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Review article

Impact of mycotoxin on immune response and consequences for pig health

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ABSTRACT

Mycotoxins are fungal secondary metabolites detected in many agricultural commodities, especially cereals. Due to their high consumption of cereals, pigs are exposed to these toxins. In the European Union, regulations and/or recommendations exist in pig feed for aflatoxins, ochratoxin A, fumonisins, zearalenone, and trichothecenes, deoxynivalenol and T-2 toxin. These mycotoxins have different toxic effects, but they all target the immune system. They have immunostimulatory or immunosuppressive effects depending on the toxin, the concentration and the parameter investigated. The immune system is primarily responsible for defense against invading organisms. The consequences of the ingestion of mycotoxin-contaminated feed are an increased susceptibility to infectious diseases, a reactivation of chronic infection and a decreased vaccine efficacy. In this review we summarized the data available on the effect of mycotoxins on the immune system and the consequences for pig health.

1. Introduction

Mycotoxins are toxic secondary metabolites produced by various molds, such as *Aspergillus*, *Penicillium* and *Fusarium*, which may contaminate food and feed at all stages of the food/feed chain. Despite the improvement of good agricultural and manufacturing practices, mycotoxin contamination cannot be avoided and contaminants are virtually ubiquitous at some concentrations in the average human and animal diets (Bryden, 2012). A recent study performed on 1100 samples collected worldwide showed that about 70% of samples tested was contaminated (Streit et al., 2013). This result was confirmed on a smaller study realized on 83 feed ingredients sampled in China (Guan et al., 2011a).

The biological reactions following ingestion of mycotoxins vary from acute, overt diseases with high morbidity and mortality to chronic, insidious disorders with reduced animal productivity. Different mycotoxins target different organs, inducing various toxic effects. At high doses, mycotoxins exposure leads to general cytotoxicity, often related to macromolecule synthesis inhibition (Maresca and Fantini, 2010). Mycotoxins induce primary biochemical lesions and impact on early cellular functions/events in the cascade of events leading to toxic cell injury or cellular deregulation (Bryden, 2012). At low doses, mycotoxins affect the functions of various tissues and organs, such as the gastrointestinal tract, liver or kidney tissues, as well as the nervous, reproductive and immune systems. Some mycotoxins also have genotoxic, carcinogenic and teratogenic effects (Maresca and Fantini, 2010).

Mycotoxins contamination levels in pig feedstuffs are usually not high enough to cause an overt disease but may result in economical loss through changes in growth, production and immunosuppression (Bryden, 2012; Oswald et al., 2005; Wild and Gong, 2010).

Pigs are very sensitive to mycotoxins. Due to their high consumption of cereals, they are exposed to these toxins and to a chronical contamination. In Europe, regulation and/or recommendations exist for 6 mycotoxins that may be present in pig feed:

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aflatoxins (AF), ochratoxin A (OTA), fumonisins (FB), zearalenone (ZEN) and trichothecenes (principally deoxynivalenol [DON], T-2 and HT-2 toxins) (Bennett and Klich, 2003).

This review summarizes the main effects induced by mycotoxins present in pig feed on immunity and determines the consequences of this immunomodulation in terms of susceptibility to infectious diseases, reactivation of chronic infection and vaccine efficacy.

2. Effect of major mycotoxins on the pig immune response

2.1. Aflatoxins

Aflatoxins are hepatotoxic and carcinogenic; they also display immunotoxic properties. These toxins impair both the innate and the acquired immune responses (Meissonnier et al., 2006; Weaver et al., 2013). The dysregulation of the antigen-presenting capacity of dentritic cells, which is starting from aflatoxin B1 (AFB1) low dose exposure, is deemed to be the mechanism by which the mycotoxin impairs cell-mediated immunity (Mehrzad et al., 2014). An exposition to AF increases the T-cell proliferation-inducing capacity of porcine monocyte-derived dentritic cells, thus enhances presenting capacity of cells (Mehrzad et al., 2015).

An alteration of the inflammatory response has been reported in pigs exposed to AF (Chaytor et al., 2011). A reduced synthesis of pro-inflammatory cytokines and an increase of anti-inflammatory ones was also demonstrated in weanling piglets fed for 4 weeks with low doses of AF (Marin et al., 2002). In utero exposure of piglets to this mycotoxin (through exposition of sows), the functional capacities of both macrophages and neutrophils were altered (Silvotti et al., 1997).

Experimentally, in a pig model vaccinated with a model antigen, which was ovalbumin (OVA), AFB1 exposure had no major effect on humoral immunity with unchanged plasma concentrations of total immunoglobulin A (IgA), IgG and IgM and the specific anti-OVA IgG. In these animals, the toxin exposure did not impair the mitogenic response of lymphocytes but delayed and decreased the OVA-specific proliferation, suggesting an impaired lymphocyte activation in pigs exposed to AFB1 (Meissonnier et al., 2008b). Similarly, in pigs vaccinated with *Mycoplasma*, the exposure to lower levels of AFB1 did not modulate the antigen-specific and total antibody response (Marin et al., 2002). Developing piglets are very susceptible to this mycotoxin. Indeed, after sows exposure to AF, the global piglets lympho-proliferative response upon mitogenic stimulation is reduced (Silvotti et al., 1997).

