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.

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:
afatoxins (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. Afatoxins

Afatoxins 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 dendritic cells, which is starting from afatoxin 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 dendritic cells, thus enhancing 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 weaning 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 activates 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, sub-clinical 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; Tarantu 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
diet (181 ng/g of feed) has shown an increased level of TNF-alpha and IL-10 in plasma, with a decreased capacity to respond with cytokine expression to ex vivo challenge with lipopolysaccharides (LPS) (Bernardini et al., 2014). By contrast, OTA has no effect on total and specific immunoglobulin concentrations (Harvey et al., 1992).

2.5. Zearalenone

Zearalenone is best known for its toxic effect on reproduction and fertility (Zinedine et al., 2007); it induces an estrogenic activity on animal (Fink-Gremmels and Malekinejad, 2007). Pigs are particularly sensitive to ZEN, which can induce edematous swelling and reddening of vulva, prolapse of the vulva, ovarian follicle damage and abortions (Schoevers et al., 2012; Zinedine et al., 2007).

Only few papers described the effect of ZEN on immunity (Eriksen and Alexander, 1998). In pigs, exposure of intestinal epithelial cells ZEN (25 μM) has a tendency to increase the synthesis of the inflammatory cytokines IL-8 and IL-10 (Marin et al., 2015). Sows exposed to high concentration of ZEN (5–250 mg/kg feed or 200–1000 μg/kg BW per day) can develop a chronic inflammation of the genital tract (EFSA, 2011).

3. Consequence of mycotoxin induced immunomodulation for pig health

3.1. Susceptibility to infectious diseases

The broad immunosuppressive effect of mycotoxins may decrease host resistance to infectious diseases (Antonissen et al., 2014). Table 1 summarizes the data obtained in pigs.

| Mycotoxin | Exposure dose | Exposure period | Pathogen | Effect compared with negative control | References |
|-----------|---------------|----------------|----------|---------------------------------------|------------|
| AFB1      | 0.07 and 0.14 mg/kg | 32 days | Brachyspira hyodysenteriae | ↓ of incubation period for dysentery, ↑ diarrhea and dysentery time, ↑ death, visible clinical signs and lesions of dysentery at necropsy | Joens et al., 1981 |
| AF        | 1.3 mg/kg feed | 25 days | Erysipelothrix rhusiopathiae | ↑ the severity of bacterial infection | Cysewski et al., 1978 |
| DON       | 2.5 mg/kg feed | 3 weeks | PCV2 | ↑ viremia and lung viral load no clinical effect | Savard et al., 2014, 2015b; Oswald et al., 2003 |
| DON       | 3.5 mg/kg feed | 3 weeks | PRRSV | ↓ weight gain, ↑ lung lesions and mortality, no effect on viral replication | Savard et al., 2014 |
| DON       | 1 μg/mL | 6 h | Salmonella typhimurium | synergistic ↑ gene expression IL-12, TNF-α, IL-10, IL-8, MCP-1 and IL-6 | Vandenbroucke et al., 2011, Verbrugghe et al., 2012 |
| T-2 toxin | 15 and 83 μg/kg feed | 23 days | Salmonella typhimurium | ↓ colonization of the cecum | Halloy et al., 2005; Oswald et al., 2003; Posa et al., 2011, 2013; Ramos et al., 2010 |
| FB1       | 10 mg/kg feed | 3 days | Bordetella bronchiseptica & Pasteurella multocida (type D) | ↑ extent and severity of the pathological changes | Posa et al., 2011 |
| FB1       | 0.5 mg/kg BW | 6 days | Escherichia coli (SEPEC) | ↑ intestinal colonization; ↑ translocation to the mesenteric lymph node, lung, liver and spleen | Oswlad et al., 2003 |
| FB1       | 1 mg/kg BW | 10 days | Escherichia coli (ETEC) | intestinal infection prolonged; impaired function of intestinal antigen presenting cells | Devriendt et al., 2009 |
| FB1       | 25.4 mg/kg feed | 42 days | Mycoplasma hyponeumoniae | ↑ severity of the pathological changes | Posa et al., 2013 |
| FB1       | 0.5 mg/kg BW | 7 days | Pasteurella multocida (type A) | ↓ growth rate and ↑ coughing; ↑ total number of cells, number of macrophages and lymphocytes in BALF, ↑ gross pathological lesions and histopathological lesion of lung | Halloy et al., 2005 |
| FB1       | 12 mg/kg BW | 18 days | PRRSV | ↑ histopathological lesions of lungs | Ramos et al., 2010 |
| FB1       | 11.8 mg/kg feed | 9 weeks | Salmonella typhimurium | Modification of the microbiota profiles | Burel et al., 2013 |
| OTA       | 3 mg/kg feed | 3 weeks | Brachyspira hyodysenteriae & Campylobacter coli | Salmonellosis arises spontaneously in animals fed the contaminated diet, clinical and patho-morphological changes (typical of salmonellosis), change of hematological and biological parameters | Stoey et al., 2000 |
| OTA       | 75 μg/kg feed | 42 days | PCV2 | ↑ PCV2 replication in serum and tissues | Gan et al., 2015 |

AFB1 – aflatoxin B1; AF – aflatoxins; DON – deoxynivalenol; FB1 – fumonisin B1; OTA – ochratoxin A; BW – body weight; PCV2 – porcine circovirus type 2; PRRSV – porcine reproductive and respiratory syndrome virus.
hydysenteriae and Campylobacter coli infections (Stoev et al., 2000). During a PCV2 infection, OTA increases the viremia in sera and tissues (Gan et al., 2015).

