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Postprint: Liver Injury and Natural Repair in Weaned Piglets Induced by Fusarium Toxin-Contaminated Feed

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Abstract

This study aimed to investigate the effects of phased feeding of Fusarium toxin-contaminated diets on serum and liver biochemical parameters, antioxidant indices, and relative mRNA expression levels of hepatic inflammatory cytokines interleukin-1β (IL-1β) and interleukin-6 (IL-6) in piglets. Thirty 35-day-old Duroc × Landrace × Yorkshire (DLY) female piglets with a body weight of $(8.45\$\pm0.94)kgwereselectedandrandomlyallocatedinto3groups, with10replicatespergroupand1pigperreplicate$ $contaminateddiet(zearalenone0.90mg/kg, deoxynivalenol1.43mg/kg, fumonisin5.85mg/kg), andthenaturalr$ $contaminateddiet.Thepre-trialperiodwas7days, andtheformaltrialperiodwas56days.Theresultsshowed$: $1)Comparedwiththecontrolgroup, therelativeliverweightofpigletsintheFusariumtoxingroupwassignificantl$ $0.05), serumalanineaminotransferase(ALT), aspartateaminotransferase(AST), andalkalinephosphatase(A$ $0.05), serumtotalprotein(TP)andglobulin(GLB)contentsweresignificantlydecreased(P <$ $0.05), serumglutathioneperoxidase(GSH-Px), serumandlivertotalsuperoxidedismutase(T-$ $SOD)activitieswesignificantlydecreased(P < 0.05), serumandlivermalondialdehyde(MDA)contentswere$ $0.05); therelativemRNAexpressionlevelsofhepaticinflammatorycytokinesIL-$ $1\$$ and IL-6 were significantly increased (P<0.05). 2) After 21 days of natural recovery, compared with the Fusarium toxin group, the relative liver weight of piglets in the natural recovery group tended to decrease (P>0.05), serum AST, ALT, and ALP activities were significantly decreased (P<0.05), serum TP and GLB contents were significantly increased (P<0.05), serum T-SOD activity was significantly increased (P<0.05), serum and liver GSH-Px, liver T-SOD activities tended to increase (P>0.05), serum and liver MDA contents were significantly decreased (P<0.05), and the relative mRNA expression levels of hepatic inflammatory cytokines IL-1β and IL-6 were significantly decreased (P<0.05). In conclusion, under the conditions of this experiment, long-term feeding of Fusarium toxins could cause liver damage in piglets, affecting hepatic antioxidant function, protein synthesis, and immune function, while after

a 21-day recovery period, the hepatic antioxidant and immune functions of piglets were improved to a certain extent.

Full Text

Study on Liver Injury Induced by Fusarium Toxin-Contaminated Diet and Natural Recovery in Weaned Piglets

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Abstract: This experiment was conducted to investigate the effects of phased feeding of Fusarium toxin-contaminated diets on serum and liver biochemical parameters, antioxidant indices, and the relative mRNA expression levels of hepatic inflammatory cytokines interleukin-1β (IL-1β) and interleukin-6 (IL-6) in weaned piglets. Thirty 35-day-old Duroc × Landrace × Large White female piglets with an initial body weight of (8.45$±$0.94) kg were randomly allocated into three groups, each consisting of 10 replicates with one pig per replicate. The control group was fed a basal diet throughout the experiment, the Fusarium toxins group received a Fusarium toxin-contaminated diet continuously (containing 0.90 mg/kg zearalenone, 1.43 mg/kg deoxynivalenol, and 5.85 mg/kg fumonisin), and the natural recovery group was switched to the basal diet after 35 days of feeding the contaminated diet. The adaptation period lasted 7 days, followed by a 56-day formal experimental period.

The results showed: 1) Compared with the control group, the Fusarium toxins group exhibited significantly increased relative liver weight ($P<0.05$), elevated serum activities of alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP) ($P<0.05$), decreased serum concentrations of total protein (TP) and globulin (GLB) ($P<0.05$), reduced activities of serum glutathione peroxidase (GSH-Px) and total superoxide dismutase (T-SOD) in both serum and liver ($P<0.05$), increased malondialdehyde (MDA) content in serum and liver ($P<0.05$), and significantly upregulated relative mRNA expression of hepatic inflammatory cytokines IL-1β and IL-6 ($P<0.05$). 2) After 21 days of natural recovery, compared with the Fusarium toxins group, the natural recovery group showed decreased relative liver weight ($P>0.05$), significantly reduced serum AST, ALT, and ALP activities ($P<0.05$), significantly increased serum TP and GLB concentrations ($P<0.05$), significantly elevated serum T-SOD activity ($P<0.05$), increased serum and liver GSH-Px activity and liver T-SOD activity ($P>0.05$), significantly decreased serum and liver MDA content ($P<0.05$), and significantly downregulated relative mRNA expression of hepatic inflammatory cytokines IL-1β and IL-6 ($P<0.05$). These findings indicate that

long-term feeding of Fusarium toxin-contaminated diets can cause liver injury in piglets, affecting hepatic antioxidant capacity, protein synthesis, and immune function, while a 21-day recovery period can partially restore these functions.

