Histological modifications induced by the mycotoxin ZEA in weaned piglets and the counteraction of its toxic effect by the use of pre- and probiotics

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Abstract
The study presented aimed to establish the morphophysiological changes induced by ZEA in certain tissues of weaned piglets and to investigate the decontamination potential of inulin and Rhodotorula rubra. For this reason we collected samples of liver and kidney from 20 weaned piglets allocated into four treatment groups: group 1 received weanling formula feed concentrate, group 2 feed concentrate supplemented with inulin and Rhodotorula rubra, group 3 feed concentrate which incorporated ZEA and group 4 feed concentrate to which ZEA, inulin and Rhodotorula rubra had been added. The experiment was carried out over an 18 day period with a level of ZEA of 250 ppb/g. A range of histological changes were observed in the liver and kidney samples taken from group 3 to whose food concentrate only ZEA had been added. Thus a slight tendency to fibrosis of the conjunctive perilobular septa was observed, the interlobular biliary canaliculi were slightly hypertrophic and most hepatocytes showing hypertrophy and having clear vacuolated cytoplasm. A frequently encountered feature of kidney tissue was the compression of the renal glomeruli. Renal parenchyma presented a disorganised aspect, with nephrocytes being dystrophic in a number of regions, while the stroma showed slight signs of interstitial and perivascular fibrosis. The synbiotic combination of inulin and Rhodotorula rubra led to a diminution of the modifications produced by ZEA, with the histopathological modifications concerned in these two types of tissue becoming less evident.

Keywords: piglets, zearalenone, inulin, Rhodotorula rubra, liver, kidney

1. Introduction
Zearalenone (ZEA) is a mycotoxin produced by many members of the genus Fusarium (Fusarium graminearum, F. culmorum, F. equiseti, and F. crookwellense) which is widely distributed as a contaminant of cereal grains and animal feedstuffs (Richardson & al., [1]; Wood, [2]; Price et al., [3]). This mycotoxin is a widely encountered contaminant, throughout the world, of cereal crops, particularly wheat and maize, but also of certain fruits and vegetables (bananas, beans, walnuts) and can even be found in products of animal origin (milk, liver, eggs) in consequence of the use of contaminated animal feed (Bennett & Klich,
Intestinal microflora are unable to break down zearalenone which is thus absorbed rapidly following oral administration.

Zearalenone metabolism occurs in the liver, an organ in which there are two major pathways of ZEA biotransformation: hydroxylation, a reaction catalysed by 3α- and 3β-hydroxysteroid-dehydrogenases (HSDs), which leads to the formation of α- and β-zearalenol (α/β ZOL); the conjugation of ZEA and its reduced metabolites with glucuronic acid, these reactions being catalysed by uridine diphosphate glucuronyl transferase (UDPGT) (Olsen & al., 1981, cited by Malekinejad et al., [5]). ZEA derivatives interact with oestrogen-specific receptors (Powell-Jones & al., [6]); as a result the major toxic effects of ZEA and its metabolites are oestrogenic, affecting the fertility and foetal development of farm animals (Boyd & al., [7]; Kuiper-Goodman & al., [8]). Porcine animals are considered more susceptible to ZEA-induced oestrogenic effects than other species (Diekman & Green, [9]; Biehl & al., [10]). It has also been shown that ZEA produces hepatic and renal lesions, including hepatocarcinoma and nephropathy, as well as being haematotoxic (NTP, [11]; Richardson & al., [12]; Maaroufi & al., [13]; Abbes & al., [14]; Zinedine & al., [15]).

Prebiotics are non-digestible food ingredients that beneficially affect the recipient, as has been shown for humans, poultry (Patterson & al., [16]), swine (Smiricky-Tjardes & al., [17]), and rats (Lobo & al., [18]). One of the principal effects of prebiotics is to improve the balance of the gastrointestinal microflora through stimulating the growth and activity of colon bacteria (Gibson & al., [19, 20]; Verdonk & al., [21]), a reduction in the species of pathogenic bacteria (Gibson & al., [19, 20]; Watzl & al., [22]) and a resulting improvement in the health of the host organism through stimulation of the non-specific immune response (Bailey & al., [23]; Gibson & al., [19, 20]). Prebiotics also increase fermentation products (Smiricky-Tjardes & al., [17]), improve mineral uptake (Bongers & al., [24]), enhance livestock performance indices (Flickinger & al., [25]), and improve disease resistance (Bailey & al., [23]).

