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Effects of Methionine on the Immune Function in Animals

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Abstract

Nutrition and immunity are the hot topics in animal's production, and the effects of methionine on the immunity are already confirmed as the deep research on the nutrition of amino acid and immune function. However, the relationship of the methionine and immunity has not been elucidated clearly, this review aims to clarify the effects of methionine on immune function in the aspects of growth and development immune organs, the histological structure of the immune organs, non-specific immunity, humoral immunity, cellular immunity and cytokines, and to provide foundations for further studies on the relationship between methionine and immune function.

Keywords

Methionine, Non-Specific Immunity, Humoral Immunity, Cellular Immunity, Cytokines

1. Introduction

As an animal essential amino acid in the daily diet, methionine possesses high nutritional value and important physiological functions [1] [2] [3], such as growth promotion [4] [5], detoxification [6], antitumor and anticancer [7] [8], resistance for coccidium infection [9], involved in methyl transfer [10] [11] [12] and synthesis of protein [13] [14] [15] [16] and so on. What's more, methionine is closely related to the immune function of livestock and poultry, which is not only has effects on the growth and development of immune organs, but also on the specific and nonspecific immune function of organism [17] [18] [19] [20] [21]. In addition, methionine plays a key role in protein synthesis and catabolism of the immune system [22]. On the other hand, the excessive methionine can also cause negative effects on animals, it is suggested that the methionine is the most toxic member of the amino acid family [23] [24] [25] [26]. This review aims to discuss the relationship between methionine and animal immune function, and to clarify the mechanism of methionine effects on the immune function ulteriorly.

2. Effects of Methionine on the Growth and Development of the Immune Organ

Immune organs mainly include bone marrow, tonsil, lymph nodes, thymus, spleen, and bursa of Fabricius (poultry). It is reported that methionine has different effect on the immune organs. Researches have pointed out that methionine can increase the relative weight of bursa of Fabricius and spleen in chicken [4] [27] [28], but methionine deficiency can lead to immune organs dysplasia [17] [20] [29], and decrease the relative weight of thymus, spleen and bursa of Fabricius [30] [31] [32]. Methionine supply can increase the weight of thymus and bursa of Fabricius of layers in the brood rearing stage, but has no significant effect on the spleen [33]. It is concluded that the development of the primary immune organs (thymus and bursa of Fabricius) may be easily affected than the secondary immune organs (spleen) by methionine [20] [34] [35]. Methionine may also affect the weight of the thymus of the early weaned piglets and meat rabbit [36] (Hou *et al*., 2001) and increase the head kidney and spleen index in juvenile Jian carp [37].

3. Effects of Methionine on the Histological Structure of the Immune Organs

Mehionine deficiency has negative effect on the imuune organs including thymus, bursa of Fabricus and spleen. Research has showed that congestion in cortex and medulla of thymic lobule were observed, and lymphocytes in the medulla was remarkably decreased in number and loosely arranged when methionine deficiency [30]. Lymphocytes were decreased in lymphoid follicles with thinner cortices and wider medullae in the bursa of the methionine-deficient [32]. Methionine deficiency reduced the lymphocytes significantly in white pulp and red pulp, also, the histological structure of spleen was disordered [31]. The swelled or vacuolated mitochondria of lymphocytes and more apoptotic lymphocytes were ultrastructurally observed in the spleens with methionine deficiency treatment in broilers [30] [31] [32].

4. Effects of Methionine on Nonspecific Immune Function

There are few researches about the effects of methionine on nonspecific immune function. Some studies showed that methionine can enhance the phagocytic activity of the leukocyte [21] [38], peripheral blood lymphocyte activity, and serum lysozyme activity [39] [40]. Methionine deficiency at the period of pregnancy or lactation will decrease the capacity of the spleen lymphocytes to the same or alloantigen nonspecific immunostimulatory [41]. We speculated that methionine may be an essential substance which maintained the nonspecific immune function.

5. Effects of Methionine on Specific Immune Function

5.1. Effects of Methionine on Humoral Immunity

Humoral immunity is mainly reflected by the recognition of B lymphocytes to antigen, and then the B lymphocytes proliferation or differentiation into plasma cells and secretion of specific antibodies. Methionine affects animals humoral immune function mainly displays in its effects on the body antibody titer and level of immunoglobulins. The appropriately methionine level can significantly increase the degree of antibody [4] [42] [43] and the sheep red blood cells antibody titer [44]. With the level of methionine increasing in the daily diet, the serum antibody increases in the broilers which infected by coccidium [45], and the leukocyte migration and antibody titer also increased in chicken which infected by Newcastle disease virus [18] [46]. However, methionine deficiency will inhibit the proliferation and differentiation of bursal lymphocytes (mainly B lymphocytes), and increase the percentage of the apoptotic cells [32].

