Nutrition and exercise can attenuate inflammatory and psychobiological changes in hypoxia?

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ABSTRACT

Exposure to hypoxia causes damage in several physiological systems, whose tissues are dependent on the O₂ supply. Recently, there has been growing attention on the immunosuppressive and inflammatory potential of the hypoxia, including stimulation, nuclear factor kappa B pathway in macrophages and Th2 response from lymphocytes. These changes may result in transient immunosuppression and happen at the same time to worsening of cognition and other psychobiological aspects. Furthermore, exercise and nutrition, especially glutamine supplementation may provide important role, not pharmacological partially reversing the effects of hypoxia. In fact, recent studies show that moderate exercise can improve cognition in people exposed to hypoxia while the exercise associated with glutamine supplementation can reverse the increase in inflammatory markers and the Th1/Th2 balance. This review aims to bring the light of the discussion about nonpharmacological ways to prevent the effects of hypoxia on the connection between the immune system and the central nervous system.

1. Introduction

Hypoxia is a common condition for people who live in high altitudes or visit these locations for work, leisure, tourism or participation in any sporting event. Furthermore, hypoxia is common in various pathophysiological conditions. For example, systemic hypoxia affects people suffering from sleep apnea, and cellular hypoxia is characteristically noted in various disease tissues, such as cancer and obesity.

The tissues that are sensitive and dependent on 21% oxygen exhibit alterations in physiological functions that impair the ability of the tissue to properly function in many cases. The magnitude of the body's response to hypoxia depends on two factors: exposure time and magnitude of hypoxia. The interest in the effects of hypoxia on the immune system has grown markedly in recent years with the emergence of evidence demonstrating that hypoxia is a potent inducer of inflammation and an immunosuppressive agent. Based on the communication between the immune system and the nervous system, more studies are needed to map the relationship between these two systems in behavioral changes caused by hypoxia. On the other hand, immunostimulatory and anti-inflammatory strategies, such as exercise and nutrition, has received minimal attention despite the importance of these agents in mitigating the effects of hypoxia. Thus, we discuss the importance of exercise and nutrition on the immune system during exposure to hypoxia and the possible impact on cognitive functioning.

2. Effects of hypoxia on the immune system and inflammation

Acute exposure to hypoxia can induce changes in several immunological parameters, including significant increases in neutrophils and lymphocytes, cell proliferation and natural killer (NK) cells [1–4]. Other studies have demonstrated that immunity...
mediated by T lymphocytes can be impaired by exposure to high altitude due to the changes in cell number and cell function, particularly cytokine expression [1,5,6]. Four hours of hypoxia may induce neutrophilia and lymphopenia, which are mainly characterized by a reduction of CD4 lymphocytes and a marked decrease in cell proliferation and activation [7]. In the innate immune response, the initial defense against pathogens depends on the activation of neutrophils, macrophages, and dendritic and NK cells. These cells can destroy the invading agents and transmit signals that amplify the adaptive immune response. The majority of gene expression after hypoxia is regulated by hypoxia-inducible factor 1 (HIF-1), a heterodimer composed of α and β subunits. Under normoxic conditions, HIF-1α is rapidly degraded by the proteasome. In hypoxic conditions, HIF-1α is not degraded. Instead, HIF-1α acts as a transcription factor for a number of genes involved in angiogenesis, vasomotor control, red blood cell maturation, energy metabolism and cell proliferation. These effects promote adaptation to hypoxia and mechanical stress [8].

In hypoxic conditions, cells are HIF-dependent. Thus, the change in HIF-1α produces adenosine triphosphate, thereby stimulating aggregation, motility, invasion and bactericidal activity as well as prolonging the life of neutrophils. With regard to adaptive immunity, increased HIF-1α production induces a phenotypic change in T helper lymphocytes (Th1) to generate Th2 cells that act by inhibiting Th1, thus reducing interferon-gamma levels (IFN-γ) and increasing interleukin 10 (IL-10) secretion [8].

