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Joint Effect of the Mycotoxins T-2 Toxin, Deoxynivalenol and Zearalenone on the Weaner Pigs against a Background of the Infection Load.

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ABSTRACT

Currently, among more than 100 000 known species of fungi about 250 species produce mycotoxins, secondary metabolites which are dangerous to human and animal health. Most of these toxins are highly resistant to physical and chemical factors, and are not destroyed even after prolonged heating of feed contaminated with mycotoxins. The aim of the present study was to investigate the joint effects of T-2 toxin, zearalenone, deoxynivalenol and infectious agents on pigs. The study was conducted inthe Federal Center for Toxicological, Radiation and BiologicalSafety. Studies have shown that the jointdietary intake T-2 toxin at a dose of 70 mg/kg, zearalenoneat a dose of 50 mg/kg and deoxynivalenolat a dose of 1000 mg/kg for 30 days against a background of the simulated Clostridium infection load causes symptomatic mycotoxicosis which is accompanied by activation of lipoperoxidation, decrease in hematological, biochemical and immunological parameters: a reduction in the number of T and B lymphocytes, titers of specific protective antibodies and the development of pathological processes in the tissues and organs of weaner pigs, slow weight gain, increase in feed conversion ratio and the development of infectious disease, confirmed with laboratory tests. The result was different in the group of animals with the same infection load but without introducing mycotoxins into the animal diet. The findings provide strong evidence that chronic intake of fuzariotoxins even at the level of permissible concentrations against a background of infection load predisposes to infectious diseases.

Keywords: a mycotoxin combination of T-2 toxin, zearalenone, deoxynivalenol, clostridium microorganisms, immunity.

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INTRODUCTION

Among natural ecotoxicants – pollutants of agricultural raw materials and products, microscopic fungi and their toxins – mycotoxins are very dangerous to human and animal health. Mycotoxins contaminate productsand feed at all stages of production, transportation, storage, processing and marketing [1, 2].

Mycotoxins are highly toxic, and many of them have immunosuppressive, mutagenic, teratogenic and carcinogenic properties [3]. Scientific studies show that livestock breeding experiences significanteconomic losses as a result of the reduction in productivity and reproduction of farm animals due tomycotoxicosis [4, 5]. The possibility of the effect of several mycotoxins or their combination with other ecotoxicantscannot be excluded [6, 7]. The clinical symptoms of the disease in animals consuming diets which contain a combination of mycotoxins in small concentrations are usually non-specific, difficult to diagnose and manifested in slow growth, deterioration in the productivity of animals and their reproductive capacity, increased susceptibility to infectious diseases, reduction in the quality of products and cause significant economic losses. This requires not only the revision of standards of maximum allowable concentrations of mycotoxins but a closer study of the concept “mycotoxin synergism” or “joint effect” [8, 9, 10].

The aim of the research was to studyjoint effect of T-2 toxin, zearalenone, deoxynivalenol and infectious agents.

METHODS AND TECHNIQUES

The experiment was conducted on farm animals: weaner pigs of the Large White. Before theexperiment the animals were under quarantine for 14 days, fed in accordance with the standards adopted in animal science. Animals were divided into two groups: control and experimental.

There were three weaner pigs (sows) in each group. The diet in the control group was mycotoxin free. The diet of the weaner pigsin the experimental group contained T-2 toxin at a dose of 70 mcg/kg, zearalenoneat a dose of 50 mcg/kg and deoxynivalenolat a dose of 1000 mcg/kg. The experiment lasted 30 days.

All animals were given vaccine against colibacillosis. The vaccine was madein FGBU “FTsTRB-VNIVI” courtesy of the head of younganimal disease laboratory Spiridonov G.N., cand.vet.sc. The vaccine was administered intramuscularly in the thigh at a dose of 1 ml on the 15 day.

In addition, all the weaner pigs were infected with pathogenic Clostridium culture (from the strain collection of FGBU “FTsTRB-VNIVI”) which had beenisolatedfrom pathologicalmaterial of dead pigs during the study of the mass death of pigs on one of the farms of the Republic of Tatarstan. Infection was performed orally in bothgroups of animals. Each weaner pig was given 2 ml of the suspension containing $1x10^6$of Clostridium.

