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REVIEW PAPER

High-altitude hypoxia induced reactive oxygen species generation, signaling, and mitigation approaches

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Abstract

Homeostasis between pro-oxidants and anti-oxidants is necessary for aerobic life, which if perturbed and shifted towards pro-oxidants results in oxidative stress. It is generally agreed that reactive oxygen species (ROS) production is accelerated with mountainous elevation, which may play a role in spawning serious health crisis. Exposure to increasing terrestrial altitude leads to a reduction in ambient O_2 availability in cells producing a series of hypoxic oxidative stress reactions and altering the redox balance in humans. Enormous literature on redox signaling drove research activity towards understanding the role of oxidative stress under normal and challenging conditions like high-altitude hypoxia which grounds for disturbed redox signaling. Excessive ROS production and accumulation of free radicals in cells and tissues can cause various pulmonary, cardiovascular, and metabolic pathophysiological conditions. In order to counteract this oxidative stress and maintain the balance of pro-oxidants and anti-oxidants, an anti-oxidant system exists in the human body, which, however, gets surpassed by elevated ROS levels, but can be strengthened through the use of anti-oxidant supplements. Such cumulative studies of fundamentals on a global concept like oxidative stress and role of anti-oxidants can act as a foundation to further smoothen for researchers to study over health, disease, and other pathophysiological conditions. This review highlights the interconnection between high altitude and oxidative stress and the role of anti-oxidants to protect cells from oxidative damages and to lower the risk of altitude-associated sickness.

Keywords Reactive oxygen species · Oxidative stress · High altitude · Oxidative stress markers · Reactive oxygen species signaling · Anti-oxidant supplements

Introduction

High altitude (HA), a special ecological environment arbitrarily defined as an elevation of 2500 m above sea level, can foster free radical formation due to resulting low partial pressure of oxygen in the blood and the resultant hypoxia. The hypoxic cells susceptible to oxidative stress, together with severe cold, high wind velocity, low humidity, high ultraviolet rays from the sun, dehydration, and lack of anti-oxidant nutrients in the diet, trigger a constellation of adverse effects, including acute mountain sickness (AMS) that can progress to potentially life-threatening complications such as high-altitude pulmonary edema (HAPE) or high-altitude cerebral edema (HACE) (Hultgren 1997; Askew 1995, 1997; Cymerman 1996; Huey and Eguskitza 2001).

Oxidative stress, a phenomenon commonly known as "Oxygen Paradox" (Goldfarb and Sen 1994) and implicated in various pathological conditions, occurs when reactive oxygen species (ROS) overwhelm the cellular anti-oxidant (AO) defense system, through either an escalation in ROS levels or a reduced capability of the cells to mount an effective anti-oxidant response. Evolutionarily, developed as an important part of the innate immune system (as a defense mechanism against bacteria), the term oxidative stress was used for the deleterious processes caused by ROS to almost all biomolecules in the 1970s and 1980s; however, later, German biochemist Helmut Sies defined it as an imbalance between oxidants and anti-oxidants in favor of the oxidants (Sies 1985, 1997; Rosen et al. 2009). One of the main sites of ROS production during high altitude–associated hypoxia could be the

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mitochondrial electron transport chain as the low availability of oxygen reduces mitochondrial respiration (Dosek et al. 2007; Mohanraj et al. 1998). At high altitude, ROS-generating systems are activated along with the repression of enzymatic and non-enzymatic anti-oxidant systems (Dosek et al. 2007; Mohanraj et al. 1998; Chang et al. 1989).

Indigenous people inhabiting mountainous high-altitude land are acclimatized to this environment through the evolution of mechanisms to relate oxygen supply and metabolism and subsequent energy generation (Hoppeler and Vogt 2001). However, individuals who travel acutely to altitude for short-to-moderate periods of time or intermittently, too high or too fast, jeopardize their normal physiology and experience reduced muscular function concomitant with hypoxia (Hoppeler and Vogt 2001; Brooks et al. 1999; Schoene 2001; Roach and Hackett 2001). Although it has been shown that performance at altitude can be eventually improved by physical training, it may not suffice to enhance performance upon return to sea level (Bailey and Davies 1997). Roach et al. (2000) have shown that exercise at altitude may aggravate AMS. Hypobaric hypoxia along with the stress generated from exercise may accentuate free radical–mediated oxidative tissue injury, thus exerting both short- and long-term consequences for health and performance (Bailey and Davies 1997; Bailey et al. 2000), and in fact, it has been suggested that the cumulative effects of hypoxic exposure may endure for some time even after return to sea level (Hornbein 2001; Neubauer 2001; Joanny et al. 2001). In the study of Operation Everest III, the level of oxidative stress was found to be parallel with the increase in altitude as the level of lipid peroxidation increased by 23% and 79% at 6000 and 8848 m, respectively (Joanny et al. 2001). In a study of US Marine Corps personnel training by Pfeiffer et al., a significant increase in oxidative stress associated with intense physical exertion, ultraviolet light exposure, and fluctuating temperatures at moderate altitudes was observed at the end of a 14-day field-training period (Pfeiffer et al. 1999). The present review draws upon the mechanisms for the generation of ROS, high altitude and oxidative stress, and the success in utilization of anti-oxidant supplements to ameliorate altitude-induced oxidative stress. Before going into detail, different reactive oxygen species source, formation, and biological significance are summarized in Table 1 along with the ROS generation that is schematically represented in Fig. 1a and b.

Hypoxia and ROS generation

With altitude barometric pressure of the atmosphere reduces and simultaneously reduces the inspired oxygen partial pressure in the environment. Thus, there is reduced partial pressure of inhaled oxygen to the cells and tissues causing hypobaric hypoxia. Acute and prolonged exposure to hypobaric hypoxia causes ROS formation resulting in oxidative stress. This stress generally comes up in any system when the free radicals and active intermediates exceed the system's ability to curb them disturbing the redox state of any aerobic cell. Normal intracellular metabolism and cytosolic enzyme systems are the source of ROS formation in both normoxic and hypoxic conditions. The only difference lies in low, normal, or higher ROS generation levels during both conditions which affect several body processes and physiological conditions accordingly (Fig. 2).

Mitochondrion-generated hypoxic ROS

The site of constant and major ROS production is mitochondria. Mitochondrial oxygen utilization and reduction through aerobic metabolism generates ROS like superoxide and hydrogen peroxide (Boveris and Cadenas 1982). This generation depends upon the resting or active mitochondrial state. As compared to cytosolic and nuclear, ROS production is about five to ten fold higher in mitochondrial matrix (especially in inner mitochondrial matrix). Furthermore, these ROS form hydroxyl radical generation (though the actual site of hydroxyl generation is not known) which depends upon the metabolic state (Richter et al. 1988; Richter et al. 1995). In mitochondria, oxygen sensing occurs at cytochrome oxidase because oxygen binds there (Bunn and Poyton 1996). Hypoxia elicits changes in the redox state of electron transport proteins of the proximal complexes upstream from the oxidase. This activity decreases the respiration rate due to limitation in ATP utilization and its hydrolysis by mitochondria during prolonged hypoxia. Majorly complex III in particular generates oxidants which stabilize the hypoxia-inducible factor -1 alpha (HIF-1α) during hypoxia (Chandel et al. 1997). Changes induced by hypoxia to redox state of cytochrome oxidase are not the sole mechanism which regulates HIF-1α activation; other mitochondrial complexes are also involved in its regulation. The vectorial transport of the ROS generation from complex III is released in such a way that more oxidants are released into the intermembrane space (IMS) and relatively less to matrix because the strong electric field is the driving force for superoxide anion to move to IMS. During hypoxia, the cytosol and IMS oxidation increases while mitochondrial matrix oxidation decreased due to increased production of ROS on the outer surface of the inner mitochondrial membrane (IMM) (Muller et al. 2004). This release of the ROS to the cytosol leads to further ROS signaling even if the effect of hypoxia has been diminished. Mitochondrial DNA (mtDNA) is more susceptible to oxidative damage as compared to nuclear DNA because of less protective histones, low DNA repair activity, and the constant formation of free radicals in mitochondria contributing to a highly reducing