2.2. Trichothecenes

Type B trichothecenes, including DON, have the capacity to up- and down-regulate immune functions by disrupting intracellular signaling within leukocytes (Pestka, 2010). Depending on the dose, frequency and duration of exposure, DON will have either an immunostimulatory or immunosuppressing effect (Pestka et al., 2004). Deoxynivalenol is able to induce an inflammatory response by acting on the ribosome, inducing a Ribotoxic stress which actives the MAPK pathway, eliciting expression of inflammation-related genes as pro-inflammatory cytokines (Pestka et al., 2004; Pestka, 2010).

In mice, this toxin induced a pronounced elevation in serum IgA (Pestka et al., 2004). In pigs, a similar increase of IgA in the serum of animals receiving DON contaminated feed has been observed (Drochner et al., 2004; Pinton et al., 2008; Swamy et al., 2003). In animals immunized with OVA, the specific immune response was investigated during a DON exposure inducing no feed refusal or reduced body weight gain. Ingestion of DON increased the plasma concentration of total and anti-OVA IgA titers. Deoxynivalenol did not modulate lymphocytes proliferation after mitogenic stimulation, but the toxin had a biphasic effect on the OVA-specific lymphocyte proliferation: An up-regulation in the days after OVA immunization but a down-regulation in the weeks following (Pinton et al., 2008).

Another study on pigs immunized with OVA showed an increase of anti-OVA IgG titers, after 42 days of exposure to a DON contaminated diet. Simultaneously, the expressions of chemokines involved in inflammatory reactions (interleukin-8 (IL-8), chemokine (C-X-C motif) ligand 20 (CXCL20), interferon-γ (IFN-γ)) were up-regulated. Deoxynivalenol also up-regulated the gene of major antioxidant glutathione peroxidase 2 (GPX-2) and down-regulated expression of genes encoding enzymatic antioxidants including GPX-3, GPX-4 and superoxide dismutase 3 (SOD-3), involved in oxidative stress (Lessard et al., 2015).

Type A trichothecenes such as T-2 toxin are cytotoxic molecules and potent protein inhibitors. In pigs immunized with OVA, subclinical doses of T-2 toxin induced an early and transient increase of total IgA plasma concentration but a decrease in the anti-OVA IgG titer (Meissonnier et al., 2008a). For higher doses of exposure, T-2 toxin had been previously shown to decrease both the mitogenic and the antigen-specific lymphocytes proliferation following a horse globulin immunization (Rafai et al., 1995).

2.3. Fumonisins

Fumonisins induce various toxic effects depending on the animal species, and there is evidence for the carcinogenicity of these toxins (Stockmann-Juvala and Savolainen, 2008). In *in vitro* and *in vivo* experiments, fumonisin B1 (FB1) modifies the Th1/Th2 (T-helper 1/T-helper 2) cytokine balance in pigs similar to an impaired humoral response (Marin et al., 2006; Taranu et al., 2005). With pigs vaccinated against *Mycoplasma* and exposed to FB1 (8 mg/kg feed for 4 weeks), a sex-related difference in the specific immune response has also been observed. In male pigs but not for female ones, exposure to the toxin reduced the vaccine-specific antibody titer (Marin et al., 2006). However, ingestion of contaminated feed had no effect on the serum concentrations of total IgG, IgA, and IgM.

Studies have also demonstrated that FB1 influences the inflammatory response. For example, incubation of swine alveolar macrophages with FB1 led to a significant reduction of the number of viable cells and cell death by apoptosis (Liu et al., 2002). An *in vivo* experiment on pigs exposed to FB (6 mg/kg feed for 5 weeks) showed a decrease of IL-1β and IL-6 genes expression in spleen tissue (Grenier et al., 2011).

Fumonisin B1 also impairs on the maturation of antigen presenting cells *in vivo* by reducing the intestinal expression of IL-12p40 and decreasing the upregulation of major histocompatibility complex class II molecule (MHC-II) with a reduction of T cell stimulatory capacity upon stimulation (Devriendt et al., 2009).

2.4. Ochratoxin A

Ochratoxin A is mainly toxic for kidney and liver. Gilts fed OTA-contaminated had reduced cutaneous basophil hypersensitivity response to phytohemagglutinin, reduced delayed hypersensitivity to tuberculin, decreased stimulation index for lymphoblastogenesis, decreased interleukin-2 production when lymphocytes were stimulated with concanavalin A, and decreased number and phagocytic activity of macrophages. Ochratoxin A was shown to be toxic on purified lymphocytes of pigs with an half maximal inhibitory concentration (IC50), concentration producing 50% inhibition of cell proliferation, of 1.3 μM (Keblys et al., 2004).

Ochratoxin A show an impact on the cytokine expression. An experiment on weaned pigs that ingested an OTA contaminated