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Forum Review

The Regulation, Control, and Consequences of Mitochondrial Oxygen Utilization and Disposition in the Heart and Skeletal Muscle During Hypoxia

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ABSTRACT

The major oxygen-dependent function of mitochondria partitions molecular oxygen between oxidative phosphorylation and reactive oxygen species generation. When oxygen becomes limiting, the modulation of mitochondrial function plays an important role in overall biologic adaptation. This review focuses on mitochondrial biology in the heart and skeletal muscle during hypoxia. The disparate mitochondrial responses discussed appear to be dependent on the degree of hypoxia, on the age at exposure to hypoxia, and on the duration of exposure. These hypoxia-induced changes include modulation in mitochondrial respiratory capacity; activation of the mitochondrial biogenesis regulatory program; induction of mitochondrial antioxidant defense systems; regulation of antiapoptotic mitochondrial proteins, and modulation of mitochondrial sensitivity to permeability transition. The mitochondria-derived reactive oxygen species signal-transduction events in response to hypoxia also are reviewed. The cardiac and skeletal muscle phenotypic signatures that result from mitochondrial adaptations include an amelioration of resistance to cardiac ischemia and modulations in exercise capacity and oxidative fuel preference. Overall, the data demonstrate the plasticity in mitochondrial regulation and function that facilitates adaptations to a limited oxygen supply. Moreover, data supporting the role of mitochondria as oxygen-sensing organelles, integrated into global cellular signal transduction are discussed.
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INTRODUCTION

THE MODERN PUBLIC FASCINATION with the human capacity to endure under environmental extremes was ignited by Amundsen and Scott's race to reach the South Pole in late 1911. Marvel at the ability to endure hypoxia was fostered by the feat of Sir Edmund Hillary and the Sherpa Tenzing Norgay in reaching the summit of Mount Everest in 1953. Although the glamour of testing the limits of human endurance excites the imagination, the ability to adapt to hypoxia has much broader physiologic and pathologic implications. These include (a) relative hypoxia during fetal development; (b) short-term hypoxia during pulmonary infections or during recreational climbing to high altitude; (c) chronic intermittent hypoxia with sleep apnea and in athletes who live at sea level and train under relative hypoxia ("live-low, train-high" paradigm); and (d) chronic hypoxia associated with chronic lung diseases and in individuals/communities living at high altitude. As mitochondria are the predominant organelles for oxygen utilization and disposal, their regulatory response to the decrement in oxygen saturation is proposed to be an important mediator of the overall functional adaptation to hypoxia.

It is now becoming evident that mitochondrial biogenesis, the regulatory program controlling mitochondrial number, func-

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tion, content, and turnover, is tissue specific and reflects mitochondrial functional requirements in specific organs (35). In the heart and skeletal muscle, the predominant roles of mitochondria pertain to oxidative phosphorylation, calcium homeostasis, reactive radical species biology, and apoptosis (35). As oxygen depletion directly modulates oxidative phosphorylation and reactive oxygen species biology, this review specifically focuses on these two aspects of mitochondrial function. Moreover, it is well established that the cellular effects of hypoxia are both time dependent [*e.g.*, acute, intermittent or chronic, and degree dependent (*i.e.*, the absolute reduction in the partial pressure of oxygen)]. These parameters differ in the numerous studies cited, thereby precluding uniformity. However, these studies collectively enhance our understanding of the modulation of mitochondrial function and regulation in response to the temporal and relative deprivation of one of their prime "substrates," oxygen. Furthermore, investigation into the effects of hypoxia on mitochondrial biology has been more extensively investigated in skeletal muscle than in the heart. We review the known data in both muscle systems, albeit with the realization that the data are less comprehensive in the heart.

The relative cardiac and skeletal muscle reliance on mitochondria is evident in that the heart is predominantly dependent on mitochondrial oxidative metabolism, whereas skeletal muscle have a plasticity in oxygen reliance based on the presence of different fiber types [*i.e.*, slow twitch (type I fibers with a high concentration of mitochondria and myoglobin) and fast twitch (type II) fibers]. Type II fibers are further subdivided into II A and II B fibers; II A fibers are defined as fast oxidative fibers (exhibiting a faster contractile velocity than type I fibers but also containing a high myoglobin and mitochondrial content), and II B fibers are described as fast glycolytic fibers with less myoglobin and fewer mitochondria and a higher storage content of glycogen.