Table 1 Important reactive oxygen species in oxidative stress

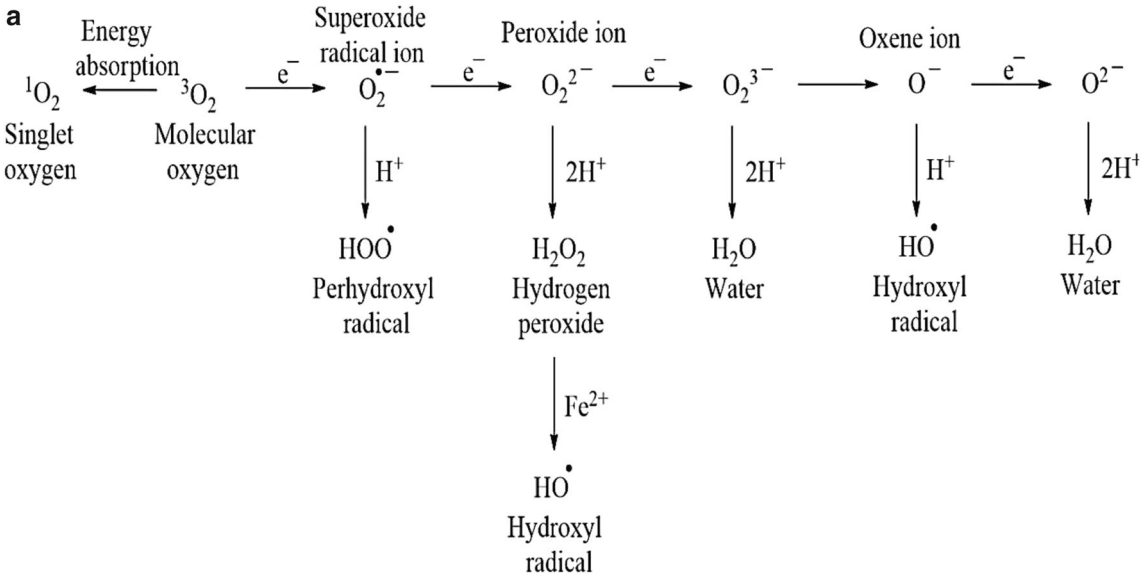
ROS	Formation	Source	Biological significance
$O_2^{\bullet-}$ (superoxide)	One-electron reduction of O_2	NADPH oxidase, cytochrome P_{450}-dependent oxygenase, xanthine oxidase, reduced coenzymes or prosthetic groups (e.g., flavins or iron sulfur clusters), reduced xenobiotics (e.g., adriamycin or paraquat), mitochondrial electron transport chain	Reaction with proteins, inhibition of mitochondrial function by inactivation of Fe-S centers
$HOO^{\bullet}$ (hydroperoxyl)	Addition of proton to $O_2^{\bullet-}$		Lipid peroxidation
H_2O_2 (hydrogen peroxide)	Addition of two protons and one electron to $O_2^{\bullet-}$, dismutation of $O_2^{\bullet-}$	Superoxide dismutase, amino acid oxidase, xanthine oxidase, NADPH oxidase, metabolic reactions in peroxisomes	Carcinogenesis
$HO^{\bullet}$ (hydroxyl)	Partial reduction of H_2O_2, Haber-Weiss and Fenton reactions, reaction of $O_2^{\bullet-}$ with H_2O_2, single-electron oxidation of water		Lipid peroxidation, damages deoxyribose backbone of DNA and all four DNA bases, induces strand breaks, base modifications, damage tumor suppressor genes, increase expression of protooncogenes
$RO^{\bullet}$ (alkoxyl)	Hydrogen abstraction from organic compound		
$ROO^{\bullet}$ (peroxyl)	Reaction of organic radical with oxygen		
ROOH (organic hydroperoxide)	Chain reaction of peroxyl radical		
$^1O_2$ (singlet oxygen)	Energy transfer		
$^3R'R''CO$ (triplet carbonyl)	Blue-green photoemission (e.g., formed via dioxetane as intermediate)		
HOCl (hypochlorous acid)	Conversion of H_2O_2 in the presence of chloride ion	Eosinophil peroxidase, myeloperoxidase	DNA-protein interactions, produce pyrimidine oxidation products, add chloride to DNA bases

environment (Ames et al. 1995). The 10609 variant is a mitochondrial SNP, and an association between the variant and high-altitude acclimatization was identified that polymorphism in the 10609 variant can affect mitochondrial function. The mtDNA 10609 variant promoted hypoxia-induced increase of intracellular ROS in Han Chinese population. mtDNA 10609T promoted hypoxia-induced increase of intracellular ROS and is a high-altitude polycythemia (HAPC) risk factor (Jiang et al. 2014). Also, there is some kind of activation of complex II of mitochondria. During hypoxia, complex II switches from succinate dehydrogenase to fumarate reductase resulting in ROS generation and succinate accumulation (Paddenberg et al. 2003). Hence, mitochondrial redox changes that track with cellular PO_2 cause ROS formation at complex III and trigger several functional responses. ROS release during hypoxia by IMM to the IMS leads to activation of transcription factors, most specifically hypoxia-inducible factors (HIF-1); also, FOXO-mediated transcription factors are activated upon cellular stress which further gets stabilized and impacts on various physiological responses of the body (Guzy and Schumacker 2006; Poyton et al. 2009; Hamanaka and Chandel 2010).

Hypobaric hypoxia activates other ROS-generating systems

During hypoxic conditions, $NO^{\bullet}$ is generated by the mitochondrial respiratory chain. Further, superoxides interact with nitric oxide radical and generate peroxynitrites (which is a strong oxidant). Peroxynitrite concentration consistently increases under hypoxia because of its dependence on oxygen level. These NO-derived free radicals are called as reactive nitrogen species. During hypoxic conditions, NO_2^- reductase pathway is activated. This pathway works during oxygen-limiting conditions which produces mitochondrial NO and further reduces NO_2^- to NO via the respiratory chain route and has been proven in rats, mouse brain mitochondria, and human endothelial cells (Zhang and Gutterman 2006).