Inulin is a naturally occurring fructooligosaccharide (FOS). It is generally extracted from the many types of plants, especially from the roots of chicory (Cichorium intybus L.) plants and belongs to a class of carbohydrates known as fructans (Goodwin & al., [26]). Fructans cannot be hydrolysed by pancreatic or brush border digestive enzymes in the proximal intestinal tract of humans or domestic animals (Pool-Zobel, [27]). It is fermented in the colon by bifidobacteria and other lactic acid producing bacteria, enhancing their relative populations (Pool-Zobel & al, [27]; Roberfroid, [28]; Flickinger, [25]). It is known that inulin stimulates the human immune system by binding to specific lectin-like receptors on leucocytes and increasing macrophage proliferation (Gildberg et al., 1998, cited by Zhang & al., [29]).

Probiotics, defined as micro-organisms or their products with beneficial effects on humans and animals (Irianto et al., 2002, cited by Zhang & al., [29]), are known for their antagonism to pathogens, enhancement of the immune response, promotion of efficiency of feed assimilation and homeostasis of intestinal microflora in humans and animals (Fuller, 1989; Fuller, 1999; Gatesoupe, 1991, cited by Zhang & al., [29]). Yeasts are among the probiotics most widely used in the rearing of porcine animals. It has been shown that the addition of Saccharomyces cerevisiae to the feed of young pigs has a positive effect on their growth, on the digestibility of food, on the enteric microbial population and on the concentration of volatile fatty acids (VFA). These effects can mainly be explained by the significant dose of enzymes, nutrients and growth factors supplied, but also, through the effects of the mannans and membrane-bound β-glucans present in the yeast supplement, there
is a reduction in the number of pathogenic bacteria and of toxic metabolites in the digestive tract (Li et al., 2006, cited by Corcionivoschi & Drinceanu, [30]).

The purpose of the investigation was to establish the morphophysiological modifications induced by the mycotoxin zearalenone (ZEA) on the liver and kidney of pigs and to investigate the potential of inulin and Rhodotorula rubra as decontaminants acting in the form of a sinbionte combination of a selected prebiotic and a probiotic product obtained through the methods of modern biotechnology.

2. Materials and methods

The experiment was carried out using 20 weaned piglets allocated to four experimental treatment groups. The control group (group 1) received weaned formula feed concentrate. Group 2 received the same concentrate supplemented with inulin and Rhodotorula rubra; group 3 received feed concentrate with added zearalenone; group 4 received feed concentrate supplemented with zearalenone, inulin and Rhodotorula rubra. The experimental feeding period was 18 days.

The experimental treatment scheme is presented in table 1. The level of ZEA added to the feed formula for groups 3 and 4 was 250 ppb/g.

Chemicals

Zearalenone was used in the form of a pure toxin purchased from the Sigma Aldrich Chemical Company, inulin was also purchased from the same supplier and Rhodotorula rubra, a reference type strain of R. rubra, was prepared by freeze-drying a culture grown at ICCF Bucharest (the Romanian National Institute for Chemical-Pharmaceutical Research and Development).

Analysis of ZEA, DON, FB and T-2/HT-2 toxins content in the feed used during the experiment

The content of zearalenone (ZEA) in the feed was analysed by high performance liquid chromatography (HPLC) with UV detection after clean-up with an immune-affinity column at a detection limit of 0.03 mg/kg (table 2). DON, FB and T-2/HT-2 toxins were analysed by ELISA using ELISA kit Veratox (Neogen, MI, 48912, USA/Canada) with detection limits of 10, 50 and 25 ppb respectively.

