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Effects of Polyunsaturated Fatty Acids on Immune Response of Avian

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ABSTRACT

Polyunsaturated fatty acids (PUFA) are important components of cell membrane phospholipids and play important roles in lipid metabolism, gene expression and cell membrane function. Changes in fatty acid composition of cell membrane phospholipids would have an impact on the immune function. In this paper, the effects on avian immune function and regulation mechanism of PUFA were summarized.

Keywords: PUFA; Immune function; Mechanism

INTRODUCTION

Polyunsaturated fatty acids (PUFA), unique biological substances, play important function in lipid metabolism, gene expression and cell membrane function. PUFA are important components of cell membrane phospholipids, which determine the flow and deformation of the cell membrane. When body was stimulated by the external antigen, the secretion of lymphokines and the generation new immune cells are dependent on the fat involved. Therefore, changes in fatty acid composition of cell membrane phospholipids will have an impact on the immune function.

PUFA are subdivided into the omega-3 (n-3) series (the first double bond is 3 carbons from the end (omega) carbon atom of the molecule) that are synthetically derived from linoleic acid (LA), and the omega-6 (n-6) series which are derived from alpha-linolenic acid (ALA), both 18 carbon atom containing fatty acids [1,2]. The three types of omega-3 fatty acids involved in animal physiology are α-linolenic acid (ALA) (found in plant oils), eicosapentaenoic acid [EPA, C20:5 (n-3)] and docosahexaenoic acid [DHA, C22:6 (n-3)] (both commonly found in marine oils). Omega-6 fatty acids are a family of pro-inflammatory and anti-inflammatory polyunsaturated fatty acids those have in common a final carbon-carbon double bond in the n-6 position counting from the methyl end, and include linoleic acid (LA), conjugated linoleic acid (CLA) and four arachidonic acids (AA) [3]. LA and ALA are termed essential fatty acids because mammalian cells are unable to synthesize these fatty acids from simpler precursors. LA can be converted sequentially via a biosynthetic pathway into other omega-6 fatty acids, the 18 carbon gamma linolenic acid (GLA), and the 20 carbon arachidonic (AA) and dihomogammalinolenic acids (DGLA). Similarly, ALA is converted into longer chain omega-3 fatty acids such as 20 carbon eicosapentaeoic acid (EPA) and 22 carbon docosahexaenoic acid (DHA).

EFFECTS OF PUFA ON AVIAN IMMUNE FUNCTION

Effects of PUFA on Immune Organs

Different growth and development status of immune organs, to a certain extent, can reflect the immune condition of livestock and poultry. Bursa of *Fabricius* is an avian-specific immune organ, and the thymus and bursa of *Fabricius* would shrink after the birds are mature, hence, the immune response of birds can only rely on lymph nodes around the spleen.

Wang et al. [4] reported that the growth of thymus, spleen and bursa of *Fabricius* was significantly affected by the dietary n-6 to n-3 PUFA ratios and n-3 PUFA composition. Increasing the content of PUFA in diets significantly could accelerate the growth of thymus, spleen and bursa of 4 weeks old chickens. The increase of

immune organs caused by PUFA in diet was not related to lymphocyte proliferation and IgG production in lymph nodes and spleen. The composition of PUFA in the bursa, thymus and bone marrow was affected by the composition of fatty acids in the diet [5,6].

Effects of PUFA on Cellular Immunity

Lymphocyte transformation rate can reflect the characteristics of the immune status as an indicator of cellular immunity through the changes of lymphocyte metabolism and morphogenesis. Several literature results show that PUFA, especially n-3PUFA can inhibit the lymphocyte proliferation. Dietary n-3 PUFA levels also influenced lymphocyte proliferation of laying hens, as the dietary n-3 PUFA level increased, the lymphocyte proliferation of laying hens were depressed more. But n-6 PUFA level seemed to have no effect on lymphocyte proliferation of laying hens. These suggest that n-3 PUFA levels were also key factors to affect lymphocyte proliferation of laying hens. One-day-old pullets were fed corn and soybean meal-based diets containing 7% by weight one of the following fat sources: lard, corn oil, canola oil, linseed oil (LO), or fish oil (FO). The proliferative response to Concanavalin A (Con A) and pokeweed mitogen (PWM) were 30 to 50% lower in chicks fed the oils rich in omega-3 fatty acids, LO and FO [5].

