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Research Progress of Vitamin D and Pathogenesis of Bronchial Asthma

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ABSTRACT

At present the incidence of bronchial asthma on the rise, its pathogenesis and the genetic immune and the relationship between social environment and other aspects are inseparable the activity of vitamin D (Vit D) in the body in the form of 1, 25 - (OH) 2 d3, mainly involved in bone metabolism and calcium absorption in addition to this, a growing number of studies show that in Vit D plays an important role in the pathogenesis of bronchial asthma, play a role in the immune function of bronchial asthma growth hormone sensitivity adjustment and airway remodeling in this paper, the development of a variety of mechanisms, such as Vit D. Review the possible mechanisms affecting bronchial asthma, hoping to provide adjuvant treatment for patients with bronchial asthma, discover new treatment approaches, and improve the quality of life for patients.

1. Function and Metabolism of Vitamin D (VitD)

Vit D is a fat-soluble steroid derivative, mainly related to the function of nutritive bones, and is often used to promote and regulate the metabolism of calcium and phosphorus in bones [1]. It has been found that a large amount of 7-dehydrocholesterol exists in human skin, and studies have shown that it is the main source of VitD[2]. The formation of cutaneous 7-dehydrocholesterol (Vit D3) by ultraviolet radiation is followed by the production of 25 (OH) D3 by liver 25 hydroxylase and 1, 25 (OH) 2D3 by kidney 1 hydroxylase. Active VitD ACTS on VitD receptors in cells through blood circulation and other pathways, and then plays a series of biological roles. In addition to the above bone functions, VitD, as an immunomodulatory molecule, also has important bone functions such as immunomodulatory, defense and repair [3]. In addition, studies have shown that patients with vitamin

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D deficiency are more likely to cause bronchiectasis, asthma and other lung diseases [4]. In addition, Esfandiar et al. found through a large number of clinical investigations that the risk of asthma in children with vitamin D deficiency was 3~16 times that of children with normal vitamin D[5],indicating that vitamin D deficiency increased the risk of asthma in children. VitD plays an important role in the occurrence and development of asthma.

2. Bronchial Asthma

Bronchial asthma is a chronic inflammation in which the respiratory tract cells are damaged, granulocytes are damaged, cells proliferate, lymphocytes and tissue cells are damaged. This chronic inflammation leads to hyperresponsiveness of the airways,often with extensive reversible airflow limitations, and leads to repeated wheezing, shortness of breath, or coughing. The main pathophysiological manifestations are chronic airway inflammation andairway remodeling, and it is now believed that the change of Th1/Th2 cell ratio is the basic mechanism of bronchial asthma, especially the most important basis of Th2 cell hyperfunction[6]. Bronchial asthma can be divided into three levels according to the severity of the disease: light, medium and severe. The most common risk groups are children or teenagers, people with allergic constitution and people with family history of bronchial asthma. In recent years, the role of Vit D as an important treatment for bronchial asthma has been gradually recognized, .but the specific mechanism of its involvement in asthma has not been clarified.

3. VitD ACTS on the Related Mechanism of Bronchial Asthma

3.1 VitD ACTS on Th2-mediated Asthma

An important immunological mechanism of asthma is the Thl/Th2 imbalance caused by the preponderance of regulatory lymphocyte responses to Th2 cytokines involved in asthma formation[7].Studies have shown that VitD plays a certain regulatory role in maintaining Th1 and Th2 balance and reducing airway inflammation[8]. In addition,studies have shown that 1,25(OH)2D3,can promote the attraction of eosinophils in non-inflammatory sites by up-regulating the expression of CXC chemotaxis cytokine receptor 4 (CXCR4) on eosinophils[9]. Therefore, when VitD is insufficient in human body, the balance of immune Thl/Th2 will shift towards Th2, leading to increased synthesis of Th2 cytokines represented by IL-4 and IL-5. Because Th2 stimulates B cells to produce specific IgE and inflammatory cytokines, which in turn stimulates the production of inflammatory mediators, such as eosinophil, leading to allergic. reactions in vivo, VitD deficiency may lead to airway hyperreactivity (AHR) and asthma[10].

