletal muscle performance in 21-month-old rats: a mitochondria-mediated pathway. *FASEB J* 2006;**20**:2439–50.
39. Sinclair DA. Toward a unified theory of caloric restriction and longevity regulation. *Mech Ageing Dev* 2005;**126**:987–1002.
40. Gerhart-Hines Z, Rodgers JT, Bare O, Lerin C, Kim SH, Mostoslavsky R, et al. Metabolic control of muscle mitochondrial function and fatty acid oxidation through SIRT1/PGC-1alpha. *EMBO J* 2007;**26**:1913–23.
41. Lagouge M, Argmann C, Gerhart-Hines Z, Meziane H, Lerin C, Daussin F, et al. Resveratrol improves mitochondrial function and protects against metabolic disease by activating SIRT1 and PGC-1alpha. *Cell* 2006;**127**:1109–22.
42. Simoneau JA, Kelley DE. Altered glycolytic and oxidative capacities of skeletal muscle contribute to insulin resistance in NIDDM. *J Appl Physiol* 1997;**83**: 166–71.
43. Ritov VB, Menshikova EV, He J, Ferrell RE, Goodpaster BH, Kelley DE. Deficiency of subsarcolemmal mitochondria in obesity and type 2 diabetes. *Diabetes* 2005;**54**:8–14.
44. Romano M, Guagnano MT, Pacini G, Vigneri S, Falco A, Marinopiccoli M, et al. Association of inflammation markers with impaired insulin sensitivity and coagulative activation in obese healthy women. *J Clin Endocrinol Metab* 2003;**88**:5321–6.
45. Furukawa S, Fujita T, Shimabukuro M, Iwaki M, Yamada Y, Nakajima Y, et al. Increased oxidative stress in obesity and its impact on metabolic syndrome. *J Clin Invest* 2004;**114**:1752–61.
46. Savage DB, Petersen KF, Shulman GI. Disordered lipid metabolism and the pathogenesis of insulin resistance. *Physiol Rev* 2007;**87**:507–20.
47. Sethi JK, Vidal-Puig AJ. Thematic submitted for publication series: adipocyte biology. Adipose tissue function and plasticity orchestrate nutritional adaptation. J Lipid Res ;48:1253–1262.
48. Kadowaki T, Yamauchi T, Kubota N, Hara K, Ueki K, Tobe K. Adiponectin and adiponectin receptors in insulin resistance, diabetes, and the metabolic syndrome. *J Clin Invest* 2006;**116**:1784–92.
49. Kern PA, Saghizadeh M, Ong JM, Bosch RJ, Deem R, Simsolo RB. The expression of tumor necrosis factor in human adipose tissue. Regulation by obesity, weight loss, and relationship to lipoprotein lipase. *J Clin Invest* 1995;**95**: 2111–9.
50. Kern PA, Di Gregorio GB, Lu T, Rassouli N, Ranganathan G. Adiponectin expression from human adipose tissue: relation to obesity, insulin resistance, and tumor necrosis factor-alpha expression. *Diabetes* 2003;**52**:1779–85.
51. Toledo FG, Menshikova EV, Azuma K, Radiková Z, Kelley CA, Ritov VB, et al. Mitochondrial capacity in skeletal muscle is not stimulated by weight loss despite increases in insulin action and decreases in intramyocellular lipid content. *Diabetes* 2008;**57**:987–94.
52. Lazzer S, Vermorel M, Montaurier C, Meyer M, Boirie Y. Changes in adipocyte hormones and lipid oxidation associated with weight loss and regain in severely obese adolescents. *Int J Obes* 2005;**29**:1184–91.
53. Sartorio A, Fontana P, Trecate L, Lafortuna CL. Short-term changes of fatigability and muscle performance in severe obese patients after an integrated body mass reduction program. *Diabetes Nutr Metab* 2003;**16**:88–93.
54. Sartorio A, Narici MV, Fumagalli E, Faglia G, Lafortuna CL. Aerobic and anaerobic performance before and after a short-term body mass reduction program in obese subjects. *Diabetes Nutr Metab* 2001;**14**:51–7.
55. Chevalier S, Marliss EB, Morais JA, Lamarche M, Gougeon R. Whole-body protein anabolic response is resistant to the action of insulin in obese women. *Am J Clin Nutr* 2005;**82**:355–65.
56. Baumgartner RN, Wayne SJ, Waters DL, Janssen I, Gallagher D, Morley JE. Sarcopenic obesity predicts instrumental activities of daily living disability in the elderly. *Obes Res* 2004;**12**:1995–2004.
57. Holloszy JO. Regulation by exercise of skeletal muscle content of mitochondria and GLUT4. *J Physiol Pharmacol* 2008;**59**(Suppl 7):5–18.
58. Long YC, Zierath JR. AMP-activated protein kinase signaling in metabolic regulation. *J Clin Invest* 2006;**116**:1776–83.