Xia et al. [7] investigated the different sources and different concentrations of PUFA on immune function in laying hens. The different levels of n-3 PUFA from linseed oil, fish oil (20, 40, 60 and 10, 30, 50 g/kg) and n-6PUFA from corn oil sources (20 40, 60 g/kg) were added in laying hens feed, peripheral blood lymphocyte proliferation rate and spleen mononuclear cell proliferation rate to ConA and stimulation of lipopolysaccharide (LPS) were detected after 5 weeks and 10 weeks. The results showed that adding n-3 PUFA in the diet could significantly inhibit laying hens spleen and peripheral blood lymphocyte transformation rate, especially the fish sources had significant effects on immune function of laying hens than that of linseed oil compared with the control group without adding fat and the treatment groups added n-6 PUFA; with the concentrations of n-3 PUFA (fish oil and flaxseed oil) increased, the degree of inhibition of lymphocyte proliferation rate also was improved, while n-6PUFA had no effect on the lymphocyte proliferation rate. Korver and Klasing [8] found that increasing dietary levels of n-3 PUFA in diets with moderate levels of n-3 PUFAs (≤ 2%) reduced late-onset hypersensitivity, while the low level of fish oil had no effect on the delayed hypersensitivity.

The source and level of dietary PUFA could alter the immune response of laying hens. Feeding laying hens diets containing high n-3 PUFA significantly enhances antibody production. Furthermore, the source of PUFA in the diet can influence lymphocyte proliferation in response to unspecific mitogens. When n-3 PUFA and n-6 PUFA ratios ranged from 0.8 to 29.0, with the increase in the ratio of n-3 PUFAs in the diet the rate of proliferation of spleen and thymus lymphocytes to ConA or PWM were significantly inhibited, which indicated that the source and level of PUFA in the diet was major factors in suppressing the immune response [4]. Xia et al. [7] showed that the antibody titers in fish oil-fed and linseed oil-fed laying hens were higher than that in laying hens fed corn oil. The proliferation response to ConA was lower in laying hens that fed oils rich in n-3 fatty acids than that in laying hens fed corn oil. Higher level n-3 fatty acids can improve immune functions of laying hens.

Effects of PUFA on Humoral Immunity

Serum antibody titer is the main indicator of humoral immune function. The dietary supplementation of PUFA had a tendency to increase the production of BSA and SRBC antibodies with a dose-dependent manner in laying hens, antibody titers after secondary challenge were higher than primary challenge. Antibody titers in fish oil-fed and linseed oil-fed laying hens were significantly higher compared with titers in laying hens fed corn oil. The results of Friedman et al. [6] demonstrated that there was a quadratic relationship between the level of anti-BSA antibody and linoleic acid in blood, that is, with the increase of linoleic acid level in the diet, the ability of hens to synthesize antibodies showed a tendency to increase first and then decrease, and the duration of antibody peak was also decreased. These suggested that the excessive linoleic acid could inhibit the chicken immune response, which was possibly due to the increase of linoleic acid level improved the presence of eicosanoids.

