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Implications of changing immune function through nutrition in poultry☆

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A B S T R A C T

Many nutrients are capable of modulating the immune system. The concept of nutritional immunomodulation goes beyond impairments in function associated with deficient or toxic levels of various nutrients, and involves using specific nutrients to achieve a functional goal. Using diet to alter immune function has become especially important in a production environment in which the use of growth promoting antibiotics is not legal or desired by consumers. The purpose of this review is not to give a catalog of nutrients capable of altering immune function. Rather, a brief introduction to immune function in poultry will be given, the balance between the innate and acquired responses is discussed, and examples of potential unintended consequences of nutritional immunomodulation are given. Examples of non-nutritional manipulation of poultry immunity will be given to give the reader context of how changing specific aspects of immune function can have effects on other aspects of immunity and production performance. The intention is not to suggest that nutritional immunomodulation is not possible or practical, rather, the reader will be made aware of points to consider when designing experiments or reading the literature in this area. Nutritional immunomodulation holds great promise as a means to increase poultry productivity and health, however, the implications on production traits, the danger of ascribing too much confidence in studies that report only a single or few measures of immunity may lead to changes in immune function that predispose the birds to other diseases, or decrease production characteristics. Several examples of nutritional immunomodulation have been used successfully in the poultry industry, but a greater understanding of the avian immune system will be required in order to take full advantage of this approach.

1. Introduction

The immune system of poultry is a complex, multi-factorial entity. Immune function is affected by bird age (McCorkle and Glick, 1979; Wells et al., 1998; Lavoie, 2006), diet composition (Korver et al., 1997, 1998; Selvaraj and Cherian, 2004; Perez-Carbajal et al., 2010), feed and energy intake (Benson et al., 1993; Jang et al., 2009), genetic potential for growth (Bayyari et al., 1997a,b; Yunis et al., 2000; Redmond et al., 2009, 2010), environment (Bartlett and Smith, 2003; Niu et al., 2009a,b) and stress (Shini and Kaiser, 2009; Shini et al., 2008a,b, 2010), among other factors. This plasticity and responsiveness to external influences have led to many efforts over the years to manipulate immune function through means such as

Abbreviations: ALA, α-linolenic acid; AGP, antibiotic growth promoter; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; LPS, lipopolysaccharide; PAMP, pathogen-associated molecular patterns; PRR, pattern recognition receptors; PUFA, polyunsaturated fatty acids; Th, T helper; TLR, Toll-like receptors.

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vaccination, reduction or elimination of specific pathogens (*e.g.* biosecurity), dietary growth promoting antibiotics, and nutritional immunomodulation.

Immunomodulation is manipulation of the immune system by pharmacologic means (Dalloul and Lillehoj, 2005). Nutritional immunomodulation can be defined as the targeted supplementation of specific dietary nutrients to alter some aspect of immune function, to accomplish an intended goal. Many examples of nutritional immunomodulation can be found in the literature (for reviews, see Kidd, 2004; Klasing, 1998, 2007; Babu and Raybourne, 2008; Kogut, 2009).

This concept is distinct from supplementation of diets with non-nutritive immunomodulators such as antibiotic growth promoters or other medications, or with prebiotics and probiotics. It is also distinct from the changes in immune function observed when nutrient deficiencies are corrected, or when nutrient toxicities interfere with normal immune function. In this review, alterations in immune function caused by nutritional deficiencies will be mentioned only briefly. Deficiencies of several nutrients can reduce immune function, including dietary protein (Jahanian, 2009), lysine (Chen et al., 2003), arginine (Jahanian, 2009), methionine (Konashi et al., 2000; Zhang and Guo, 2008), vitamin D (Aslam et al., 1998), vitamin E (Erf et al., 1998), phosphorus (Liu et al., 2008). The immune system is highly complex and tightly regulated, and therefore a profound understanding of how the avian immune system works is necessary to take full advantage of nutritional immunomodulation. Likewise, mistaken assumptions regarding a "more is better" approach to manipulating immune function, disregarding the balance between innate and acquired immunity, or assuming a change in one measure of immunity represents an "improvement" in immunity can lead to unintended consequences. The current state of knowledge of avian immunity lags behind that of many mammalian species (Erf, 2004; Ly et al., 2010), thus making the field of nutritional immunomodulation in poultry somewhat of an inexact science at this point. Although the genetic coding (Hughes and Friedman, 2008; Sardiello et al., 2008), and mechanisms (Staeheli et al., 2001; Lillehoj et al., 2004) of immune function and regulation differ in many respects between birds and mammals, the ultimate functional endpoints are usually the same (Erf, 2004; Davison, 2003). Based on what is currently known about avian immunity, however, it is still possible to effectively achieve specific outcomes through nutritional immunomodulation. This review will provide a basic overview of immunity in poultry, show a few of the many ways in which dietary nutrients can be used to alter immune function, and demonstrate examples of unintended consequences can arise when immune function is modified. This latter objective may become more and more important to the poultry industry, given the current interest in using non-drug means to support the health and rapid and efficient growth in poultry (Gabriel et al., 2006; Huff et al., 2004, 2006; Lee et al., 2010). Selected examples of non-nutritive will also be used to demonstrate principles, limitations and opportunities for immunomodulation in poultry.

