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Review article

Performance and altitude: Ways that nutrition can help

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ABSTRACT

High altitudes are a challenge for human physiology and for sports enthusiasts. Several reasons lead to deterioration in performance at high altitudes. Hypoxia owing to high altitude causes a breakdown of homeostasis with imbalance in several physiological systems, including the immune system. The reduction in mucosal immunity and inflammation and the predominance of the humoral immune response causes a condition of immunosuppression and an increased likelihood of infection. In addition, it is known that worsening of the immune response is associated with reduced performance. On the other hand, immunonutrition plays an important role in modulating the effects of physical exercise on the immune system. However, to our knowledge, few studies have evaluated the effect of nutrition on the immune system after exercise in hypoxia. Although the association between exercise and hypoxia has been shown to be more severe for the body owing to the sum of stressful agents, supplementation with carbohydrates and glutamine seems to play a relevant role in mitigating immunosuppressive effects. These findings, although limited by the fact that they are the result of very few studies, shed light on a relevant theme for sports physiology and nutrition and suggest that both supplements may be useful for athletes, visitors, and workers in high-altitude regions. The aim of this review was to discuss the effects of high-altitude hypoxia on the human body from the point of view of exercise immunology because it is known that transient immunosuppression after strenuous exercise and competition should be followed by reduction in training overload and worse performance.

Introduction

High-altitude regions are associated with sports, especially football and climbing. However, tourists, workers such as miners and pilots, and residents of these regions also suffer from the same rigors [1]. In South America, for example, each year ~4000 people visit the Aconcagua Provincial Park in the Argentine Andes, where the maximum altitude can reach 6960 m. Curiously, only 60% of these people visit the park because of the climbing options it offers. The other 40% are attracted to the park because of its natural beauty, despite the risks inherent to these regions. In the Himalayan region, during the second half of the 20th century, 784 people died in activities >6000 m. The highest risk in these regions is the reduction in oxygen partial pressure, which causes hypoxia [2].

The lower barometric pressure reduces the partial pressure of oxygen per unit volume, which, in turn, decreases the amount of available oxygen in the blood and tissues, characterizing hypoxia. It has been shown that, at high altitudes, body homeostasis breaks down, inducing physiological, biochemical, and behavioral alterations. Although the majority of the time these alterations are transient and reversible after return to normoxia, in some cases they may worsen and lead to death [1].

In this context, the aim of this review was to discuss the effects of high-altitude hypoxia on the human body from the point of view of exercise immunology as it is known that transient immunosuppression after strenuous exercise and competition should be followed by reduction in training overload and worse performance.

A review of the literature was carried out using source articles indexed by the ISI, PubMed, and Medline published between 1985 and 2018. We used the following terms: *high altitude, hypoxia, immune system, immune response, inflammation, supplementation, glutamine, carbohydrate,* and *physical exercise*. Based on the abstracts, we selected 80 articles with approaches that fell within the scope of this review. All descriptors were searched by the Boolean operators "or, and, not" in various arrangements to maximize the search and quality. No restrictions were made on age, sex, or experimental design, including studies with humans or experimental animals.

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High altitudes and hypoxia

At sea level, the barometric pressure (Pb) is ~760 mm Hg and reduces proportionally to the increase in altitude. With increases in altitude, the decrease in available oxygen for the cellular metabolism compromises the permanence and performance of the human being. The reduction in available oxygen includes several repercussions in the homeostasis of the biological systems. In this situation, the organism generates diversified responses to try to restore balance [3,4].

The first effects of hypoxia occur soon after the onset of altitude exposure. In a few minutes, different adjustments are made in various systems, including cardiovascular, endocrine, immune, skeletal muscle, and brain operation. Thus, there is a ventilatory response and increased heart rate and cardiac output, as well as an increase in the number of erythrocytes and hemoglobin and loss of muscle mass, among other changes [5].

In addition, heat loss, dehydration, and thermal imbalance may occur [6]. At an altitude of 8000 m, hypothermia may occur, because of the effect of cold usually present at high altitudes, as well as sudden death, which is closely associated with cerebral edema, predominantly caused by failure of vascular fluid endothelial regulation after a reduction in arterial oxygen [7].