Hosseini-Mansoub and Bahrami [9] evaluated the influence of fish oil (FO) supplementation in the diet of broiler chickens on the humoral immune response as well as some blood parameters. Two hundred and sixteen one day old broiler chickens were divided into four dietary groups 0, 1, 2, or 4% FO with 3 replicates of 18 birds. Four chicks randomly selected and marked from each replicate were immunized intramuscularly with 0.2 ml of 5% sheep red blood cells (SRBC) as a non-infectious antigen, at the ages of 15 and 35 days and blood samples were taken 7 days after each immunization. The highest BW was observed in the 2% FO dietary group (T3), followed by T2 ($P<0.01$). The serum cholesterol and triglyceride levels significantly decreased in the FO groups at the age of 42 days ($P<0.01$). In addition, the inclusion of FO in broiler diets significantly increased the blood glucose (G) level and decreased the total protein (TP), albumin (A) and globulin (GL) concentrations. Fish oil-treated birds had significantly more serum antibody (predominantly immunoglobulin M, IgM) to SRBC than the control group. The highest response to primary and secondary injections of SRBC after 7 days, were detected for group 4 (4% FO), followed by 2% FO group ($P<0.05$). The results indicate that the addition of 2%

FO to broiler chick's diet may stimulate the development of the immune response and improve blood indices, while 4% level was not recommended because of probable off-flavours in the product.

Effects of PUFA on the Production of Cytokines

Cytokines are a class of small molecule polypeptides or proteins with immunomodulatory and effect functions produced by immune cells in the process of inflammation and immune response. PUFA can inhibit the production of cytokines. Korver et al. [8] found that adding fish oil rich in n-3 PUFA to broiler diets exhibited inflammatory inhibition and reduced the content of plasma tumor necrosis factor (TNF) and interleukin-1 (IL-1) released from peripheral macrophages.

Previous studies have demonstrated that proinflammatory cytokines could increase muscle protein degradation, reduce muscle protein synthesis, divert nutrients to the synthesis of components in the immune system, and suppress animal growth [10]. Studies in animal models and in human subjects generally reported a decreased production of proinflammatory cytokines in immune cell in peripheral blood and spleen after fish oil supplementation [11]. Further study revealed that the immunomodulatory effect was caused by the n-3 PUFA, especially, EPA and DHA in the fish oil. Remarkably, n-3 PUFA could decrease the proinflammatory cytokines (IL-1, IL-6 and TNF-α) expression and secretion in peripheral immune cells and suppress animals' inflammatory response. PUFA could attenuate the growth inhibition effect by reducing the production of proinflammatory cytokines in several species. Fowler et al. [12] demonstrated that feeding mice relatively low amounts of purified ethyl esters of EPA and DHA (i.e., 10 g/kg of diet) for only 10 days significantly reduced delayed-type hypersensitivity response and altered *in vitro* lymphocyte proliferation.

MECHANISM OF PUFA REGULATION ON IMMUNE FUNCTION

Lipid bilayers, proteins and sugars are the main components of cell membrane. PUFA in diets could affect the membrane lipid composition, and the alteration of membrane composition could lead to changes of the membrane fluidity, the type and quantity of arachidic acid, the signal transduction and the gene expression, which could ultimately result in the function change of immune cell.

Changes in Lipid Membrane Fatty Acid Composition and Mobility

The certain ratio of PUFA in membrane phospholipids can ensure the integrity, normal structure and physiological function of membrane. The deficiency or excess of PUFA will affect the composition of membrane phospholipids, thereby affecting the membrane structure. The composition of fatty acids in the membrane phospholipids can also affect the fluidity of membrane, and in turn, the alteration of membrane fluidity can affect immune function by affecting immune cell activity. Peck [13] showed that phagocytosis of macrophages had high correlation with the content of saturated fatty acids in the phospholipid membrane. Fish oil could improve the expression of IL-2 receptor in lymphocytes by increasing membrane fluidity, and inhibit the mitosis of lymphocyte.

Changes in Generation of the Eicosanoid

LA is an essential fatty acid. Dietary LA has been beneficial in reducing atherosclerosis and coronary heart disease (CHD). Humans and other animals (unlike plants) lack the enzymes that can synthesize LA and/or α-LNA. Thus, these essential fatty acids (EFA) must be provided in the diet. In the absence of these dietary unsaturated fatty acids, growth is impaired and structural and metabolic perturbations are evident. The deprivation of α-LNA results in decreased brain docosahexaenoic acid (DHA) and is associated with impaired learning and visual activity. α-LNA and its desaturation/elongation products, eicosapentaenoic acid (EPA) and DHA, may play an important role in modulating the synthesis of arachidonic acid (AA), prostanoids, leukotrienes (LTs). These desaturated/elongated products may serve as substrates for the formation of prostanoids and LTs with activities that are weaker than the effects of their AA-derived counterparts [14].