Histopathology

For histopathological study samples of liver and kidney tissue were taken from the slaughtered animals, fixed in formalin 10% and processed for histological paraffin wax embedding. Paraffin blocks were sectioned with manual rotary microtome Leica at the thickness of 5 μ. The section stained with hematoxylin – eosin and trichromic Mallory methods (Bancroft & Stevens, [31]) were then examined under an Olympus CX41 optical research microscope fitted with a digital camera and image analysis software.

Table 1 Experimental treatment scheme

<table>
<thead>
<tr>
<th>Composition of feed formula</th>
<th>Group 1 control</th>
<th>Group 2 Inulin + Rhodotorula rubra</th>
<th>Group 3 ZEA</th>
<th>Group 4 ZEA + Inulin + Rhodotorula rubra</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maize / Corn</td>
<td>64.31</td>
<td>64.18</td>
<td>64.309975</td>
<td>64.179975</td>
</tr>
<tr>
<td>Soya meal</td>
<td>16</td>
<td>16</td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td>Rapeseed meal</td>
<td>8</td>
<td>8</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Milk powder</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Gluten</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Salt (sodium)</td>
<td>0.20</td>
<td>0.20</td>
<td>0.20</td>
<td>0.20</td>
</tr>
</tbody>
</table>

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3. Results and discussions

ZEA. Table 2 presents the results for ZEA levels as determined by high performance liquid chromatography (HPLC).

Table 2 Determined levels of ZEA

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>ZEA (ng/g) ppb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1 (control)</td>
<td>40.92</td>
</tr>
<tr>
<td>Group 2 (feed + inulin + R. rubra)</td>
<td>54.64</td>
</tr>
<tr>
<td>Group 3 (feed + ZEA)</td>
<td>316.01</td>
</tr>
<tr>
<td>Group 4 (feed + ZEA + inulin + R. rubra)</td>
<td>325.16</td>
</tr>
</tbody>
</table>

The control and inulin plus Rhodotorula diets contained 40.92 and 54.64 ppb ZEA respectively, which was considered negligible taking into consideration the literature data and EU recommendation 576/2006 [32].

Although ZEA was added at a concentration of 250 ppb by weight to the feed for groups 3 and 4, the disparities between this and the measured concentrations (316.01 ppb and 325.16 ppb respectively) can be attributed to pre-existing contamination of the maize / corn used in the feed mix.

DON, FB and T-2/HT-2 toxins. ELISA test analyses, using the Veratox ELISA kit (Neogen, MI, 48912, USA/Canada), detected no traces of contamination of the feed formula with DON, FB or T-2/HT-2 toxins.

Histopathological study of the liver

Histological sections of liver from individuals in the control group show the presence of hepatic lobules that have parenchyma arranged as regular cords of hepatocytes delimited by slightly distended sinusoidal capillaries. The hepatocytes are polygonal in form with central or eccentric spherical nuclei, deeply staining, and with finely granulated cytoplasm. Within the hepatic parenchyma hepatocytes undergo hypertrophy, especially in the peripheral part of the hepatic lobules. The cytoplasm of these cells contains small lipid vesicles, conferring upon it a vacuolated appearance (Fig. 1a). In some areas, around the lobules, there are signs of a slight degree of fibrosis, with numerous fibroblasts to be found among the collagen fibres. The interlobular Kiernan spaces are somewhat enlarged due to the hypertrophy of the venules and biliary ducts (Fig. 1b) and to the proliferation of the periductal connective tissue, which is infiltrated with lymphocyte cells.
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In the case of individuals from group 2 (fed on compound to which both inulin and Rhodotorula rubra had been added as supplements), transverse sections through the liver lobules showed their hexagonal or pentagonal form and separated from each other by thin connective tissue septa (Fig. 2a). In the connective tissue of the Kiernan interlobular spaces, although the interlobular biliary canaliculi were of normal diameter the venules and arterioles showed a degree of hypertrophy. The hepatocytes are arranged in regular cords converging on the centrolobular vein. They show a polygonal aspect, having 1-2 spherical, intensely staining nuclei and finely granulated cytoplasm (Fig. 2b). In the extralobular zone the hepatocytes have a hypertrophic aspect, often exhibiting eccentric nuclei, sometimes pyknotic, with clear vacuolated cytoplasm.

