High-altitude hypoxia. A challenging strain targeting cellular redox homeostasis

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ABSTRACT
After putting forward some evidence of hypobaric hypoxia as a particular stimulus causing systemic, tissue and cellular challenging strains, the present short review is focused on the current findings relating the reasoning of increased tissue generation of reactive oxygen and nitrogen species (RONS) when humans and animals organisms are exposed to high-altitude environments. In contrast to earlier concepts, hypobaric hypoxia-induced decreased physiological oxygen availability seems to be a prompt condition to cellular loss of *redox* homeostasis resulting in increased oxidative stress, which does not further augment upon reoxygenation. The apparently paradoxical condition of hypoxia-induced free radical production is regulated by very particular and specific cellular mechanisms, being mitochondria special sources and targets of RONS as well as critical organelles related to cellular death mediated by apoptosis.

Key-words: hypoxia, free radicals, oxidative damage, mitochondria, apoptosis

RESUMO
Hipóxia de altitude.
Um estímulo indutor de alterações na homeostasia redox
Após considerar evidências da hipoxia hipobárica enquanto um estímulo particular indutor de alterações deletérias a nível sistémico, tecidual e celular, a presente breve revisão focar-se-á sobre os principais mecanismos associados à produção adicional de espécies reactivas de oxigénio e nitrogénio (ERON) em humanos e animais submetidos a condições ambientais de hipóxia. Em oposição aos conceitos pioneiros, a diminuição da disponibilidade de oxigénio que se verifica em condições de hipoxia hipobárica é uma condição favorável à perda da homeostasia redox celular resultando num incremento do stress oxidativo, o qual não é agravado após períodos de reoxigenação. Esta aparente condição paradoxal de geração adicional de radicais livres é regulada por mecanismos celulares específicos, sendo as mitocôndrias fontes e simultaneamente alvos das ERON, bem como organelos críticos associados à morte celular mediada por apoptose.

Palavras-chave: *hipoxia, radicais livres, lesão oxidativa, mitocôndrias, apoptose*

1. INTRODUCTION

Oxygen deprivation, usually known as hypoxia is a constant threat to the animal kingdom. Acute or chronic exposure to conditions of high-altitude hypoxia has been considered an important challenge for the organism compromising body functioning, including cardiorespiratory, endocrine, metabolic, nutritional and thermal homeostasis[14, 38, 41, 46, 47, 56, 79, 94, 103, 113]. In the last years, evidence of systemic and local oxidative stress and damage, resulting from a wide imbalance between oxidant production and the antioxidant capacity, has also been reported during and after hypoxia exposure. Actually, under several distinct set up conditions conducted with humans and animals, data have revealed increased free radical production and signs of oxidative damage to lipids, proteins and DNA in several tissues. The present short review focuses on the effects of hypoxia on free radical production and on related disturbances of *redox* homeostasis. The impact of reoxygenation upon hypoxia, the main mechanisms behind RONS production in oxygen-deprived environments with particular emphasis on mitochondria both as source and target of free radical as well as the role of acclimatization on hypoxia-related oxidative deleterious effects will also be discussed.