ROS formation in vascular compartments affects the redox-dependent cell signaling functions and also decreases NO availability by its direct interaction with superoxide. Xanthine oxidoreductase (XOR) is a significant source of cellular ROS and further promotes oxidant-induced cell signaling reactions in hypoxic conditions. When the oxidative phosphorylation declines during low oxygen concentration, anaerobic glycolysis occurs which leads to raised concentration of



b

$O_2^{\bullet-} + O_2^{\bullet-} + 2H^+ \longrightarrow H_2O_2 + O_2$ (Non-enzymatic production of H_2O_2) (Equation 1)

$O_2^{\bullet-} + O_2^{\bullet-} + 2H^+ \xrightarrow{SOD} H_2O_2 + O_2$ (enzymatic production of H_2O_2) (Equation 2)

$H_2O_2 + e^- \longrightarrow HO^{\bullet} + OH^-$ (Partial reduction of H_2O_2) (Equation 3)

$Fe^{3+} + O_2^{\bullet-} \longrightarrow Fe^{2+} + O_2$ (Haber-Weiss reaction) (Equation 4)

$Fe^{2+} + H_2O_2 \longrightarrow Fe^{3+} + HO^{\bullet} + OH^-$ (Fenton Reaction) (Equation 5)

$Cu^{2+} / Fe^{3+} + O_2^{\bullet-} \longrightarrow Cu^{+} / Fe^{2+} + O_2$ (oxidation of reduced transition metals) (Equation 6)

$O_2^{\bullet-} + H_2O_2 \longrightarrow HO^{\bullet} + OH^- + O_2$ (production of hydroxyl radical) (Equation 7)

$H_2O \longrightarrow HO^{\bullet} + H^+ + e^-$ (Single electron oxidation of H_2O) (Equation 8)

Fig. 1 **a** Schematic representation of reactive oxygen species generation. **b** Reactive oxygen species production: Dismutation of $O_2^{\bullet-}$ to H_2O_2 occurs either non-enzymatically (Eq. **1**) or through a reaction catalyzed by superoxide dismutases (SODs) (Eq. **2**). H_2O_2 may be fully reduced to water or partially reduced to hydroxyl radical (Eq. **3**), one of the strongest oxidants in nature, break down to $HO^{\bullet}$ in the presence of transition metals like Fe^{2+} or Cu^{2+}, called Haber-Weiss and Fenton reactions. In the first step, Fe(III) is reduced by $O_2^{\bullet-}$ (Eq. **4**), followed by oxidation by H_2O_2 (Eq. **5**). The reduced transition metals catalyzing the formation of $HO^{\bullet}$ in turn may be oxidized by $O_2^{\bullet-}$, propagating this process (Eq. **6**). The hydroxyl radical is also produced when $O_2^{\bullet-}$ itself reacts with H_2O_2 (Eq. **7**) or by single-electron oxidation of water (Eq. **8**)

hypoxanthine and xanthine and they both act as xanthine dehydrogenase enzyme system. Xanthine oxidoreductase exists in two isoforms: XO (xanthine oxidase) and xanthine dehydrogenase (a cytosolic enzyme) (XDH). XDH can be converted to XO by thiol oxidation reactions or phosphorylation. Only XO produces ROS, which causes oxidative phosphorylation of purine substrates with the formation of O_2^- and H_2O_2 and under the influence of hypoxia, H_2O_2 is formed more than O_2^- (Poss et al. 1996; Lanzillo et al. 1996; Lance et al. 1997; Teradat et al. 1992). Prolonged hypoxia increases XO and its precursor XDH activity in cultured lung endothelial cells. Hypoxia induced increase in both XDH and XO activities but did not convert XDH to XO. This hypoxia-induced increase in activity of XO (present in endothelial cell (EC)) is related to the release of superoxide by EC. Furthermore, superoxide increases intracellular hydroxyl radical in EC. Oxidative damage caused to EC by XO influences albumin passage by depleting intracellular ATP levels by altering calcium homeostasis and cytoskeletal architecture.

NADPH oxidase too leads to the formation of free radicals, given hypoxic conditions for 3 weeks. Also, chronic exposure in rats causes an increase in NOX4 mRNA. NOX enzyme

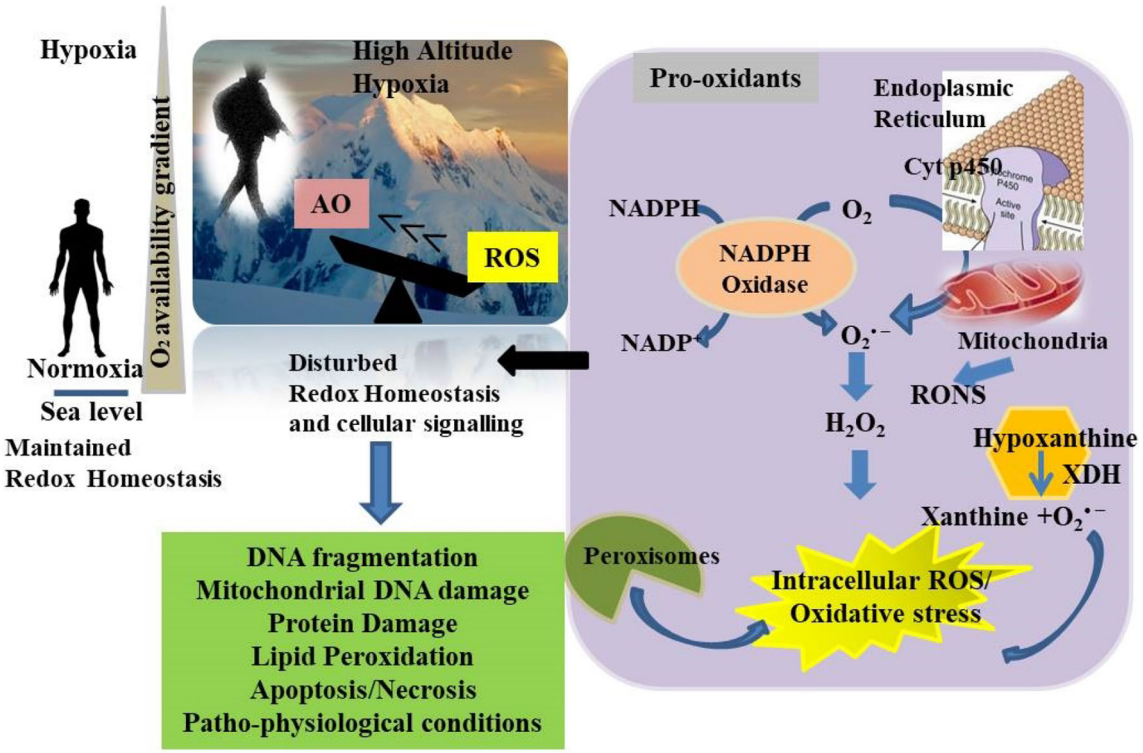


Fig. 2 ROS generation and disturbed redox homeostasis at high altitude. ROS: reactive oxygen species; AO: anti-oxidants; XDH: xanthine dehydrogenase

reduces the NO levels by reacting with it and forming peroxynitrite (Liu et al. 2006). Cytochrome P450–dependent microsomal electron transport system in mammals is another major source of ROS generation. CYP enzymes function as a part of NADPH/O_2-dependent microsomal electron transport system and one of the most important cellular sources of reactive oxygen species. CYP enzymes localized in the smooth endoplasmic reticulum of the liver contain heme prosthetic group in the form of iron protoporphyrin IX, and this group is essential for enzymatic activity. P450 reaction cycle yields different forms of reactive oxygen like superoxides and peroxides (Liu et al. 2006; Lewis 2002).