To do research, crystal T-2 toxin, deoxynivalenol, zearalenonewith mycotoxin purity 99.8, 96.7 and 98.3% respectively were used which had been produced in the mycotoxin laboratory of FGBU “FTsTRB-VNIVI”. *Fusarium sporotrichioides* strain *2M15* was used as a producer of T-2 toxin and zearalnone, courtesy of A.N.Kotik,Doctor of Biological Sciences, *Fusarium graminearum* strain *W32* was used as a producer of deoxynivalenolwhich was taken from the microscopic fungi collection of FGBU “FTsTRB-VNIVI”.

Toxins were included in the diet of animals being thoroughly mixed with the feed. The dosages were at the maximum allowable concentrations level adopted in Russia. Control animals received the same diet, but without mycotoxins. Feed was also pre-checked for mycotoxins which are regulated in Russia and for biological safety – the presence of pathogenic and opportunistic pathogenic microorganisms, the feed met the requirements of Safe Quality Food Certification.

Clinical condition of the animals, feed intake, hematological, biochemical and immunological parameters, the change in body weight were studied,lifespan and pathological changes were recorded. In the experimental and control animals, blood samples were taken from the tail vein.

Haematology research on the determination of the number of erythrocytes, leukocytes, hemoglobin, monocytes, lymphocytes, platelets was conductedwith Mythic 18 haematology analyzer; total protein, bilirubin, glucose, enzyme activities of alanineaminotransferase, aspartateaminotransferase, alkaline phosphatase in animal serum were determined with Microlab 300 biochemistry analyzer.

T and B-lymphocytes count in the peripheral blood was identified with E-rosette test. Antibody titers to colibacillosis vaccine were determined withserum agglutination test. The degree of intensity of lipid peroxidation (LPO) was identified by the accumulation of secondary products of lipid peroxidation – malondialdehyde (MDA) in the reaction with 2-thiobarbituric acid.

Material for pathological studies was fixed in 5% neutral formalin, ethanol-formalin (9:1), a buffer solution of 10% formalin, pH-8.0. After dehydration, compression of the material and preparation of units,histological sections (8 microns thick) were made. Stained with hematoxylin and eosin, histological specimens were studied by assessing changes in the structure of organs and tissues, as well as morphometric parameters.

Digital material processing was performed withanalysis of variance and Student's t-test.

RESULTS AND DISCUSSION

Haematological parameters of weanerpigs against a background oflong-term intakeof mycotoxins were studied. The results of the study of leukocyte,lymphocyte, monocyte, granulocyte count are shown in Table 1.

As can be seen in Table 1, there was a fluctuation in leukocyte numbers. So, on thetenth day of the studythe total number of leukocytes in the animals of the experimental group was 17.2% more than in the animals of the control group, on the twentieth day it was68.9% more, by the end of the experiment it was 6.4% more than in the animals of the control group.

On thetenth day of the study the total number of lymphocytes in the animals of the control group was36.5% more than in the animals of the experimental group, on the twentieth day it was 41.4% more, then it was a decline in the number of lymphocytes in the animals of this group and by the end of the experiment it was only 17.77% more than in the animals of the experimental group.

The number of granulocytes in the animals of the second group on the tenth day was 102.3% more than in the animals of the control group,on thetwentieth day it was 181.5% more than in the first group, at the end of the experiment the number of granulocytes in the second group was 112% more than in the control group.

Dynamics of the parameters indicates that a significant increase in the number of leukocytes on the tenth and twentieth days of the experiment in the animals of the second group was due to several factors: the effect of mycotoxins (the number of formed elements usually increases at the beginning of intoxication), signs of animal diarrhea (clotting factors) and infection load which wasproved during the experiment. The increasein the number of granulocytes can be explained by allergenic effect of mycotoxins and the reaction of the body to bacterial toxins.