Changes in Lipid Peroxidation Status

Dietary supplemented with large doses of PUFA in deposition could cause lipid peroxidation in the organs, particularly increasing free radicals or byproducts of lipid peroxidation may change the structure and function of cell membrane, which significantly affects the body's immune function. Adding the natural antioxidants VE in animal diets can reduce free radicals and peroxide generating and maintain the integrity of the structure and function of cell membranes, eventually maintain the normal immune function [15].

Changes in Signal Transduction and Gene Expression

PUFA can alter the signal transduction through changing the fatty acid composition in phospholipids' of cell membrane, which has significant influence on the fluidity and membrane function of signal molecules, enzymes and receptors. There was direct relation between PUFA and intracellular signal transduction pathways, for

instance, phosphatidylinositol 4, 5-bi-sphosphate (PIP2) and phosphatidylcholine (PC) can generate the second messenger, diacyl-sn-glycerol (DAG) through hydrolysis process. In addition, several lipids have important effects on intracellular signal-related enzymes, such as phosphatidyl serine (PS) is the required material during the activation process of proteinkinase C (PKC). Supplementation with n-3 PUFA had been demonstrated to lower TNF-alpha and IL-1 production in mononuclear cells [16].

Jolly et al. [17] reported that the suppressed proliferative response in EPA- and DHA-fed mice was preceded temporally by a significant reduction in IL-2 secretion. DAG production was significantly suppressed in EP- and DHA-fed mice relative to the SAF and AA groups. The reduced DAG mass was paralleled by reduced ceramide mass following EPA and DHA feeding compared to the SAF and AA groups. Thus, low dose, short term dietary exposure to highly purified EPA or DHA appears to suppress mitogen-induced T-lymphocyte proliferation by inhibiting IL-2 secretion, and these events are accompanied by reductions in the production of essential lipid second messengers, DAG and ceramide.

The n-3 PUFA in fish oil was primarily responsible for the effects on IL-12 and IFN-γ [18] and n-3 PUFA-fed mice had significantly lower circulating IL-12 p70 and IFN-γ than mice fed the olive oil ethyl esters control diet. Cytokine mRNA for IL-12 p40, tumor necrosis factor-alpha and IL-1beta were lower in infected mice fed n-3 PUFA-containing diets than in mice fed the control diet [19]. Xia et al. [6] documented that feeding high n-3/n-6PUFA diets in laying hens inhibited the secretion of IL-2 and decreased the expression of IFN-γ mRNA in spleen of laying hens. Fernandes et al. [20] investigated the mechanisms by which marine lipids rich in long chain omega-3 fatty acids inhibit autoimmune disease and prolong the survival rate in female (NZB/NZW) F1 (B/W) mice. The results showed that splenocytes from the fish oil group when stimulated with Con A had higher IL-2 and lower IL-4 production similar to that of young (3.5 mo) mice; significantly lower c-Myc and c-Ha-Ras proteins were detected in spleens of fish oil-fed mice than that of corn oil-fed mice, which indicated that changes in membrane fatty acid composition may contribute to the altered immune function and gene expression during the development of murine SLE.

CONCLUSION

The immune function of the body was affected by the dietary fatty acid saturation and addition level, meanwhile, the different type and amount of unsaturated fatty acids could generate influence on cellular immunity, humoral immunity as well as the secretion of cytokines and antibodies. Added too high or too low of unsaturated fatty acids of will cause the decline in immune function, only a moderate amount of supply can improve the body's immune function. In the animal production, the feed industry should fully take into account the dietary type and dose of PUFA in order to achieve better results and economic benefits.

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