This review focuses on three main areas of mitochondrial biology in hypoxic cardiac and skeletal muscle. These include (a) the molecular regulatory events associated with the control of mitochondrial function and their response to hypoxia, (b) the adaptive effects of hypoxia and the specific role of mitochondrial changes in these programs, and (c) the role of the mitochondrion in oxygen sensing and redox signaling. Collectively these data should convey the current knowledge pertaining to mitochondrial adaptation and its regulation in enabling the heart and skeletal muscle to maintain contractile function despite changing oxygen saturation and delivery. As important, the deficits in our knowledge regarding the mitochondrial response to hypoxia are presented, and areas requiring further investigation are identified.

Areas not discussed in this review include mitochondrial NO biology; the role of myoglobin or the effects of hypoxia on oxygen delivery to muscle (*e.g.*, via sarcopenia or modulation in capillary density) and hypoxia-mediated modifications in mitochondrial subcellular distribution.

MITOCHONDRIAL REGULATION

Regulatory control of mitochondrial biogenesis

Mitochondrial biogenesis is defined as the regulatory control of mitochondrial turnover, content, function, and number to maintain diverse homeostatic demands across tissue types (56). The molecular machinery orchestrating this biogenesis program requires exquisite communication between the mitochondrial genome (which encodes for 13 proteins in four enzyme complexes of the electron-transfer chain) and the nuclear genome [which encodes for the majority of proteins necessary for homeostatic functions, including oxidative phosphorylation, reactive oxygen species (ROS) biology, and apoptosis (38)]. The conductors of intergenomic regulation of mitochondrial biogenesis include the nuclear regulatory proteins: nuclear respiratory factors (NRF) 1 and 2, the cAMP response element–binding protein (CREB), and transcription factor A of mitochondria (TFAM). These transcription factors regulate genes encoding the electron transfer chain complexes (27, 45, 79). Upstream, the transcriptional coactivators peroxisome proliferator–activated receptor γ coactivator 1 α and β (PGC1s) and the PGC1-related coactivator modulate the aforementioned nuclear regulatory proteins. This regulatory program activates target genes encoding regulatory enzymes of fatty-acid β-oxidation, oxidative phosphorylation (33, 34, 94), and genes that modulate antioxidant defenses, including nuclear-encoded mitochondrial antioxidant enzymes and the uncoupling proteins (83, 84, 87).

In the postnatal heart, mitochondria are highly abundant, constitut ~40% of total cardiomyocyte volume (7), and produce >90% of the cell's energy. The cardiac mitochondrial biogenesis program parallels the developmental changes in oxygen tension, hemodynamic load, and substrate preference, as evidenced by the acceleration of mitochondrial biogenesis in the perinatal period, with a peak in young adulthood and subsequent decline during senescence (7, 40, 49). In skeletal muscle, the mitochondrial content is dependent on muscle fiber type, and the relative proportion of fiber types appears to be partially modifiable, as evidenced by the augmentation of slow-twitch fibers in endurance athletes (86).

The biochemical/hormonal modulators of this program include ROS, AMP kinase activity, nitric oxide (NO), thyroid hormones, and fatty acid metabolites (43, 66, 91, 99). The complex interplay between the molecular and biochemical mediators is epitomized by NO, which not only upregulates the transcriptional machinery driving biogenesis (67) but also concurrently reduces oxidative phosphorylation flux *via* competitive inhibition of respiratory chain electron transfer (65).