Results of the researchon erythrocytesand hemoglobin are shown in Table 2. As can be seen in Table 2, there was a fluctuation in erythrocyte numbers. However, it was less than a fluctuation in leukocyte numbers. More significant changes are the following: the number of erythrocytes, hemoglobin and platelets was lower in the second group than in the group of biological control, by 41.5%, 22.5% and 76% respectively. Thus, these data indicate the negative impact of mycotoxins on haematological parametersof animals when they are given to animals with the feed for a long period of time in the concentrations close to the maximum allowable and against a background of infection load.

The study of biochemical parameters of weaner pig serum against a background of long-term jointintake of mycotoxins was carried out. The results are given in Table 3.

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As can be seen from the data presented in Table 3, there was a slight fluctuation in total protein numbers in both groups of animals. However, greater decrease was in the second group on the twentieth and thirtieth days, it was 8.21% and 13.1% respectively.

A similar pattern was in the case withglucose concentration – a greater decrease was in the second group on the twentieth and thirtieth days, it was 56.8% and 40.5% respectively. In mycotoxicosis, the higher degree of intoxication,the higher rate of decrease in the amount of glucose in the blood, that was observed in our experiment. Hypoglycemia is probably the result of glycolysis enhancement or glucose malabsorption in the intestine. So, Suneja S. et al. (1984) observed a significant decline in glucose absorption in the small intestine.

Hepatotoxic effect of mycotoxins is well-known –an increase in the number of such hepatobiliary enzymes as aspartate aminotransferase and alanine aminotransferase in the serum indicates a significant damage of the hepatocyte membrane. In the serum of weaner pigs of the experimental group, the activity of alanine aminotransferase and aspartate aminotransferase increased by 41% and 70% respectively, itcorresponds to the data of scientific works (Fekete S., 1993; Garies, M., Hashen, A. et al, 1998). The decline in AST:ALT ratio to 0.95 with a coefficient of 1.31 in the control indicates liver disorder in animals of the experimental group. The amount of bilirubin increased by 408% in the second group that indicates the toxic load on the liver.

Table 1: Leukocyte,lymphocyte, monocyte, granulocyte count in the weaner pig blood against a background of long-term joint intake of mycotoxins (n = 3)

Indicator	The group of animals / The day of the study							
	1 (control)				2 (experimental)			
	1	10	20	30	1	10	20	30
Total number of leukocytes, $x10^9$/l	14.75 ±0.45	16.47 ±0.51	15.93 ±0.48	17.96 ±0.44	15.63 ±0.42	19.3 ±0.51*	26.9 ±0.44***	19.1 ±0.49
Lymphocytes, %	76.1 ±2.3	69.7 ±2.6	72.6 ±2.5	67.4 ±2.7	68.6 ±2.1	66.8 ±2.9	60.8 ±3.2*	52.1 ±2.7*
Monocytes, %	19.2 ±1.9	25.0 ±2.2	22,3 ±1.8	26.6 ±1.3	26.5 ±1.7*	29,7 ±1.9	30.7 ±2.0*	35.9 ±2.4*
Granulocytes, %	4.7 ±0.56	5.3 ±0.47	4,6 ±0.49	6.0 ±0.52	4.9 ±0.51	7.5 ±0.64*	8.5 ±0.32**	12.0 ±0.66**

* –p ≤ 0.05 ** p ≤ 0.01 *** p ≤ 0.001

Table 2: Erythrocyte, hemoglobin, platelet count in the weaner pig blood against a background of long-term joint intake of mycotoxins (n = 3)

Indicator	The group of animals / The day of the study							
	1 (control)				2 (experimental)			
	1	10	20	30	1	10	20	30
Erythrocytes, $x10^{12}$/l	5.33 ±0.13	5.45 ±0.15	5.61 ±0.12	6.43 ±0.15	5.37 ±0.15	6.1 ±0.13 *	5.8 ±0.11	4.06 ±0.18 ***
Hemoglobin, g/l	92.0 ±1.9	93.0 ±1.6	95.0 ±1.8	99.0 ±1.9	92.0 ±2.0	95.0 ±1.4	91.0 ±1.3	79.0 ±2.2 **
Platelets, $x10^9$/l	225.5 ±8.13	225.0 ±8.71	226.0 ±8.64	262.6 ±7.36	236.0 ±6.72	393.0 ±7.93 ***	639.6 ±8.85 ***	62.0 ±11.4 ***

