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Research on Restoration Strategies for Human Body Functions Due to Gut Microbiota Dysbiosis in High-Altitude Hypoxia

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Abstract: High-altitude hypoxia can cause dysbiosis of the gut microbiota and disrupt its functional equilibrium. Subsequently, the gut microbiota causes multi-organ dysfunction due to "gut-organ axis" disruption. This review discusses the mechanisms underlying high-altitude hypoxia-induced gut microbiota and body dysfunction. The study systematically discusses the possible effects and applications of microbiota-focused therapeutic approaches, such as nutrition, probiotics/prebiotics, traditional Chinese medicine, and scientific exercise training, for maintaining gut microbiota homeostasis and bodily function. Finally, the study discusses future research directions focused on personalized intervention technologies to protect health at high altitude.

Keywords: High-altitude hypoxia; Gut microbiota; Functional repair; Microecological modulation

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1. Introduction

The hypoxic environment of high altitude is a major challenge for human physiology. Among all the body systems involved, the gut microbiota is an essential modulator of host physiology, and its dysbiosis is increasingly reported to be a pivotal factor involved in high altitude responses [1]. Dysregulated composition and function of microbiota not only aggravate gastrointestinal symptoms, but also induce further functional damage in remote organs through the "gut-brain axis" and "gut-lung axis". Therefore, it is of great importance to elucidate the mechanisms underlying high altitude hypoxia-induced dysregulation of gut microbiota and host functional impairment. In addition, the study of microbiota modulation-based intervention is of great theoretical and applied significance for high altitude adaptation, as well as for the prevention and treatment of altitude illnesses, acute and chronic.

2. The Impact of high-altitude hypoxia on gut microbiota and human physiology

2.1. Characteristics of high-altitude hypoxia and its effects on human physiology

The most prominent high-altitude condition is the gradual decrease in atmospheric pressure and partial oxygen pressure with altitude, which causes low oxygen intake. This is the main problem of high-altitude hypoxia. This physical condition of hypoxia activates a series of complex physiological stress responses in the body (**Figure 1**).

Figure 1. Mechanism of high-altitude hypoxia impact on human physiology via gut microbiota dysbiosis.

In order to get more oxygen to the vital organs such as the heart and brain, the body compensates for hypoxia by increasing respiration and heart rate and constricting peripheral blood vessels to redirect blood flow. Meanwhile, the kidneys release erythropoietin (EPO) to promote hematopoiesis in the bone marrow, increase the number of red blood cells and the concentration of hemoglobin and improve oxygen intake and transportation [2]. This compensation may also bring the potential risk of blood viscosity. In the acute process, the individuals will present typical acute high-altitude symptoms, such as headache, weakness, sleeplessness and indigestion. In the later period, high altitude can induce chronic pathological changes, such as high-altitude pulmonary hypertension and polycythemia. Moreover, hypoxia can directly or indirectly affect the energy metabolism, oxidative stress and immune function, which cause multiple organ dysfunction, providing a basis for subsequent dysbiosis of gut microbiota.

2.2. Changes in the structure and function of gut microbiota under high-altitude hypoxia

High-altitude hypoxia exerts a substantial and complicated effect on the composition and function of gut microbiota. At the phylum level, high-altitude hypoxia presents an imbalance in the F/B ratio, in which the relative abundance of Firmicutes increases while the relative abundance of Bacteroidetes decreases [3]. This change is closely related to energy absorption disturbance. At the genus level, high-altitude hypoxia causes a substantial decrease in the relative abundance of probiotics, such as Lactobacillus and Bifidobacterium, which have anti-inflammatory effects and can maintain the intestinal barrier, while the relative abundance of probiotics may decrease or the relative abundance of pathogenic microorganisms, such as Desulfovibrio and Escherichia-Shigella, may increase. In addition, high-altitude hypoxia can also affect the metabolic activity of the microbiota. One aspect is that the relative abundance of metabolites with protective effects on the intestinal barrier, such as butyrate and propionate, decreases, while the anti-inflammatory action of these metabolites is weakened [3].

The other aspect is that the metabolism of amino acids and bile acids is disturbed, and the microbiota may produce more pro-inflammatory metabolites that participate in systemic inflammatory responses.

2.3. Mechanisms linking gut microbiota dysbiosis to abnormal human physiology

Gut microbiota dysbiosis induces functional dysregulation in the human body via "gut-axis" pathways and cross-talk with multiple systems. The essence of gut microbiota dysbiosis may be focused on the intestinal barrier damage and the activation of the inflammatory response [4]. When gut microbiota dysbiosis is induced by hypoxia damage, the amount of SCFA decreases, which may lead to energy deficit in colon epithelial cells, down-regulation of expression of tight junction proteins, increased intestinal permeability, and "leaky gut." Endotoxin (such as lipopolysaccharide, LPS) and other microbiota metabolites translocate into the blood and cause a low-grade whole-body inflammatory state. Inflammatory mediators not only directly damage the function of target tissues, but also affect the central nervous system through the "gut-brain axis" and aggravate cognitive dysfunction and mood disorders [5]. In addition, microbiota dysbiosis may increase metabolic burden in the liver and disturb immune homeostasis in the whole body. At the same time, the disturbance of microbiota metabolites, such as bile acid and tryptophan metabolites, may also interfere with energy metabolism, neuroendocrine regulation, and immune regulation of the host. These vicious cycles finally lead to dysfunction of the gut and digestive system, immune system, nervous system, and metabolic system.