Oxidative stress markers and high altitude

Oxidative stress is a mechanism which damages cellular molecules and imposes several toxicological implications. High altitude imposes excessive ROS production by various mechanisms which are capable of damaging proteins, nucleic acids, polysaccharides, and lipids. Several studies have mentioned the existence of markers which can be set as indicators of stress induced by hypoxia-generated ROS in aerobic organisms (Strapazzon et al. 2016). At high altitude under hypobaric hypoxia, ROS production is increased (Irarrázaval et al. 2017). Among damages to aerobic cell, they are most susceptible to membrane oxidation commonly called as lipid peroxidation. High-altitude climbing/trekking/exercise (Debevec et al. 2017) all causes increase in lipid peroxidation during metabolically induced cell damage. Lipid peroxidation in membranes of various cells of humans or animals causes an increase in exhaled pentane gas. Free radicals generated during hypoxia-induced oxidative damage cause changes in membrane lipids and proteins and affect the membrane fluidity (Kappus 1985). Majorly affected by oxidative stress in membranes are the polyunsaturated fatty acids (PUFAs). This attack of ROS on membrane PUFAs causes the normal cell functions to alter (Magalhães et al. 2005). Besides lipid peroxidation of cellular membranes, the red cell membrane fluidity changes and filterability deteriorates at high altitude. A major factor behind this phenomenon is vitamin E deficiency/depletion during stress conditions. Level of vitamin E or extent of its depletion is directly proportional to membrane damage (Simon-Schnass 1994). Red cell membrane enzymatic activity is also affected during exercise at HA. Exercise at HA influences the RBC's anti-oxidant defense enzymes like superoxide dismutase and catalase (CAT) activity (Güzel et al. 2000). Higher concentration of thiobarbituric acid reactive substances (TBARS) in blood plasma was observed after the training exercise probably due to increase in lipid peroxidation and also oxygen-associated injury to muscle cell membranes (Wozniak et al. 2001; Ramazan et al. 2000; Bernabucci et al. 2002; Vani et al. 2010). Rats and mice exposed to intermittent hypoxia have

increased blood pressure and higher ROS generation. Redox stress generated during intermittent hypoxia exposure leads to activation of hypoxia-inducible factors and several consequences like increased levels of endothelin in blood which causes vasoconstriction, production of inflammatory cytokines, and abnormal lipid metabolism (Friedman et al. 2014; Gangwar et al. 2020).

It has been of no contradiction that, during the hypoxic condition, there is decrease in reduced glutathione (GSH) and increase in oxidized glutathione. Glutathione disulfide (GSSG) concentration in plasma is a potent indicator of oxidative stress and is closely related to cellular redox changes in body. GSSG levels increased significantly during high-altitude exposure (Magalhaes et al. 2004). A decrease in GSH and an increase in GSSG were also reported in humans exposed to high altitude (Vats et al. 2008). Decreased activities of glutathione peroxidase, cytochrome c oxidase, and superoxide dismutase in mitochondrial lung are reported during HA exposure and are good indicators of oxidative stress (Lemoine et al. 2018). Oxidative DNA damage can be detected by measuring formamidopyrimidine DNA glycosylase (FPG), 8-oxoguanine DNA glycosylate 1 (OGG1), 4-hydroxynonenal (HNE), F2 isoprostanes, 8-OHDg, and 8-iso-PGF 2 alpha (Moller et al. 2001; Janocha et al. 2017; Jefferson et al. 2004).

Oxygen and oxygen-derived species in cell signaling

ROS are intracellular chemical species which are able to trigger various biological and signaling events (Finkel 2011). ROS plays a role in proliferation, differentiation, and other cellular events in the body. At a low concentration, ROS initiate biological processes, regulate several intracellular signaling, cause cell-to-cell communication, and are a stimulus to pass biological information from the cell surface to nucleus causing a signal transduction or cell signaling. While oxidative stress results in a significant increase in ROS and this accumulation of ROS is more associated with oxidative damage of lipids, proteins, and DNA (Glasauer and Chandel 2013; Schieber and Chandel 2014; Cross et al. 1987). ROS appear to modulate a number of kinases and phosphatases, redox-sensitive transcription factors, and genes associated with it. Thus, for ROS to act as a secondary messenger, its production and utilization must be in a controlled manner. During normal conditions, this activity is controlled tightly but during hypoxic conditions, this activity is imbalanced. Cells when stimulated by ROS undergo the same signaling activation as when experienced during growth factor signaling, but the problem with ROS signaling is that they are a bit small in size and highly reactive. ROS reacts very randomly and rapidly too within very short distances. The first signaling molecules to be considered redox sensitive are transcription factors, NF-κB, AP-1 Sp-1, c-Myc, p53, c-Myc and early growth response factor 1 (EGR-1), metal-responsive transcription factor (MIF-1) and upstream stimulatory factor, glucocorticoid receptor (GR), and cyclic AMP response element-binding protein (CREB). ROS are involved in the receptor signaling propagation and are increased by ligand binding of epidermal growth factor (EGF), platelet-derived growth factor (PDGF), transforming growth factor beta 1 (TGFβ1), etc. (Martindale and Holbrook 2002). Non-receptor tyrosine kinases and serine/threonine phosphorylation are activated by several ROS species like H_2O_2 and O_2^-. One electron reduction produces O_2^- and this is converted to H_2O_2 by superoxide dismutase. H_2O_2 is a good signaling molecule as it can easily pass through membranes.

HIF stabilization during ROS signaling in hypoxic conditions

HIF-1 is a heterodimer which consists of two subunits, i.e., HIF-1α (oxygen regulated) and HIF-1β (constitutively expressed and not oxygen regulated). HIF complex is regulated by oxygen-dependent hydroxylation of specific hydroxylases by HIF prolyl hydroxylases (PHDs, member of family 2-oxoglutarate-dependent dioxygenase) like PHD1, PHD2 and PHD3. After hydroxylation, VHL (von Hippel-Lindau, a component of E3 ubiquitin ligase) protein binds and subsequent degradation of α subunit occurs by ubiquitin proteasome pathway. These PHDs cause α subunit to degrade during oxygen conditions, while it cannot degrade in oxygen-deficient conditions, resulting in dimerization and stabilization of HIF-1α with HIF-1β (Schofield and Ratcliffe 2005). When one moves to high altitude, there is attenuated PHD2 hydroxylase activity resulting in increased HIF-1α levels. Thus, it is very much clear that HIFs are key players in cellular responses in relation to limited O_2 supply. It is of no conflict that all PHD forms are essential in regulating HIF. It has been observed that PHD2 suppression alone can augment the level of HIF-1α more than HIF-2α and PHD3 suppression alone can increase the level of HIF-2α more than HIF-1α (Appelhoff et al. 2004). Silencing of PHD2 with siRNAs alone is sufficient to stabilize HIF-1α in normoxic human cells while silencing PHD1 and PHD3 in both normoxic and hypoxic conditions has no effect on the stability of HIF-1α (Berra et al. 2003). Thus, PHD2 can be called as a critical oxygen sensor. ROS and HIF-1α are involved in the hypoxic signaling processes. In humans, ROS could be involved in the first phase of regulation of HIF-1α gene expression, as indicated by the positive correlation between both HIF-1α gene expression and DNA oxidation markers (Kietzmann and Görlach 2005). ROS directly inhibit PHDs and thus overall increase in HIF-1α mRNA accumulation (Pialoux et al. 2009).