However, all signs and symptoms resulting from exposure to high altitude are proportional to exposure time and hypoxia intensity, that is, the higher the altitude reached and the longer the stay, the more the body will respond to intense physiological responses compared with lower altitudes for less time [8–11].

Some studies may report this relationship when they demonstrate an increase in basal metabolic rate (BMR) in a manner that is dependent on altitude and time of exposure as well as generally reduced food consumption (i.e., the individual's energetic need). In fact, hypoxia may increase daily energy requirement by $\leq$600 kcal/d [10–12]. A reduction in body mass of $\leq$3% during 8 d of exposure to an altitude of 4300 m or $\leq$15% after a period of 3 mo at an altitude between 5300 and 8000 m have been described [4,12]. One of the causes of this phenomenon is the reduction in appetite and food consumption owing to the possible anorectic effects of hypoxia [10].

Reduced food intake and increased calorie expenditure may exert a negative effect on physical performance, even at moderate altitudes of 2000 to 4500 m [13]. It also may have secondary consequences, such as depletion of muscle glycogen stores and negative nitrogen balance [10]. Acute exposure to an altitude of 4300 m for 2 d increased the BMR by ~30% and even after a 21-d acclimatization, remained 17% higher than the BMR at sea level [9].

Sympathetic responses in high-altitude conditions in the Pikes Peak Mountains in Colorado at 4300 m during acute and chronic exposure have been extensively documented [8]. After 4 h on the mountain, the epinephrine serum was higher at rest compared with sea-level values. The release of epinephrine immediately contributes to improved oxygen supply via increased heart rate and systolic volume, thus increasing cardiac output, vasodilation, and tissue bronchodilation. It also contributes to an elevation in the metabolic rate associated with acute exposure to high altitude.

In contrast, the norepinephrine level found during acute exposure at rest is generally similar to that observed at sea level [14]; however, it is elevated when the exposure lasts for several days. The constant increase in the activity of the sympathetic nervous system (SNS) and level of norepinephrine over time exerts effects mainly through α-adrenergic receptors and directly influences arterial tissue flow, vascular resistance, blood pressure, and BMR [14].

Hypoxia and performance

Hypoxia owing to high altitudes dramatically reduces physical and sports performance [15]. There are some mechanisms proposed to reduce performance. Among them are the quick depletion of substrates more, cardiovascular overload, oxygen deficit, neuroendocrine alterations, energy deficit, and accumulation of metabolites such as hydrogen ions (H^+) and reactive oxygen species (ROS).

Despite these limitations, hypoxia can be an important strategy to improve performance. Therefore, strategies such as "sleep high and train low" or "sleep low and train high" have been used [16]. In light of the possible benefits stimulated by these strategies, they can have consequences for immune and inflammatory responses. This is a topic of great relevance as immunosuppression and infections are limiting to the practice of exercise, forcing the athlete to reduce the training overload or even interrupt it [17]. Consequently, adaptations to training and performance improvement are known to be associated with training overload. Ultimately, recurrent episodes of infections could result in less training, which could lead to worse performance.

Certain factors related to the relevance of the immune response and pro- or anti-inflammatory balance for performance during exercise, the effect that hypoxia has on the immune system, and how immunonutrition can contribute to the maintenance of ideal conditions for training in hypoxia conditions are discussed here.

Immune system and performance

Acute exposure to hypoxia for a few hours may change various immunologic parameters, including worsening of the innate immune response and elevated neutrophil numbers and natural killer (NK) cells [8,18,19]. It has been reported that acute exposure to hypobaric hypoxia at 5500 m for 20 min and 2 h of recovery in normoxia induced the same effects on neutrophil numbers and function. In vitro production of interleukin (IL)-1β and IL-2 in the supernatant of mononuclear cells obtained after lipopolysaccharide (LPS) stimulation was not affected [18].

Other studies have demonstrated that T lymphocyte–mediated immunity may be impaired [8,20], although the number and function of B lymphocytes does not appear to be altered by hypoxia. In addition, women exposed to altitudes of 5050 m for 1 and 21 d presented a decrease in $CD4^+$ T cells, without $CD8^+$ T-cell alteration [21].