2. Overview of immune function

There are several review papers that will give the reader more complete information on general and specific aspects of immune function in poultry (Lamont, 1998; Qureshi et al., 1998; Kogut, 2000; Erf, 2004; Klasing, 2005; Korver, 2006; Reese et al., 2006; Bennoune et al., 2009) than is intended in this paper. The basic function of the immune system is to protect the bird from infectious and non-infectious challenges from "non-self" molecules or organisms. To do this, the immune system of the bird has two main components: innate immunity and acquired (or acquired) immunity.

Acquired immunity involves a specific, targeted response following exposure to and recognition of specific activators of immune function (antigens). The acquired immune response can involve B cells that produce antibodies to antigen and cytotoxic T cells that actively kill specific invading pathogens. The acquired response results in memory, meaning that the next time a particular antigen is encountered a much more rapid response is possible. The acquired response itself typically has a minimal effect on energy and nutrient requirements of the bird, because the nutrients used for antibody production and expansion of B cell populations is minimal (Henken and Brandsma, 1982; Henken et al., 1982, 1983; Klasing and Calvert, 1999), and the effectors of acquired immunity have little in the way of systemic effects observed with inflammation. Nutritional immunomodulation of acquired immunity generally targets antibody production (Bartlett and Smith, 2003; Bartell and Batal., 2007; Biswas et al., 2006; Chou et al., 2009; Ruiz-Feria and Abdukalykova, 2009), and will be discussed in more detail later in the paper.

Innate immunity is a group of non-antigen specific mechanisms meant to exclude or eliminate pathogens from the bird, and is one of the earliest defense mechanisms against any infectious agent (Fearon and Locksley, 1996; Babiuk et al., 2003). The body has many barrier defenses such as the skin and mucosal surfaces (*i.e.* gut-associated, bronchus-associated and mucosa-associated lymphoid tissues), which prevent foreign material from gaining access to the bird (Bar-Shira et al., 2003; Bar-Shira and Friedman, 2005, 2006; Yun et al., 2000). If pathogens evade these barriers, pathogen-associated molecular patterns (PAMP) present on the cells are recognized by the cells of the innate immune system through Toll-like receptors (TLR) and pattern recognition receptors (PRR; Werling and Coffey, 2007; Kogut and Klasing, 2009). The localized activation of innate immunity can lead to inflammation, which involves the release of chemical signals that result in the recruitment of phagocytic cells. The phagocytes of poultry such as heterophils, (the avian equivalent of the mammalian neutrophil), dendritic cells, and macrophages (Maxwell and Robertson, 1998; Millet et al., 2007) kill pathogens through the release of toxic chemicals such as reactive oxygen species and nitric oxide and through degranulation (He et al., 2006, 2008; Swaggerty et al., 2009). The phagocytes also process and present antigen to cells of the acquired immune system (Aderem, 2002). Other innate immune cells protect the host through activation of complement proteins, which targets pathogens for elimination by other cells (Baelmans et al., 2006; Schou et al., 2010), and the release of histamine and heparin from mast cells, which dilates blood vessels and further recruits phagocytic cells to the site of inflammation (Holgate, 2000). Unlike the acquired