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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 O_2 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

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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 acts 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 4 350-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 4 300 m [11,12].

McNamee *et al.* submitted their volunteers to a vacuum chamber for 20 min at 5 500 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 5 500 m with 4 h of acclimatization to 4 000 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 O_2 caused activation of the NF-κB 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 3 600 m, 4 400 m and 5 000 m.

Wu *et al.* also investigated the effects of hypoxia in 18 adolescents in normoxia and hypoxia equivalent to 2 800 m, 4 400 m and 3 600 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 4 554 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 7 600 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 5 000 m can cause neuroinflammation via production of pro-inflammatory cytokines by microglia [20]. A recent study demonstrated that exposure to moderate hypoxia (equivalent to 2 500 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 5 000 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 cytotoxic 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 VO_2max at an altitude of 4 300 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 1 500 Kcal caloric 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 [43].

Exercise associated with hypoxic environments (equivalent ~5 070 m followed by 20 min of exercise on a bicycle to 60% VO_2max) 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% VO_2max and 60% VO_2max) in both normoxic (PiO_2 = 20.94%) and hypoxia (PiO_2 = 14.65%, equivalent ~4 000 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 2 000 and 4 500 m [45]. Some studies indicate that acute exercise at moderately high altitudes (< 3 000 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 VO_2max 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 1 640 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]. Akisu *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 4 500 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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References

[1] Walsh NP, Oliver SJ. Exercise, immune function and respiratory infection: an update on the influence of training and environmental stress. *Immunol Cell Biol* 2015; http://dx.doi.org/10.1038/icb.2015.99.

[2] Pedersen BK, Steensberg A. Exercise and hypoxia: effects on leukocytes and interleukin-6-shared mechanisms? *Med Sci Sports Exerc* 2002; **34**: 2004-13.

[3] Mishra KP, Ganju L. Influence of high altitude exposure on the immune system: a review. *Immunol Invest* 2010; **39**(3): 219-34.

[4] Ramsey G, Cantrell D. Environmental and metabolic sensors that control T cell biology. *Front Immunol* 2015; http://dx.doi.org/10.3389/fimmu.2015.00099.

[5] Hartmann G, Tschop M, Fischer R, Bidlingmaier C, Riepl R, Tschop K, et al. High altitude increases circulating interleukin-6, interleukin-1 receptor antagonist and C-reactive protein. *Cytokine* 2000; **12**: 246-52.

[6] Oliver SJ, Macdonald JH, Harper Smith AD, Lawley JS, Gallagher CA, Di Felice U, et al. High altitude impairs *in vivo* immunity in humans. *High Alt Med Biol* 2013; **14**(2): 144-9.

[7] Thake CD, Mian K, Garnham AW, Mian R. Leukocyte counts and neutrophil activity during 4 h of hypocapnic hypoxia equivalent to 4000 m. *Aviat Space Environ Med* 2004; **75**: 811-7.

[8] Eltzschig HK, Carmeliet P. Hypoxia and inflammation. *N Engl J Med* 2011; **364**(7): 656-65.

[9] Caris AV, Lira FS, de Mello MT, Oyama LM, dos Santos RV. Carbohydrate and glutamine supplementation modulates the Th1/Th2 balance after exercise performed at a simulated altitude of 4500 m. *Nutrition* 2014; **30**(11–12): 1331-6.

[10] Klausen T, Olsen NV, Poulsen TD, Richalet JP, Pedersen BK. Hypoxemia increases serum interleukin-6 in humans. *Eur J Appl Physiol Occup Physiol* 1997; **76**: 480-2.

[11] Kauser H, Sahu S, Kumar S, Panjwani U. Guanfacine is an effective countermeasure for hypobaric hypoxia-induced cognitive decline. *Neuroscience* 2013; **254**: 110-9.

[12] Mazzeo RS, Donovan D, Fleshner M, Butterfield GE, Zamudio S, Wolfel EE, et al. Interleukin-6 response to exercise and high-altitude exposure: influence of β-adrenergic blockade. *J Appl Physiol* 2001; **91**: 2143-9.

[13] McNamee EN, Korns Johnson D, Homann D, Clambey ET. Hypoxia and hypoxia-inducible factors as regulators of T cell development, differentiation, and function. *Immunol Res* 2013; **55**(1-3): 58-70.

[14] Fritzenwanger M, Jung C, Goebel B, Lauten A, Figulla HR. Impact of short-term systemic hypoxia on phagocytosis, cytokine production, and transcription factor activation in peripheral blood cells. *Mediat Inflamm* 2011; http://dx.doi.org/10.1155/2011/429501.

[15] Himadri P, Kumari SS, Chitharanjan M, Dhananjay S. Role of oxidative stress and inflammation in hypoxia-induced cerebral edema: a molecular approach. *High Alt Med Biol* 2010; **11**(3): 231-44.