Heme-containing oxidases control ROS levels and HIF-1α under hypoxia. Heme-containing oxidase like NADPH oxidase converts O_2 to $O_2^{\bullet-}$ and afterward to H_2O_2, and it acts as signaling molecules mediating response to hypoxia. Heme-containing enzymes such as NADPH oxidases or cytochrome b-type NAD(P)H oxidoreductase or mitochondria may produce ROS depending on the PO_2 (Kietzmann and Görlach 2005). As discussed in the previous section, mitochondria produce ROS and during hypoxia redox potential of mitochondria changes which lead to overproduction of ROS and this may lead to participation in other transcriptional responses. Mitochondrial ROS is required in HIF-1α DNA binding activity (Chandel et al. 1998). It has been observed that in p° cells (deficient in mitochondrial DNA), there is no rise in ROS generation, HIF-1α protein accumulation and HIF-1α-dependent gene expression during hypoxia (Agani et al. 2000). Complex III of mitochondrial electron transport chain is required for the hypoxic stabilization of HIF-1α and HIF-2α and an increase in ROS links this complex to HIF stabilization. Using siRNA to suppress the expression of the Rieske iron-sulfur protein of complex III, hypoxia-induced HIF-1α stabilization is attenuated. Further, ROS production decreased as measured by a novel ROS-sensitive fluorescence resonance energy transfer probe. It is thus clear that mitochondria work as O_2 sensors and also signal hypoxic HIF-1α and HIF-2α stabilization by generating and releasing ROS to the cytosol (Guzy et al. 2005; Chandel et al. 2000). Crosstalk among various signaling cascades triggered by high or low ROS levels might influence the stability and further activity of HIF-1α.

Nuclear factor erythroid-related factor 2 as guardian to redox homeostasis during hypoxia

The transcription factor nuclear factor erythroid-related factor 2 (Nrf2) regulates anti-oxidant, anti-inflammatory, and cytoprotective genes during hypobaric hypoxia and is the guardian to redox homeostasis. During stress condition, Nrf2 is released from KEAP1 (Kelch-like erythroid cell–derived protein with CNC homology [ECH]–associated protein 1) (Oh and Jun 2017; Huang et al. 2002). After its release, it is translocated to the nucleus and activates genes which confer resistance to a variety of oxidative stress–related neurodegenerative molecules. All these genes contain this cis-acting ARE. Nrf2-ARE activation is a neuroprotective pathway providing short-term protection against chronic hypobaric hypoxia (Kensler et al. 2007; Rushmore et al. 1991). Other targets downstream to Nrf2, heme oxygenase (HO-1), SOD, thioredoxin (Trx), glutathione S-transferase (GST), and glutamate-cysteine ligases (GCLC and GCLM) are upregulated in response to hypobaric hypoxia (Sethy et al. 2011; Satoh et al. 2006; Innamorato et al. 2008).

Hypoxia and oxidative stress caused due to fluctuations in cellular oxygen affect HIF-1α (involved in the regulation and expression of genes important for cells to hypoxia) and Nrf2 (induced in response to oxidative stress and exert a cytoprotective role). Lung adenocarcinoma cell line (A549) expresses the high levels of NADPH oxidase 1 (NOX1) which is crucial for increased ROS production during intermittent hypoxia and further induces HIF-1α and Nrf2. It also regulates Nrf2 target unit thioredoxin 1 (Trx1). Inhibition of endogenous NOX1 inhibits the targeted expression of Nrf2 and Trx1 while overexpression of NOX1 recombinant protein results in an increase in Nrf2 and Trx1. Dual upregulation of both the factors overall increases HIF-1α signaling during intermittent hypoxia, establishing the fact that Trx1 may probably set a link between Nrf2 and HIF-1α. Nrf2 is considered a transcription factor regulating anti-oxidant and detoxification genes (Malec et al. 2010).

Cells surviving H_2O_2 treatment showed reduced mitochondrial components like cytochrome c/b. Cells showing Nrf2 overexpression prevented H_2O_2 from decreasing mitochondrial-related morphological changes and cytochrome b/c. Nrf2 is linked to the outer mitochondrial membrane as it has been proven that mitochondria produced from the myocardium of Nrf2 knockout mice undergo permeability transition, hypersensitive to mitochondrial toxins and has decreased mitochondrial membrane potential. Direct interaction of Nrf2 with mitochondria resulted in decreased oxidative stress in mitochondria (Strom et al. 2016). Also, in cardiomyocytes and mouse embryonic fibroblast culture, Nrf2 gene KO produces high ROS levels. It has been demonstrated that induction of HO-1 and NOX-1 causes removal of damaged mitochondrial units and maintains its function. Thus, Nrf2 has possibly the role in preventing oxidative stress–induced increase in calcium overload and preventing mitochondrial membrane integrity by preventing its membrane transition (Lee et al. 2003; Kovac et al. 2015; Piantadosi et al. 2008).

Peroxisome proliferator–activated receptor-gamma coactivator (PGC)-1alpha and SIRT are associated with HIF-1α activity in hypoxic ROS signaling

Hypoxic signaling increases HIF stabilization in cells and enhances ROS signaling in hypoxic cells. Mitochondria exposed to hypoxia are self-destructed via autophagy which helps in reducing ROS and provides sufficient oxygen supply to the remaining mitochondria. In skeletal muscle cells, PGC-1alpha activity is tightly coupled with HIF-1α activity. Mitochondrial biogenesis increases with rise in PGC-1alpha; this leads to increase oxygen consumption and intracellular hypoxia and thus HIF-1α stabilization. It is important to match the mitochondrial biogenesis and mitochondrial autophagy to match oxygen demand and oxygen supply (Ohagan et al. 2009;

Murray 2009). Sirtuins (SIRT, NAD-dependent deacetylases) are regulated in terms of ratio of NAD and NADH. High NAD levels activate sirtuins while high NADH levels suppress its activity. SIRT1 is known to downregulate HIF-1α activity by deacetylating it during hypoxia. This process of deacetylation is dependent on the NAD levels during hypoxia (Lin and Guarente 2003). Another member of the same family, SIRT6, is known to downregulate HIF-1α-mediated transcription by binding to chromatin on hypoxia response element (HRE) (Zhong et al. 2010). SIRT3 is most studied and its overexpression downregulates the ROS production and HIF stabilization. Similarly, if SIRT3 is downregulated, then it stabilizes HIF-1α and starts downstream signaling during exposure to hypoxia. SIRT3 downregulation during hypoxia increased levels of all putative HIF-1 α targets such as VEGF-A, phosphoglycerate kinase 1 (PGK-1), and phosphoinositide-dependent protein kinase-1 (PDK-1) (Bell et al. 2011). Physical exercise–induced ROS generations are important in modulating the several factors of mitochondrial biogenesis like MAP kinases, SIRT1 and PGC-1alpha. All these are modulated by redox state changes in the body. PGC-1alpha decreases ROS generation by activating anti-oxidant enzyme or by increasing the mitochondrial production. ROS-mediated increase in HIF-1α and its stabilization resulted in controlled angiogenesis during exercise. Also, exercise-induced ROS cause methylation in DNA and histone-associated post-translational modification (Radak et al. 2013).

