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Review article

Mycotoxins and the intestine

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ABSTRACT

Fungal biochemical pathways can yield various compounds that are not considered to be necessary for their growth and are thus referred to as secondary metabolites. These compounds have been found to have wide ranging biological effects and include potent poisons (mycotoxins). Mycotoxins invariably contaminate crops and (thus) animal feeds. The intestine is the key link between ingested mycotoxins and their detrimental effects on the animal. Effects on the intestine, or intestinal environment, and immune system have been reported with various mycotoxins. These effects are almost certainly occurring across species. Most, if not all, of the reported effects of mycotoxins are negative in terms of intestinal health, for example, decreased intestinal cell viability, reductions in short chain fatty acid (SCFA) concentrations and elimination of beneficial bacteria, increased expression of genes involved in promoting inflammation and counteracting oxidative stress. This challenge to intestinal health will predispose the animal to intestinal (and systemic) infections and impair efficient digestion and absorption of nutrients, with the associated effect on animal productivity.

1. Introduction – mycotoxins and their diversity

Fungal biochemical pathways can yield various compounds that are not considered to be necessary for their growth and are thus referred to as secondary metabolites. These compounds have been found to have wide ranging biological effects and include potent poisons (mycotoxins). Fungi frequently infect crops and the subsequent contamination with mycotoxins poses a significant health risk to both humans and animals consuming the crop material. Currently, there are around 500 known mycotoxins. Recent work, using liquid chromatography-tandem mass spectrometry (LC-MS/MS) and analysing 83 different feed and feed raw materials, revealed that all of the samples contained a multitude of mycotoxin metabolites (Streit et al., 2013), with 26 to 30 different metabolites most frequently detected. Seven was the lowest number of metabolites detected in a sample, while 69 was the highest. The total number (range) of different metabolites that were detected was 139. These recent data, using the latest analytical techniques, are supporting the views expressed previously about the presence of mycotoxins. In 2005, Devegowda and Murthy suggested that "under practical conditions, no poultry feed is completely free of mycotoxins" and that "no feed can be expected to contain only one mycotoxin". Similarly, Professor Tom Scott from the University of Saskatchewan, Canada, has been quoted as saying "mycotoxins, they are everywhere". The reality is that nutritionists, producers, etc. are routinely dealing with crops/feeds with multiple mycotoxin contamination, even if their (perhaps older) analytical tests do not indicate/confirm this.

Silages (preserved forages or cereals) are a major component of ruminant feed rations worldwide. It is sometimes overlooked that silages can become contaminated with an array of mycotoxins from the field to feeding. It has become noteworthy that numerous 'emerging' mycotoxins (e.g., roquefortine C and mycophenolic acid) are being found. Given the prominence of silages in a ruminant's diet and their normally significant levels of mycotoxin contamination, the very significant contribution of silages to the overall mycotoxin challenge of a ruminant is often overlooked.

2. Effects of mycotoxins

At the cellular level, toxins can catastrophically interfere with numerous pathways and processes. Some better understood

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mycotoxins are known to inhibit protein synthesis (Creppy, 2002). Therefore, cells that are rapidly multiplying or synthesising/secreting protein(s) (e.g., intestinal, immune, etc.) would be particularly vulnerable to the effects of mycotoxins. There are excellent reviews available that consider the physiological (e.g., reproductive) effects of mycotoxins in animals (e.g., Cortinovis et al., 2013). Where data are perhaps lacking is in translating physiological effects into quantifiable performance effects. Recently, there have been two large studies that have employed meta-analysis techniques to assess the effects of mycotoxins on broilers (Andretta et al., 2011) and growing pigs (Andretta et al., 2012). The meta-analysis for broilers encompassed 98 published articles, consisting of over 1,400 diets and 37,000 birds. The analysis showed that, on average, mycotoxins reduced broiler feed intake by 12% and weight gain by 14%, with ochratoxins (OT) and aflatoxins (AF) having the greatest effect on these parameters. Effects were greatest on younger animals and, unsurprisingly, the type of mycotoxin and its concentration influenced the magnitude of the effect. For growing pigs, the meta-analysis encompassed 85 published articles, consisting of over 1,000 diets and 13,000 pigs. The effects of mycotoxins appear to be greater on growing pigs, with an 18 and 21% reduction in feed intake and weight gain, respectively. Aflatoxins were still mycotoxins having a greater impact but this time alongside deoxynivalenol (DON). Effects were, again, greater on younger animals, with mycotoxin type and concentration obviously key factors determining the size of the effect. For growing pigs, there seems to be a gender effect, with mycotoxins affecting males more than females. Both meta-analyses identified that nutritional factors (e.g., methionine concentration for growing pigs) affected the magnitude of the mycotoxin effect. Whilst this needs consideration, permitting the utilisation of expensive dietary components to minimise the effects of mycotoxins is unlikely to be cost effective. With ruminants, there is a general lack of data relating to effects on performance. In 1979, Noller et al. reported that DON and zearalenone (ZEA) reduced bodyweight gain of lactating cows by up to 44%, while DON at 6 mg/kg reduced milk fat by over 1 per cent from 3.92 to 2.77 (Trenholm et al., 1985). In other work, ZEA reduced the conception rate of heifers by 25% (Weaver et al., 1986). Typically, acute mycotoxin intoxications that cause death are uncommon. What is more common are the (chronic) negative effects of mycotoxin contamination on animal performance and health.