Keywords: Fusarium toxins; piglets; liver injury; interleukin-1β; interleukin-6

Fusarium toxins are secondary metabolites produced by Fusarium fungi during growth and represent the most economically damaging class of mycotoxins to the global feed and livestock industries. The most common Fusarium toxins include zearalenone (ZEN), deoxynivalenol (DON), and fumonisins (FUM). These toxins exert broad toxic effects on animals, including reduced growth performance and nutrient digestibility, metabolic disorders in tissues and organs, and cytotoxic effects on various cell types. Following dietary ingestion, Fusarium toxins are transported to the liver for catabolism, making hepatic morphological and functional changes important diagnostic markers for subclinical mycotoxicosis. Previous studies have demonstrated that Fusarium toxins can impair liver function, induce oxidative stress and inflammatory responses, and cause histopathological damage such as hepatocellular swelling and degeneration, as well as vascular wall thickening and lumen dilation. While liver injury has been associated with increased cytokine production, few studies have examined changes in cytokine expression in weaned piglets with Fusarium toxin-induced liver injury, and the natural recovery process following such injury remains unclear. Therefore, this study investigated the effects of Fusarium toxins on various indicators of liver function damage and the relative mRNA expression of cytokines interleukin-1β (IL-1β) and interleukin-6 (IL-6) at the molecular level, to explore both the impact of Fusarium toxins on piglet liver injury and the potential for natural recovery, thereby providing a theoretical basis for swine production.

1.1 Experimental Animals and Design

Thirty 35-day-old Duroc × Landrace × Large White female piglets with an initial body weight of (8.45$±$0.94) kg were randomly divided into three groups with no significant differences in initial body weight among groups (P>0.05). Each group contained 10 replicates with one pig per replicate. The control group received a basal diet throughout the experiment, the Fusarium toxins group was fed a Fusarium toxin-contaminated diet (containing 0.90 mg/kg zearalenone, 1.43 mg/kg deoxynivalenol, and 5.85 mg/kg fumonisin), and the natural recovery group was switched to the basal diet after 35 days of feeding the contaminated diet. The adaptation period lasted 7 days, followed by a 56-day formal experimental period. Piglets were housed individually in pens equipped with feeders and nipple drinkers, allowing ad libitum access to feed and water. The experiment was conducted at the experimental facilities of the College of Animal Science and Technology, Shandong Agricultural University.

1.2 Experimental Diets

The basal diet was formulated according to NRC (2012) nutrient requirements for piglets and adjusted based on practical production conditions. The Fusarium toxin-contaminated diet was prepared by replacing 50% of the corn and corn gluten meal in the basal diet with naturally moldy corn and moldy corn gluten meal. The diet composition and nutrient levels are presented in Table 1 . All experimental diets were prepared in a single batch before the trial began, and samples were collected at the start and end of the experiment for analysis of mycotoxin and crude protein content. Zearalenone, aflatoxin (AFL), fumonisin, and T-2 toxin concentrations were determined using enzyme-linked immunosorbent assay (ELISA) and fluorescence techniques, while deoxynivalenol was measured by high-performance liquid chromatography (HPLC). The main mycotoxin concentrations in the experimental diets are shown in Table 2 ; aflatoxin and T-2 toxin were not detected.

1.3 Sample Collection

On the final day of the experiment, blood samples were collected from the anterior vena cava before morning feeding after an overnight fast. Blood samples were allowed to clot for 30 minutes, then centrifuged at 3,000 r/min for 10 minutes to obtain serum, which was aliquoted into Eppendorf tubes and stored at -20°C for subsequent analysis. Following blood collection, piglets were euthanized by electrical stunning and exsanguination. The abdominal cavity was immediately opened, and two liver tissue samples were collected from the same location on the inner side of the right liver lobe into cryovials, snap-frozen in liquid nitrogen, and then stored at -80°C for antioxidant analysis and RNA extraction. The entire liver was subsequently removed and weighed to calculate relative liver weight using the formula: Relative liver weight (g/kg) = Liver weight (g) / Live body weight (kg).

1.4 Analytical Methods

1.4.1 Serum Biochemical Parameters Serum activities of alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP), as well as concentrations of total protein (TP) and globulin (GLB), were determined using a Cobus-Mira-Plus automatic biochemical analyzer according to the kit instructions (Nanjing Jiancheng Bioengineering Institute).