3.2 Vit D Acted on Treg Cells

Treg cells can inhibit excessive immune response, and a study has found that Treg cell population is damaged in asthma patients, which is directly related to low vitamin D level[11]. Forkhead box P3(FoxP3) is a transcription factor that plays an important role in T cell development and function, and is also involved in the maintenance of human autoimmune tolerance. The effect of 1,25-(0H) 2D3 is to up-regulate the expression of FoxP3 in Treg cells, increase the production of il-10, and exert an anti-inflammatory effect by affecting the balance of Th1/ Th2 cells[12],suggesting that vitamin D can promote the secretion of il-10. On the contrary, inadequate differentiation and functional defects of Treg cells are the key causes of hyperfunction of Th2 cells and asthma[13]. A mouse experiment showed that CD4+CD25+Treg cells were significantly increased in mice given topical 1,25-(OH) 2D3 treatment or ultraviolet B(UVB) radiation, and the immunosuppressive effect of CD4+CD25+Treg cells in vivo was also significantly enhanced compared with the control mice[14]. In addition, vitamin can promote the production of Treg cell chemokine CCL22 by myeloid dendritic cells and up-regulate the activation of Treg cells[15]. On the contrary, inadequate differentiation and functional defects of Treg cells are the key causes of hyperfunction of Th2 cells and asthma[13]. A mouse experiment showed that CD4+CD25+Treg cells were significantly increased in mice given topical 1,25-(OH) 2D3 treatment or ultraviolet B(UVB) radiation, and the immunosuppressive effect of

CD4+CD25+Treg cells in vivo was also significantly enhanced compared with the control mice[14]. In addition, vitamin can promote the production of Treg cell chemokine CCL22 by myeloid dendritic cells and up-regulate the activation of Treg cells[15].

3.3 VitD ACTS on Th17 Cell Mediated Asthma

In recent years, more and more studies have found that Th17/Treg imbalance plays an important role in asthma[16]. Pfeffer et al. found that VitD can play an anti-inflammatory role by regulating the response of epithelial cells to stimulation[17]. Among them, IL-35 secreted only by regulatory T cells has important inhibitory properties on cells, especially Th17 cells. Th17 cells secrete IL-6 and IL-17, which are involved in the inflammatory response of asthma by promoting prostaglandin and acute phase protein synthesis. 1I1-17 is a proinflammatory cytokine that

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can act on airway epithelial cells, etc., and can promote the recruitment of neutrophils and macrophages by stimulating chemokines and other cytokines to trigger inflammatory responses[18]. In addition, Zhong Jie et al. found that SOCS-1 and SOCS-3 were related to Th17/Treg imbalance and were associated with allergic asthma. This further elucidates the mechanism by which VitD ACTS on Th17 cells to mediate asthma[19]. This further elucidates the mechanism by which VitD ACTS on Th17 cells to mediate asthma.

3.4 Vit D Affects the Sensitivity of Glucocorticoids

The preferred long-term treatment for asthma is inhaled corticosteroids (ICS), but long-term use of ICS can contain many side-effects, including inhibiting growth, causing osteoporosis and lowering the immune system. The study of Kelly et al [20] showed that the average height of children receiving ICS treatment was 1.2cm lower than that of the control group in adult follow-up. To alleviate the symptoms of bronchial asthma, ICS activates effective anti-inflammatory genes by encoding related cytokines, chemokines, and enzymes and receptors involved in inflammation[21]. However, it is difficult to control asthma symptoms of some patients after long-term use of ICS, namely, corticosteroid resistant Asthma (SRA)[22]. On the one hand, studies have shown that SRA is related to the functional expression of Th17 cells, while Vit D can reduce the production of Th17 cells[23]. Vit D can have a synergistic effect with ICS in the treatment of bronchial asthma, and the mechanism is that Vit D can up-regulate the production of ICS-induced IL-10, so as to affect the balance of Th1/Th2 cells and thus exert an anti-inflammatory effect[24]. On the other hand, the occurrence of SRA may include a decrease in the affinity of ICS to its receptor[25]. A large number of studies have found that Vit D plays an anti-inflammatory role of ICS by down-regulating the expression of NF- B in lymphocytes to enhance binding affinity between ICS and hormone receptors[26]. In addition, Xiong's study showed that Vit D can increase the expression of MAPK phosphatase 1 activated by mitogen and reduce the expression of chemokines, thus reducing the phosphorylation of ICS receptors and enhancing the anti-inflammatory effect of ICS[27].