Hypoxia-mediated effects on mitochondrial gene expression

Studies in the 1970s suggested that cardiac and skeletal muscle mitochondria adapt and augment mitochondrial oxidative phosphorylation capacity in response to chronic hypobaric hypoxia (57, 70, 75). This concept has been challenged by more recent literature that suggests that hypoxia alone is insufficient to induce augmentation in mitochondrial function (6). Rather, additional biologic stressors or cues such as concurrent exercise, cold exposure, early life (neonatal period) and/or intermittent normoxia must coexist with hypoxia to augment mitochondrial oxidative phosphorylation and ROS-modulating machinery (32). These biologic triggers and their underlying regulatory control are discussed further under the section on adaptive effects of hypoxia.

The effect of pure hypoxia on the mitochondrial machinery has been most comprehensively defined in animals and in cell-culture experiments. In adult rats exposed to hypobaric hypoxia

for 14 or 21 days, a progressive reduction in mitochondrial size and increase in mitochondrial number, without an overall change in the total cardiomyocyte mitochondrial volume, has been demonstrated (68). In these studies, a modest, albeit significant reduction in electron transfer chain complex activity and mitochondrial copy number was found after 21 days of hypobaric hypoxia (68). Similar studies have shown that genes encoding enzymes involved in fatty acid import and β-oxidation are also downregulated in response to chronic hypobaric hypoxia (20, 64). Together these studies suggest a modest reduction in mitochondrial respiratory capacity, although the functional consequences of these changes do not appear to be dramatic. This is borne out by the paucity of long-term consequences for communities living at high altitude (28, 30, 53).

The effects of 48 h of severe hypobaric hypoxia on skeletal muscle respiratory function and oxidative damage were evaluated in mice (46). After this subacute exposure, skeletal muscle analyses demonstrated increased oxidative stress, as measured by the degree of protein carbonylation, aconitase activity, and sulfhydryl groups, and a reduction in ADP-dependent respiration (46), as depicted in Fig. 1. Our understanding of the mechanisms modulating ROS generation (31) and the control of oxidative phosphorylation (21) under hypoxic conditions is advancing, although not yet complete. Undoubtedly, the nuanced balance between the ROS generation and oxidative phosphorylation in the mitochondria will depend, in part, on the degree and duration of hypoxia and the adaptive plasticity of the heart and skeletal muscle.

Despite these uncertainties, these studies show that in adult rodents, neither brief nor prolonged exposure to hypobaric hypoxia activates the mitochondrial biogenesis program but, conversely, induces mitochondrial damage from oxidative stress and shows a modest downregulation in oxidative phosphorylation capacity. The negative regulatory effect on mitochondrial biogenesis is also evident in hypoxic cell culture studies (74, 89).

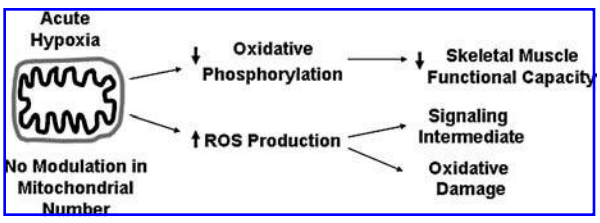

FIG. 1. Schematic of adaptive mitochondrial perturbations in response to acute hypoxia. These data have been more extensively assessed in skeletal muscle, and how the cardiac mitochondria respond to acute hypoxia appears not to have been well characterized.

ADAPTIVE EFFECTS OF HYPOXIA

Adaptive effects of hypoxia on mitochondria and concomitant cardiac ischemia/reperfusion injury