* –p ≤ 0.05 ** p ≤ 0.01 *** p ≤ 0.001

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Table 3: Biochemical parameters of the weaner pig serum against a background of long-term joint intake of mycotoxins (n = 3)

Indicator	The group of animals / The day of the study							
	1 (control)				2 (experimental)			
	1	10	20	30	1	10	20	30
Total protein, g/l	62.5 ±0.93	63.2 ±0.91	63.3 ±0.93	63.9 ±0.92	62.3 ±0.92	62.6 ±0.90	58.1 ±0.82*	55.5 ±0.94**
Total bilirubin, mcmol/l	1.6 ±0.18	1.5 ±0.16	3.2 ±0.19	2.5 ±0.17	1.5 ±0.1	4.2 ±0.15***	4.9 ±0.22**	12.7 ±0.57***
Glucose, mmol/l	3.6 ±0.16	3.5 ±0.14	4.2 ±0.15	4.4 ±0.14	3.2 ±0.11	2.9 ±0.14*	2,5 ±0.13***	1.9 ±0.17***
Cholesterol, mol/l	3.6 ±0.16	3.2 ±0.13	3.6 ±0.14	1.8 ±0.09	2.5 ±0.13**	5.0 ±0.15***	4.2 ±0.17	1.5 ±0.11
ALT, IU/L	28.6 ±1.94	33.2 ±1.58	29.2 ±1.92	51.9 ±1.84	27.4 ±1.85	46,3 ±1.92**	80.6 ±1.63***	59.2 ±1.91
AST, IU/L	33.1 ±2.49	36.9 ±2.43	35.2 ±2.49	55.3 ±2.55	34.6 ±2.42	60.2 ±2.23**	75.2 ±2.48***	56.4 ±2.47
Alkaline phosphatase, IU/L	145.3 ±14.6	137.9 ±15.3	143.4 ±14.8	175.3 ±15.5	165.4 ±9.2	312.2 ±19.2**	267.7 ±18.6**	102.6 ±14.4*

* –p ≤ 0.05; ** p ≤ 0.01; *** p ≤ 0.001

Lipid peroxidation is a normal metabolic process in all organs and tissues, which plays an important role in the physiological and biochemical homeostasis of normal cells, and also acts as a universal mechanism for the development of various pathological conditionsin the organism. Therefore, malondialdehyde count was an indicator of activation of lipid peroxidation. According to many works devoted to the study of the antioxidant status and immunity,activation of lipid peroxidation plays a key role in the pathogenesis of pathological changes in the mycotoxicoses (Surai P.F., 2005). Our research also proves the activation of lipid peroxidation under the influence of mycotoxins on weaner pigs. Results of the research on products of lipid peroxidation (MDA) in animal blood are presented in Table 4.

Table 4: Malondialdehyde count in the weaner pig blood (n = 3)

The group of animals	The day of the study	MDA, mcmol/l
1 (control)	1	1.86±0.17
	10	1.92±0.19
	20	3.35±0.1
	30	5.19±0.15
2 (experimental)	1	1.65±0.16
	10	3.07±0.21*
	20	7.32±0.22***
	30	8.69±0.19***

* - p ≤ 0.05; ** p ≤ 0.01; *** p ≤ 0.001

As can be seen from the data presented in Table 4, there was an increase in malondialdehyde count in both groups, butin theexperimental group it was more significant. So, an increase in malondialdehyde count in the animals of the second group was 59.9% more than in the animals of the control group on the tenth day, on the twentieth day it was 118.5% more than in the first group, at the end of the experiment an increase in malondialdehyde count in the second group was 67.4% more than in the control group.