The environmental stress exclusively caused by high altitude is sufficient to cause increased IL-6 in the circulation, which is likely mediated by IL-6’s hematopoietic action [9]. Klausen et al. examined the influence of exposure to a 4350-m altitude for four days in 10 humans, and IL-6 levels in the serum were significantly increased compared with other pro-inflammatory agents, such as the cytokines IL-1β, TNF-α and C-reactive protein, which remained unchanged [10]. Other studies revealed an increase in circulating IL-6 levels for 12 days at an altitude of 4300 m [11,12]. McNamee et al. submitted their volunteers to a vacuum chamber for 20 min at 5500 and reported an increase in white blood cell count, lymphocyte and absolute and relative CD16 NK-expressed receptor concentrations [13]. The number of these cells returns to pretest values after 2 h of recovery in normoxia. In vitro production of IL-1β and IL-2 in the supernatant of mononuclear cells obtained after stimulation with lipopolysaccharide was not affected.

During a 2-h exposure to 5500 m with 4 h of acclimatization to 4000 m in a hypobaric chamber, an increase in the rate of phagocytosis by neutrophils was noted, whereas phagocytosis by monocytes was not affected. A reduction in TNF-α produced by monocytes and IFN-γ produced by CD4 lymphocytes was noted in addition to the increase in HIF-1α expression by mononuclear cells. Moreover, exposure of blood mononuclear cells to hypoxia exclusively caused nuclear translocation of the A subunit p50, indicating that 10% of available O2 caused activation of the NF-kB pathway [14], which plays a central role in the stimulation of inflammation-mediated increases in TNF-α and IL-6 [15].

3. Effects of hypoxia and inflammation on cognition

Recent studies from our laboratory and other groups have drawn attention to the impact of hypoxia on cognitive aspects, which comprise a set of intellectual skills that facilitate reasoning, perception, communication, problem solving, learning, memory, attention, executive function and monitoring in addition to psychomotor functioning (reaction time, movement time, and speed of performance) [16–18].

A study by Wu et al. assessed the effects of acute exposure to hypoxia on the arithmetic performance of 16 teenagers exposed to different altitudes [19]. The authors demonstrated that the mean error calculating (addition and subtraction) and the reaction time increased significantly 30 min after 1 h of exposure to 3600 m, 4400 m and 5000 m.

Wu et al. also investigated the effects of hypoxia in 18 adolescents in normoxia and hypoxia equivalent to 2800 m, 4400 m and 3600 m in hypobaric chamber [20]. The volunteers were exposed to each altitude for 1 h. The researchers found that memory and reaction time deteriorated at all altitudes compared with normoxic conditions, and this effect was proportional to the worsening hypoxia.

The mechanisms responsible for worsening of cognition in hypoxia are not fully understood. Bijursten et al. investigated the effect of altitude on cognitive function and release of the S-100b protein in seven volunteers who climbed a mountain corresponding to 4554 m of altitude [21]. The participants performed cognitive tests. Acute mountain syndrome was assessed in these patients, and blood samples were obtained to measure S-100b levels [21]. The results indicate that an 80% increase in the serum concentration of S-100b protein occurred at the start of the ascent. In addition, the symptoms of acute mountain sickness progressed and cognitive functions were reduced, suggesting that neuronal death may be a mechanism.

Kohman and Rhodes suggest that pro-inflammatory cytokines, such as IL-1, IL-6 and TNF-α, contribute to the reduction of neuron survival in inflammatory processes, such as hypoxia, thus decreasing the proliferation and neuronal differentiation in new cells in the hippocampus and subsequently compromising various psychobiological aspects [22]. In fact, cytokines can act in the central nervous system to control hypothalamic functions and in the hippocampus and other brain structures that control mood, cognition, satiety, temperature, and sleep [23,24].

