HIGHLIGHTED TOPIC | Aging and Exercise

In vivo mitochondrial function in aging skeletal muscle: capacity, flux, and patterns of use

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Kent JA, Fitzgerald LF. In vivo mitochondrial function in aging skeletal muscle: capacity, flux, and patterns of use. J Appl Physiol 121: 996–1003, 2016. First published August 25, 2016; doi:10.1152/japplphysiol.00583.2016.—Because of the fundamental dependence of mammalian life on adequate mitochondrial function, the question of how and why mitochondria change in old age is the target of intense study. Given the importance of skeletal muscle for the support of mobility and health, this question extends to the need to understand mitochondrial changes in the muscle of older adults, as well. We and others have focused on clarifying the age-related changes in human skeletal muscle mitochondrial function in vivo. These changes include both the maximal capacity for oxidative production of energy (ATP), as well as the relative use of mitochondrial ATP production for powering muscular activity. It has been known for nearly 50 yr that muscle mitochondrial content is highly plastic; exercise training can induce an ∼2-fold increase in mitochondrial content, while disuse has the opposite effect. Here, we suggest that a portion of the age-related changes in mitochondrial function that have been reported are likely the result of behavioral effects, as physical activity influences have not always been accounted for. Further, there is emerging evidence that various muscles may be affected differently by age-related changes in physical activity and movement patterns. In this review, we will focus on age-related changes in oxidative capacity and flux measured in vivo in human skeletal muscle.

bioenergetics; biomechanics; glycolysis; mitochondria; physical activity

In the intact organism, physiological processes are influenced at a wide range of levels in a continuum that scales up from the molecular to the population level. These influences extend to mitochondrial function in humans, which can make evaluation of the magnitude and mechanisms of age-related changes in mitochondrial function a daunting challenge. In addition to the many factors that can influence mitochondria, in recent years our understanding of what is meant by “mitochondrial function” has expanded from the aerobic production of energy to also include signaling and sensing roles (71). For example, mitochondrial production of reactive oxygen species (ROS) may increase with age and thus possibly influence the development of sarcopenia (11). Likewise, mitochondria play a role in sensing the energy state of the cell, including the need for increased mitochondrial biogenesis to meet short- and long-term fluctuations in cellular energy demands (12, 95, 96).

In biology, structure and function are inextricably linked. Early papers discussed mitochondria as existing in a reticulum (2, 48); this concept was illustrated recently in an elegant study by Glancy et al. that showed the multiple morphologies and extensive mitochondrial network found in skeletal muscle (23). In addition to ensuring that mitochondria are localized near sites of high energy demand, the existence of a reticulum also serves the need for communication along the mitochondrial network regarding regions of increased need or impaired function (70). It is presumably this communication that facilitates the ongoing processes of fission and fusion (94), which act to enlarge the reticulum or discard damaged regions, respectively (95).

A variety of experimental approaches and methods, from molecular to whole body, have contributed to our understanding of the effects of old age on mitochondrial biology. Since the 1950s, respiration has been examined directly in isolated mitochondria using respirometry, a technique that quantifies oxygen consumption in each of the various stages or “states” of mitochondrial oxidative phosphorylation (14). The effects of aging on the rate of respiration can be determined for each of these states by varying the substrates to which the mitochondria are exposed (52, 58). Respirometry has been applied increasingly to the study of aging, as commercial development of reliable and sensitive respirometers has allowed greater use of this sophisticated approach. In addition to isolated mitochondria, respirometry can also be used to quantify oxidative function in permeabilized muscle fiber bundles (86). In fact, the sample used in these studies was demonstrated years ago by Saks et al. (86), and more recently by Picard and colleagues (72, 73), to be a critically important one. These
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In addition to direct measurement of oxygen consumption by respirometry, many early studies used the maximal activities of enzymes known to participate in oxidative metabolism as proxies for mitochondrial content (3, 36). Genomic and metabolomic approaches likewise have become important tools for studying the effects of old age on mitochondrial function. These methods provide information about the networks of genes and proteins involved in oxidative metabolism; as such, they can be used to examine age-related changes in mitochondrial content and function (31). Finally, studies of muscle mitochondrial function in situ have used animal model preparations to query function by measuring oxygen consumption across the muscle bed, while accounting for variations in blood flow and oxygen delivery (33, 35). Studies of enzyme activities, isolated mitochondria, permeabilized fibers, genomics, and proteomics all make use of tissue samples obtained by biopsy, in the case of humans, or with excised muscle, in the case of animal models of aging.