Microscopic sections from the liver of individuals in group 3, which was fed with compound to which ZEA had been added, showed a degree of fibrosis of the perilobular conjunctive septum (Fig. 3a), while in the Kiernan spaces the interlobular biliary canaliculi show some degree of hypertrophy. Within the lobules the cords of hepatocytes are in a regular arrangement and converge on the centrolobular vein. In these structures are to be found very few hepatocytes with finely granulated, more deeply staining, cytoplasm; hypertrophic hepatocytes, with a clear appearance and vacuolated cytoplasm, predominate (Fig. 3b).
Neutrophilic polymorphonuclear leucocytes and macrophages are to be found between these cells. The nuclei of hepatic cells may be located centrally, slightly eccentrically or entirely eccentrically. Hypertrophic sinusoidal capillaries run between the hepatic cords (Fig. 3b).

Exposure of hepatocytes to ZEA raises the concentration of hepatic aminotransferases (ALT, AST) in blood plasma – a rise which confirms the hepatotoxicity of this mycotoxin (Stadnik & Borzecki, [33]). Jiang & al., [34] have established that, in storks, while the liver, kidneys and spleen are tissues targeted by ZEA, the genital organs are not. They have also shown that ZEA interferes with the functioning of the hepatic antioxidant system and causes a series of hepatic lesions. The tendency to fibrosis of the connective perilobular septa and, consequently, a growth in the quantity of collagen fibres, could be a consequence of the assimilation of iron, a process known as haemosiderosis, without however resulting in anaemia. In excess, hepatic iron can have oxidative effects which may stimulate fibrinogenesis, a process which may lead to the development of hepatic cancer (Andrews 1999, cited by Tiemann & al., [35]). Irving & al., [36] have shown that a super-loading with iron leads to a stimulation of the synthesis of collagen fibres, associated with a higher level of the mRNA which codes for the synthesis of hepatic procollagen. Morphofunctional alteration of hepatic cells has been confirmed by ultrastructural studies which indicate that in such situations a proliferation of the smooth endoplasmic reticulum (SER) occurs in the hepatocyte cytoplasm along with a loss of ribosomes from the rough endoplasmic reticulum (RER), a loss of glycogen and an increase in the number of lipid vesicles (Tiemann & al., [35]). A rough endoplasmic reticulum (RER) with intact ribosomes is needed for the synthesis of the lipoproteins which transport triglycerides in the hepatocytes. Thus a failure in the formation of the protein moiety can lead to the loss of triglyceride transport functionality, leading to an accumulation of lipids in the cytoplasm of the hepatic cells which results in an imbalance of lipid metabolism (Tiemann & al., [35]). As a consequence of their highly hydrophobic character lipids accumulate as droplets in the cytoplasm, giving it a vacuolised appearance.

Individuals from group 4, to the feed of which had been added ZEA, inulin and Rodotorula rubra, showed, in the ground tissue of the liver, slight degrees of interlobular, perivascular and pericanalicular fibrosis (Fig. 4a). Hepatic lobules are formed from orderly cords of hepatocytes in which hepatocytes with finely granulated cytoplasm are predominant (Fig. 4b). Only in the periphery of the hepatic lobule do the hepatocytes show hypertrophy, their cytoplasm being vacuolated and assuming a clear appearance.
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Fig. 4. Liver – Group 4. a - slight pericentrolobular fibrosis (1000x; Mallory trichrome stain); b - extralobular hepatocytes with finely granulated cytoplasm. In this region hypertrophic hepatocytes with clear cytoplasm can also be observed (1000x; haematoxylin-eosin stain)