Additionally, hypoxia may activate glial cells in the hippocampus, and these cells can release factors involved in neuronal death and cognitive impairment [25]. One of the key cellular pathways of neuronal injury involves inflammation [26]. The neuronal damage induced by a simulated altitude of 7600 m for 7 days are potentially implicated in perception, memory and attention deterioration [11]. These results confirm those reported in a study by Chiu et al. indicating that hypoxia leads to neuronal death and reduced cognitive abilities [27].

Four hours of exposure to 5000 m can cause neuroinflammation via production of pro-inflammatory cytokines by microglia [28]. A recent study demonstrated that exposure to moderate hypoxia (equivalent to 2500 m) for 6 h per day for a 3-day period generated oxidative stress and an inflammatory response that lead to neuronal apoptosis in the hippocampus region and subsequent memory loss [28]. In addition, Smith et al. reported that hypoxia equivalent to 5000 m for 8 h during a 14-day period can lead to neuronal apoptosis in the frontal cortex of rats that exhibit cognitive functions caused by neuroinflammation [29].

4. Effects of exercise in hypoxia conditions on the immune system

Even when performed at sea level, exercise can stimulate or inhibit the immune response. Thus, moderate exercise has
immunostimulatory and anti-inflammatory properties, whereas exhaustive exercise is immunosuppressive and inflammatory. The immunomodulatory effect of physical exercise is described by two hypotheses that are not exclusionary [30,31]. The first hypothesis is related to the release of stress hormones during and after exercise, such as catecholamines and cortisol. These stress hormones are released in greater amounts during acute physical exercise [32-35]. The second hypothesis concerns the relationship among the immune system, exercise and nutrition [36,37], notably the role of glutamine, which is an amino acid that is sensitive to strenuous exercise and an indispensable substrate for immune cells [30,38,39].

The effect of exercise on the immune system includes a variety of physical reactions to stress, including thermal injury, such as trauma that causes changes like neutrophilia and lymphopenia induced by high plasma cortisol levels, changes in the pro/anti-inflammatory balance, reduced salivary IgA and changes in cytokotic NK cells [40]. These studies suggest that the immune system can be suppressed after intense and prolonged exercise [33,36]. Regarding the pro/anti-inflammatory balance, the concentration of cytokines and other inflammatory markers have been the subject of studies [41,42]. Notably, IL-6 levels increased 2, 4 and 20 h after a moderately intense workout with 55% of VO2max at an altitude of 4300 m compared with the same exercise at sea level [43]. On the other hand, no changes in TNF-α plasma concentrations were noted. However, in this study, the authors imposed voluntary additional exercise and a diet with a 1500 Kcal calorific restriction to simulate the conditions noted in athletes and workers at high altitudes, thus preventing definitive conclusions regarding the unique effects of exercise versus caloric restriction [44].

Exercise associated with hypoxic environments (equivalent ~5070 m followed by 20 min of exercise on a bicycle to 60% VO2max) results in a more severe effect on the response of NK cells than exercise under normoxic conditions [13]. Exercise under hypoxic conditions induced a more pronounced immune response than exercise performed at sea level conditions.

More recently, Blegen et al. conducted a study with two different intensities (40% VO2max and 60% VO2max) in both normoxic (PiO2 = 20.94%) and hypoxia (PiO2 = 14.65%, equivalent ~4000 m) conditions, and the results suggested no difference between TNF-α and IL-1 levels after 60 min of exercise in hypoxia and normoxia conditions [44]. These results were in contrast to those reported by at altitudes of 2000 and 4500 m [45]. Some studies indicate that acute exercise at moderately high altitudes (< 3000 m) does not induce more immune system stress than exercise performed at sea level given that the exercise is performed with moderate intensity. Thus, 40% and 60% of VO2max were calculated at sea level [1,40,44,46].