The main advantage of the techniques discussed above is that specific sites of altered mitochondrial content and function in young vs. older tissue can be identified. The main disadvantage of these techniques is the risk of reducing the scope of the preparation to the extent that it does not reflect conditions in vivo and thus may not provide an accurate understanding of age-related changes in mitochondrial function. The different techniques are susceptible to this problem to varying degrees (32, 72, 73). In contrast to biopsy-based methods, in vivo studies of muscle mitochondrial energetics using phosphorus-31 nuclear magnetic resonance spectroscopy (31P MRS) query oxidative function of a volume of muscle tissue noninvasively and continuously (1, 29, 44, 50, 66, 89). Notably, the advantages and disadvantages of 31P MRS are the reverse of the in vitro preparations: the main advantage of MRS is that it interrogates muscle oxidative function with all systems intact; indeed, these measures reflect overall oxidative function of the system (including but not exclusively mitochondrial function), and so the term “oxidative” rather than “mitochondrial” function or capacity is more appropriate in this case. The primary disadvantage of 31P MRS is that it examines a volume of tissue (1 to ~250 cm³), which thus precludes a detailed mechanistic analysis. While these in vitro and in vivo methods provide information about different aspects of mitochondrial function, it should be noted that measures of enzyme activities (59, 64) and respirometry estimates of mitochondrial oxygen consumption (52) are highly correlated with 31P MRS measures of oxidative capacity. In sum, both in vitro and in vivo approaches contribute to a fuller understanding of the complex performance of mitochondria and the impact of old age on this performance. There are many excellent reviews of the literature pertaining to mechanistic studies of mitochondrial function in aging (32, 81). This review is devoted to a discussion of age-related changes in mitochondrial function, with a particular emphasis on the information provided by in vivo measures of human skeletal muscle oxidative capacity.

MUSCLE MITOCHONDRIAL CAPACITY IN VIVO

First discovered by physicists in 1946 (5, 76), the application of phosphorus nuclear magnetic resonance techniques to the study of human muscle energetics in vivo dates back to the early 1980s (13, 78). This method typically involves a small copper coil positioned over the tissue of interest and used to send and receive radiofrequency pulses into the muscle. When the coil and tissue volume of interest are positioned in the isocenter (i.e., region where the magnetic field strength and orientation are homogenous) of a static magnetic field, this radiofrequency signal can be used to measure the compounds of interest in the cytosol of the sample volume. The technique applies principles from quantum and classical physics to exploit the known properties of nuclear spin for each compound of interest. As a result, phosphorus-containing compounds such as ATP, phosphocreatine (PCr), and inorganic phosphate (Pi) can be followed with rapid (2–10 s) temporal resolution in resting and contracting muscle, as shown in Fig. 1. The relative concentration of metabolites such as ADP, H+, and diprotinated Pi also can be calculated on the basis of information from the 31P spectrum.

PCr recovery method. Early adoption of 31P MRS by world-class biochemists such as B. Chance, G. Radda, M. Kushnerick, and R. Shulman ensured the rigorous development of this technique for applications related to muscle energetics. Arnold et al. were the first to suggest that PCr recovery kinetics might be used for interrogating muscle mitochondrial function in vivo (1). The “PCr recovery” method was developed by Meyer and colleagues (65–67) and is now considered by investigators around the world to be the gold standard for in vivo oxidative capacity measures. The protocol for this method involves inducing a decrease in [PCr] in the muscle of interest to ~50% of resting concentration, typically using a brief, maximal contraction that activates the entire muscle but causes little change in cytosolic pH. Because [ATP] is maintained constant under these conditions, nonoxidative glycolysis ends when the contraction stops, and no PCr recovery occurs in the absence of blood flow, the recovery of PCr is accomplished solely by oxidative phosphorylation (66, 77). The recovery of PCr follows a monoexponential function, which can be fit, and a rate constant (kPCr) can be calculated. Further, the maximal velocity for oxidative phosphorylation can be estimated as kPCr multiplied by resting [PCr] (50, 65).