The ability of hypoxia to induce mitochondrial biogenesis may be dependent in part on the developmental stage, which in turn may reflect enhanced mitochondrial plasticity of cardiac and skeletal muscle mitochondria in the young. This is illustrated in neonates, where the mitochondrial biogenesis program is activated by the persistence of a hypoxic environment (16, 73). Four-week-old rats adapt to high-altitude prolonged hypoxia by exhibiting increased cardiac mitochondrial number with a modest reduction in mitochondrial mean volume and no change in state III respiration, compared with normoxic control rat hearts (16). In neonatal swine, persistent hypoxia drives increased myocardial cytochrome c oxidase I (COX I) activity associated with elevated COX I mRNA and protein levels (73). COX I forms complex IV of the electron-transport chain and is central for pumping protons across the inner mitochondrial membrane to maintain the proton motive force necessary for ATP synthesis. These mitochondrial adaptations to chronic hypoxia suggest the existence of an enhanced capacity to preserve oxidative phosphorylation for ATP generation during hypoxia in the neonatal heart. Furthermore, these adaptations to hypoxia in neonatal mammals confer increased tolerance to cardiac ischemia (5, 18). Immature rabbits adapted to chronic hypoxia exhibited improved cardiac ischemic tolerance associated with both increased bioenergetics, as measured by enhanced postischemic recovery of mitochondrial ATP and by enhanced mitochondrial K^+ ATP-sensitive channel (K_{ATP}) activity (5, 18). Proposed mechanisms whereby mitochondrial KATP channel activation enhances postischemic mitochondrial energetic recovery include the reversible inhibition of electron transfer during acute ischemia (72), resulting in blunted ROS generation (14, 78), or the ameliorative effects of K^+ influx into the mitochondrial matrix modulating the matrix volume or ionic content or both, and thereby promoting bioenergetic recovery during reperfusion (15, 72). This is schematized in Fig. 2.

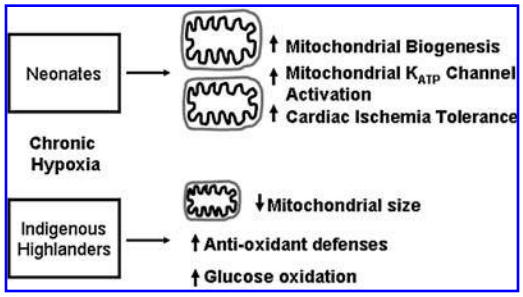

FIG. 2. Mitochondrial perturbations that accompany exposure to chronic hypoxia. The effects in the neonate differ substantially from those that develop in indigenous highlander communities that have lived at high altitude for thousands of years.

Adaptation to intermittent high-altitude hypoxia has been shown to confer protection against cardiac ischemia-induced arrhythmias and against myocardial infarction, thereby improving postinfarction survival in rats (3, 41, 57, 63, 97). This adaptive phenotype is proposed to result from activation of the mitochondrial biogenesis program [reviewed (56)] or via modulation of mitochondrial pore and/or channel biology or both. Interestingly, studies to demonstrate directly that the mitochondrial biogenesis program is operational in the heart in response to intermittent high-altitude hypoxia do not appear to have been performed. Nevertheless, this biologic stress is known to enhance cardiac resistance to ischemic injury (57). Conversely, data to support the modulation of mitochondria per-

meability transition pore (MPTP) function and mitochondrial KATP channel activity in cardiac ischemia resilience are more robust. The MPTP has a critical role in determining mitochondria and cell survival, and its inhibition has been shown to augment tolerance to ischemic injury (26). Consequences of MPTP opening include the entrance of water and solutes into the mitochondria, leading to matrix swelling, collapse of the inner membrane potential, uncoupling of the respiratory chain, efflux of Ca^{2+}, and release of small proteins such as cytochrome *c* [reviewed (9)]. Intermittent hypoxia reduces ischemia/reperfusion Ca^{2+} overloading and, in isolated mitochondria, prevents the opening of the MPTP and release of cytochrome c in the presence of high Ca^{2+} concentrations (97). In addition to its potential role in mitochondrial adaptation to chronic hypoxia, the mitochondrial K_{ATP} channel may also participate in mediating ischemic tolerance induced by intermittent hypoxia (3, 62, 95). Diazoxide, a mitochondrial K_{ATP} channel opener, afforded protection to ischemic injury in normoxic hearts but had no effect on the intermittent high-altitude hypoxic hearts, suggesting constitutive K_{ATP} channel activation in the latter group (3, 62). Conversely, selective mitochondrial K_{ATP} channel blockers abolished the protective effects of intermittent hypoxia but had no significant effect in normoxic groups (3, 62, 95). The effects of intermittent hypoxia on cardiac mitochondria are shown in Fig. 3.