[16] Chu CH, Chen AG, Hung TM, Wang CC, Chang YK. Exercise and fitness modulate cognitive function in older adults. *Psychol Aging* 2015; **30**(4): 842-8.

[17] Lemos Vde A, dos Santos RV, Lira FS, Rodrigues B, Tufik S, de Mello MT. Can high altitude influence cytokines and sleep? *Mediat Inflamm* 2013; http://dx.doi.org/10.1155/2013/279365.

[18] de Aquino-Lemos V, Santos RVT, Antunes HKM, Lira FS, Luz Bittar IG, Caris AV, et al. Acute physical exercise under hypoxia improves sleep, mood and reaction time. *Physiol Behav* 2016; **154**: 90-9.

[19] Wu X, Li X, Han L, Wang T, Wei Y. Effects of acute moderate hypoxia on human performance of arithmetic. *Space Med Med Eng (Beijing)* 1998; **11**(6): 391-5.

[20] Wu Z, Zhu A, Takayama F, Okada R, Liu Y, Harada Y, et al. Brazilian green propolis suppresses the hypoxia-induced neuroinflammatory responses by inhibiting NF-κB activation in microglia. *Oxid Med Cell Longev* 2013; http://dx.doi.org/10.1155/2013/906726.

[21] Bijursten H, Ederoth P, Sigurdsson E, Gottfredsson M, Syk I, Einarsson O, et al. S100B profiles and cognitive function at high altitude. *High Alt Med Biol* 2010; **11**(1): 31-8.

[22] Kohman RA, Rhodes JS. Neurogenesis, inflammation and behavior. *Brain Behav Immun* 2013; **27**(1): 22-32.

[23] Vizi ES. Receptor-mediated local fine-tuning by noradrenergic innervation of neuroendocrine and immune systems. *Ann N Y Acad Sci* 1998; **851**: 388-96.

[24] Weisberg SP, Hunter D, Huber R, Lemieux J, Slaymaker S, Vaddi K, et al. CCR2 modulates inflammatory and metabolic effects of high-fat feeding. *J Clin Invest* 2006; **116**: 115-24.

[25] Lee W, Moon M, Kim HG, Lee TH, Oh MS. Heat stress-induced memory impairment is associated with neuroinflammation in mice. *J Neuroinflammation* 2015; **23**(12): 102.

[26] Bhalala US, Koehler RC, Kannan S. Neuroinflammation and neuroimmune dysregulation after acute hypoxic-ischemic injury of developing brain. *Front Pediatr* 2015; http://dx.doi.org/10.3389/fped.2014.00144.

[27] Chiu GS, Chatterjee D, Darmody PT, Walsh JP, Meling DD, Johnson RW, et al. Hypoxia/reoxygenation impairs memory formation via adenosine-dependent activation of caspase 1. *J Neurosci* 2012; **32**(40): 13945-55.

[28] Malairaman U, Dandapani K, Katyal A. Effect of Ca2EDTA on zinc mediated inflammation and neuronal apoptosis in hippocampus of an *in vivo* mouse model of hypobaric hypoxia. *PLoS One* 2014; **9**(10): e110253.

[29] Smith SM, Friedle SA, Watters JJ. Chronic intermittent hypoxia exerts CNS region specific effects on rat microglial inflammatory and TLR4 gene expression. *PLoS One* 2013; **8**(12): e81584.

[30] Costa Rosa LFBP. Exercise as a time-conditioning effector in chronic disease: a complementary treatment strategy. *Evid Based Complement Altern Med* 2004; **1**: 63-70.

[31] Cosio-Lima LM, Desai B, Stelzer JW, Schuler PB. Effects of 4:1 carbohydrate/protein solution versus a carbohydrate-alone solution on IL-6, TNF-α, and cortisol during prolonged cycling in hot environmental conditions. *Open Access J Sports Med* 2012; **3**: 21-6.