The rate of PCr recovery postcontraction is sensitive to changes in oxidative capacity due to exercise training and disuse (46, 49, 55) but cannot identify the mechanisms for differences in oxidative capacity across groups. Mitochondrial content cannot be discerned by this method, and thus mechanistic studies require the use of in vitro methods (see introduction). The PCr recovery measure requires the assumption that oxygen delivery to the mitochondria is not limited. In cases such as peripheral vascular disease (28) or trained athletes (30), this assumption may be violated because of insufficient tissue perfusion, and so this method may not be appropriate for
evaluating oxidative capacity in those cases. For example, Haseler et al. (30) showed that PCr recovery kinetics following plantar flexion exercise in trained male athletes increased as the fraction of inspired oxygen was increased, indicating that insufficient oxygen delivery under normoxic conditions can limit this measure of muscle mitochondrial capacity in highly trained muscle. By limiting the degree of intracellular acidification, any influence of acidosis on the rate of enzyme activities is eliminated, and so the rate of PCr recovery can be used to infer the capacity of the mitochondria, or more correctly, the capacity of the entire oxidative system of the muscle. The validity and reliability of this method have been clearly established with enzyme activity and respirometry measures of tissue samples (52, 59, 64). Thus the PCr recovery method is a relatively simple and highly reliable technique for the noninvasive measurement of muscle oxidative capacity.

We note here that recent advances in near-infrared spectroscopy (NIRS) technology, particularly the development of simultaneous multifrequency data collection capabilities (83), may soon provide an additional noninvasive method for evaluating muscle oxidative capacity in vivo. By sampling at multiple frequencies, the problem of signal loss or alteration due to scatter is significantly reduced. The question of the relative contribution to the signal from oxy-/deoxyhemoglobin vs. oxy-/deoxymyoglobin remains, but reasonable assumptions about this are possible (84). At present, this technique requires additional validation in populations with significant subcutaneous, intermuscular, and intramyocellular fat stores, but early reports (83, 84) suggest that multifrequency NIRS may become an additional tool for probing age-related changes in muscle oxidative capacity.

**Application of 31P MRS to studies of aging.** Taylor et al. were the first to investigate the effects of old age on muscle bioenergetics using 31P MRS (88). In this early study using dynamic contractions of the finger flexor muscles, they observed no difference by age in contraction-induced changes in PCr or intracellular pH, nor in postcontraction PCr recovery kinetics. Following development of this technique by Meyer (66), we used the PCr recovery method to evaluate ankle dorsiflexor (tibialis anterior) muscle oxidative capacity, along with measures of whole-body peak oxygen consumption (V\textsuperscript{\text{\textregistered}}O\textsubscript{2peak}), in groups of young and older men and women with similar low levels of habitual activity, as quantified by accelerometry (44). As expected (75), the older group had a V\textsuperscript{\text{\textregistered}}O\textsubscript{2peak} during treadmill exercise that was ~25% lower than that of young adults, and the generally low V\textsuperscript{\text{\textregistered}}O\textsubscript{2peak} values in both groups confirmed their sedentary status. Despite lower V\textsuperscript{\text{\textregistered}}O\textsubscript{2peak} in the old, muscle oxidative capacity was not different between the age groups, suggesting that decreased oxidative capacity is not a de facto occurrence in old age. Because the groups were matched for similar daily activity, the results also suggested that habitual use of a muscle (as, e.g., locomotion in the case of the dorsiflexors) may be important in preserving its oxidative capacity in aging humans. Other investigators who have examined a variety of muscles also have reported similar oxidative capacity in young and older adults, using both in vivo (15, 29, 38) and in vitro (26, 27) methods; in many cases, these studies have accounted for the activity characteristics of their study cohorts (16, 26, 27, 29, 44, 50, 51, 56, 60, 90, 91).

In contrast to reports indicating no age-related deficits in oxidative capacity in muscle, numerous in vivo (18, 40, 56, 61) and in vitro (74, 87, 92) studies have found significantly lower capacity in older compared with younger adults. A comparison of studies in the literature reporting these disparate results showed that in most cases they could be distinguished by differences in either the muscle studied (most studies of vastus lateralis reported lower oxidative capacity in the old) or the lack of objective measures of physical activity, or both. Thus, to test the hypothesis that detection of age-related differences in mitochondrial capacity might be influenced by the muscle under study and the habitual activity level of the study groups, we used 31P MRS to measure in vivo muscle oxidative capacity in the tibialis anterior and vastus lateralis muscles of young and older men and women who were classified as sedentary, highly active, or mobility-impaired (55, 56). Habitual activity was quantified by accelerometry. Notably, although the sedentary young and older groups were matched for overall physical activity (counts/day), the older adults engaged in fewer minutes of moderate-vigorous activity (MVPA) each day (Fig. 2). As expected, overall activity and MVPA were lower in the older impaired group. Muscle PCr recovery kinetics showed an age-by-muscle interaction such that oxidative capacity was preserved (or higher) in the tibialis anterior but lower in the vastus lateralis of the older compared with younger groups.