Immunoglobulin A (IgA), immunoglobulin G (IgG), immunoglobulin M (IgM), immunoglobulin D (IgD), immunoglobulin E (IgE) are the mainly immunoglobulin subtypes in animals. Methionine can affect humoral immune function by the immunoglobulin levels. Dietary methionine has significant influence on the content of serum IgM and IgA of 2-month New Zealand meat rabbit [47]. Another study points out that methionine has positive effects on the IgG levels of the blood in weaning piglets [36]. Wu *et al.* (2012a) [30] reported that methionine deficiency can decrease serum IgG, IgA and IgM content significantly, which suggests that the humoral immune function is injured. In addition, the level of the methionine is higher in the immune response than normal condition [48] [49] [50], which suggesting that it has close relationship between the methionine and immune response or disease resistance. Increase the dose of methionine in the diet of chicken which infected by Newcastle disease virus, the level of IgG increased too [51]. Methionine also has a protective role in the toxicological effect of aflatoxin [52]. Studies also point out that methionine can promote young carp intestinal humoral immune function by affecting the activity of lysozyme, hemagglutination titer, total iron binding capacity, complement 3 (C3) or complement 4 (C4) content and the IgM content [53].

5.2. Effects of Methionine on Cellular Immunity

Animal cellular immunity is mainly achieved by differentiation of cytotoxic T lymphocytes and producing of the cytokines which activated by antigen of the T lymphocytes. At the same time, the cellular immunity refers to the phagocytosis of macrophage, cell-mediated cytotoxic effect of the killer (K) cells and natural killer (NK) cells. Diets supplemented with digestible methionine could improve the cellular immune response of broiler chicks [54] [55]. Methionine can promote T lymphocyte proliferation ability of the peripheral blood, thymus and spleen, and methionine deficiency will reduce the transformation of T lymphocyte proliferation ability [56] [57]. Research shows that the methionine can promote the thymus T lymphocyte cells differentiation which induced by phytohaemagglutinin (PHA) and enhance the cellular immune function [45]. Wu *et al*. (2012a) found that methionine deficiency can affect the relative percentage of T lymphocyte subsets ($CD3^+$ and $CD3^+$ $CD8^+$ and $CD3^+$ $CD4^+$) of chicken broilers [30]. The superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px) activities, and abilities to inhibit hydroxyl radicals were greatly decreased while the malondialdehyde (MDA) contents were markedly increased when methionine deficiency [31], and it shows that methionine deficiency can induced oxidative damage and lipid peroxidation, which leads to the accumulation of free radicals and eventually injure the biofilm structure of lymphocytes and finally affects the cellular immunity.

Methionine deficiency will reduce PHA reactivity, reduce the stimulus reaction of spleen lymphocytes to concanamycin A (ConA) and mitogenesis of thymic cells. Researcher also points out that methionine deficiency can decrease the PHA reactivity of animal [9], but after supplement of methionine, the lymphocyte transformation reaction enhanced in different degree [58], which can also significantly increase the reaction of peripheral blood lymphocytes to ConA and proliferation of conversion rate which induced by PHA [59].

5.3. Effects of Methionine on Cytokines

There are few reports about the methionine on cytokines in animals. The generation of the Interleukin 1 (IL-1), interleukin 6 (IL-6) and tumor necrosis factor (TNF) has closely relationship to the metabolism of sulfur-containing amino acids including methionine [60] [61] [62]. Methionine is a necessary factor for the generation of IL-1 [63]. Though the research about how methionine directly affect the interleukin 2 (IL-2) is uncommon, some studies reported that methionine may affect peripheral blood IL-2 through the pathways of provision of thiol and promotion of lymphcytes division [64]. Wu (2012) have found that methionine deficiency can significantly reduce the content of serum IL-2 in chicken broilers [30].

6. The Mechanism of the Effect of Methionine on Immune Function

The mechanism of effect of methionine on the immune response has not been fully elucidated, here we speculate that some possible mechanisms may be involved: methionine can be act as immune regulatory factor, such as IL-1 [65] or hormone (insulin-like growth factor-I, triiodothyronine and thyroxine) [66] [67] can be regulated by the methionine; Methionine as a donor of methyl groups, and it participates in the methylation of DNA and proteins, involving in the synthesis of spermine and spermine, and thereby regulate immune related genes expression [68]. Methionine also can indirect regulate the lymphocytes proliferation and differentiation by polyamine [69]. Methionine is the substrate of the synthesis of choline, therefore, phosphatidyl choline and acetylcholine play key roles in the metabolism of leukocyte [6]. As a glutathione precursor amino acids, methionine can protect cells from oxidative damage [70] [71] [72] [73], which may be play important role in the effect of methionine on immune organs or function.