Four hours at 4,000 m can induce neutrophilia and lymphopenia, similar to that occurring in a single exercise session [22,23], characterized mainly by a reduction in $CD4^+$ lymphocytes and a marked decrease in cell proliferation and activation [23]. However, as discussed in several studies, when individuals are at rest under conditions of hypoxia, there is an increase in the number and activation of NK cells and an imbalance in the T-helper (Th) 1/Th2 balance toward the Th2 response owing to the greater sympathetic-adrenal activation [22,24].

The environmental stress caused by elevated altitude alone is already sufficient to increase IL-6 serum, even under conditions of independent effort [25,26]. The influence of altitude for 4 d at 4350 m in 10 humans was examined. The results indicated that the level of serum IL-6 was elevated, whereas other proinflammatory cytokines, such as IL-1β, tumor necrosis factor (TNF)-α, and other inflammatory markers as C-reactive protein (CRP) remained unchanged [25]. Other studies observed elevation in IL-6 levels at 4300 m [8]. This increase can last 12 d after acclimatization [26]. Three nights at 4000 m promoted an increase in IL-6, IL-1 ra, and CRP, associated with elevated altitude-induced pulmonary edema [20].

Most of the genes expressed after hypoxia are regulated by hypoxia inductor factor-1 (HIF-1), a heterodimer composed of an α- and β-subunit. In normoxia, HIF-1α is rapidly degraded by the proteasome. However, HIF-1α does not undergo degradation, but instead acts as a transcription factor for genes involved in angiogenesis, vasomotor control, red cell maturation, energy metabolism, and cell proliferation [27,28].

In hypoxia, cells of innate immunity are HIF-dependent, that is, the HIFα causes them to produce ATP, stimulating aggregation, motility, invasion, and bactericidal activity, in addition to prolonging the life of neutrophils. HIFα can also modulate the acquired immune response by inducing the phenotypic shift from Th1 to Th2 cells because of the reduction in interferon (IFN)-γ production and the elevation of IL-10 secretion [28].

Fritzenwanger et al. found increased phagocytosis by neutrophils, decreased production of TNF-α and IFN-γ by monocytes and $CD4^+$ cells, respectively, and increased HIF-1α expression by peripheral blood mononuclear cells after 4 h of exposure to an altitude of 5500 m [29]. Furthermore, in the leukocytes, hypoxia provoked nuclear translocation of the p50 subunit, indicating that the 10% oxygen concentration in the air caused activation of the NF-κB pathway [29], responsible for the central role in cytokine stimulation proinflammatory drugs, TNF-α, and IL-6 [30].

In summary, the majority of published studies show that hypoxic environments stimulate monocytes and in vitro sensitization of T lymphocytes, resulting in increased production of inflammatory cytokines. On the other hand, in a culture of cells maintained in hypoxia (1% oxygen) for 18 h, there may be high TNF-α synthesis from healthy volunteer monocytes stimulated with LPS [31].

Immune system and exercise

The relationship between exercise and the immune system is based on neuroimmuno-endocrine interactions and immunonutrition because cells of the immune system express receptors for various hormones and neurotransmitters [32] and are influenced by the availability of energetic substrate [33]. The first hypotesis is production of catecholamines and cortisol increased by physical exercise to explain the immunomodulatory effect of physical exercise is related to production of catecholamines and cortisol directly affecting the immune system. The release or inhibition in cytokine production by immune and muscle cells also plays the role of modulating the neuroendocrine response, such as the immune response itself, owing to the well-described neuroimmuno-endocrine relationship [32,34].

Catecholamines (epinephrine and norepinephrine) are secreted by the adrenal medulla, binding to α- and β-adrenergic receptors. Their action increases quickly at the beginning of physical exercise and remains elevated during their performance, with the increase directly proportional to intensity. However, at the end of exercise they return rapidly to resting levels [35,36]. These hormones play a key role during physical exercise, acting to maintain nutrients for the muscles and brain and facilitating the transport of oxygen [37]. The actions on the immune system are mainly related to leukocytosis during exercise and decreased immune response after exercise [35].

Epinephrine and norepinephrine can decrease the cellular functions as immunologic cells exposed to catecholamines undergo alterations in the surface expression of molecular adhesion [38,39]. This action on the immune system is seen in vitro studies, demonstrating that in macrophages, catecholamines activate and modulate adrenergic receptors that inhibit LPS binding. The mechanism of action directly affects the phagocytic capacity of macrophages and inhibits the production of proinflammatory cytokines [40,41].