3. Microbiota regulation-based strategies for functional repair under high-altitude hypoxia

3.1. Nutritional intervention and dietary adjustment strategies

Nutritional intervention and dietary regulation are two repair strategies that focus on enhancing gut microbiota homeostasis and recovery of human physiological functions in hypoxic environments at high altitudes. The essential principle of these strategies is to provide adequate dietary support to supply nutrients for beneficial bacteria and to simultaneously reduce the gastrointestinal burden. One fundamental strategy is to increase the intake of complex carbohydrates and dietary fibers, such as whole grain, vegetables, and fruits [6]. These foods act as prebiotics that are preferentially fermented by beneficial gut bacteria (mainly Bifidobacterium and Lactobacillus) to produce short-chain fatty acids (SCFAs), which can further repair the intestinal barrier, suppress inflammation, and regulate energy metabolism. In addition, an adequate amount of high-quality protein should be consumed to maintain tissue repair and immune function; meanwhile, the intake of red meat, which may stimulate the growth of harmful bacteria, should be reduced. Moreover, the intake of foods or supplements rich in polyunsaturated fatty acids (e.g., Omega-3) should be increased to reduce inflammatory responses [7]. Adequate intake of vitamins (e.g., Vitamin D, C, and E) and trace elements (e.g., zinc and iron) is essential to reduce oxidative stress and maintain the normal function of both the microbiota and host cells. Only with a well-balanced dietary structure can the study improve our gut microenvironment and lay the foundation for implementing other repair strategies.

3.2. Application of probiotics and prebiotics

The use of probiotics and prebiotics is a precise approach to directly regulate the composition of gut microbiota and stimulate the proliferation of beneficial microbiota through exogenous supplementation (**Figure 2**). Probiotics are viable microorganisms that can provide a health benefit to the host at a defined dose, usually Bifidobacterium and Lactobacillus [8]. At high altitude, taking specific probiotics can directly supplement beneficial microbiota, compete with pathogenic microbiota for colonization sites, and keep the microbiota in a balanced state through their metabolic products, such as bacteriocins. More importantly, probiotics can improve the intestinal epithelial barrier, reduce endotoxin translocation, and regulate the host's immune response, thereby eliminating systemic inflammation. Prebiotics are non-digested dietary substances (such as inulin and oligosaccharides) that can serve as "fuel" and selectively stimulate the proliferation and activity of beneficial microbiota [9]. When probiotics and prebiotics are used in combination, they often exhibit synergistic effects, and the overall effect of altering the microbiota structure and producing short-chain fatty acids is more pronounced, which can systematically regulate digestive, immune and metabolic abnormalities caused by high-altitude hypoxia. This is an effective and safe approach to microbiota manipulation.

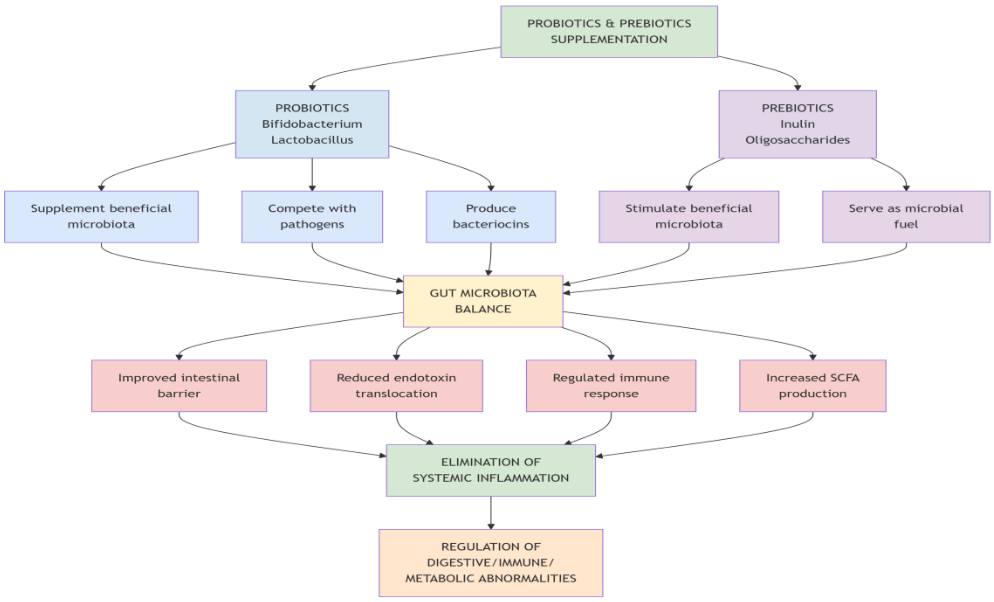

Figure 2. Mechanism of probiotics and prebiotics in regulating gut microbiota dysbiosis under high-altitude hypoxia.