3. Mycotoxins and the gastrointestinal tract

When considering mycotoxins, the focus is normally only on the post absorptive effects of mycotoxins, whether they manifest in chronic or acute signs. This is a major oversight of the impact mycotoxins have in the intestinal environment. The gastrointestinal tract (GIT) is the initial site for interaction of ingested mycotoxins with the animal. Mycotoxins have varying bio-availabilities (Grenier and Applegate, 2013). Some will be more rapidly absorbed, whilst others will get further along the GIT. This is very important for a number of reasons. Firstly, whether absorbed into the systemic circulation or not, the cells of the GIT will potentially be exposed to the full range of ingested mycotoxins and in the highest concentrations. Secondly, toxins that get further along the GIT will have had more opportunity to interact with the microbial cells present in the intestine. These cells can also be vulnerable to the effects of mycotoxins. Recent work by Alassane-Kpembi et al. (2013) studied the effects of the Type B trichothecenes on intestinal epithelial cell viability. They demonstrated that these mycotoxins have a negative effect on the viability of the intestinal cells. When discussing feed mycotoxins, low concentrations are often dismissed as being of very little significance. The work of Alassane-Kpembi et al. would suggest otherwise, as the effects on cell viability, per unit of mycotoxin, were much greater at the lower concentrations than at higher ones. They also reported that in almost all cases, the effects of combinations of the toxins were either additive or indeed synergistic, reinforcing the fact that it's inappropriate to consider any single mycotoxin in isolation. Obviously, the importance of intestinal cell viability in maintaining the performance and health of the animal cannot be overstated.

With techniques available to study gene expression, it is possible to evaluate the activity of cells in more detail than whether they are only viable or non-viable. Very recent work by Taranu et al. (2015) studied the effects of low concentrations (10 μM) of ZEA on gene expression of porcine intestinal cells (IPEC-1). Due to its oestrogenic activity, ZEA is typically associated with reproductive problems and is reported to have low toxicity when ingested. Although low concentrations of ZEA did not affect cell viability, Taranu et al. reported that 1,954 genes had an altered profile compared with the control. Of these, 190 genes were significantly differentially expressed, of which 70% were up-regulated. Genes coding for glutathione peroxidase enzymes (GPx6, GPx2, GPx1) were among those up-regulated, which provides further evidence for mycotoxins inducing oxidative damage. The real-time reverse transcription polymerase chain reaction revealed increased expression of cytokines involved in inflammation (e.g., tumor necrosis factor alpha, interleukin-6, and interleukin-8) and immune cell recruitment (e.g., interleukin-10). The increased expression of these molecules would demonstrate that ZEA modulates intestinal cell immune and/or cellular repair pathways. Inflammation has an energy and nutrient cost and can compromise the integrity of the intestine.

The intestinal microbiota also plays a crucial role in determining the health and performance of the animal. An optimal microbiota prevents colonisation of the intestinal epithelium by pathogens and penetration of the gut barrier, modulates the gut-associated lymphoid tissue (GALT) and systemic immunity, and influences gastrointestinal development. The combined effects are better digestive efficiency and utilisation of nutrients. It goes without saying that microbial cells can be susceptible to mycotoxins. Recent work by Ouethrani et al. (2013) demonstrated that ochratoxin A (OTA) significantly reduced acetic, butyric and total short chain fatty acid (SCFA) concentrations in a dynamic simulation model of the descending human colon. This would indicate that OTA is able to affect the composition and/or metabolism of the colonic microbiota. Moreover, and in support of this, the work of Ouethrani et al. revealed that OTA eliminated a strain of *Lactobacillus reuteri* from the descending colon microbiota, which was permanent. *L. reuteri*, which produces the bacteriocin, reuterin, can be a key resident of the GIT, having been shown to have positive effects on intestinal disorders, infection and immune responses. There are limited other data documenting the effects of mycotoxins on (intestinal) bacteria. Tenk et al. (1982) reported that T-2 caused an increase in the aerobic intestinal bacteria count, while chronic exposure to low doses of DON in pigs also increased aerobic intestinal bacteria (Waché et al., 2009). Recently, ZEA and DON administered individually, or in combination, negatively affected mesophilic aerobic bacteria (Piotrowska et al., 2014). Clearly, mycotoxins can influence the composition and/or fermentation products of the intestinal microbiota and, in doing so, affect the health and performance of the animal.

4. Effects on the immune system

There are various very good reviews outlining the effects of mycotoxins on the immune system, which the reader is referred to (e.g., Girish and Smith, 2008). It is, therefore, not necessary to say