7. Methionine and Cancer

It is reported that many cancers or tumors has closed relationship with the methionine. In animals, methionine restriction may impair cancer growth and carcinogenesis. The requirement for methionine is a common feature of some cancers, which is known as "methionine dependence" [74]. Thus, the restriction of methionine may be a useful strategy in limiting cancer cellular growth. Dietary restriction of methionine in combination with other nutrients that are known to aid cancer growth may have an additive effect in limiting growth and metastases of cancers [75]. Therefore, methionine requirements may be more elevated in cancer cell, because of increased protein synthesis and an increase of transmethylation reactions [76]. Dietary methionine restriction may also extend life-span. In mice, a methionine-deficient diet prolongs life-span and slows immune system [77].

8. The Metabolism of Methionine Pathways

Methionineis partitioned between protein synthesis and the *de novo* pathway in every cell, which also referred to as the methylation cycle or recycling pathway where it is converted to S-adenosylmethionine (SAM), the principal methyl donor [78] under the influence of methionine adenosyltransferase [79]. In the process of methylation, SAM is converted to S-adenosyl-homocysteine and a large range of proteins and other molecules [80] in the presence of methyltransferases. Homocysteine, biosynthesized from methionine, can condense with serine to form cystathionine [11] [81]. Both powder and liquid forms consist of an L-isomer and a D-isomer at a ratio of 1:1. In the metabolic pathway of poultry, 70% - 100% of the D-isomer of DLM or LMA is converted to L-isomer [82] [83] [84] [85] and utilized by the body.

9. Source of Methionine

Many foods contain high level of methionine, such as milk, meat, seeds, peanut, soybean, rice, wheat, sweet basket, broccoli, chives, garlic, watercress, pineapple, apple and so on. But in the breeding industry, the level of the methionine in the feed can't meet the need of the animals, it needs to be added by artificial. As a feed additive, the DL-methionine (DLM) is produced from a complex chemical synthetic process, and the starting material for its production is acrolein derived from propylene [86]. Industrially, the powder and liquid forms of methionine sources are mainly used. It is known as DLM (powder form) and DL-2-hydroxy-4-[methyl] butanoic acid (LMA: liquid form).

10. Other Uses of Methionine

Methionine is not only used as the feed additives in the poultry, but also widely used in some other aspects. In the medical industry, methionine can be clinically used for the prevention and treatment for the chronic hepatitis, cirrhosis, fatty liver disease, or cholestatic liver disease [87], and adjuvant therapy for the poisoning of the sulfa drugs, arsenic or benzene [88] [89] [90]. In addition, methionine also can be used as a cholagogue medicine, adjusting the pH of urine, reducing adipose accumulation [91], and methionine is an important composition of the medical amino acid infusion. In the medical cosmetic, methionine can promote formation of skin collagen and keratin protein, promote growth hormone secretion and skin healthy [92] [93]. Methionine is also a kind of antioxidant, sulfur atomic in methionine molecule can scavenge free radicals. In addition, methionine has a wide application in the field of foods, biochemical research, photography and so on [94] [95] [96].

11. Perspectives

11.1. Research Contents Should Be Diversified

At present, the research on the immune system of methionine mainly focuses on the immune organ weight, growth index, the production of some antibodies and lymphocyte proliferation. However, very few studies focus on the morphological pathology or genes changes of the immune system or immune organs which are induced by methionine deficiency, so more work needs us to do.

11.2. The Mechanism of the Effect of Methionine on Immune System Needs to Be Further Studied

The mechanism of the effect of methionine on immune function is still in the preliminary phase, and the mechanism is not clear reported, which needs to be studied further. Meanwhile, the molecular level or methods should be used to clarify the mechanism, such as cell culture *in vitro* should be used to study the mechanism.

11.3. Research Methods Should Be Diversified

At present, traditional ways are mainly used to study the effects of methionine on immune system, such as organ weight, the determination of blood biochemical index and some enzyme activities by some certain kits, and a variety of new technologies should be used in the research. All above questions that remain are challenging and will require the innovation of new tools and approaches. It is necessary to draw lessons from new technology in human medical research, and promote the research development of the methionine effect on the immune system in the direction of standardization and accuracy, such as introduction of immune histochemical staining, cell culture techniques or flow cytometry assay method, next-generation sequencing technology and so on.

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