Mounting evidence has shown mitochondria to be targets of cardioprotective signals and to participate in the protective effects orchestrated by ischemic preconditioning, a biologic phenomenon whereby transient ischemic episodes confer subsequent cellular tolerance to ischemic and oxidative stress (54, 55, 60). Hypoxic preconditioning demonstrated improved tolerance to anoxic injury associated with decreased degradation of mitochondrial membrane potential (92). The maintenance of the inner mitochondrial membrane potential seen in preconditioned mitochondria is indicative of an increased capacity to produce ATP after ischemia/reperfusion (52, 55, 69, 90). Mitochondria are also the target for various signals mediating intrinsic apoptosis, resulting in the release of the proapoptotic signal cytochrome *c* (8, 44). Hypoxic preconditioning significantly decreased the degree of apoptosis after severe anoxia (93). This resistance to anoxia is associated with the concomitant increase in the antiapoptotic protein Bcl-2 after hypoxic preconditioning (93), as shown in Fig. 3.

Taken together, these data suggest a multifaceted mitochondrial capacity to respond to ischemic injury after hypoxia-mediated perturbations either in neonatal tissue or in response to transient hypoxia-mediated signaling. The mitochondrial changes include (a) upregulating the mitochondrial biogenesis program, (b) modifying mitochondrial bioenergetics, (c) activation of the mitochondrial K_{ATP} channel, (d) abrogation of cell death processing *via* apoptosis by the upregulation of antiapoptotic proteins such as Bcl-2, and by (e) augmenting resilience to opening of the mitochondrial permeability transition pore. Additional mitochondrial adaptive programs that may underpin hypoxia-mediated "cardioprotection" include augmentation of antioxidant defenses. Ischemic preconditioning has been shown to upregulate mitochondrial antioxidant defense programs [reviewed (96)], but appear not to have been studied in the context of hypoxia-induced cardioprotection.

Effects of hypoxia on exercise capacity

The comparison of the relative maintenance of anaerobic and aerobic exercise capacity in response to hypoxia reflects, in part, mitochondrial function. Moreover, these changes can be assessed to evaluate the temporal effect of hypoxia on skeletal muscle aerobic capacity and, by inference, mitochondrial function. On ascent to altitude, it is well established that anaerobic performance is maintained and that aerobic performance is diminished (12). To test whether this balance is altered before acclimatization, exercise capacity was compared in individuals within hours of reaching an altitude of 10,500 feet and then again 3 days later (12). Anaerobic capacity was similar on both occasions; however, aerobic capacity, which was diminished by ~12% within the first few hours of ascent, recovered by ~50% at day 3 (12). These data may reflect altered mitochondrial function and demonstrate partial recovery before the restoration of P_{O_2} or the induction of the hematocrit or both. Direct evaluation as to whether this is due to modulation of mitochondrial oxidative activity has not been performed.

Exposure to intermittent hypoxia and concurrent exercise is a physiologic state in which the mitochondrial biogenesis program is operational. This state, termed the "live-low, train-high" paradigm, is transactivated by strenuous training under hypoxic conditions in athletes living at sea level. Here, it appears that a component of skeletal muscle adaptation to reduced oxygen availability at the time of maximal oxygen demand augments mitochondrial volume density and increases citrate synthase activity (23, 59). This increase in mitochondrial function is associated with an induction in $V_{O_{2,max}}$ in numerous studies (4, 58, 98), although it has been disputed by others (59). The discrepant effects on $V_{O_{2,max}}$ may be due to differences in the type and extent of training in these studies. The enhanced mitochondrial function is, however, strongly supported by the uniform induction of citrate synthase activity in all of these studies (4, 58, 59, 98). Moreover, the mitochondrial biogenesis regulatory program has now been directly implicated in orchestrating these changes, in that the upregulation of genes encoding PGC-1α, citrate synthase, and manganese superoxide dismutase has been shown to parallel the induction of $VO_{2,max}$ in endurance runners living at low altitude and training under hypoxic conditions (98); this is depicted in Fig. 3.