Cortisol is known as a hormone with high anti-inflammatory and immunosuppressive action, causing inhibition of lymphocyte proliferation, apoptosis of immature T and B lymphocytes, thymocytes, and splenocytes. In addition, the cortisol reduces NK cell activity [42,43]. Unlike catecholamines, during exercise cortisol has a late effect, acting mainly in the recovery phase, and its concentration is directly proportional to the intensity and volume of physical exercise [36,44].

One of the main mechanisms of action of glucocorticoids is the inhibition of IL-12 production by monocytes and macrophages. In fact, the IL-12 favors the cellular immune response against viruses and bacteria, with consequent inflammatory action. In addition, cortisol reduces the expression in IL-12 receptors in T lymphocytes and NK cells. IL-12 is an important cytokine for differentiation of the immune response. Its inhibition induces changes in the profile of circulating cytokines, leading to an effective decrease in IFN-γ and increase in IL-4. With the change in the cytokine profile, the cellular immune response is impaired, favoring the humoral immune response. The humoral response in turn is characterized by the production of anti-inflammatory cytokines IL-4, IL-10, and IL-13 and act in an antagonistic way to the cellular immune response [34].

The alteration in the cytokine profile characterized by the inhibition of IL-12 can generate cellular modifications, inhibiting the activation of macrophages and proliferation of T cells [34]. Cortisol also exerts a strong influence on the interaction of immune cells with the endothelium, affecting leukocyte trafficking to inflamed tissues. The mechanism of action occurs through inhibition of the expression of adhesion molecules in endothelial cells, which in turn affect the adhesion of leukocytes in the endothelium, reducing the immune system's response capacity [45].

Immune system and exercise in hypoxia

Several studies have demonstrated changes in the immune system after prolonged exertion [36]. When physical exercise is added to hypoxia, there may be a more pronounced effect on immune function [8]. It has been observed that a hypoxic environment alone can modulate the immune response similarly to physical exercise performed under normal atmospheric pressure conditions. However, exercise in high-altitude environments becomes a challenge for the body because hypoxia and physical exercise are considered stressors. The junction of two stress factors will result in a more pronounced effect on immune function, inflammation, and immunity of the oral mucosa [46,47].

In relation to pro- or anti-inflammatory balance, the concentration of cytokines and other inflammatory markers has been the subject of some studies [5,48]. IL-6 and acute-phase proteins showed high concentrations at 2, 4, and 20 h after a moderate exercise session on a bicycle for 3 h at 55% intensity of the maximum rate of oxygen consumption (VO_2 max) after 1 d at 4300 m [49]. However, there was no change in plasma TNF-α concentration. In this study, in addition to exercise, the authors imposed a diet with caloric restriction of 1500 kcal to participants to simulate the condition found by athletes and workers at high altitudes [49].

The combination of hypoxic exercise (11.8% oxygen = ~5070 m for 10 min, followed by 20 min of bicycle exercise at 60% VO_2 max) results in a more severe effect on the NK cell response compared with exercise in normoxia [18]. One study comparing two exercise intensities (40% and 60% VO_2 max) in both normoxia (partial pressure of inspired oxygen [PiO_2], 20.94%) and hypoxia (PiO_2, 14.65% = ~4000 m) indicated that there was no difference between TNF-α or IL-1 after 60 min of exercise in normoxia or hypoxia at the two intensities [50]. However, the concentration of TNF-α showed a tendency to increase at both intensities when the exercise was in hypoxia.

However, some studies have shown that acute exercise performed at a moderately elevated altitude (<3000 m) does not impose greater stress on the immune system than exercise at sea level, provided that the intensity is <60% of the VO_2 max calculated at normoxia [8,50–52].

With respect to monocytes, moderate exercise decreases the relationship between non-classical (inflammatory) and classical cells, reducing the expression of toll-like receptor (TLR)4 in non-classical cells and therefore reducing inflammatory response. In addition, the moderate exercise reduces serum TNF-α concentration and increses production of IL-1 ra, IL-6, IL-10, and TGF-β by T lymphocytes [53].

In relation to mucosal immunity, it has been shown that participants exposed for 2 d to 4350 m presented increased salivary flow and norepinephrine after exercise and recovery [54]. More recently, it was observed that 2 wk of exposure to 3000 m, three sessions/wk, four sets of five sprints of 10 s, with a 20 s interval of active recovery in hypoxia did not alter salivary immunoglobulin (Ig)A [55].