**Histopathological study of the kidney**

Microscopic sections of the kidneys of individuals in the control group (group 1) show the presence of a renal capsule rich in parallel-lying collagen fibres with numerous fibroblasts distributed between them. Beneath the capsule the connective tissue extends, in the form of richly vascularised bands, into the renal parenchyma which makes the stroma. The renal cortex is distinguished by the presence of renal corpuscles and of transverse sections of the proximal and distal convoluted tubules of the nephrons. Specimens in this group showed a slight degree of interstitial, peritubular and perivascular fibrosis (Fig. 5a), a process more marked towards the border of the medulla and towards the pelvis. Infiltration of leucocytes can be also be observed in the connective tissue around the corpuscles and in the neighbourhood of the pelvis. Over wide areas there may be seen a series of morphostructural modifications in the nephrons. These consist of processes of glomerular compression (Fig. 5a), an enlargement of the capsular space, in which a granulo-serous exudate is present, and lesions in external layer of the Bowman’s capsule. A feature frequently encountered is a thickening of the outer layer of the Bowman’s capsule, a process which is due to the metaplasia of its simple pavement epithelium, transforming it into a simple cuboidal or even columnar epithelium. Infrequently, in the parenchyma of the renal cortex, the renal corpuscles become reduced to being simply the external layer of the capsule.

Microscopic study of a large number of histological sections of kidney has allowed us to observe the heterogeneous character of the renal corpuscles, with these showing a range of dimensions (Fig. 5b). This feature suggests a compensatory functional response of entire corpuscles, which undergo hypertrophication while the corpuscles affected become smaller, and undergo modification with respect to both their structure and their functioning.

The renal tubules of the nephron are lined with a simple cuboidal epithelium resting on a basement membrane. Nephrocytes present with large, spherical, centrally positioned heterochromatic nuclei, with finely granulated cytoplasm. In limited areas the nephrocytes are hypertrophic, with strongly vacuolated cytoplasm, due to the intracellular accumulation of lipid and a degree of peritubular oedema is also evident.
Fig. 5. Kidney – Group 1. a - glomerular compression and atrophy (400x; Mallory trichromic stain); b - renal corpuscles of different dimensions (100x; Mallory trichromic stain)

Low power views of kidney sections from group 2, which received feed compound, inulin and *Rhodotorula rubra*, show a lower degree of heterogeneity in the renal corpuscles as compared with the control; the corpuscles are more homogeneous in both size and structure (Fig. 6a, 6b). In more limited regions the presence of renal corpuscles of reduced size may be observed, with the glomeruli appearing compressed and the capsule space enlarged (Fig. 6b).

The process of fibrosis is not manifested in the cortical zone of the renal parenchyma but only in the medulla, where the parenchyma adjoins the renal pelvis, a zone in which local leucocyte infiltration may be seen.

It is known that inulin, particularly in its long-chain form, stimulates the human immune system by binding to the specific lectin-like receptors on the leucocyte membrane and stimulating the proliferation of macrophages. It has also been shown in mice that feeding with inulin increases both the number of NK lymphocytes and the kinetic response of the macrophages (Causey & al, 1998, Kelly-Quagliana & al., 1998, cited by Rebeca Cerezuela & al., [37]). It has likewise been shown that the insoluble gamma form of inulin is capable of triggering the presence of C3 fraction complement receptors on the surface of macrophages (Cooper, 1995, cited by Rebeca Cerezuela & al., [37]).

These microscopic observations show that, without the administration of exogenous ZEA mycotoxin, the synbiotic combination of inulin and *Rhodotorula* has a protective effect on the kidney, the changes manifest being much less marked than those seen in individuals from group 1.

Fig. 6. Kidney – Group 2. a - general view – renal corpuscles of the same size (200x; haemotoxylin-eosin stain); b - detail fig. 6.a. (400x; haemotoxylin-eosin stain)
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In the case of group 3, which received feed compound and ZEA, the renal corpuscles evident in the parenchyma of the renal cortex are heterogeneous in both size and appearance (Fig. 7a). Thus while some corpuscles are small with a compressed glomerulus others present a hypertrophic aspect (Fig. 7b). One frequently encountered feature is the compression of the glomeruli to the point of their complete disappearance, with the corpuscle thus being reduced to no more than the external layer of the Bowman’s capsule. Likewise, another feature to be noted is a partial or entire thickening of the external layer of the Bowman’s capsule resulting from the metaplasia of its simple pavement epithelium into a simple cuboidal epithelium. The renal parenchyma appears disorganised (Fig. 7a), due to the modifications that take place both in the renal corpuscles and in the nephron tubules. A frequently encountered feature is that of nephrocyte dystrophy: the nephrocytes of the nephron epithelium become detached from the basement membrane, under hypertrophy, and their cytoplasm vacuolates, with ensuing degeneration. In limited areas the processes of dystrophy are more marked, leading to an attenuation of the renal parenchyma. In the stroma a slight tendency to interstitial and perivascular fibrosis is seen, a process which also extends to the external layer of the Bowman’s capsule.