2. HYPOBARIC HYPOXIA. A GREAT SYSTEMIC AND TISSUE CHALLENGE

High-altitude exposure has been considered an important challenging strain for the organism compromising the homeostasis of several physiological features such as cardiorespiratory, endocrine, metabolic, nutritional and thermal[14, 38, 41, 46, 47, 56, 79, 94, 103, 113]. Actually, in addition to hypoxia associated with the low barometric pressure, distinct environmental stimuli are also imposed by high-altitude, including extreme cold, temperature shifts, very low absolute humidity, increased ultraviolet radiation, lead to an exacerbated physiological stress[6, 51, 113, 116]. Barometric pressure decreases in an inverse proportion to altitude[117] resulting in the decrease of the partial pressure of inspired oxygen, which affects the "oxygen cascade" and diminishes oxygen diffusion capacity from the atmospheric air to the lungs, blood and tissues, i.e., inducing systemic and local oxygen deprivation[51, 95]. Dioxygen molecule is vital for mammalian cells serving as the ending electron acceptor in the oxidative process that mediates energy generation in mitochondria. Therefore, to counteract the limit oxygen availability, a compensatory fine tuning of the hypoxia sensing and signal transduction pathways eliciting central respiratory, circulatory and several peripheral processes is triggered[45, 46]. However, depending on the severity, the duration and the rapidity of the onset of hypoxia, the decreased levels of oxygen might severely compromise body metabolism promoting reversible or irreversible loss of tissue and cell homeostasis and leading to organic and functional decay. Given that even the acclimatized body remains hypoxic at certain severe altitudes[118], an organic deterioration is a condition that is often described in animals and humans after some time spent at severe high-altitude[13, 113, 125]. This deleterious organic phenomenon is frequently attributed to distinct factors usually experienced by dwellers in high-altitude sojourns, such as dehydration, starvation, physical exhaustion and extreme cold[118]. However, it seems that oxygen unavailability *per se,* if sufficiently severe, brisk or prolonged, plays a major role causing mental and physical deterioration. In fact, hypoxia exposure seems to result in significant weight loss, skeletal muscle degradation, poor appetite, slow recovery from fatigue, lethargy, irritability, an increasing lack of willpower to start new tasks[1, 15, 17, 30, 50, 80, 119], and, ultimately, in a benign illness related to neurological and respiratory symptoms that might result in high-altitude cerebral[41] or pulmonary edema[12]. Nevertheless, despite the scientific worldwide efforts to find out and better understand the specific mechanisms underlying these hypoxia-mediated deterioration occurrences, there are still many doubts and unanswered questions.

3. *REDOX* CHANGES INDUCED BY HYPOXIA - INCREASED OXIDATIVE STRESS AND DAMAGE

Amongst many potential biological mechanisms suggested to explain the different physiological constrains associated with high-altitude exposure, increased cellular oxidative stress has been reported during the last years. In fact, high-altitude hypoxia has been associated with enhanced generation of reactive oxygen and nitrogen-based species (RONS)

in both animals and humans. Probably linked to an increased production of RONS and to an inability of the antioxidant systems to counteract RONS effects, evidence of lipid peroxidation, protein oxidation and oxidative DNA damage have been described in humans exposed to altitude environments[7, 66, 77, 87]. It is important to note that in high-altitude other factors besides hypoxia, such as intense UV radiation, brisk air temperature variations and physical activity may also be related to RONS formation leading to enhanced oxidative stress[105]. For example, physical activity, such as that associated to mountaineering itself, could be an exacerbating factor of the oxidative stress and damage observed in many climbers and high-altitude dwellers.

Attempting to emphasize the role of hypoxia, a number of acute, chronic and intermittent hypoxia studies with rats[22, 97, 106] and humans[7, 9, 54] have been conducted in both hypobaric and normobaric conditions confirming high-altitude hypoxia *per se* as an independent modulator of cell and tissue *redox* status. Data from Magalhães and co-workers in humans and rats, both in plasma[69, 73] and skeletal muscle[70-72], are consistent with others reporting increased oxidative damage and an inability of the antioxidant system to cope with the increased production of RONS under hypoxia[7, 23, 52, 54, 66, 77, 89, 98, 106]. Increased lipid peroxidation measured by thiobarbituric acid reactive substances (TBARS) or malondialdehyde (MDA), and enhanced protein oxidation estimated by carbonyl derivatives groups or sulfhydryl groups (SH) were found at distinct levels of cell organization[69-73]. Moreover, DNA damage expressed as increased strand breaks and endonuclease III-sensitive sites was described in human skeletal muscle after 2 weeks of hypoxia[107].