Geographically distinct communities that have lived at high altitude for generations demonstrate common physiologic traits that implicate evolutionary selection for similar genetic variants that evoke metabolic pathway adaptations advantageous in long-term hypobaric hypoxic environments (28, 77). The one physiologic adaptation to chronic hypobaric hypoxia that is evident in both the heart and skeletal muscle is the enhanced reliance on glucose oxidation at the expense of fatty acid oxidation, thereby improving the yield of ATP generated per mole of oxygen consumed (2, 29, 30, 76). In parallel with these perturbations in mitochondrial substrate preference, the Sherpas exhibit reduced mitochondrial volume density (37). Interestingly, an additional adaptation to attenuate the oxidative stress associated with living at high altitude is the upregulation of antioxidant defenses in muscle, as shown by the elevation of glutathione-*S*-transferase levels in Tibetans living at high altitude compared with those living at low altitude (22). These changes are shown in Fig. 2. Furthermore, the mitochondrial biogene-

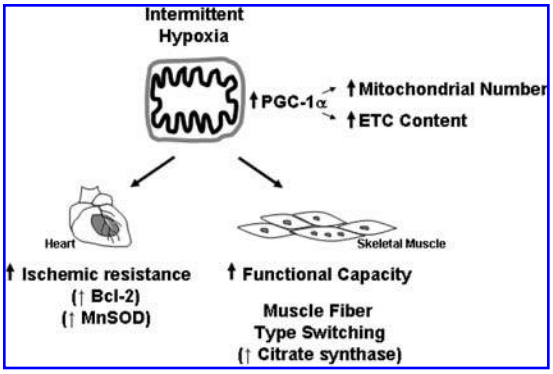

FIG. 3. Mitochondrial adaptations to intermittent hypoxia and to the "live-low, train-high" paradigm. Modulations under these conditions appear to align with the classic induction of the mitochondrial biogenesis gene regulatory program.

sis program appears to be "recruitable" in response to exercise training by individuals who live for prolonged periods at high altitude (17).

Overall, it appears that short-term hypoxia blunts exercise capacity because of limitations in aerobic capacity. Intermittent hypoxia coupled to increased exercise promotes the mitochondrial biogenesis gene regulatory program that augments exercise capacity and promotes skeletal muscle isoform switching. Mitochondria appear to adapt to chronic hypoxia by enhancing the preference for oxygen-efficient glucose oxidation and by upregulating their antioxidant defenses to prevent excessive oxidative stress under low-oxygen-saturation conditions.

THE ROLE OF THE MITOCHONDRION IN OXYGEN SENSING, SIGNALING, AND CELLULAR INJURY

Mitochondria, oxygen sensing, and reactive oxygen species–mediated signal transduction

An emerging concept evokes hypoxia-mediated mitochondrial orchestration of signal-transduction events modifying subsequent cellular responses. This paradigm inserts mitochondrial function into a "mediator role" in facilitating cellular adaptations to low-oxygen conditions. This notion is explored after the discussion of hypoxia-mediated perturbations in mitochondrial respiration that modulate hypoxia inducible factor 1-α (HIF-1α).