Oxidative stress and inflammation in the brain at high altitude

There are cerebral symptoms like HACE and AMS at high altitude for which subclinical inflammation has been speculated in the brain. Upregulation of aquaporin 4 in astrocytes and water permeability by toll-like receptors has been seen to cause systemic inflammation in the brain by activation of corticotropin-releasing hormone receptor type-1 in central microglia, followed by local secretion of corticotrophin-releasing hormone in the brain (Song et al. 2016). Also, hypoxic stress and associated inflammation cause alteration in the functional integrity of the blood-brain barrier which is essential to maintain the central nervous system homeostasis. The blood-brain barrier disruption by increased paracellular permeability may cause alteration in the tight junctions and further systemic central nervous system drug uptake (Lochhead et al. 2017). It has also been observed that intermittent hypoxia induced injury in the brain and specifically affects cortical, subcortical, and hippocampal regions and causes apoptosis of neurons. This process selectively happens via oxidative stress and inflammatory pathways (Zhang et al. 2012). Thus, hypoxia and oxidative stress have severe pathological and neurological consequences.

Anti-oxidant defense system and its status in body

Detoxification of ROS is paramount to the survival of all aerobic life forms. In order to ameliorate the deleterious effects engendered by oxidants, the human body is equipped with an impressive repertoire of anti-oxidants, which can be classified as enzymatic and non-enzymatic or can be exogenously supplied through foods and supplements (Table 2). They play an effective role as free radical scavengers by donating their own electrons to ROS, thus counteracting the adverse effects of the latter (Fig. 3) (Kunwar and Priyadarsini 2011; Shinde et al. 2012; Birben et al. 2012). Anti-oxidant may work at three different levels in the body: (a) prevention, maintaining ROS formation to a minimum level; (b) interception, scavenging reactive species by using either catalytic or non-catalytic molecules; and (c) repair, removing and repairing damaged biomolecules (Sies 1986). On adaptation to stress conditions, they hold the capability to generate appropriate AO enzymes and transfer these enzymes to the right site at a specific time period and at a right concentration. The activity of anti-oxidants also produces free radicals which sometimes acts as pro-oxidant. Thus, it is necessary that a complete chain reaction occurs so that the generated radical is stabilized by resonance or steric hindrance. This is important in determining the efficacy of anti-oxidants. Supplementation can be given in the form of single vitamin, which sometimes may inhibit the radical load, or as mixture of anti-oxidants which provides a synergistic effect (by interaction between anti-oxidants). It has been observed that the anti-oxidant defense system weakens at high altitude, which, however, can be overcome by anti-oxidant supplementation or by natural anti-oxidant production in the body (Poljsak et al. 2013; Halliwell 2011).

Anti-oxidant supplementation studies to reduce the effect of hypoxic ROS

Free radical load generated at high altitude induces several metabolic and physiological changes. Oxidative stress acts as a pathogenic factor in various respiratory diseases and lungs by activation of several ROS-generating systems like xanthine oxidase. At HA, the effect of oxidative stress can be mitigated by exogenous nutritional supplements like β-carotene, quercetin, resveratrol, vitamin C and vitamin E that quench the singlet oxygen and other free radicals (Stellingwerff et al. 2019; Koivisto et al. 2019). Literature report reveals that the ventilatory threshold (VT) decreases upon ascent to HA, but improves with acclimatization. Subjects exposed to 4300 m of hypoxia with prior AO supplementation were shown to have improved VT upon acute, but not chronic exposure (Subudhi et al. 2006; Masella et al.

Table 2 Anti-oxidant defense in biological systems

System	Remarks	Role/function
Non-enzymatic		
α-Tocopherol (vitamin E)	Membrane-bound receptors Regeneration from chromanoxyl radical	Interferes with the propagation of free radical–mediated chain reactions
Ascorbic acid (vitamin C)	Water-soluble	Transforms vitamin E free radicals back to vitamin E, breaks the chain reaction of lipid peroxidation
Glutathione (GSH)		Reduces lipid peroxides and H_2O_2 leading to further oxidation of GSH to GSSG; participates in synthesis of proteins, nucleic acids, and leukotrienes and in detoxification of xenobiotics; regulates and activates transcription factors, such as AP-1, NF-κB, and Sp-1
Flavonoids	Plant anti-oxidants (rutin, quercetin, etc.)	Strong capacity to donate electrons or hydrogen atoms, chelate transition metal ions, inhibit lipid peroxidation by trapping lipid alkoxyl radical
Chemical anti-oxidants	Food additives, e.g., BHA (butylated hydroxyanisole) and BHT (butylated hydroxytoluene)	
β-Carotene (vitamin A)		Singlet oxygen quencher, reacts with peroxyl, hydroxyl, and superoxide radicals
Uric acid		Singlet oxygen quencher, radical scavenger
Plasma proteins	e.g., Ceruloplasmin	Binds copper and iron and ions, prevents $HO^{\bullet}$ formation
Enzymatic		
Superoxide dismutases (CuZn-SOD, Mn-SOD, extracellular (EC-SOD))	Cytoplasm, mitochondria, extracellular fluids	Dismutates superoxide anions to hydrogen peroxide and molecular oxygen
Glutathione peroxidase (GPx)	Cytosol and mitochondria1 matrix	Reduces hydrogen peroxide and lipid hydroperoxides to their corresponding alcohols using GSH as substrate
Catalase (CAT) (Heme enzyme)	Peroxisomal matrix and heart mitochondria	Reduces hydrogen peroxide to water and oxygen
Peroxiredoxin I, II, III, IV, V, VI (Prx)	Cytosol (Prxs I, II, III, V, and VI), peroxisomes (Prx IV and V), lysosomes, (Prx IV and VI), endoplasmic reticulum, extracellularly, Golgi apparatus (Prx IV), and mitochondria (Prxs III and V)	Reduces peroxides to corresponding alcohol
Thioredoxin (Trx)	Cytosol and mitochondria	Reduces hydrogen peroxide to oxygen and water, electron donor to peroxiredoxin I–V and glutathione peroxidases
Thioredoxin reductase (TrxR)	Extracellular space, nucleus, cytoplasm, plasma membrane, and mitochondria	Catalyzes the reduction of oxidized Trx
Glutathione transferase (GT)	Cytosol and mitochondria	Inactivates secondary metabolites, such as unsaturated aldehydes, epoxides, and hydroperoxides
Ancillary enzymes		
NADPH-quinone oxidoreductase	Dicoumarol sensitive	2-electron reduction of quinones
Epoxide hydrolase		
Conjugation enzymes	UDP-glucuronyl transferase Sulfotransferase GSH transferases	
Glutathione reductase (GR)	Cytoplasm and mitochondria	Reduces oxidized form of glutathione
Glutamate-cysteine ligase		Catalyzes the first production step of glutathione
NADPH	Glucose 6-phosphate dehydrogenase 6-Phosphogluconate dehydrogenase Isocitrate dehydrogenases Malate enzyme Energy-linked transhydrogenase	Acts as reducing equivalents
Transport systems	Liver and heart	GSSG and conjugate export for detoxification
Semidehydroascorbate reductase		
Methionine sulfoxide reductase		
DNA repair enzymes	Mitochondria	Correct errors resulting from oxidative damage