This apparent physiological paradox was confirmed by *in vivo* direct measurements and *in vitro* assay of reactive oxygen species (ROS) production in different tissues and experimental conditions of hypoxia. Using electron paramagnetic resonance spectroscopy, Bailey et al.[10] identified a clear increase in blood and cerebral spinal fluid concentration of ROS in humans exposed for 18h to 12% of oxygen. Additionally, rats exposed to 10-min of normobaric hypoxia (10% O_2) revealed an increase in ROS-dependent dihydrorhodamine 123 fluorescence signal in mesenteric circulation by nearly 200% above control values (120). In isolated rat diaphragm strips loaded with dihydrofluorescein-DA, Zuo et al.[127] showed that the transition to low intracellular oxygen pressure prompt a burst of intracellular ROS. Vanden Hoek et al.[109] and Damerau et al.[28] also observed increased ROS production during hypoxia in cardiac myocytes. These data are consistent with earlier observations by Park et al.[84] using electron spin resonance (ESR) in intact hearts during ischemia and Kevin et al.[58] using *redox* sensitive fluorescent probes in the intact heart. Moreover, Duranteau et al.[33] showed that the extent of increase in dichlorofluorescin fluorescence in cardiomyocytes was proportional to the severity of hypoxia. These responses were attenuated by inhibitors that block the generation of ubiquinol at mitochondrial complex I and II, which suggest that hypoxia increases ROS production at complex III of mitochondrial electron transport chain.

In accordance, data from distinct studies dealing with antioxidants in humans[8, 23, 87, 102] and rats[52, 70, 97, 98] submitted to hypoxia clearly demonstrated benefits of such supplementation against oxidative stress and damage. Additionally, RONS produced in skeletal muscle during hypoxia contribute to decreased force production and both intracellular and extracellular antioxidants markedly attenuated the decline and loss of contractile function observed during hypoxia[76, 122].

Similar to other studies dealing with systemic[reviewed in 31, 67] or local[78, 88, 109] hypoxic or anoxic pathophysiological states, one can argue that hypoxia truly engenders a biological paradox, i.e., too less molecules of stable oxygen seem to generate more molecules of unstable and reactive oxygen with systemic and tissue deleterious consequences to organism. Therefore, although the use of oxygen as metabolic fuel allows a vital and attractive harvest of energy-rich phosphates per molecule of glucose, amino-acids or fatty acids, it seems that in oxygen depressed environments, such as high-altitude, a significant fraction of the oxygen utilized by the body undergoes a univalent reduction, resulting in the formation of RONS[6, 11].

4. SUB-CELLULAR SITES AND MECHANISMS OF FREE RADICAL GENERATION IN HYPOXIC TISSUES

Despite the considerations on hypoxia-induced oxidative stress and damage, many important questions concerning the possible mechanisms involved in this exceeded production of RONS under hypoxia remain to be adequately addressed. Currently, work on this research topic suggests that some of the mechanisms able to explain, at least in part, the increased RONS production in humans and rats submitted to hypoxia are: (i) a rapid microvascular inflammatory response resulting in increased formation of the pro-inflammatory mediator leukotriene B4 and in leukocyte endothelium adherence and migration into perivascular space via nitric oxide depletion[107, 120, 121]; (ii) the increased xanthine oxidase activity, resulting from cellular energetic and metabolic inefficiency and excessive calcium levels[49]; (iii) the increased spontaneous epinephrine oxidation[2, 55]; (iv) the enhanced nitric oxide ($NO^{\cdot}$) production stimulated by elevated levels of cytosolic calcium[42] or by increased activity of constitutive NO synthase[123] occurring during hypoxia, and (v) the accumulation of reduced equivalents in the electron transport chain (ETC) – the so-called condition of reductive stress[33, 57].

Despite the relevance of all the other above-mentioned mechanisms, this section will focus in particular on mitochondria as a RONS source and target during hypoxic conditions.

Mitochondria produce the energy required to drive the endergonic and vital biochemical processes of cell life through a rather well-coupled mechanism of oxidative phosphorylation[16]. Additionally, mitochondria are also critical organelles in the modulation of cellular osmotic regulation, *redox* status and pH control, signal transduction, and in the establishment of cellular calcium homeostasis[112].