The regulatory control of HIF-1α and its transcriptional modulatory effects are central to the adaptive cellular response to hypoxia and include, in part, the upregulation of genes promoting glucose uptake, glycolysis, erythropoiesis, and angiogenesis [see reviews (42, 81)]. This regulatory role of HIF-1α in response to hypoxia is not discussed here except to review the role of mitochondrial control of HIF-1α stability. HIF-1α stabilization is required for its subsequent adaptive cellular regulatory control. The normal response to hypoxia promotes HIF-1α stability, which then promulgates HIF-1α transactivated adaptive gene-regulatory programs. However, under hypoxic conditions in cells depleted of mitochondrial DNA (ρ° cells) and in cells treated with mitochondrial respiratory inhibitors, numerous investigators have shown that HIF-1α stabilization is not evident (1, 13, 51). In contrast, other groups have shown a dissociation between ρ° cells and HIF-1α stabilization (19, 82, 88). These conflicting data may reflect differing oxygen concentrations in experiments or possibly cell-specific regulatory control. The effect of varying oxygen saturation is shown by Chandel and colleagues (80), who demonstrated that hypoxia permits HIF-1α degradation in ρ° cells, whereas anoxia promotes HIF-1α stabilization. The mechanism attenuating HIF-1α degradation under anoxic conditions is mitochondria and oxygen independent, and here prolyl hydroxylases rather than the electron-transport chain complexes function as the direct oxygen sensors (10, 36). Further to define the mitochondrial components that modulate HIF-1α stability, investigators have used genetic disruption of electron-transport chain components to determine their contribution to HIF-1α stability in response to changes in oxygen saturation. Cytochrome c null cells are unable to stabilize HIF-1α under hypoxic conditions (48). Furthermore, the genetic depletion of Rieske iron-sulfur protein in mitochondrial complex III also negates hypoxia-induced HIF-1α stabilization (11, 24). However, it appears that oxidative phosphorylation does not play a role in HIF-1α stabilization, but rather, complex III ROS signaling mediates adaptive HIF-1α regulation (11). This is supported by studies showing that electron-transfer chain perturbations that disrupt HIF-1α stabilization can be rescued *via* the introduction of ROS intermediates (13). Conversely, the stabilization of HIF-1α under hypoxic conditions can be disrupted by the administration of antioxidant compounds or enzymes (11) or *via* the direct attenuation of electron-transfer chain ROS generation or both (24). Despite conflicting data, the weight of evidence supports electron-transfer chain–mediated ROS signaling as a mitochondria-dependent component in HIF-1α stabilization and also suggests that fully competent oxidative phosphorylation may not be necessary for this mitochondria-mediated signal transduction (11). These data illustrate the "oxygen sensor" function of mitochondria whereby ROS generation facilitates the subsequent cellular transactivation of diverse HIF-1α–dependent adaptive events.

Hypoxia, mitochondria, and oxidative stress

The upregulation of antioxidant enzymes in skeletal muscle of Sherpas suggests that increased oxidative stress accompanies hypobaric hypoxia (22). The direct measurement of the consequences of hypoxia on oxidative stress in human skeletal muscle has not been extensively studied. However, electron microscopic examination of vastus lateralis muscle from individuals before and after completion of an 8-week sojourn in the Himalayas at an altitude >16,400 feet shows a doubling of the volume of lipofuscin deposits (50), a marker of oxidative damage to mitochondria (85). Additional studies in human subjects demonstrate that acute hypobaric hypoxia increases the burden of oxidative stress, as measured by plasma markers such as total glutathione content, lipid peroxidation, and thiol groups after 4 h of simulated high altitude (47). This is again supported by an increase in lymphocytic DNA strand breaks in individu-

als exercising to exhaustion at high-altitude compared with those exercising at sea level (61). Hypoxia-mediated oxidative stress in mouse skeletal muscle was directly examined (46). Here, 48 h of hypobaric hypoxia resulted in skeletal muscle oxidative stress, as seen by increased protein carbonylation and reductions in aconitase activity and sulfhydryl group content (46). Interestingly, preemptive therapy with vitamin E supplementation attenuated the evidence of enhanced oxidative stress (46).

Interestingly, the role of HIF-1α in the modulation of hypoxia-mediated mitochondrial ROS production has recently been suggested (39, 71). The mechanism underpinning this modulation of ROS results from HIF-1α transactivation of pyruvate dehydrogenase kinase 1 (PDK 1) (39, 71). PDK 1 upregulation inhibits the activation of pyruvate dehydrogenase, resulting in reduced glucose oxidation, an attenuation of tricarboxcylic acid cycle flux, and less reducing equivalents production (39, 71). Consequently, this leads to diminished electron transfer and less mitochondrial ROS generation (39). The composite of the interactions between ROS signaling and HIF-1α activity is illustrated in Fig. 4. Whether this regulatory control is operational in chronic hypoxia is unknown, but it does not align with the augmentation of glucose oxidation evident in the hearts of Sherpas (30).