$$O_2^{\bullet-} + \text{Cu (II)/Zn-SOD} \longrightarrow \text{Cu(I)/Zn-SOD} \quad \textbf{(Equation 9)}$$

$$O_2^{\bullet-} + \text{Cu (I)/Zn-SOD} + 2H^+ \longrightarrow H_2O_2 + \text{Cu(II)/Zn-SOD} \quad \textbf{(Equation 10)}$$

$$\text{Catalase-Fe}^{3+} + H_2O_2 \longrightarrow \text{Compound I} + H_2O \quad \textbf{(Equation 11)}$$

$$H_2O_2 + \text{Compound I} \longrightarrow \text{Catalase-Fe}^{3+} + H_2O + O_2 \quad \textbf{(Equation 12)}$$

$$\text{E-SeH} + H_2O_2 \longrightarrow \text{E-SeOH} + H_2O \quad \textbf{(Equation 13)}$$

$$\text{E-SeOH} + \text{GSH} \longrightarrow \text{E-Se-SG} + H_2O \quad \textbf{(Equation 14)}$$

$$\text{E-Se-SG} + \text{GSH} \longrightarrow \text{E-SeH+ GSSG} \quad \textbf{(Equation 15)}$$

Fig. 3 Effective role of anti-oxidants as free radical scavengers: CuZn-SOD dismutation mechanism comprises two stages: (i) reduction of Cu(II) form of the enzyme by superoxide, releasing di-oxygen (Eq. **9**), and (ii) oxidation of reduced Cu(I) by another superoxide anion and two protons, generating H_2O_2 (Eq. **10**). (i) Reduction of H_2O_2 to H_2O by heme Fe^{+3} generating covalent $Fe^{+4}=O$ species with a porphyrin π-cation radical (compound I) (Eq. **11**) and (ii) oxidation of second peroxide molecule to O_2 by compound I releasing the ferryl oxygen species as H_2O (Eq. **12**). Oxidation of selenol gives selenenic acid (E-SeOH) (Eq. **13**), which reacts with reduced GSH to form a selenenyl sulfide adduct (E-Se-SG) (Eq. **14**). The active form of the enzyme is regenerated by a second GSH via the attack of E-Se-SG forming oxidized glutathione (GSSG) (Eq. **15**)

2005). In a study by Xu et al., rats supplemented with resveratrol, a natural non-flavonoid polyphenol phytoalexin, were exposed to a high-altitude hypoxia environment. The results revealed that resveratrol ameliorated the enlargement of the lung and spleen mediated by hypobaric hypoxia. Moreover, lowering of serum and liver malondialdehyde, plasma high-density lipoprotein and cholesterol levels, liver CCAAT/enhancer-binding protein alpha (C/EBPa), peroxisome proliferator–activated receptor g (PPARg), and HIF-1α and HIF-2β expression levels were observed. In addition, resveratrol increased liver SOD and fat hormone-sensitive lipase (HSL) activity, and Sirt-1 expression levels, together with the suppression of fat acetyl-CoA carboxylase (ACC), carnitine palmitoyltransferase (CPT-I) and fatty acid synthetase (FAS) activity. Thus, the data demonstrated the effective alleviation of hypoxia-induced oxidative stress by resveratrol along with the modulation of lipid metabolism, which is associated with the HIF signaling pathway (Xu et al. 2016). Sarada et al. evaluated the effect of β-carotene on oxidative stress induced by hypoxia on male albino rats. The increasing trend of malondialdehyde levels in plasma and tissues, and a concurrent decrease in blood glutathione, glutathione peroxidase, and plasma protein on hypoxia exposure were reversed on supplementation with β-carotene, suggesting it to possess potent anti-oxidant activities in reducing the oxidative stress induced by hypobaric hypoxia (Sarada et al. 2002). Quercetin, a flavonol widely present in fruits and vegetables, has been reported to exhibit anti-oxidant effects as free radical scavengers, hydrogen-donating compounds, singlet oxygen quenchers, and metal ion chelators, and lowers oxidative stress and lipid peroxidation. The reduction in hypoxia-induced increase in ROS and MDA production together with the restoration of anti-oxidant enzyme levels, such as GPx, GSH and SOD, by quercetin has been well documented in literature (Patir et al. 2012). A possibility of the use of cobalt for the prevention of oxidative stress induced by hypoxia has also been explored. According to a report by Shrivastava and co-workers, it was found that the administration of cobalt chloride attenuated the generation of ROS, and oxidation of lipids and proteins, while maintaining the GSH/GSSH ratio. The reduction in hypoxic oxidative stress by cobalt supplementation was achieved through the maintenance of higher cellular HO-1 and metallothionein (MT) levels mediated by HIF-1α signaling mechanisms (Shrivastava et al. 2008).

Pfeiffer et al. studied the effect of anti-oxidant supplement consisting of a daily dose of 20,000 IU β-carotene, 400 IU vitamin E, 500 mg vitamin C, 100 μg selenium, and 30 mg zinc in mitigating oxidative stress induced in US Marine Corps personnel training at moderate altitudes along with ultraviolet light exposure and fluctuating temperatures. Some diminution of oxidative stress indicators was brought about by AO supplementation; however, it was not effective in reducing all oxidative stress indicator levels back to baseline values (Pfeiffer et al. 1999; Chao et al. 1999). Furthermore, the efficiency of an anti-oxidant mixture comprising vitamin E, β-carotene, ascorbic acid, selenium, α-lipoic acid, *N*-acetyl 1-cysteine, catechin, lutein, and lycopene to reduce oxidative stress in US Marines undergoing 24 days of cold-weather field training at a moderate altitude was examined by Schmidt and co-workers. The results concluded that the supplement under investigation was not effective in attenuating the mean levels of oxidative stress in the entire test group; however, few individuals with low initial anti-oxidant status might have derived some benefit from it (Schmidt et al. 2002). In an investigatory study of L-arginine and anti-oxidant vitamins E and C on the cardiovascular performance of broiler chickens grown under chronic hypobaric hypoxia, it was found that arginine supplementation improved the pulmonary vascular performance of hypoxic chickens, with its enhanced effects observed on the addition of vitamins E and C. It was speculated that NO

bioavailability increased and oxidative damage decreased as a consequence of synergistic roles of arginine and anti-oxidant vitamins, thus improving cardiopulmonary performance (Bautista-Ortega and Ruiz-Feria 2010). On the other hand, in a study by Hagobian et al., no rise in plasma cytokines, primarily IL-6, TNF-α, and CRP concentrations, was observed for the AO-supplemented group at 4300 m (Hagobian et al. 2006). The effects of anti-oxidant vitamins on new born and placental traits in gestations at high altitude were studied by Parraguez et al., wherein it was concluded that vitamin C and E supplementation during pregnancy prevented hypoxia-induced oxidative stress and, thus, improved pregnancy outcomes (Parraguez et al. 2011). ROS production–associated oxidative stress at high altitude results in memory impairment, with the hippocampus being the most vulnerable towards hypoxic damage. Barhwal et al. investigated the effect of acetyl-L-carnitine on spatial working memory deficits together with oxidative and apoptotic damage in rats exposed to chronic hypobaric hypoxia at a simulated altitude of 6100 m. It was revealed that supplementation with acetyl-L-carnitine ameliorated working memory impairment, reduced oxidative stress, and inhibited hypoxia-induced apoptotic cascade (Barhwal et al. 2007). Alga *Spirogyra porticalis* inhabiting the Trans-Himalayan Region has immense potential to counter oxidative stress as a nutraceutical supplement (Kumar et al. 2019).