1.4.2 Serum and Liver Antioxidant Indices Liver tissue samples were thawed on ice and homogenized in physiological saline at a 1:9 weight-to-volume ratio using mechanical homogenization (10,000–15,000 r/min) in an ice-water bath. The homogenate was centrifuged at 3,000 r/min for 15 minutes, and the supernatant was collected for analysis. Activities of glutathione peroxidase (GSH-Px) and total superoxide dismutase (T-SOD), as well as malondialdehyde (MDA) content, were measured in serum and liver homogenate supernatants

using commercial kits purchased from Nanjing Jiancheng Bioengineering Institute.

1.4.3 Relative mRNA Expression of Hepatic Inflammatory Cytokines IL-6 and IL-1β Total RNA was extracted from liver tissue using the Trizol reagent kit (TaKaRa, Dalian) according to the manufacturer' s instructions. RNA concentration and purity were determined using a UV spectrophotometer (OD260/OD280 ratio: 1.8–2.0). Based on the measured concentration, the required amount of RNA for the reverse transcription system was calculated, and cDNA was synthesized using the PrimeScript® RT reagent Kit (TaKaRa, Dalian) following the kit protocol. Relative mRNA expression levels of IL-6 and IL-1β were quantified by real-time fluorescent quantitative PCR using the SYBR Green I method. The PCR reaction system was prepared according to the SYBR Premix Ex TaqTM (Tli RNaseH Plus) kit (TaKaRa, Dalian) instructions: SYBR Premix Ex Taq (Tli RNaseH Plus) (2×) 10 L, PCR Forward Primer (10 mol/L) 0.4 L, PCR Reverse Primer (10 mol/L) 0.4 L, ROX Reference Dye II (50×) 0.4 L, cDNA template 2.0 L, and sterile double-distilled water to a final volume of 20 L. Primer sequences for IL-1β, IL-6, and glyceraldehyde-3-phosphate dehydrogenase (GAPDH) are listed in Table 3 and were designed and synthesized by Sangon Biotech (Shanghai) Co., Ltd. The reaction was performed on an ABI 7500 real-time PCR system under the following conditions: pre-denaturation at 95°C for 30 s, followed by 45 cycles of denaturation at 95°C for 5 s, annealing/extension at 60°C for 34 s, then 95°C for 15 s, 60°C for 1 min, and 95°C for 15 s. Relative gene expression was quantified using the 2-$\Delta\Delta$Ct method.

1.5 Statistical Analysis

Experimental data were analyzed using SAS 9.2 software with one-way ANOVA. Duncan' s multiple range test was used for post-hoc comparisons, with $P<0.05$ considered statistically significant.

2.1 Relative Liver Weight

As shown in Figure 1 [Figure 1: see original paper], the relative liver weight of piglets in the Fusarium toxins group was significantly higher than that in the control group ($P<0.05$). The natural recovery group exhibited lower relative liver weight compared to the Fusarium toxins group but higher than the control group, though these differences were not statistically significant ($P>0.05$).

2.2 Serum Biochemical Parameters

Table 4 presents the serum biochemical results. Compared with the control group, the Fusarium toxins group showed significantly increased serum AST, ALT, and ALP activities ($P<0.05$) and significantly decreased serum TP and GLB concentrations ($P<0.05$). Following natural recovery, the natural recov-

ery group demonstrated significantly reduced serum AST, ALT, and ALP activities ($P<0.05$) and significantly increased serum TP and GLB concentrations ($P<0.05$) compared to the Fusarium toxins group, though these values remained significantly different from the control group ($P<0.05$). These findings indicate that Fusarium toxins impair hepatic protein synthesis function, which can be partially restored after discontinuation of the contaminated diet.

2.3 Serum and Liver Antioxidant Indices

As presented in Table 5 , compared with the control group, the Fusarium toxins group exhibited significantly decreased activities of serum GSH-Px, serum T-SOD, and liver T-SOD ($P<0.05$), along with significantly increased MDA content in both serum and liver ($P<0.05$). After natural recovery, the natural recovery group showed significantly increased serum T-SOD activity ($P<0.05$) and significantly decreased MDA content in serum and liver ($P<0.05$) compared to the Fusarium toxins group, with values not significantly different from the control group ($P>0.05$). Serum GSH-Px activity and liver T-SOD activity in the natural recovery group did not differ significantly from either the control or Fusarium toxins groups ($P>0.05$). These results demonstrate that Fusarium toxins cause oxidative damage in piglet liver, which can be partially ameliorated by feeding the basal diet.

