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Biological properties of coronaviruses of farm, domestic animals and birds: comparative characterization of pathology they induce (review)

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SUMMARY

Coronavirus induced diseases can cause significant damage to agriculture that is associated with high (up to 100%) lethality in young animals. Members of the family *Coronaviridae* are characterized by the fact that they infect a wide range of animals and birds with expressed species-limited pathogenicity. One more coronavirus specificity involves their ability to simultaneously affect more than one organ. The disease severity is also strongly correlated with the age of the susceptible animal and degree of pathology. Thus, the coronavirus induced diseases are most often acute in newborn and young animals, while such diseases often develop into chronic and latent forms in adult animals. The general property of all coronavirus-induced diseases involves acute impairement of capillary circulation in the affected organ thus leading to the development of further pathology. The proposed review demonstrates brief overview of the history of discovery and examination of the viruses of *Coronaviridae* family and describes the coronavirus taxonomy. The paper reviews the virus structure, physico-chemical and biological properties; it describes specific features of their cultivation *in vitro*, some biochemical aspects of the virus replication and analyses the process of their propagation in the sensitive cells. Some data on the virus antigen structure and immunogenicity, on the presence of related antigens in the coronaviruses infecting humans, animals and birds are demonstrated as well. The paper provides data on the significant role the coronaviruses play in the pathology of farm animals and stresses their economic relevance, in particular for the commercial pig and poultry production.

Keywords: review, coronaviruses, mammals, avian, immunity, clinical picture

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Биологические особенности коронавирусов сельскохозяйственных, домашних животных и птиц: сравнительная оценка характера вызываемых ими патологических процессов (обзор)

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РЕЗЮМЕ

Болезни, вызываемые коронавирусами, могут наносить значительный ущерб сельскому хозяйству, обусловленный высокой (доходящей до 100%) летальностью среди молодняка. Представители семейства *Coronaviridae* характеризуются тем, что поражают широкий спектр животных и птиц, при этом отмечается выраженное видовое ограничение патогенности. Еще одной особенностью коронавирусов является способность поражать не один, а сразу несколько органов. Также существует четкая зависимость тяжести течения болезни от возраста восприимчивого животного и интенсивности патологических процессов. Так, заболевания, вызываемые данными вирусами, чаще всего имеют острое течение у новорожденных животных и молодняка, у взрослых особей они нередко переходят в хроническую и латентную формы. Общее свойство всех болезней, индуцированных коронавирусами, – острое нарушение капиллярного кровообращения в пораженном органе, становящееся основой развития дальнейшего патологического процесса. В предлагаемой обзорной статье представлена краткая информация об истории открытия и изучения вирусов семейства *Coronaviridae*, приведена таксономия коронавирусов. В работе рассматривается строение, физико-химические и биологические свойства данных вирусов, изложены особенности их культивирования *in vitro*, некоторые биохимические аспекты репликации, анализируется процесс размножения в восприимчивых клетках. Кроме того, обобщены некоторые данные об антигенной структуре и иммуногенности, о наличии родственных антигенов у коронавирусов, поражающих человека, животных и птиц. В статье приводятся данные о значительной роли коронавирусов в патологии сельскохозяйственных животных и подчеркивается их экономическое значение, особенно в условиях промышленного свиноводства и птицеводства.

Ключевые слова: обзор, коронавирусы, млекопитающие, птицы, иммунитет, клиническая картина

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INTRODUCTION

While considering the background of the issue one should mention that coronaviruses infecting animals and mostly birds were detected and studied before the human coronaviruses. Some of them were actively investigated and used as a model system in the studies of the molecular biology of the whole group of these viruses [1].

The first representative of the coronavirus family was isolated during the studies of avian infectious bronchitis etiology, and it was Infectious bronchitis virus (IBV). The viral nature of the highly contagious disease, often lethal for young chickens, was substantiated by the American researchers [2, 3]. Other researchers later detected the viral particles by means of negative-contrast electron microscopy of the IBV suspension [4]. The viral particles were mostly of round or oval shape and possessed thick membrane with club-shaped protrusions – spikes (Fig. 1).