To the best of our knowledge, there are no data available concerning the effect of ZEN on vivo analysis on mice which were fed 10 mg/kg ZEA (1.5 mg/kg BW per day) during 2 weeks, infected with Listeria monocytogenes, and showed a decreased resistance to Listeria with increasing trend of the splenic bacterial counts, compared with control animals (Pestka et al., 1987).

3.2. Reactivation of chronic infection

The effect of mycotoxin intoxication on the reactivation of chronic infection was also investigated. However, the experiment was not performed with pigs but with rodents. In the immunocompetent host, Toxoplasma gondii infection progresses to a chronic phase characterized by the presence of encysted parasites. Cyst rupture may occur, but infection remains latent and reactivation is prevented. In immunosuppressed animal and human subjects, such as patients infected with the human immunodeficiency virus, rupture is associated with the formation of new cysts and disease. Low and repeated doses of either AFB1 or T-2 toxin are able to accelerate Toxoplasma cyst rupture in previously infected mice (Venturini et al., 1996).

3.3. Vaccination efficacy

Immunity acquired through vaccination can also be impaired by mycotoxin ingestion (Table 2). For example, AFB1 interferes with the development of acquired immunity in swine following erysipelas vaccination with bacterin preparation (a suspension of killed bacteria) of E. rhusiopathiae (Cysewski et al., 1978). As already mentioned, ingestion of feed contaminated with AFB1 or T-2 Toxin reduced the vaccine response to the model antigen, ovalbumin, acting on the cellular and the humoral response respectively (Meissonnier et al., 2008a, 2008b). Ingestion of low doses of another mycotoxin, FB1, decreases the specific antibody response mounted during Mycoplasma vaccination in pigs (Taranu et al., 2005). In pigs exposed to OTA or FB1 and vaccinated against Aujesky disease (Suid Herpesvirus 1 [SuHV1]), the humoral immune response was greatly disturbed, with a strong decrease in antibody observed (Stoev et al., 2012). In diet contaminated with DON or FB1, pigs showed an alteration of the specific immune response upon vaccination with OVA (Grenier et al., 2011).

Likewise, feeding pigs a DON-contaminated diet was shown to inhibit the vaccination efficiency of PRRSV modified live vaccine by severely impairing viral replication (Savard et al., 2015a).

It should also been mentioned that the vaccine immune response is altered at mycotoxin doses that do not alter the global immune response (Meissonnier et al., 2008a, 2008b; Taranu et al., 2005). The breakdown in vaccine immunity and may lead to the occurrence of disease even in properly vaccinated flocks. These reactions are of considerable consequence in animals for which we rely on an effective vaccination program for disease prevention.

4. The problem of mycotoxins co-contamination

In the above paragraphs, the effects of single mycotoxin on immunity were described. However, mycotoxins often co-occur and animals are exposed to several mycotoxins at the same time. Indeed, raw materials can be contaminated by several fungi, which are able to simultaneously produce several mycotoxins, and in addition, the diet of animal is composed of several commodities (Alassane-Kpembi et al., 2015, 2016). A worldwide survey on 7049 samples reported that 48% of feed and feedstuff samples are contaminated by 2 or more mycotoxins (Rodrigues and Naehrer, 2012). Other studies showed that 75%–100% of animal feed samples are contaminated with more than one mycotoxin (Guan et al., 2011a; Streit et al., 2012).

The toxicity of mycotoxins mixtures cannot always be predicted based upon their individual toxicities. It can be antagonistic.