Nonetheless, mitochondria respiratory function has been considered a relevant mechanism involved in cellular ROS production under conditions of oxygen deprivation[64, 85, 108]. In such hypoxic conditions, reducing equivalents seem to accumulate throughout the mitochondria ETC due to an inefficacy to transport electrons to oxygen. Actually, a hypoxia-induced decrease in V_{max} of cytochrome *c* oxidase seems to favour an increase in the reductive state of mitochondrial electron carriers upstream of cytochrome aa_3[33] favoring electron leakage and increased univalent reduction of oxygen with formation of ROS[20, 29, 33, 57, 76, 100]. Nevertheless, cytochrome *c* oxidase can hardly be considered as a prompt oxygen sensor under hypoxic conditions. Cytochrome *c* oxidase in rat hepatocytes required 90–120 min under hypoxia to undergo a decrease in *V*max[19], yet data from Chandel et al.[21] revealed that cells displayed hypoxia-inducible factor-1alpha (HIF-1a) protein accumulation, a key regulator of transcriptional responses to hypoxia, within 30 min. Based on the difference between the duration of hypoxia needed to elicit alterations in cytochrome *c* oxidase *V*max and the time required to stabilize HIF-1a, it is not credible that cytochrome *c* oxidase could serve as the primary oxygen sensor in hypoxia. Rather, it appears that mitochondrial complex III must possess inherent sensitivity to distinct oxygen concentrations allowing it to adjust its generation of ROS inversely with the oxygen tension[21, 39]. In fact, mediated by some hypothetical mechanisms that ultimately increase the transfer of an electron from the ubisemiquinone to molecular oxygen, complex III seems to be the primary site of ROS production during hypoxia, and a competent cellular oxygen sensor[for review see 40].

Depending on the severity and the duration of the hypoxia conditions, mitochondria themselves may also become targets from ROS resulting in the peroxidation of membrane lipids, protein oxidation and DNA cleavage[25, 61, 86], which can culminate in the down-regulation of the respiratory function[59, 90, 115], impaired ATP synthesis (5) and, eventually, in cellular death[24, 53, 59]. Data from Magalhães and coworkers[70] support the role of skeletal muscle mitochondria as a potential ROS source and as an oxidative target organelle under severe but physiological hypoxic conditions. In mice exposed to 48h of severe hypoxia equivalent to an altitude of 8500m, skeletal muscle mitochondria significantly increased superoxide radical production and protein oxidation. The activity of the superoxide-sensitive enzyme aconitase significantly dropped by approximately 30% in animals exposed to simulate high-altitude when compared to control. Moreover, vitamin E supplementation protected mitochondria from both the over-pro-

duction of carbonyl groups and aconitase inactivation induced by hypoxia. These results were consistent with data obtained elsewhere confirming the role of mitochondria as an important ROS source[64, 65, 108] and target[83, 124] under hypoxic conditions.