2.4 Relative mRNA Expression of Hepatic IL-1β and IL-6

Figure 2 [Figure 2: see original paper] illustrates that the Fusarium toxins group had significantly elevated relative mRNA expression levels of hepatic IL-1β and IL-6 compared to the control group ($P<0.05$). Following natural recovery, the natural recovery group showed significantly decreased expression of both cytokines compared to the Fusarium toxins group ($P<0.05$), with levels not significantly different from the control group ($P>0.05$).

Discussion

In 2013, our research team collected and analyzed 153 feed ingredient samples from multiple feed mills and farms in Shandong Province for mycotoxin contamination. Naturally moldy corn and corn gluten meal were selected to prepare the Fusarium toxin-contaminated diet, while ingredients with toxin levels below detection limits were used for the basal diet. However, trace amounts of toxins were still detected in the basal diet, highlighting the widespread contamination of feed ingredients with Fusarium toxins in China. Since the toxin concentrations in the basal diet were far below the limits specified in Chinese feed hygiene standards (<0.5 mg/kg for zearalenone per GB 13078.2–2006; <1 mg/kg for deoxynivalenol per GB 13078.3–2007; no standard established for fumonisin) and EU maximum limits for piglet diets (<0.1 mg/kg zearalenone, <0.9 mg/kg deoxynivalenol, and <5.0 mg/kg fumonisin), and the toxin levels in the Fusarium toxins group exceeded these standards, we conclude that the basal diet toxin

content did not confound the interpretation of results for the Fusarium toxins group.

The liver is a vital organ for detoxification in both humans and animals, and changes in its function have significant implications for animal health. Relative organ weight is widely used to assess toxin-induced toxicity. This study found that long-term feeding of Fusarium toxin-contaminated diet significantly increased relative liver weight in piglets, which differs from our previous 35-day feeding trial and may be attributed to compensatory liver enlargement due to prolonged toxin exposure. Alterations in serum ALT, AST, and ALP activities represent a hepatic response to injury, while serum TP and GLB concentrations directly reflect hepatic protein synthesis capacity, both serving as indicators of hepatotoxicity. Previous studies demonstrated that feeding piglets a Fusarium toxin-contaminated diet for 35 days significantly increased serum AST and ALT activities within normal reference ranges (AST: 32–84 U/L; ALT: 31–58 U/L), with histopathological evidence of liver damage. In the current study, while serum ALT, AST, and ALP activities were significantly elevated, they remained within normal ranges, indicating mild hepatic injury requiring further investigation. The significant reduction in serum TP and GLB concentrations suggests impaired hepatic protein synthesis, further confirming liver dysfunction. Serum T-SOD and GSH-Px activities reflect systemic antioxidant capacity, while MDA is a lipid peroxidation metabolite. Previous research on the combined cytotoxicity of deoxynivalenol and zearalenone demonstrated that Fusarium toxins can accelerate cellular peroxidation by damaging antioxidant systems and promoting free radical generation, leading to oxidative damage in various organs. Consistent with Jiang et al.' s findings in broiler chickens, our results showed significantly decreased T-SOD and GSH-Px activities and increased MDA content in serum and liver, indicating that Fusarium toxins induced oxidative stress and oxidative damage in piglet liver.

Liver injury triggers the release of numerous cytokines from resident innate and adaptive immune cells, initiating cascades of inflammatory responses. Studies on trichloroethylene-sensitized guinea pigs demonstrated elevated hepatic IL-1 and IL-6 mRNA expression during liver injury. In this study, the significant upregulation of hepatic IL-1β and IL-6 mRNA expression in the Fusarium toxins group provides molecular evidence that Fusarium toxins can induce inflammatory cytokine expression in liver tissue, potentially leading to immune dysfunction and hepatocellular damage, though the specific mechanisms warrant further investigation.

Following 35 days of Fusarium toxin exposure and subsequent feeding of the basal diet, piglets showed reduced relative liver weight and improved hepatic functional indices, protein synthesis capacity, and antioxidant status. These recovery effects are similar to those observed with functional amino acids (such as glutamate and arginine) and mycotoxin adsorbents, indicating partial alleviation of liver injury. The significant reduction in hepatic IL-1β and IL-6 mRNA expression to levels comparable with the control group provides molecular evi-

dence that Fusarium toxin-induced liver injury can be mitigated through dietary intervention, though the underlying mechanisms require further elucidation.

Conclusion

Under the conditions of this study, long-term feeding of a Fusarium toxin-contaminated diet (0.90 mg/kg zearalenone, 1.43 mg/kg deoxynivalenol, and 5.85 mg/kg fumonisin) caused liver injury in piglets, impairing hepatic antioxidant capacity, protein synthesis, and immune function. A 21-day recovery period after discontinuing the contaminated diet partially restored these hepatic functions.

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