3.5 VitD and Respiratory Tract Infection

Respiratory tract infection is an important factor that induces asthma. Vit D is closely related to upper respiratory tract infection and can play a role in resisting the invasion of respiratory tract pathogens by enhancing the innate immunity of human body[28]. The research results of BERRY et al. also proved the same conclusion, that when the level of 25(OH)D was increased by 4ng/mL, the risk of respiratory infection was correspondingly reduced by 7%[29]. In addition, VitD can also affect the pathogenesis of asthma by influencing; the cell cycle of airway smooth muscle (ASM) cells and regulating ASM cells to participate in the genetic transcription of airway remodeling.

3.6 Vit D ACTS on Airway Remodeling

Airway remodeling is an experience of a series of pathophysiological changes from airway epithelial injury, increase of airway smooth muscle cells (ASMCs), and angiogenesis during the progression of asthma. No effective control method is available[30]. Many studies have confirmed that in patients with asthma, the expression of the nf-kappa B increases significantly and participate in the process of airway remodeling, in asthma model in mice, Vit D treatment reduced the airway remodeling, reduced the airway of a series of physiological and pathological changes, inhibit the nf-kappa B p65 nuclear transfer, at the same time by inducing increased I kappa alpha B predominate mRNA level and reduce I kappa alpha phosphorylation B predominate in order to increase the I kappa alpha B protein levels predominate[31]. Cupta et al[32] found that the low level of Vit D in children with asthma was significantly correlated with the increase of ASMCs, which alleviated a series of pathophysiological changes in the airway, inhibited the nuclear translocation of NF- B P65, and increased the level of I B protein by inducing increased I B mRNA levels and reduced I B phosphorylation[31]. Cupta[34] et al. found that the low level of Vit D in asthmatic children was significantly correlated with the increase of ASMCs, which alleviated a series of pathophysiological changes in the airway, inhibited the nuclear translocation of NF- B P65,and increased the level of I B protein by inducing increased I B mRNA levels and reduced I B phosphorylation[31]. Cupta[32] et al. found that the low level of Vit D in children with asthma was significantly correlated with the increase of ASMCs, which alleviated a series of pathophysiological changes in the airway, inhibited the nuclear translocation of NF- B P65, and increased the level of I B protein by inducing increased I B mRNA levels and reduced I B phosphorylation[31].Cupta et al.[32] found that the low level of Vit D in children with asthma was significantly correlated with the increase of ASMCs, which alleviated a series of pathophysiological changes in the airway, inhibited the nuclear translocation of NF- B P65,and increased the level of I B protein by inducing increased I B mRNA levels and reduced I B phosphorylation[31]. Cupta et al. [32] found that the low level of Vit D in children with asthma was significantly correlated

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with the increase of ASMCs. 1,25-(OH) 2D3 can reduce the proliferation of ASMCs by inhibiting the phosphorylation of retinoblastoma protein (Rb) and cell cycle monitoring point kinase 1(Chk1)[33]. Vit D can down-regulate the expression and mRNA levels of the two proteases in ASMCs sensitized by Adistintegrin and metalloproteinase 33, ADAM33 and matrix metalloproteinase9, MMP9,and effectively inhibit ASMAS proliferation[34].

4. Conclusion

As an immunomodulator, Vit D may inhibit the pathways involved in the occurrence and development of asthma, thus playing a certain role in the occurrence and development of bronchial asthma. Qu Jumei et al. showed that the level of Vit D in children with bronchial asthma was significantly lower. After supplementing with Vit D, asthma symptoms were significantly relieved[35],which further verified the close relationship between vitamin D and bronchial asthma. Therefore, the revelation of the mechanism of Vit D's influence on asthma opens up a new horizon for the treatment of asthma.

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