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**Fig. 1.** In vivo quantitation of muscle mitochondrial capacity by phosphorus-31 magnetic resonance spectroscopy. In human vastus lateralis muscle: spectrum at rest shows metabolites of interest (A); stack plot shows changes in PCr and P\textsubscript{i} during a 24-s maximal contraction followed by recovery (B); and exponential fit of PCr recovery provides the rate constant for PCr recovery (k\textsubscript{PCr}), which reflects the oxidative capacity of the muscle and can be used to estimate the maximal velocity (V\textsubscript{max}) for oxidative phosphorylation (C).
(Fig. 2). Further, the strong correlation between vastus lateralis capacity is higher in the vastus lateralis than the tibialis anterior in active (runners) and sedentary young groups but the opposite is the case in the older groups. Differences in moderate-vigorous activity (MVPA, middle) across the age groups likely contribute to these effects by altering the amount and intensity of muscle recruitment to different degrees. That is, maintenance of mitochondrial capacity in the mixed-fiber type vastus muscle may require more MVPA than in the predominantly slow-fiber type tibialis anterior muscle. Values are means ± SE. Data compiled from Larsen et al. (55, 56).

As discussed above, the body of literature over the past ~20 yr reveals a good deal of heterogeneity with regard to the question of in vivo muscle oxidative capacity in aging. Researchers have variously invoked differences in subject characteristics, the muscle studied, and the experimental protocols applied as potential explanations for these differences in results. While the studies of Larsen et al. (55, 56) shed some light on this controversy, we sought to gain additional clarity on this important question and so performed a formal systematic review and metaanalysis of this literature (21). The results showed that overall, there is in fact a small positive effect of old age on oxidative capacity, as measured by PCR recovery kinetics (Fig. 3). Examination of the moderators of this effect indicates that muscle group, in particular, has a significant effect on the outcome, wherein oxidative capacity is lower in the knee extensor muscles of older adults, but higher in the dorsiflexors and upper extremity muscles. Thus the results of this metaanalysis provide clarity and consensus about the existing literature regarding age-related differences in human skeletal muscle oxidative capacity in vivo. Additional significant moderators of oxidative capacity included physical activity and sex, and therefore these factors should also be accounted for in future studies. Finally, there exists a lack of information about in vivo mitochondrial capacity in “older-old” adults, i.e., those over ~75 yr of age. Given the striking increase in morbidity and mobility dysfunction beyond the age of 75–80 yr, it is important that researchers include this segment of the population in future studies, in order to fully determine how aging affects human skeletal muscle mitochondrial function in vivo.

Fig. 2. In vivo mitochondrial capacity varies by muscle and habitual physical activity in aging humans. Note the age-by-muscle interaction, such that oxidative capacity is higher in the vastus lateralis than the tibialis anterior in active (runners) and sedentary young groups but the opposite is the case in the older groups (kPCR, right), even when young and older groups are matched for similar overall physical activity (left). This effect is exaggerated in mobility-impaired older adults. Differences in moderate-vigorous activity (MVPA, middle) across the age groups likely contribute to these effects by altering the amount and intensity of muscle recruitment to different degrees. That is, maintenance of mitochondrial capacity in the mixed-fiber type vastus muscle may require more MVPA than in the predominantly slow-fiber type tibialis anterior muscle. Values are means ± SE. Data compiled from Larsen et al. (55, 56).

**Physical Activity, Muscle Group, and Patterns of Use: Is Mitochondrial “Dysfunction” in Aging a Behavioral Issue?**

The classic work of muscle physiologists such as P. Gollnick, J. Holloszy, G. Brooks, and others provides a strong foundation for understanding the effects of long-duration exercise training on muscle mitochondrial content and function (19, 24, 25, 36). These seminal studies, which examined muscle from both humans and animal models, showed that the capacity for mitochondrial respiration can increase multifold in response to exercise training and that this generally occurs via an increase in mitochondrial content, typically measured by the activity of enzymes involved in oxidative phosphorylation. More recently, the work of Gibala and colleagues (22, 37) and others (39, 54, 57) has shown that long-duration training
programs are not necessary to evoke a significant increase in mitochondrial capacity. Indeed, short-term, high-intensity interval training can also increase mitochondrial biogenesis and the capacity for oxidative phosphorylation (10, 37, 62). Likewise, the reverse occurs with disuse, such that markers of mitochondrial function are reduced by immobilization and paralysis (4, 63, 80). Thus, while technological advances have provided us with sophisticated research tools to address the question of mitochondrial function in aging, we must continue to bear in mind the fundamental role of exercise and physical activity in affecting muscle mitochondrial function and the systems (e.g., cardiovascular, neural) that support it.