Collectively, the data show that hypoxia-mediated mitochondrial ROS generation appears to have both signaling and oxidative damaging effects. The determination of which consequence of ROS generation dominates remains unresolved. Interestingly, even the mechanism whereby the electron-transfer chain generates ROS under hypoxic conditions remains speculative, and three separate hypothetical scenarios have been proposed [reviewed (25)].

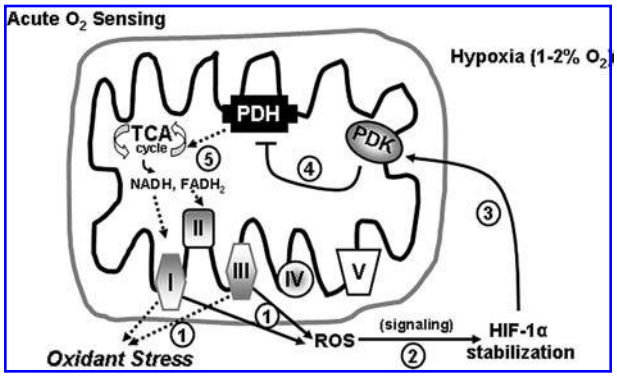

FIG. 4. Mitochondrial functioning as an intracellular signaling intermediate in response to acute/subacute hypoxia. A schematic of proposed mechanisms whereby mitochondria modulate cellular regulatory events through reactive oxygen species, signal transduction, and oxidative stress pathways. The numeric sequence shows that electron-transfer chain ROS production can promote oxidative stress or facilitate HIF-1α stabilization or both. HIF-1α upregulates PDK-1, which in turn inhibits pyruvate dehydrogenase. This slows the tricarboxcylic acid cycling and decreases the generation of reducing equivalents, resulting in the attenuation of electron transfer and subsequent ROS production. The *dashed arrow lines* depict pathways moderated by PDH phosphorylation of PDK.

CONCLUSIONS

Mitochondrial biology has a fundamental role in maintaining energetic and ROS homeostasis. The modulation of mitochondrial regulation and, by extension, function in response to hypoxia has important ramifications for cardiac and skeletal muscle function. A gathering body of evidence supports the concept that mitochondria exhibit varying degrees of plasticity in their response to hypoxia. This plasticity appears to relate in part to the age at the time of exposure and to the chronicity and number of exposures to hypoxia. Moreover, the selection of genetic variants over generations may be operational in augmenting tolerance to hypoxic environs in communities living at high altitude. The ability of mitochondria to adapt to hypoxic conditions can confer improved tolerance to cardiac ischemia through a variety of mechanisms, including upregulation of the mitochondrial biogenesis and antiapoptotic programs, via mitochondrial K_{ATP} channel activation, and *via* the enhanced resilience against mitochondrial permeability transition. Furthermore, skeletal muscle remodeling ranges from a decrease in aerobic capacity, a switch in muscle fiber type, the modulation in fuel preference for oxidative metabolism, to an induction of antioxidant defense programs. The role of mitochondria in ROS production in response to hypoxia is also addressed and shows that the regulation of ROS engenders both adaptive and maladaptive effects. Finally, the mitochondrial response to hypoxia is not restricted solely to changes in mitochondrial function *per se* but may help orchestrate signal-transduction events modifying cellular responses as a whole to low-oxygen conditions.

Although a significant body of work delineates mitochondria function, areas remain in which a relative lack of understanding in mitochondria biology exists, sometimes further confounded by conflicting data. This review has sought to summarize the current literature examining the regulation, control, and adaptive responses of mitochondria in heart and skeletal muscle during hypoxia.

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ABBREVIATIONS

COX I, cytochrome c oxidase I; CREB, cAMP response element–binding protein; HIF-1α. hypoxia inducible factor 1 alpha; MPTP, mitochondria permeability transition pore; NRF, nuclear respiratory factor; PDK 1, pyruvate dehydrogenase kinase 1; PDH, pyruvate dehydrogenase; PGC-1, peroxisome proliferator–activated receptor γ coactivator 1; ROS, reactive oxygen species; TFAM, transcription factor A of mitochondria.

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