5. HYPOXIA-INDUCED MITOCHONDRIAL DYSFUNCTION AND INCREASES THE LEVELS OF APOPTOSIS

Under severe conditions of hypoxia, the oxidative-mediated mitochondrial dysfunction may contribute, at least partially, to some of the described skeletal muscle morphological changes[for review see 18, 48], including mitochondrial swelling, cristae degeneration and relevant accumulation of lipofuscin-like pigments[3, 68, 75], which have also been described in several other tissues[62, 96, 99] as being related to abnormal mitochondrial functionality and to cellular death fate. Some studies reported that under conditions of oxidative stress and increased cytosolic free calcium, mitochondria function can become severely affected[reviewed in 27]. In fact, decreased activity of some of the ETC protein complexes and/or citric acid-cycle enzymes[124], and inner membrane phosphoslipid peroxidation, including cardiolipin[81, 82] mediated by free radical oxidation seems to correlate well with depressed mitochondrial function. In accordance, hypoxia-induced oxidative stress significantly impaired mitochondrial respiration as demonstrated by decreased state 3, respiratory control ratio and ADP/O, and by increased state 4 with both complex I and II-linked substrates[70], which contributed to decreased mitochondrial phosphorylation efficiency and coupling between respiration and ATP synthesis. These assumptions were confirmed by the decreased respiratory rate in the presence of the uncoupler CCCP (carbonyl cyanide m-chlorophenylhydrazone) and by increased respiration in the presence of the ATP synthase inhibitor oligomycin. Vitamin E supplementation was able to attenuate most of the mitochondrial functional changes induced by hypoxia, which further supports the oxidative nature of mitochondrial dysfunction. Moreover, depending on the magnitude of the insult, alterations in mitochondrial membrane permeability mediated by distinct aetiologies may predispose to the activation of the intrinsic pathway of apoptotic cell death. In fact, the dysfunction of the adenine nucleotide translocases[44, 110] and/or the opening of the mitochondrial permeability transition pore (mPTP)[for refs see 26, 44, 60] might result in important bioenergetic consequences, namely (i) the loss of mitochondrial transmembrane potential, (ii) the uncoupling of the respiratory chain, (iii) the increased production of the superoxide radical, (iv) the disturbance of mitochondrial biogenesis, (v) the outflow of matrix calcium and glutathione, (vi) the release of soluble intermembrane proteins, and (vii) a burst of mitochondrial oxygen consumption, among other effects. Eventually, this scenario of mitochondrial dysfunction might entail a bioenergetic collapse that can culminate in the disruption of plasma membrane integrity (necrosis) and/or in the activation of specific cysteine apoptogenic proteases (caspases) that trigger the mitochondrial intrinsic pathway of apoptosis[for review see 43, 63]. In accordance, prolonged simulated conditions of high-altitude decreased inner and outer mice skeletal muscle mitochondrial membrane integrity and increased Bax/Bcl-2 ratio suggesting that severe and persistent hypobaric hypoxia exposure predisposes skeletal muscle to cell death[74]. In clear contrast, Riva and coworkers[92] showed an over-expression of Bax and Bcl-2 in skeletal muscle of young rats growing under moderate chronic hypoxia conditions (10% O_2). In this case, the graduate and less severe level of hypoxia exposure was translated into an increase of the Bcl-2/Bax ratio allowing a better protection against apoptosis. In fact, no sign of apoptosis was detected by TUNEL, annexin V-binding and DNA electrophoresis analysis. However, the protective effect of the acclimatization process against skeletal muscle oxidative stress already demonstrated elsewhere[71] and/or the hypoxia severity might probably explain, at least in part, this discrepancy in the results. In fact, recent data from molecular analysis brought by Schroff and Chandel[104] suggest that the outcome of the mixed signals generated by hypoxia is determined by the level of the hypoxic stimulus. The authors described a pathway whereby severe but not moderate hypoxia promotes apoptosis. The anti-apoptotic gene Mcl-1 is induced by hypoxia through HIF-1; however, under severe hypoxia, Mcl-1 is targeted for degradation by the proteasome, whereas under mild hypoxia remains elevated favoring sur-

vival. Nonetheless, mitochondria isolated from ventricular myocytes of rats exposed to intermittent hypoxia (6h/day at 5000m for 42 days) seem to be more resistant to the opening of the mPTP and to cytochrome *c* release after reperfusion injury[126]. Enhancement of the mitochondrial tolerance against calcium overload, most likely through the activation of mitochondrial ATP-sensitive potassium channels, might underlie the protective mechanism of intermittent hypoxia on cardiomyocytes submitted to reperfusion injury.

Unfortunately, studies concerning the influence of less severe hypoxic conditions, equivalent to those that many humans face around the world, on muscle mitochondrial function are still missing.

Nevertheless, data regarding the impact of such hypoxic conditions on whole muscle tissue, blood or plasma oxidative stress and damage markers suggest that less intense alterations would probably occur at mitochondrial level[74].

6. DOES REOXYGENATION UPON HYPOXIA CAUSES FURTHER INCREASE IN OXIDATIVE STRESS AND DAMAGE?

The injury perpetrated by the mechanism of ischemia/reperfusion is perhaps the supreme example of pathologic atavism in which intracellular RONS production exceeds the cellular defenses and can trigger massive stress and damage to the affected cells[114]. In fact, while RONS may be generated in a smaller extent during the ischemic period, far greatest production of these compounds occurs after reintroduction of oxygen during the period of reperfusion[34, 36, 111]. Accordingly, ultrastructural and metabolic cellular disturbances related with the decreased oxygen availability during ischemia and aggravated oxidative-mediated tissue harmful effects during the reperfusion period have been reported in several tissues[34, 36, 111]. In fact, enhanced capillary permeability, endothelial ROS production, and polymorphonuclear leukocytes mobilization with endothelial adherence and tissue infiltration have been described in post-ischemic reperfused tissues[4, 32, 101].