[32] Walsh NP, Gleeson M, Shephard RJ, Gleeson M, Woods JA, Bishop NC, et al. Position statement. Part one: immune function and exercise. *Exerc Immunol Rev* 2011; **17**: 6-63.
[33] Ortega E, Giraldo E, Hinchado MD, Martín L, García JJ, De la Fuente M. Neuroimmunomodulation during exercise: role of catecholamines as stress mediator and/or danger signal for the innate immune response. *J Neuroimmunomodulation* 2007; **14**: 206-12.
[34] Nieman DC, Henson DA, Garner EB, Butterworth DE, Warren BJ, Utter A, et al. Carbohydrate affects natural killer cell redistribution but not activity after running. *Med Sci Sports Exerc* 1997; **29**(10): 1318-24.
[35] Kippelen P, Fitch KD, Anderson SD, Bougault V, Boulet LP, Rundell KW, et al. Respiratory health of elite athletes – preventing airway injury: a critical review. *Br J Sports Med* 2012; **46**(7): 471-6.
[36] Nieman DC. Immunonutrition support for athletes. *Nutr Rev* 2008; **66**(6): 310-20.
[37] Lira FS, De Aquino Lemos V, Bittar IG, Caris AV, Dos Santos RV, Tufik S, et al. Physiological and cytokine response to acute exercise under hypoxic conditions: a study pilot. *J Sports Med Phys Fit* Forthcoming 2016.
[38] Xiao W, Chen P, Dong J, Wang R, Luo B. Dietary glutamine supplementation partly reverses impaired macrophage function resulting from overload training in rats. *Int J Sport Nutr Exerc Metab* 2015; **25**(2): 179-87.
[39] Neto JC, Lira FS, de Mello MT, Santos RV. Importance of exercise immunology in health promotion. *Amino Acids* 2011; **41**(5): 1165-72.
[40] Walsh NP, Gleeson M, Pyne DB, Nieman DC, Dhabhar FS, Shephard RJ, et al. Position statement. Part two: maintaining immune health. *Exerc Immunol Rev* 2011; **17**: 64-103.
[41] Shay JE, Celeste Simon M. Hypoxia-inducible factors: crosstalk between inflammation and metabolism. *Semin Cell Dev Biol* 2012; **23**(4): 389-94.
[42] McNamee L, Mead G, MacGillivray S, Lawrie SM. Schizophrenia, poor physical health and physical activity: evidence-based interventions are required to reduce major health inequalities. *Br J Psychiatry* 2013; **203**(3): 239-41.
[43] Hagobian TA, Jacobs KA, Subudhi AW, Fattor JA, Rock PB, Muza SR, et al. Cytokine responses at high altitude: effects of exercise and antioxidants at 4300 m. *Med Sci Sports Exerc* 2006; **38**: 276-85.
[44] Blegen M, Cheatham C, Caine-Bish N, Woolverton C, Marcinkiewicz J, Glickman E. The immunological and metabolic responses to exercise of varying intensities in normoxic and hypoxic environments. *J Strength Cond Res* 2008; **22**(5): 1638-44.
[45] Turner CE, Barker-Collo SL, Connell CJ, Gant N. Acute hypoxic gas breathing severely impairs cognition and task learning in humans. *Physiol Behav* 2015; **142**: 104-10.
[46] Tiollier E, Schmitt L, Burnat P, Fouillot JP, Robach P, Filaire E, et al. Living high-training low altitude training: effects on mucosal immunity. *Eur J Appl Physiol* 2005; **94**: 298-304.
[47] Bailey N, Clark M, Nordlund M, Shelton M, Farver K. New paradigm in nutrition support: using evidence to drive practice. *Crit Care Nurs Q* 2012; **35**(3): 255-67.
[48] Bailey DM, Castell LM, Newsholme EA, Davies B. Continuous and intermittent exposure to the hypoxia of altitude: implications for glutamine metabolism and exercise performance. *Br J Sports Med* 2000; **34**(3): 210-2.
[49] Akisu M, Baka M, Huseyinov A, Kultarsay N. The role of dietary supplementation with L-glutamine in inflammatory mediator release and intestinal injury in hypoxia/reoxygenation-induced experimental necrotizing enterocolitis. *Ann Nutr Metab* 2003; **47**(6): 262-6.
[50] Han T, Li X, Cai D, Zhong Y, Chen L, Geng S, et al. Effect of glutamine on apoptosis of intestinal epithelial cells of severe acute pancreatitis rats receiving nutritional support in different ways. *Int J Clin Exp Pathol* 2013; **6**(3): 503-9.
[51] Wischmeyer PE, Kahana M, Wolfson R, Ren H, Musch MM, Chang EB. Glutamine reduces cytokine release, organ damage, and mortality in a rat model of endotoxemia. *Shock* 2001; **16**(5): 398-402.
[52] Arwert LI, Deijen JB, Drent ML. Effects of an oral mixture containing glycine, glutamine and niacin on memory, GH and IGF-I secretion in middle-aged and elderly subjects. *Nutr Neurosci* 2003; **6**(5): 269-75.
[53] de Kieviet JF, Oosterlann J, van Zwol A, Boehm G, Lafeber HN, Elburg RM. Effects of neonatal enteral glutamine supplementation on cognitive, motor and behavioral outcomes in very preterm and/or very low birth weight children at school age. *Br J Nutr* 2012; **108**(12): 2215-20.
[54] Spielman LJ, Little JP, Klegeris A. Inflammation and insulin/IGF-resistance as the possible link between obesity and neurodegeneration. *J Neuroimmunol* 2014; **273**: 8-21.
[55] Svensson M, Lexell J, Deierborg T. Effects of physical exercise on neuroinflammation, neuroplasticity, neurodegeneration, and behavior: what we can learn from animal models in clinical settings. *Neurorehabil Neural Repair* 2015; **29**(6): 577-89.