| Mycotoxin | Exposure dose | Antigen | Effect compared with negative control | References |
|-----------|---------------|---------|--------------------------------------|-------------|
| AF        | 1.3 mg/kg feed| Erysipelothrix rhusiopathiae | Interfered on the development of acquired immunity | Cysewski et al., 1978 |
| AFB1      | 385–1807 µg/kg feed | OVA | Decreased and delayed cell-mediated immunity | Meissonnier et al., 2008b |
| DON       | 3.5 mg DON/kg feed | OVA | Increased OVA-primary IgG antibody response | Lessard et al., 2015 |
| DON       | 2.5–3.5 mg/kg BW | PRRSV | Decreased PRRSV post-vaccinal viremia and reduced vaccinal efficacy | Savard et al., 2015b |
| DON       | 2.2–2.5 mg DON/kg feed | OVA | Increased concentration of OVA specific IgA and IgG | Pinton et al., 2008 |
| DON       | 0.6–4.7 mg DON/kg | Human serum albumin, sheep red blood cells, paratuberculosis vaccine, tetanus toxoid and diphtheria toxoid | Significant dose-dependent reduction in secondary antibody response to tetanus toxoid | Ovens et al., 1997 |
| DON + ZEN | 2.1–3.2 mg DON/kg diet and 0.06–0.25 mg ZEN/kg diet | Parvovirus | No effect | Gutzwiller et al., 2007 |
| DON or FB1 | 3 mg DON/kg feed or 6 mg FB1/kg feed | OVA | Reduced anti-OVA antibody production with a decrease of lymphocytes proliferation | Meissonnier et al., 2008a |
| T-2 toxin | 1324–2102 µg/kg feed | OVA | Reduced anti-OVA antibody production without significant alteration to specific lymphocyte proliferation | Taranu et al., 2005 |
| FB1       | 8 mg/kg BW | Mycoplasma agalactiae | Decreased specific antibody titre | Stoev et al., 2000 |
| OTA       | 1 mg/kg feed | Salmonella choleraesuis | Immunosuppression and delayed response to immunization | Stoev et al., 2012 |
| OTA or FB1 | 0.5 mg OTA/kg feed or 10 mg FB1/kg feed | Suid Herpesvirus 1 (Aujesky disease) | Decreased anti-SuHV1 antibody production after vaccination | Stoev et al., 2012 |

AF – aflatoxins; AFB1 – aflatoxin B1; DON – deoxynivalenol; ZEN – zearalenone; OTA – ochratoxin A; BW – body weight; OVA – ovalbumin; PRRSV – porcine reproductive and respiratory syndrome virus; OVA – ovalbumin.
additive or synergistic and increase the impact of each mycotoxin. The studies concerning the toxicity of mycotoxins mixture on pig immune response are scarce. Reduction of lymphocyte proliferation has been investigated in several pig in vivo studies, and different type of interaction were observed: additivity (co-exposure to AF and FB [0.05 and 30 mg/kg feed] for one month; co-exposure to OTA and T-2 toxin [2.5 and 8 mg/kg feed] for 30 days) or synergy (co-exposure to FB and DON [50 and 4 mg/kg feed] for 28 days) (Grenier and Oswald, 2011). In animals co-exposed to DON and FB (6 and 3 mg/kg of feed) for 35 days, synergistic interaction was observed on lymphocytes proliferation upon mitogenic stimulation, additive interaction on cytokines expression (IL-8, IL-1β, IL-6 and macrophage inflammatory protein 1β) and antagonistic interaction on levels of specific IgA and cytokine expression (Grenier et al., 2011).

In animals co-exposed to DON and FB (6 and 3 mg/kg of feed) for 35 days, additive interaction on specific IgG, on lymphocytes proliferation upon mitogenic stimulation and on cytokines expression (IL-8, IL-1β, IL-6 and macrophage inflammatory protein 1β) was observed, and antagonistic interaction on levels of specific IgA was observed (Grenier et al., 2011).

5. Conclusion

Mycotoxins can contaminate many raw materials and cause significant health risk to animals. Numerous strategies are used to minimize mycotoxins contamination throughout the feed chain. In the fields, resistant crops associated as well as agronomic control measures can be used. Similarly, during feed storage and processing, physical, chemical and biological methods can reduce mycotoxin contamination. However once mycotoxins are present in feed, it’s difficult to reduce their concentrations and their toxicity due to the stability of these compounds (Bryden, 2009). The simultaneous presence of several mycotoxins, not sensitive to the same detoxification procedure, also increases the difficulty to control animals’ exposure to mycotoxins (Bryden, 2012). Recently, new detoxification biological methods showed that the use of bacteria (Grenier et al., 2012, 2013; Guan et al., 2011b), feed additives such as arginine or glutamate were effective to decrease the toxic effects of mycotoxins in young pigs (Duan et al., 2014; Wu et al., 2013, 2015), even for exposition to mycotoxins mixtures (Yin et al., 2014; Grenier et al., 2015).

Pig, a species very sensitive to mycotoxins, is really exposed due to a cereal rich diet. At the European level, regulation or recommendations exist for 6 mycotoxins that are often present in pig feed. They are FB, AF, OTA, DON, T-2/HT-2 toxins and ZEN. Exposure to these toxins induces several toxic effects on pig, including a modulation of the immune response. This later effect increases the susceptibility and severity of infectious diseases, and reduces the efficacy of vaccines. This is of particular note for animal husbandry because during infection, nutrients are used for the immune system instead of growth and development (Klaasing, 2007). Consequently, mycotoxin contamination also has an indirect effect on animal productivity (Klaasing, 2007; Oswald et al., 2005).

The presence of new mycotoxins (emerging, masked, modified toxins, etc.) revealed by new analytical methods can also increase the risk for pig health. Currently, very few studies document the occurrence and toxicity of these toxins, thus there is a need to determine the risk they represent in pig production (Broekaert et al., 2015; Pierron et al., 2016).

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Conflict of interest

The authors declare that they have no competing interests.
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