During HA exposure, there is increase in body's AO defense system such as increase in urate/uric acid (most abundant aqueous AO), which is responsible for contributing to 2/3rd of total anti-oxidant capacity in the human body. The factors which are responsible for increase in urate during hypoxia augment xanthine oxidase–associated increase in free radical load. Breakdown of adenosine by XO also induces increase in urate during hypoxia (Sinha et al. 2009b). There is a significant correlation between urate (present in plasma) and anti-oxidant capacity at HA hypoxia (Baillie et al. 2007). A decrease in GSH and an increase in GSSG were reported in humans exposed to high altitude affecting glutathione metabolism. These changes can be enhanced by supplementation of *N*-acetyl cysteine and vitamin E (Vats et al. 2008). Lifelong exposure to hypoxia results in a higher GSH/GSSG ratio, higher SOD activity, and overall higher anti-oxidant status in the body for proper acclimatization to HA (Sinha et al. 2009a). Vij et al. (2005) reported that sojourners traveling to HA and acclimatizing there for around 3 months may not show a protective AO defense system. TBARS were higher; non-enzymatic anti-oxidants like ascorbic acid and ceruloplasmin were significantly lower, along with marginal alteration in plasma total anti-oxidant status (TAS), glutathione levels, and SOD activity as compared to their basal values. However, a longer stay for more than a year at altitude led to a reversion of the TBARS levels back to pre-exposure levels. The improvement in TAS, SOD activity, glutathione, ascorbic acid and ceruloplasmin levels was observed, suggesting the activation of anti-oxidant defense system during prolonged high-altitude exposure (Vij et al. 2005). In a recent study, high altitude–induced fatigue was ameliorated using phenylethanoid glycosides from *Gansu Maxianhao* as they are potential anti-oxidants and regularize energy metabolism by controlling the adverse metabolic products, upsurge energy substances reserve thus help lessen fatigue caused by hypoxia exposure (Yu et al. 2020).

Patterson et al. suggested four possible reasons behind the lack of a measurable effect attributable to anti-oxidant supplementation: (1) vitamin anti-oxidant formulations based upon in vitro studies may be inefficient scavengers in vivo; (2) detrimental ROS may be compartmentalized at sites within the cell that are inaccessible by the administered anti-oxidant; (3) anti-oxidants may possess toxicities that mask their advantageous effect, such as pro-oxidant effects or scavenging free radicals useful for other processes such as cell signaling; and (4) only a group of people may be at a risk of increased oxidative stress (Patterson et al. 2000).

Thus, the determination of appropriate combination and amounts of anti-oxidant nutrients to mitigate oxidative stress yet permitting critical adaptations to hypoxia involving ROS and cell signaling to occur is a challenge that needs to be addressed.

Anti-oxidant supplementation in prevention of altitude-associated sickness

ROS, responsible for alterations in vascular endothelial permeability, results in high altitude–associated pathophysiological conditions like AMS, HAPE and HACE, which can be attenuated by AO supplementation. The treatments of choice include descent and supplementary oxygen; however, in case of severe illness, the combination proves to be an optimal therapy. In fact, de-induction may reduce symptoms of pathophysiological conditions; however, medical therapy comes into play when descent is not possible or supplementary oxygen is not available. Botao and co-workers showed that *Ginkgo biloba* (GB) extract exhibited a protective effect on HACE in rats, which could be attributed to its anti-oxidant properties and suppression of the caspase-dependent apoptosis pathway. It was observed that GB-treated subjects possessed reduced MDA concentration and active caspase-3 expression along with the increase in SOD activity and GSH concentration (Botao et al. 2013).

Patir et al. elucidated the role of quercetin in reducing hypoxia-induced cerebral edema using male Sprague Dawley rats as an animal model. It was demonstrated that quercetin-administered hypoxia-exposed rats exhibited no edema and inflammation in their brain sections. Moreover, the study revealed that quercetin possessed superior drug in

ameliorating high-altitude cerebral edema as compared to dexamethasone by acting as a potent anti-oxidant as well as an anti-inflammatory agent without any side effects (Patir et al. 2012).

Similarly, the general altitude-related sickness called as acute mountain sickness can be lowered by AO supplementation. An anti-oxidant mixture of L-ascorbic acid, α-tocopherol acetate and α-lipoic acid resulted in a reduced Lake Louise AMS score, increased arterial oxygen saturation levels, and calorie intake, suggesting that the attenuation of AMS and improvement in the physiological profile of mountaineers at high altitude could be achieved by exogenous delivery of water- and lipid-soluble anti-oxidant vitamins at the prescribed doses (Bailey and Davies 2001). AMS development with a gradual ascent to an altitude of around 5000 m directly correlated with an increase in serum hydroperoxides. Vascular damage was also observed with increased AMS symptoms. AO supplementation like AO vitamins had a major prophylactic effect, reduced oxidative markers and enhanced total GSH, and overall redox oxidative condition during HA hypoxia (Magalhaes et al. 2004; Araneda et al. 2005).

Supplementation with GB can probably act as a better alternative to acetazolamide, which is also used to curb symptoms of AMS. Prophylactic action of GB leads to hypoxic tissue protection, maintains the AO activity in tissues and prevents AMS with no probable side effects (Gertsch et al. 2004). As a consequence of oxidative damage to the endothelium, there occurs the leakage of cerebrovascular fluid resulting in AMS. In a study by Baillie et al., lowland volunteers ascended to 5200 m were given a dose of ascorbic acid, α-tocopherol acetate, and α-lipoic acid; however, it was observed that 69 and 66% of the anti-oxidant and placebo groups, respectively, had AMS, revealing that there was no benefit from AO supplementation at high altitude (Baillie et al. 2009).

Henceforth, it can be said that there are prophylactic benefits of these pharmacological agents, but the strategies to combat pathophysiological conditions at altitude must intend to define dosage, use, and combination of anti-oxidants which all can help enhance or benefit the near to healthy stay at high altitude for sojourns.

Conclusion

High altitude and free radical production leading to oxidative damage have received considerable attention. Increasing evidence from studies on cell line, rat and human models generate data which implicate the presence of ROS during acute and prolonged high-altitude exposure. ROS overload has a major impact from cell surface to cell signaling downstream to it affecting overall physiological profile of individuals at or exposed to high altitude. Dietary anti-oxidant or vitamin supplementation is evidently safe and a possibly effective intervention that can attenuate the ROS load and can prevent the occurrence of altitude-associated sickness. Thought has to be given to recognize when oxidative damage become possibly damaging enough to provide anti-oxidant therapy. Appropriate blend and quantity of anti-oxidant supplementation essential to provide control of excess ROS and also allow cell to execute cell signaling for critical adaptation to hypoxia is perplexing. Thus, understanding the pharmacological profile of reactive oxygen species, redox-sensitive intracellular signaling pathways, anti-oxidant enzyme family importance and anti-oxidant supplementation to detoxify ROS is imperative.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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