Supplementation and immune system in hypoxia

Glutamine

Glutamine may be classified as a non-essential amino acid (AA), that is, the need can be synthesized by the organism. It is the most abundant free AA in plasma and muscle tissue and plays a role in the immune system, acid–base balance, transport of ammonia, carbon skeleton donation for gluconeogenesis, nucleotide synthesis, and induction of the gene expression of a wide variety of proteins [56].

It is known that glutamine acts as a nutrient for rapidly dividing cells, such as enterocytes and leukocytes. Therefore, when supplementation is oral, high consumption by intestinal cells can make its availability to other regions of the organism unviable. Therefore, one way to attenuate enterocyte consumption is to administer supplementation at night, when immunosuppressive hormones are in reduced concentrations and immune-related activities begin to stand out against other tissues [57].

Numerous studies have demonstrated reduced plasma and tissue glutamine concentrations during and after intense and prolonged exercise. Among the mechanisms involved in this decrease, we highlight the elevation of cortisol concentration, which stimulates both muscle glutamine efflux and glutamine uptake by the liver. As a result, the increased supply of hepatic glutamine combined with the reduction in hepatic glycogen stores and increased cortisol concentration promote greater stimulus for hepatic gluconeogenesis from glutamine [58–60].

Another mechanism implicated in the reduction of glutaminemia during prolonged physical exercise is the change of the blood pH (metabolic acidosis) and favors increased uptake of glutamine by the kidneys [61]. The elimination of H^+ by the kidneys involves the use of ammonia from glutamine. Thus, loss of H^+ helps to maintain the acid–base balance [33,62]. The glutamine-buffering role may be especially important under high-altitude conditions because there is greater use of anaerobic pathways for energy production [63,64]. In addition, the increase in glutamine uptake by immune cells, especially when activated, may contribute to the reduction in exercise-induced glutaminemia, as previously demonstrated [65,66].

In metabolic terms, at the cellular level, the importance of glutamine is evidenced by the high activity of the glutaminase-phosphate–dependent enzyme that is the main enzyme in the process of degradation of glutamine and other enzymes of the glutaminolytic pathway. In fact, cells with a high capacity for glutamine degradation, such as lymphocytes, macrophages, and neutrophils, use glutamine at high rates to provide energy substrate for energy production, purine synthesis, and purimidines [67,68].

On the other hand, exercise induces an increase in the activity of immunologic cells; that is, the demand for energetic substrates including glutamine increases, so the decrease in substrates can drastically impact cell functionality, explaining in part transient immunosuppression after exercise [56,69].

Marathon and ultra-marathon runners supplemented with 5 g of glutamine in 330 mL of water just before and 2 h after exercise presented a reduction of the incidence of infections over a period of 7 d after exercise. Of the athletes who received supplementation, only 19% reported an infection, whereas 51% of the athletes who received placebo mentioned some type of infection during the study period [70].

Athletes investigated after oral ingestion of a glutamine solution (100 mg/kg body weight) presented elevation in glutaminemia after 30 min. which could return to baseline after up to 2 h [69]. In another study with physically active participants distributed into three groups (18.5% glucose polymer, a placebo of glutamine, and a polymer of glucose of 18.5% + 8 g of glutamine) showed that the oral glutamine supplementation elevated glutaminemia after intensive exercise and during the recovery period, suggesting that only one part of ingested glutamine was taken up by enterocytes [71].

Other study not found effetc of glutamine suplemmentation (5g in 330 ml of water) on IL-1, IL-2, TNF-α and pro/anti-inflammatory balance during marathon, no change was found or IL-1, IL -2, TNF-α, and inflammatory response [69].

Rzywkowski et al. investigated the action of supplementation of L-glutamine (17.5 g) and protein (68.5 g) offered during and after exercise and found a correlation between glutaminemia reduction and salivary IgA concentration after 2 h of exercise at 75% VO_2 max [72]. There was also a 15% reduction in glutamine concentration 2 h after exercise in the placebo group, whereas this reduction was not observed in the other groups that received L-glutamine and protein, without altering the concentration of salivary IgA.