Similar results have also been reported by Mona H. K. Al-Jibouri & al. [38]) from their studies of the effect of ZEA and of ZEA in combination with soya on the kidney and liver of albino mice. The histopathological modifications seen in the nephrocyte epithelium are the consequence of lesions caused by ZEA to the membranes of the epithelial cells, through their impact on the Na⁺ - K⁺ exchange pump, with a consequent disturbance in intra- and extracellular fluid composition. ZEA also acts on the mitochondria, with implications for ATP synthesis (Abbes & al., [14]; Salah-Abbes, 2008, cited by Mona Al-Jibouri & al., [38]).

**Fig. 7. Kidney – Group 3. a - renal corpuscles heterogeneous in dimensions and appearance (100x; Mallory trichromic stain); b – disorganized renal parenchyma, glomerular compression and atrophy (400x; haematoxylin-eosin stain)**

Individuals in group 4, fed with feed compound to which ZEA, inulin and *Rodotorula rubra* had been added, have renal parenchyma of relatively homogeneous appearance, a feature due both to the renal corpuscles, which have perceptibly similar sizes, and also to the nephron tubules, whose epithelium is uniform, being a simple one of pavement, cuboidal or columnar pattern, depending upon which segment of the nephron is in view in the section (Fig. 8a, 8b). The peritubular arterial capillary network is visible, and, in limited areas, a slight degree of peritubular oedema is noticeable. Infrequently, in the cortex of the renal parenchyma, smaller corpuscles with highly compressed vascular glomeruli are encountered, but so are glomeruli whose capsules show evidence of thickening. Fibrosis is only to be
observed in isolated areas in the stroma, around the renal corpuscles and perivascularly. For specimens in this group the synbiotic combination of inulin and *Rhodotorula rubra* has the effect of decontaminating the influence of the ZEA by greatly attenuating its toxic effects on the parenchyma and the renal stroma.

Fig. 8. Kidney – Group 4. a - renal parenchyma of fairly homogeneous appearance (100x; haemotoxylin-eosin stain); b - renal parenchyma of fairly homogeneous appearance, renal corpuscles and nephron tubules (400x; haematoxylin-eosin stain)

4. Conclusions

This study provides evidence that the rearing of weanling piglets on a feed concentrate contaminated with ZEA mycotoxin originating from fungi of the *Fusarium* genus, over a period of 18 days, can produce histopathological modifications in both liver and kidney. In the liver the principal modifications are a slight tendency towards fibrosis of the peribiliary conjunctive septa, mild hypertrophy of the interlobular biliary ducts, hepatocyte hypertrophy with clear, vacuolated cytoplasm, and hypertrophy of the sinusoidal capillaries. The renal parenchyma presents a disorganised appearance, in comparison with the group which did not receive ZEA in its feed, with the renal corpuscles being of heterogeneous dimensions and the frequent occurrence of renal glomerular compression, sometimes to the extent of the complete disappearance of the glomerulus and the reduction of the corpuscle to the external layer of the Bowman’s capsule. In some small areas there is hypertrophy accompanied by nephrocyte cytoplasmic vacuolation leading to degeneration of the cells affected. The kidney stroma shows a slight tendency towards interstitial fibrosis.

Our study shows that the supplementation of feed concentrate with a synbiotic combination of inulin and *Rhodotorula rubra* reduces the alterations produced by ZEA, with histopathological alterations in these two types of tissues becoming less evident.

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