In later years, the new family was persistently supplemented with the infectious agents isolated from humans and animals [5]. Starting from 1965, publications appeared that reported on the virus isolation from diseased people demonstrating acute respiratory signs [6]. One of such viral agents isolated from the diseased teenager and subjected to three passages in volunteers was identified as B814. This strain and strains 229E, OC38, OC43, isolated by the American researchers D. Hamre and J. J. Procknow [7] in human embryonic kidney cell line turned out to be similar in structure. Their further examination demonstrated common morphology of the isolates and IBV. Therefore, that enabled their incorporation in the same taxonomic group.

Comparative studies carried out by the group of researchers demonstrated such integration. It was additionally confirmed that murine hepatitis virus can be also included in this group as it has similar shape and structure [8].

Despite different natural hosts and diseases caused, they share not only structure but also a number of biological properties. Five key identification criteria were selected:

– average size of the virion is 80–160 nm;
– single-stranded RNA;
– membrane;
– virions are shaped as rounded bodies with typical crown of club-shaped protrusions;
– virus replication in cytoplasm with budding into the cytoplasmic vacuoles.

In 1968, the group of infectious agents having similar structure were proposed to be named coronaviruses thus emphasizing their specific shape. In 1976, the International Committee on Taxonomy of Viruses (ICTV) assigned the coronaviruses the status of the family. Hereafter, the family was supplemented with other viruses isolated from animals and birds as well as agents detected as a result of studies of contamination of cell cultures of different origin.

GENERAL DESCRIPTION OF CORONAVIRUSES

Coronaviruses (CoV; family *Coronaviridae*) belong to order *Nidovirales*, which includes large enveloped RNA-viruses. According to D. K. Lvov et al., this order comprises three families, one of which (*Coronaviridae*), in its

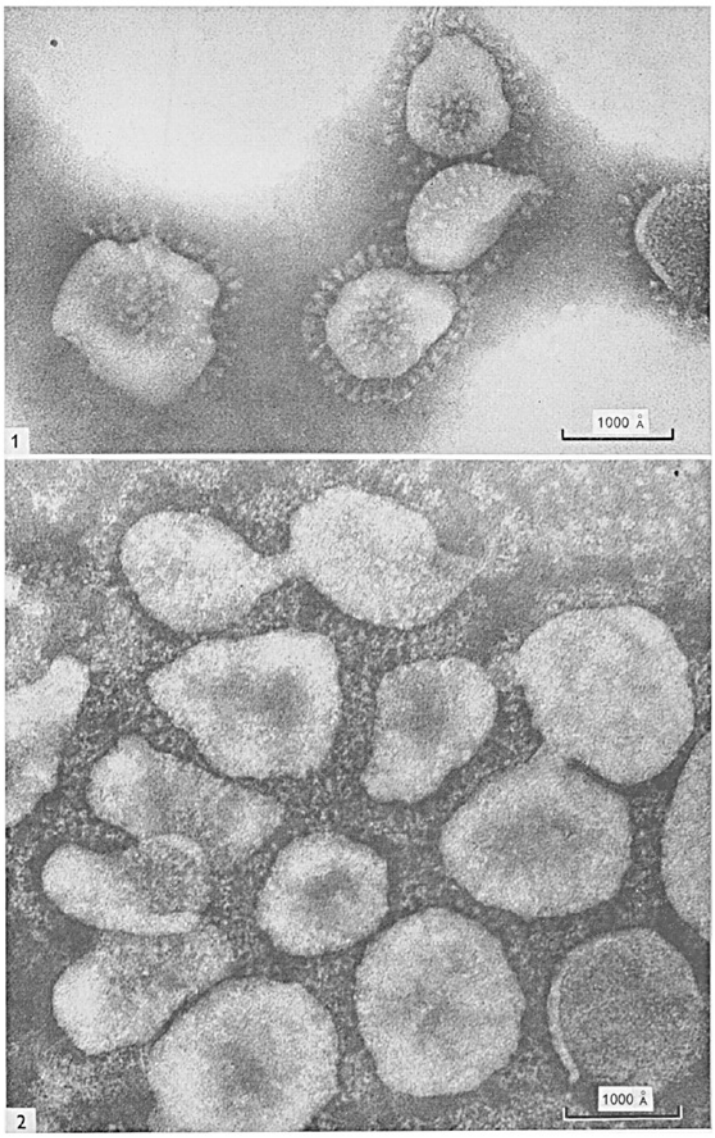

Fig. 1. General view of the infectious bronchitis virus virion. Negative staining [4]