The results of T- and B-lymphocytesblood test in animals against a background of mycotoxins are shown in Table 5.

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Table 5: The amount of T- and B-lymphocytes in the weaner pig blood (n = 3)

The group of animals	The day of the study	Indicator	
		T-lymphocytes	B-lymphocytes
1 (control)	1	55.2±2.45	25.9±1.64
	10	53.2±2.39	26.5±1.38
	20	51.4±2.84	25.3±0.92
	30	46.7±3.02	28.5±1.33
2 (experimental)	1	52.8±2.36	27.4±1,12
	10	53.7±2.83	28.6±1.49
	20	48.3±2.14	26.1±0.38
	30	32.1±2.97*	23.2±1.81

*–p ≤0.05; ** p ≤0.01; *** p ≤0.001

As can be seen from the data presented in Table 5,there was a decrease in T-lymphocytes in both groups, but it was more significant in the experimental group.

Health condition of the animals during the experiment was as follows. During the first 2 weeks of the experiment general health of the animals of both groups was good.The animals of the first group which were given feed without any mycotoxins were active and ate well.

Mycotoxins had a harmful effect on the animals of the experimental group, provingtheir name “silent killers”, when negative impact dramatically manifested itself clinically after toxinswere accumulated.

Animals in the second group ate less feed than animals in the first group, after 6-8 days they partially refused their feed, it lasted 3-4 days, then weaner pigsbeganto consume the feedagain but in smaller amounts and were significantly less active. This is probably due to the development of feed refusal and poor absorption (malabsorption) syndromes. T-2 toxin inhibits protein synthesis of the liver, that leads to hyperaminoacidemia– an excess of free amino acids in the bloodstream, increased concentration of tryptophan in the brain, serotonin in the midbrain tissue andthe cerebral cortex, which affects a sense of fullness (Smith, 1992).The second syndrome is causedby apoptosis in the gastrointestinal tract by trichothecenes (Bondy, Pestka, 2000) and by reduced amount of pancreatic enzymes and bile acids required for the emulsification and digestion of fats.

This was particularly evident in the second half of the experiment– the animals of the experimental group were weak, kept together, pursed their stomachs, had an upset stomach. Onthe 21-23 days they were worth,had a high temperature, one weaner pig died. While studying pathological material (internal organs) in the young animal disease laboratory, *Clostridium* pathogens were identified.The animals of the control group were active and ate well during the whole experiment.

Zootechnical performance parametersin animals are shown in Table 6.

Table 6: Zootechnical performance parameters in the weaner pigs (n = 3)

Indicator	The group of animals	
	1 (control)	2 (experimental)
Body weight at the beginning of the experiment, kg	14.9 ±0.22	14.65 ±0.22
Body weight at the end of the experiment, kg	22.22 ±0.36	19.1 ±0.64*
Weight gain after 30 days, kg	7.32	4.45
Average daily gain, g	244.0	148.3
Feed intakeper headfor 30 days, kg	26.0	22.6
Feed conversion ratio	3.55	5.07
Animal preservation, %	100	66.6

* –p ≤ 0.05; ** p ≤ 0.01; *** p ≤ 0.001

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The data presented in Table 6 show that the highest weight gain was in the biological control group – 244 g, the weight gain in the second group was less– 148.3g (<39.2%). Feed conversion ratio was also different in the first and second groups, 3.55 and 5.07 respectively.

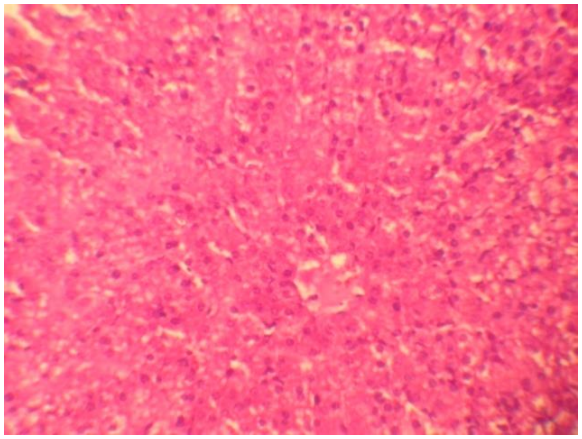

Figure 1: The liver of the weaner pig with dietary mycotoxin intake.Large areas of hepatocyte necrosis, edema, plasmorrhagiaof the wall of the centralvessel, swelling space of Disse. H & E stain, x 200.