The amount and intensity of daily physical activity are lower in older adults (93). However, the influence on mitochondrial function of age-related changes in daily patterns of muscle activation (intensity, duration, timing) is not known. For example, a hallmark characteristic of older adults is their slowed gait speed (6). In addition, there are striking alterations in gait mechanics in older compared with young adults (9, 20, 47). As illustrated in Fig. 4, these alterations, including greater anterior pelvic tilt, less plantar flexion, and a redistribution of joint moments from distal to proximal joints (20, 79), translate to differing patterns of muscle use in young and old, including changes in the intensity and timing of contractions of the various locomotory muscles. These muscle-specific alterations in gait set the stage for differing effects of “aging” on, for example, the knee extensor muscles compared with the ankle dorsiflexors, as discussed above. It should be noted that this change in pattern occurs even in healthy, mobile older men and women and thus may represent a subtle adaptation that subsequently impacts muscle use and therefore mitochondrial energetics in aging.

The question of why essentially all species exhibit a decline in spontaneous physical activity in senescence is perhaps one of the most fascinating questions in gerontology today (34). In the meantime, by accounting for the known effects of decreased habitual activity on muscle mitochondrial function, future in vitro and in vivo studies will advance the field by providing more accurate estimates of the magnitude and mechanisms of this fundamental problem.

**OXIDATIVE ENERGY PRODUCTION DURING MUSCLE CONTRACTIONS IN VIVO**

In addition to determining the maximal capacity of the mitochondria to produce energy in the form of ATP, we have examined the question of whether there are age-related changes in the relative contribution of oxidative metabolism to the overall energy demand of the muscle in vivo (17, 50, 53, 91). Building on the early work of Boska (7, 8) and others (42, 85), we have applied $31^P$ MRS measures of in vivo ATP production by oxidative phosphorylation, nonoxidative glycolysis, and the creatine kinase reaction to the question of how ATP production is accomplished during muscular activity (17, 50, 53, 82, 91). Briefly, changes in PCr during contraction indicate the direct contribution of the creatine kinase reaction to net energy production; for each PCr molecule broken down, one ATP is formed. Nonoxidative glycolysis is measured by changes in cytosolic [H$^+$], while accounting for the effects of intracellular buffering, efflux of protons from the myocyte, proton consumption by the breakdown of PCr, and the very small amount of proton production associated with oxidative phosphorylation. Oxidative ATP production can be measured by PCr recovery kinetics postcontraction or by changes in the phosphorylation potential during contraction. Thus, under conditions in which ATP consumption $=$ ATP production, the rates of ATP production (mM/s) and total ATP produced from each pathway can be determined and used to calculate the total cost of contraction, as well as the relative contribution of each pathway (17, 50, 53, 91). This approach can also be used to evaluate muscle metabolic economy (force per ATP, adjusted for fat-free muscle mass; N-m-ATP$^{-1}$-cm$^{-2}$) (17, 43, 53, 91).

The observation of greater acidosis and accumulation of mono- and diprotomated $P_i$ during fatiguing contractions in young compared with older adults (45) prompted a series of studies in the tibialis anterior muscle designed to address the question of whether ATP production by each energetic pathway may be altered in old age. We first identified an effect of age on the relative contribution of each pathway to overall ATP production during a maximal contraction (50) and then performed a series of studies designed to determine the potential sources of this difference (17, 53, 91). During a maximal voluntary contraction sustained for 60 s, ATP synthesis from the creatine kinase reaction and oxidative phosphorylation were similar in young and older adults, while glycolytic ATP production was higher in the young group (50). Thus the older group produced relatively more energy by oxidative metabolism. Notably, there was no difference in oxidative capacity ($K_{PCr}$) between the age groups.