3.3. Traditional Chinese Medicine (TCM) regulation strategy

The strategy of TCM regulation is based on the holistic view and differential treatment principle, and uses multiple components and multi-target actions to regulate microbiota dysbiosis induced by high-altitude hypoxia through the spleen and stomach dysfunction, qi and blood imbalance. According to the TCM theory, "high-altitude insufficient clear qi" would impair the spleen and stomach qi and cause "spleen dysfunction in transportation" and "poor gastric intake", and then regulate the transformation of "food essence" and nourish the whole body, which is the TCM pathophysiology of microbiota dysbiosis [10]. Therefore, the therapeutic strategy usually focuses on "tonifying qi, strengthening the spleen, harmonizing the stomach, expelling dampness, and promoting blood circulation". TCM herbs like Astragalus and Codonopsis can enhance the anti-hypoxia capacity and metabolic ability of the body. Poria and Atractylodes can regulate the spleen and stomach dysfunction and restore the function of transportation and absorption, and then improve the internal environment. Rhodiola and other herbs that tonify qi and promote blood circulation can enhance the body's oxygen transport and microcirculation. These compound herbal medicines and their active ingredients (polysaccharides, flavonoids, and saponins) can directly regulate the composition of gut microbiota and promote the growth of beneficial bacteria and inhibit the growth of harmful microbes. Meanwhile, they can also improve the anti-inflammatory, antioxidant, and gut barrier repair functions, and then adjust the "gut-lung" and "gut-brain" axis by these multiple ways and improve the functional interactions of the axis by TCM strategy, so as to regulate microbiota and enhance the ability of the body to adapt to high-altitude hypoxia.

3.4. Combined application of exercise and adaptation training

Strategically combining exercise and adaptation training comprehensively improves the body's repair capacity and overall hypoxic tolerance through physiological reconstruction of higher hypoxic tolerance, and directly adjusts gut microbiota by proactive intervention through regulating the gut microbiota–host interaction. This strategy is based on a scientific and gradual approach. Pre-adaptation training (intermittent hypoxic training) before ascent to a high-altitude environment activates the HIF signaling pathway, improves cardiopulmonary function, enhances the ability of red blood cells to carry oxygen and improves the body's own resistance to oxidative damage, and thus creates a physiological basis for adapting to real high-altitude environment. After arriving at high altitude, individualized, moderate-intensity regular exercise (brisk walking, jogging, yoga) can improve intestinal peristalsis, promote the circulation of abdominal blood and protect intestinal barrier function and microbiota transport, creating a better mechanical and chemical environment for the proliferation of beneficial bacteria. Regular exercise can increase the amount of short chain fatty acid-producing bacteria and decrease the amount of inflammatory factors. Meanwhile, exhaustive exercise of high intensity may further damage the intestinal mucosa and induce ischemia, increase oxidative stress and aggravate microbiota homeostasis imbalance. Therefore, combining scientific exercise and stepwise adaptation training can improve the physiological function, maintain the internal environment and provide a better guarantee for microbiota reconstruction.

4. Application and prospects of high-altitude gut microbiota regulation strategies

Although the results of various intervention strategies for regulating gut microbiota at high altitude show some potential, their effects are significantly limited, and further comprehensive assessment is warranted. Nutritional dietary regulation is the most basic support method and is highly safe with easy implementation; however, its effects are low and gradually manifested based on the dependence of individuals' long-term compliance. The effects of probiotic/prebiotic intervention on regulating gut microbiota are evident in terms of enhancing the proportion of certain microbiota (such as Lactobacillus and Bifidobacterium) and ameliorating gastrointestinal hypoxia symptoms; however, the effects of this intervention are strain-specific and highly individualized. The long-term safety of this intervention and its effect on native microbiota remain unclear. The advantage of TCM formulations lies in their multi-target regulation, and they have a long history of application in ameliorating hypoxia symptoms and gastrointestinal function [11]. However, the advantages of TCM intervention are obscured by its composition complexity and unclear action mechanism, and the effect of TCM on microbiota is unclear. Furthermore, large samples and RCTs are lacking, making it difficult for TCM to be accepted by evidence-based medicine. The standardization and dose determination are also challenging issues for its widespread application. Exercise and adaptation training offer the most basic benefits; however, their application is limited by individuals' fitness levels and training conditions, and inappropriate exercise may increase the body's burden. In summary, existing strategies are single interventions without microbiota-based combinatory treatment based on individual differences, and their long-term effect and cost-effectiveness should be further assessed by comprehensive clinical studies.

5. Conclusion

In summary, high-altitude hypoxia causes obvious dysbiosis of gut microbiota and further leads to multisystem dysfunction via the "gut-organ axis." Nutritional regulation, probiotic/prebiotic intake, TCM regulation, and scientific exercise mode exhibit great potential in regulating dysbiotic gut microbiota and physiological function. In the future, researchers should focus on the "personalized medicine" principles to explore the underlying mechanisms in more detail and advance the development and translation of precise and effective microbiome intervention strategies. This will offer more theoretical basis and practical guidance for high altitude residents to maintain their health.

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Disclosure statement

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