However, despite evidence demonstrating that systemic physiological hypoxia induced by real or simulated high-altitude exposure exacerbate cellular RONS production and oxidative stress, some studies also demonstrate that, in contrast with to the model of ischemia/reperfusion[for review see 35], the levels of RONS production[120] and oxidative stress and damage[54, 73] do not increase further during or after the reoxygenation period subsequent to hypoxia. A report from Magalhães and coworkers[73] revealed that 4 hours of simulated high-altitude exposure equivalent to 5500m significantly increased the burden of oxidative stress during the hypoxic period in humans; nevertheless, no additional signs of oxidative stress or damage were observed at the end of the pressurization/reoxygenation period. In fact, increased levels of protein and lipid oxidation, as well as reduced total antioxidant capacity were observed during the hypobaric hypoxia exposure, but no additional oxidative modifications were found after the reoxygenation period when compared with values obtained after the 4h of hypobaric hypoxia. In conformity with this findings, data from a study in which 8 male subjects were continuous and gradually exposed for 31 days to a simulated Everest ascend in a hypobaric chamber and re-pressurized in 2 days until sea level conditions (Operation Everest III-Comex'97) revealed that the conditions of oxidative stress and damage observed during the hypoxic period were not exacerbated after reoxygenation[54]. Moreover, in a study with rats submitted to 10-min *in-vivo* normobaric hypoxia (10% O_2) followed by a 10-min normoxic (21% O_2) recovery period, Wood and coworkers[120] showed an increase in ROS-dependent dihydrorhodamine 123 fluorescence signal in mesenteric circulation by nearly 200% above control values during hypoxia, which did not further increase, instead it progressively decreased towards control, during the recovery room air breathing period. Consistently, a report from Risom and coworkers[91] also demonstrated that the levels of DNA strand breaks and oxidatively damaged purine bases in human mononuclear blood cells significantly increased after 2h of hypoxia corresponding to 5500m above sea level, but did not further increase after 2h of reoxygenation.

All together, these data suggest fundamental differences in the underlying mechanisms responsible for *redox* status disturbances in humans and rats during conditions of physiological hypoxia-reoxygenation vs. the classical model of ischemia/reperfusion.

Actually, in clear contrast with studies dealing with ischemia/reperfusion[for review see 34, 93, 111], in which oxidative stress and cellular injury are severely aggravated during reperfusion, data suggest that the reoxygenation period does not further increase the levels of oxidative stress and damage induced by the previous hypoxic period. Nevertheless, data from Gonzalez and coworkers[37] demonstrated that, in contrast with previous reports expressed above, humans exposed during 3 days to an altitude of 3500m revealed enhanced erythrocyte membrane oxidative damage one day upon returning to sea level when compared to values obtain at altitude. Discrepancies in the timing of data collection upon returning to sea level conditions, tissue susceptibility and the sensitivity of the different techniques are possible explanations for these differences. Additional studies are required to clarify this important topic. Moreover, no data has been published regarding the impact of this phenomenon on skeletal muscle. Considering the heterogeneity of response of distinct tissues to the same insult and the fact that skeletal muscle has been considered very resistant to ischemia/reperfusion, additional studies should address the impact of hypoxia/reoxygenation in this tissue.

7. CONCLUSION

Despite being an apparent paradox, accumulating evidence demonstrate that oxygen deprived environments favour increased RONS generation and the occurrence of enhanced cellular oxidative stress. Data obtained in distinct experimental settings, models and tissues, including skeletal muscle, have reported unequivocal clues of RONS production by distinct cellular sources, including by mitochondria with consequent signs of oxidative macromolecular damage of lipids, proteins and DNA. Nevertheless, moderate hypoxia-induced RONS may be an adaptive cellular reaction to the disproportion between oxygen supply and demand, and play a yet incompletely defined role in the physiological response to hypoxia. As an example, mitochondria are currently considered determinant cellular hypoxic-oxygen sensors contributing with RONS for cellular adaptation depending on important *redox*-dependent signaling mechanisms. On the other hand, under severe hypoxic conditions, tissues may fail to maintain a normal *redox* homeostasis, which might result in cell dysfunction and, ultimately, in the activation of cell death pathways.

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