To determine whether this difference in ATP flux was due to a limitation in glycolytic capacity in older muscle or a “preference” for oxidative metabolism, we next measured ATP production during intermittent maximal contractions with
blood flow intact or restricted by cuff ischemia (53). Ischemia was used to eliminate oxidative ATP production to determine whether older muscle could increase glycolytic ATP production to match overall muscle energy needs. During contractions with intact blood flow, the older group again showed a greater reliance on oxidative ATP production compared with young. During ischemia, glycolytic flux was similar in young and old [1.3 ± 0.2 (SE) and 1.4 ± 0.2 mM ATPs, respectively], indicating that there was not a limitation in glycolytic ATP production in the old and thus suggesting that a greater reliance on oxidative metabolism under free-flow conditions was indeed a “preference” of the older muscle. To test whether this energetic difference was an intrinsic property of older muscle, we next evaluated ATP production during continuous supramaximal stimulation of the peroneal nerve at a fixed frequency (25 Hz, 60 s) and at the frequency eliciting 50% of maximal tetanic force for each participant (~15 Hz in young and 11 Hz in old, 90 s (91)]. Notably, the shift to a lower frequency in the old was roughly comparable in magnitude with the lower motor unit discharge rates observed during maximal voluntary contractions of this muscle group in older adults (41). This approach interrogated muscle energetics absent of the influence of the nervous system and accounted for age-related shifts in the force-frequency curve (68, 69). The results indicated that ATP production from each pathway was similar in young and old at the fixed stimulus of 25 Hz. In contrast, during stimulation at the adjusted frequencies, older muscle produced relatively more ATP via oxidative phosphorylation and the creatine kinase reaction and less through glycolysis than did the young. Once again, there was no difference between age groups in the oxidative capacity (kO2) of the muscle. These results suggested that the manner of activation of the muscle could influence the emergence of an age-related difference in energetic pathway use.

To follow up on the potential influence of neural factors on energetic pathway preference, we evaluated the effects of contraction intensity, and thus potential age-related differences in motor unit recruitment and discharge rates, on ATP production (17). Isometric contractions at 20, 50, and 100% of maximal voluntary force were used to impose varying levels of recruitment (complete recruitment at ~50% maximum) and discharge rates (from submaximal to maximal). In this study, the older group once again showed no difference in oxidative capacity, but a greater reliance on oxidative energy production than the young group, and this difference increased with contraction intensity. In contrast, the young group had greater glycolytic flux overall compared with the older group, particularly at 50 and 100% of maximal contractile force.

This line of research has generated many interesting additional questions about the influence of aging on energy pathway selection during muscular work. Clearly, adequate mitochondrial function and a vascular network to support it are necessary elements for successfully meeting the energy demands of the muscle. Likewise, acute and chronic changes in neural activation of muscle seem likely to play a role in the relative dependence of older muscle on each energetic pathway. Mechanistic studies that investigate the integration of metabolism, particularly as it relates to mitochondrial function, will be important contributions to our understanding of energetics in aging muscle.

CONCLUSIONS AND WHAT IS NEXT?

The variety of approaches available for the study of mitochondrial structure and function, along with our growing understanding of the multiple roles that mitochondria play in vivo, make this a highly relevant and very exciting time for the study of muscle mitochondria and oxidative metabolism in our aging population. “Team science” approaches that clarify the interactions along the continuum of function from molecular to behavioral bring the promise of new insight about potential targets for preventing or reversing age-related challenges to bioenergetics. Emerging topics such as the role of age-related changes in neural function on muscle energetics, including neuronal mitochondrial function; the effects of factors such as reactive oxygen species production, chronic inflammation, and sarcopenia on mitochondrial structure and function; and the potential mediating effects of exercise training all require investigation. The importance of habitual physical activity is clear, and much progress has been made in this area in the past decade. Future study designs must include this essential factor to then allow an accurate focus on the remaining, direct effects of old age on mitochondrial function. Additional questions include potential sex-based differences in energetics (82) and how age-related changes in vascular function and perfusion of muscle may influence mitochondrial function in older adults.

Certainly, exercise cannot prevent all of the changes in muscle function that occur in old age, including mitochondrial function. It seems clear that mechanistic studies of ROS production, mitochondrial DNA copy number, mitophagy, protein modifications, etc., tell us “why” mitochondrial function is altered, while behavioral studies are needed to fully understand “why” this occurs. By applying a combination of approaches, researchers from a variety of perspectives have advanced our understanding of mechanistic changes in mitochondrial function at the molecular and cellular levels, as well as the functional changes in mitochondria observed in vivo. Our review of the literature highlights the point that in many cases, “altered” mitochondrial function may not necessarily mean mitochondrial “dysfunction” when it comes to aging skeletal muscle.

DISCLOSURES

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AUTHOR CONTRIBUTIONS


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