59. Wojtaszewski JF, MacDonald C, Nielsen JN. Regulation of 5'AMP-activated protein kinase activity and substrate utilization in exercising human skeletal muscle. *Am J Physiol Endocrinol Metab* 2003;**284**:E813–22.
60. Adhihetty PJ, Irrcher I, Joseph AM, Ljubicic V, Hood DA. Plasticity of skeletal muscle mitochondria in response to contractile activity. *Exp Physiol* 2003;**88**:99–107.
61. Finck BN, Kelly DP. PGC-1 coactivators: inducible regulators of energy metabolism in health and disease. *J Clin Invest* 2006;**116**:615–22.
62. Holloszy JO. Biochemical adaptations in muscle. Effects of exercise on mitochondrial oxygen uptake and respiratory enzyme activity in skeletal muscle. *J Biol Chem* 1967;**242**:2278–82.
63. Short KR, Vittone JL, Bigelow ML, Proctor DN, Rizza RA, Coenen-Schimke JM, et al. Impact of aerobic exercise training on age-related changes in insulin sensitivity and muscle oxidative capacity. *Diabetes* 2003;**52**:1888–96.
64. Neubauer O, Reichhold S, Nersesyan A, König D, Wagner KH. Exercise-induced DNA damage: is there a relationship with inflammatory responses? *Exerc Immunol Rev* 2008;**14**:51–72.
65. Vichaiwong K, Henriksen EJ, Toskulkao C, Prasannarong M, Bupha-Intr T, Saengsirisuwan V. Attenuation of oxidant-induced muscle insulin resistance and p38 MAPK by exercise training. *Free Radic Biol Med* 2009;**47**:593–9.
66. Greiwe JS, Cheng B, Rubin DC, Yarasheski KE, Semenkovich CF. Resistance exercise decreases skeletal muscle tumor necrosis factor alpha in frail elderly humans. *FASEB J* 2001;**15**:475–82.
67. Petersen AM, Pedersen BK. The anti-inflammatory effect of exercise. *J Appl Physiol* 2005;**98**:1154–62.
68. Lanza IR, Short DK, Short KR, Raghavakaimal S, Basu R, Joyner MJ, et al. Endurance exercise as a countermeasure for aging. *Diabetes* 2008;**57**:2933–42.
69. Johnston AP, De Lisio M, Parise G. Resistance training, sarcopenia, and the mitochondrial theory of aging. *Appl Physiol Nutr Metab* 2008;**33**:191–9.
70. Balakrishnan VS, Rao M, Menon V, Gordon PL, Pilichowska M, Castaneda F, et al. Resistance training increases muscle mitochondrial biogenesis in patients with chronic kidney disease. *Clin J Am Soc Nephrol* 2010;**5**:996–1002.
71. Kouidi E, Albani M, Natsis K, Megalopoulos A, Gigis P, Guiba-Tziampiri O, et al. The effects of exercise training on muscle atrophy in haemodialysis patients. *Nephrol Dial Transplant* 1998;**13**:685–99.
72. Gosker HR, Schrauwen P, Broekhuizen R, Hesselink MK, Moonen-Kornips E, Ward KA, et al. Exercise training restores uncoupling protein-3 content in limb muscles of patients with chronic obstructive pulmonary disease. *Am J Physiol Endocrinol Metab* 2006;**290**:E976–81.
73. Tyni-Lenné R, Gordon A, Jansson E, Bermann G, Sylvén C. Skeletal muscle endurance training improves peripheral oxidative capacity, exercise tolerance, and health-related quality of life in women with chronic congestive heart failure secondary to either ischemic cardiomyopathy or idiopathic dilated cardiomyopathy. *Am J Cardiol* 1997;**80**:1025–9.
74. Gielen S, Adams V, Linke A, Erbs S, Möbius-Winkler S, Schubert A, et al. Exercise training in chronic heart failure: correlation between reduced local inflammation and improved oxidative capacity in the skeletal muscle. *Eur J Cardiovasc Prev Rehabil* 2005;**12**:393–400.
75. Raguso CA, Kyle U, Kossovsky MP, Roynette C, Paoloni-Giacobino A, Hans D, et al. 3-year longitudinal study on body composition changes in the elderly: role of physical exercise. *Clin Nutr* 2006;**25**:573–80.
76. Short KR, Vittone JL, Bigelow ML, Proctor DN, Nair KS. Age and aerobic exercise training effects on whole body and muscle protein metabolism. *Am J Physiol Endocrinol Metab* 2004;**286**:E92–101.
77. Østergård T, Andersen JL, Nyholm B, Lund S, Nair KS, Saltin B, et al. Impact of exercise training on insulin sensitivity, physical fitness, and muscle oxidative capacity in first-degree relatives of type 2 diabetic patients. *Am J Physiol Endocrinol Metab* 2006;**290**:E998–1005.