In one of the few studies on the importance of glutamine to the immune system in hypoxia, elite runners were exposed to an altitude of 1640 m for 4 wk and a considerable elevation was observed in the incidence of upper respiratory tract infections (URTIs), accompanied by a reduction in plasma glutamine [73]. We recently evaluated the possible role of glutamine supplementation (20 g over 6 d) on the adaptive immune response after strenuous exercise in hypoxia, simulating an altitude of 4500 m. Our results indicate that supplementation influenced the Th1/Th2 balance toward the Th1 response after exercise, thus avoiding the immunosuppression that characterizes exposure to altitude, especially after strenuous exercise. In addition, supplementation prevented an increase in the concentration of IL-6, suggesting an immunomodulatory and anti-inflammatory role [74]. These results suggest that nutritional strategies, classically studied at sea level [36,58,60] can be efficient in high-altitude altitudes.

Regarding the immunity of the mucosa, hypoxia added to the exercise was not able to change the IgA concentration; however, under these conditions, supplementation with 20 g of glutamine at night for 6 d promoted improvement in the pro- or anti-inflammatory balance, stimulating an increase in inflammatory cytokines in the oral mucosa [75]. The significance of these results is not yet fully clarified, but an inflammatory environment may contribute to the early elimination of pathogens, which may result in a lower incidence of URTI.

Carbohydrates

Ingestion of carbohydrates (CHOs) during exercise has been associated with reduced cortisol responses, an influence in leukocyte count, and maintenance of phagocytic and oxidative activity of granulocytes and monocytes, which may attenuate the immunosuppression derived from exercise [33,36].

During exercise, CHO is taken up by skeletal muscle to resynthesize ATP, and during recovery it is used to resynthesize glycogen after exercise [76]. With changes in the CHO metabolism during exercise, the skeletal muscle produces and releases cytokines, notably IL-6, which act primarily on the liver, stimulating the hepatic release of glucose. In addition, IL-6 stimulates the cortisol production by adrenal glands to increase the availability of circulating glucose [77].

Because of this, CHO intake during prolonged exercise can influence the immune system through its effects on the level of plasma glucose and production of the stress hormone. Carbohydrate 6% solution supplementation was offered with 650 mL CHO or placebo before and after the run. The CHO group demonstrated an attenuated increase in plasma cortisol concentration and anti-inflammatory cytokines, IL-10, and IL-1 ra, which are involved in inhibiting inflammation [78]. In addition, CHO supplementation during exercise exerts an effect on the level of circulating IL-6 after prolonged exercise [79]. Robson-Ansley et al. conducted a randomized, double-blind study with nine participants who consumed a placebo or CHO solution (2 mL/kg body weight of a solution 8%) 2 h before, every 20 min during, and after exercise, performing 5 km on a treadmill running at 60% VO_2 max. The authors observed that supplementation was able to reduce the IL-6 after exercise [80].

Supplementation with CHO during strenuous exercise in hypoxia similar to a 4500 m altitude reduced IL-4 production by lymphocytes during and after exercise and induced the Th1 response mediated by the increase in heat shock protein-70, which reached highest levels after 2 h of recovery. No change was observed in serum cortisol concentration [74]. CHO supplementation also may contribute to improvement in mucosal immunity, increasing salivary flow after exercise, reducing TNF-α, and increasing IL-10 after 2 h of recovery [75].

Conclusion and perspectives

Hypoxia due to high altitude represents a challenge to human physiology and can be a constraint on performance. In high-altitude conditions, the immune system undergoes alterations that lead to immunosuppression, especially owing to inflammation and predominance of the adaptive humoral immune response, as demonstrated by the increase in Th1 response. Supplementation with glutamine and CHOs, which are important strategies at sea level, could be a useful tool to mitigate the effects of hypoxia. Preserving the immune response can help maintain high training overloads and thus ensure improved performance. However, more studies are needed to understand the role of sports nutrition and immunonutrition from a broader perspective, in relation to different sports modalities, times of exposure to hypoxia, intensity of hypoxia, and level of physical conditioning. In addition, special attention should be given to the application of the laboratory findings for studies on mountains. Unlike the laboratory, where environmental conditions are controlled, on mountains hypoxia is combined with other environmental conditions such as temperature and humidity and the effect of this set of conditions may result in responses partially different from those found in laboratory studies.

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