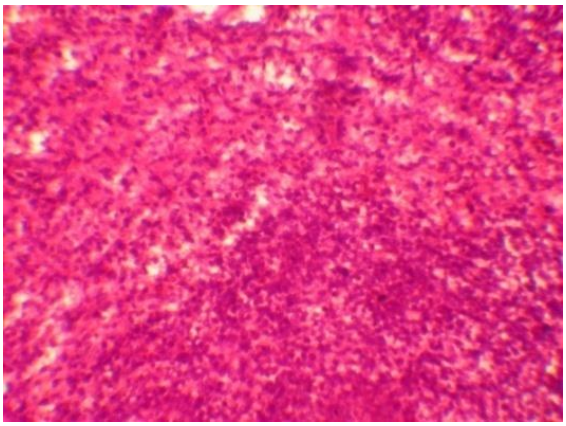

Figure 2: The spleen of the weaner pig with dietary mycotoxin intake.White pulp depletion. H & E stain, x 200.

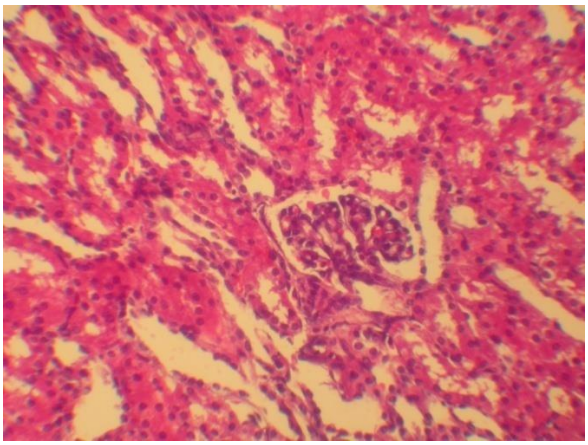

Figure 3: The kidney of the weaner pig with dietary mycotoxin intake.Areas of necrosis of the tubular epithelium, edema, plasmorrhagiaof the capillaries of malpighian tufts, desquamation of the tubular epithelium.H & E stain, light microscopy, 200mm lens.

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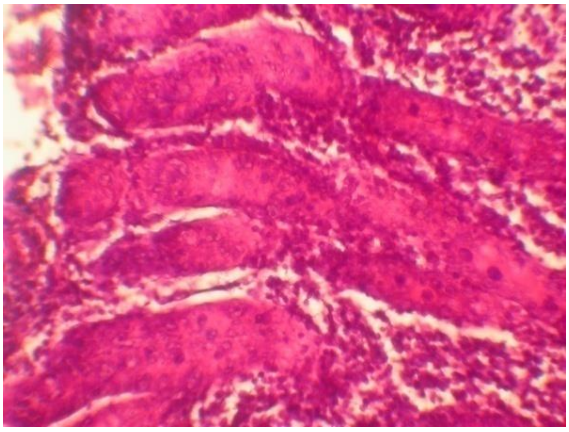

Figure 4:The duodenum of the weaner pig with dietary mycotoxin intake.Focal necrosis of mucous membrane, polymorphocellular infiltration (deep layer).H & E stain, light microscopy, 200mm lens.