5. Benefits of nutritional strategy on inflammation

Glutamine is an amino acid that acts as a nutrient for cells, such as enterocytes, leukocytes and tumor cells. Considering the anti-inflammatory effects of glutamine before stressors, such as physical exercise, extreme environments and physiopathology conditions (including diseases such as cancer, sepsis, burn and trauma) [47], the maintenance of normal levels of glutamine can reverse the signs of inflammation caused by such conditions and that are related to life expectancy in severe conditions. However, little is known about the impact of hypoxia on the concentration of glutamine. Hypoxia is a stress factor for the body. Hypoxia in combination with physical exercise can trigger an imbalance in homeostasis.

Bailey et al. evaluated elite runners exposed to a moderate altitude of 1640 m for 4 weeks and observed a significant increase in the incidence of upper respiratory tract infection accompanied by a reduction in plasma glutamine [48]. Aksu et al. evaluated the influence of glutamine supplementation on the release of inflammatory mediators and intestinal injury in rodents under hypoxic conditions and demonstrated that the group under hypoxic conditions with supplementation exhibited attenuated gastrointestinal injury and a reduction in TNF-α concentrations compared with animals under hypoxic conditions without supplementation [49]. The anti-inflammatory effects of glutamine supplementation were similar to those noted under pathophysiological conditions characterized by severe inflammation [50,51].

Furthermore, some studies suggest that glutamine per se may have central role in modulating neurotransmitter synthesis and consequently altering cognitive function and mood. Cognitive function and mood state were assessed in the context of glutamine (5 g) nutritional supplementation for 3 weeks on growth hormone and insulin-like growth factor 1. Glutamine supplementation during two periods, morning and evening, in 42 volunteers with severe psychiatric histories was effective in improving short-term memory, concentration, attention and mood compared with the placebo group. These results highlighted the effect of supplementation on the release of insulin-like growth factor 1 [52].

The effects of glutamine are also noted in children, as demonstrated by the study by Kieviet et al. in which glutamine supplementation (0.3 g/kg per day) was administered to low weight babies from Day 3 to Day 30 after birth [53]. After 7 years, the same volunteers performed motor and cognitive tests. Beneficial effects with respect to attention, working memory, information processing and reaction time were noted in the test results for the children receiving supplementation.

6. New perspectives

Interestingly, strategies to minimize the effects of hypoxia on inflammation and cognition can be of great practical importance. As discussed above, hypoxia can induce inflammation, which may subsequently worsen psychobiological aspects. Nutritional strategies and exercise can stimulate the anti-inflammatory response by at least partially reversing the damage caused by hypoxia.

Recently, our group demonstrated that the performance of an acute session of exercise with moderate intensity was sufficient to reverse cognitive worsening, mood and sleep caused by 29 h under hypoxic conditions, which are similar to those at 4500 m [18]. To explain these results, we cannot exclude the partial contribution of moderate exercise on reversing the inflammation caused by exposure to hypoxia. As previously discussed, moderate exercise increased IL-10 levels and decreases TNF-α levels, thus creating an anti-inflammatory condition. Moreover, other studies demonstrate that acute exercise induces similar changes in the central nervous system, thereby reversing neuroinflammation caused by conditions, such as obesity [54,55].

However, exercise and nutrition can have even better effects. Our group evaluated the effects of glutamine supplementation on the regulation of lymphocyte-mediated responses and
inflammation in humans exposed to 5 h of 4500 m to simulate altitude hypoxia with and without strenuous exercise. The volunteers received 20 g of glutamine nightly for 6 days prior to hypoxia. Supplementation mitigated the effects of hypoxia on the parameters studied by stimulating the Th1 response, inhibiting the Th2 response and partially reversing the increases in IL-6 and TNF-α [9]. In view of the broad spectrum of consequences attributed to hypoxia, non-pharmacological strategies may be important to mitigate these effects. In this review, we propose that the worsening of cognition caused by hypoxia is due in part to the neuroinflammation, which can be subsequently mitigated by exercise and glutamine supplementation. However, experimental studies are needed to assess the validity of this hypothesis and ensure that this treatment is effective from a practical point of view.

**Conflict of interest statement**

We declare that we have no conflict of interest.

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