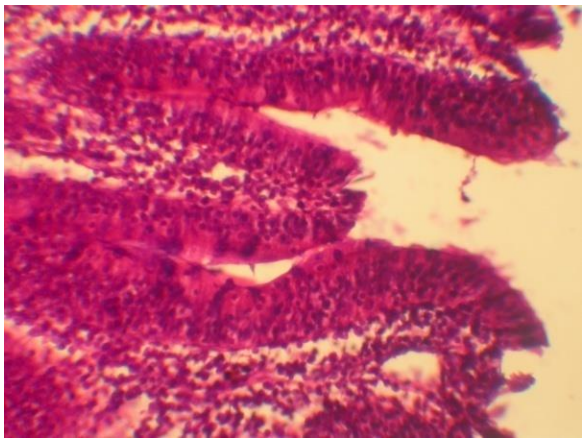

Figure 5: The duodenum of the weaner pig with dietary mycotoxin intake.Focal necrosis of mucous membrane, polymorphocellular infiltration (surperficial layer).H & E stain, light microscopy, 200mm lens.

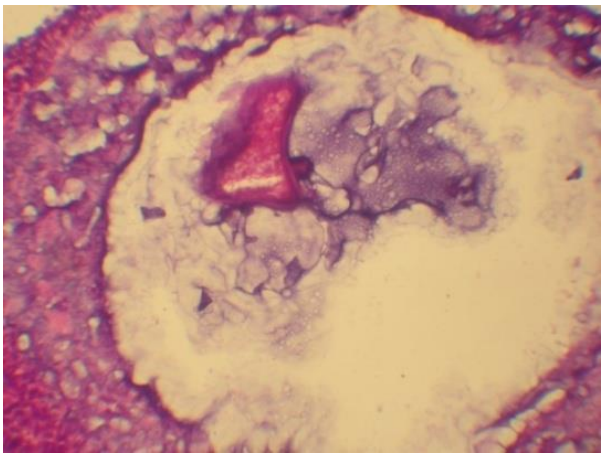

Figure 6: The ovary of the weaner pig with dietary mycotoxin intake.Colliquativefollicular necrosis with cellular reaction.H & E stain, light microscopy, 200 mm lens.

Histological studyshowed that feed intake with mycotoxins against a background of infection load causes pathological changes in some organs. Albuminous degeneration with focal necrosis reaching one-third of hepatic lobule cellsdeveloped in the liver. The reaction of Kupffer cells, which increased slightly and deformed, was observed, the space under the Kupffer cells (the space of Disse) expanded. However, there was no high sensitivity ofmacrophage cells. In the kidneys, albuminous degeneration developed, accompanied by desquamation of epithelial cells into the lumen of the tubules, clusters of protein masses in tubular lumina.

Focal necrosis of the tubular epithelium was observed. Capillaries of malpighian tufts were slightly thickened andedematic. In the lungs, a focal serous edema in interalveolar septum was observed. There was white pulp depletion in the spleen. Increased polymorphocellular infiltration with numerous lymphocytes from lymph follicles could be seen in the duodenum wall,focal necrosis of mucous membrane occured. In the wall of the stomach,infiltration of lymphoid cells, focal necrosis of the gastric mucosa wereidentified. In the heart, there were small areas of interstitial serous edema with slight polymorphocellular reaction involving lymphocytes, histiocytes and macrophage-like cells.Colliquativefollicular necrosis with cellular reaction developed in ovaries. The data of histological study of organs and tissues are presented in Fig. 1-2.

CONCLUSION

The joint dietary fuzariotoxin intake: T-2 toxin at a dose of 70 mg/kg, zearalenone at a dose of 50 mg/kg and deoxynivalenol at a dose of 1000 mg/kg for 30 days against a background of the simulated Clostridium infection load causes symptomatic mycotoxicosis which is accompanied by activation of lipoperoxidation, decrease in hematological, biochemical and immunological indicators: a decline in the number of T and B lymphocytes, titers of specific protective antibodies and the development of pathological processes in the tissues and organs of weaner pigs.

The data show the negative joint effect of mycotoxins on immunological, biochemical and haematological parameters, weight gain of the weaner pigs, their preservation even at the level of permissible concentrations, we consider these data particularly relevant as negative joint effect of mycotoxins on animals is often recorded on pig farms.

It is necessary to consider poor body resistance under the influence of small amounts of mycotoxins entering the bodywith feed as an independent type of mycotoxicosis which has perhaps more practical importance than the acute types.

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