turn, consists of two subfamilies and eight genera [9]. The ICTV proposed to use Greek alphabet letters (alpha, beta, gamma and delta) for designation of four genera of the coronavirus family [10]. As mentioned above, the viruses belonging to the family *Coronaviridae* have common biological properties and they are similar in their morphology. The coronavirus virion has a spherical shape (120–160 nm) and typical protrusions – peplomers (15–20 nm) forming serrated framing. Their shape and distance between the club-shaped protrusions serve as the differential structural properties, which allow to distinguish between coronaviruses and ortho- and paramyxoviruses by negative staining.

Coronavirus nucleocapsid is a long flexible helix containing the genomic positive-sense RNA (molecular weight 5.5×10^6) and a large number of molecules of phosphorylated nucleocapsid protein N (50–60 K). The virus envelope consists of lipid biolayer formed of the intracellular membrane of the host cells and two viral glycoproteins: E1 (20–30 K) and E2 (180–200 K); peplomers are formed of E2 molecules. The matrix glycoprotein E1 passes through the lipid biolayer and interacts with the nucleocapsid inside the viral particle [11] (Fig. 2).

PHYSICAL AND CHEMICAL PROPERTIES OF THE CORONAVIRUSES

Coronaviruses are infectious agents with moderate persistence in the environment. All members of the family have high tolerance for the vacuum freeze-drying, and being freeze-dried they can survive for several years at 4 °C. The coronaviruses can be UV-inactivated. The period necessary for the complete loss of infectivity depends on the distance from the UV-exposure source. Longer exposition (100–120 min) results in complete destruction of the virion of the porcine hemagglutinating encephalomyelitis virus (PHEV), loss of its infectivity and hemagglutination activity [12]. Sun rays also destruct the coronaviruses, however this procedure is rather slow, at least 3 hours at 37–38 °C are necessary for the complete inactivation of the virus [13].

Data on the hydrogen ion effect on the coronavirus stability are diverse. The majority of the researchers hold to an opinion that pH range from 7.0 to 7.5. is optimal for all members of the family. All coronavirus species are destructed by the fat solvents: when treated with Tween, ether, chloroform the viruses are completely inactivated [14].

Ionic and non-ionic detergents (Triton X-100, sodium dodechyl sulphate, deoxycolate, Nonidet P-40) destruct coronaviruses [15]. Members of this coronavirus family are relatively resistant to proteases (trypsin, pepsin) and amylases, but they are destructed by phospholipase C.

The coronaviruses are inactivated by the following disinfecting agents: 1% solutions of phenol, cresol and formalin, 70% ethanol, carbolic soap solution and 10% soda solution, upon 3–10 min exposure [16].

The coronavirus survival in the environment was modeled on IBV by T. T. Satylganov, and the test demonstrated the coronaviruses maintained infectivity for 8–10 hours in aerosols, much longer in drinking water (up to 9 days) and up to 12 days on hard and soft objects (down, feathers, eggshells, wood) [17].

Outdoors the virus inactivates within 4–11 days in spring at 0–18 °C and relative humidity 49–84%; in 3–9 days in summer at 10–23 °C and humidity 68–90%; in winter the virus maintains activity for 33–44 days. Six hours were required for effective disinfection in case of treatment of infected surfaces with bleach solution containing 3% of active chlorine; it took three hours in case of treatment with 0.5% formaldehyde and 3% tetrachloride, while sodium hypochlorite solution with 1.5% active chlorine resulted in disinfection of the surfaces in one hour. Exposure time increased with the use of aerosols. Thus, safe IBV inactivation required 12-hour exposure of the disinfected surface to the sodium hypochlorite aerosol (5% active chlorine) [17].

CORONAVIRUS REPRODUCTION FEATURES

Biochemical aspects of coronavirus replication were first studied by W. B. Becker et al. while examining IBV infected chick embryo chorioallontoic membrane (CAM) cells [18]. The virus was found to bud into the cisterns of cytoplasmic reticulum and cytoplasmic vesicles but not

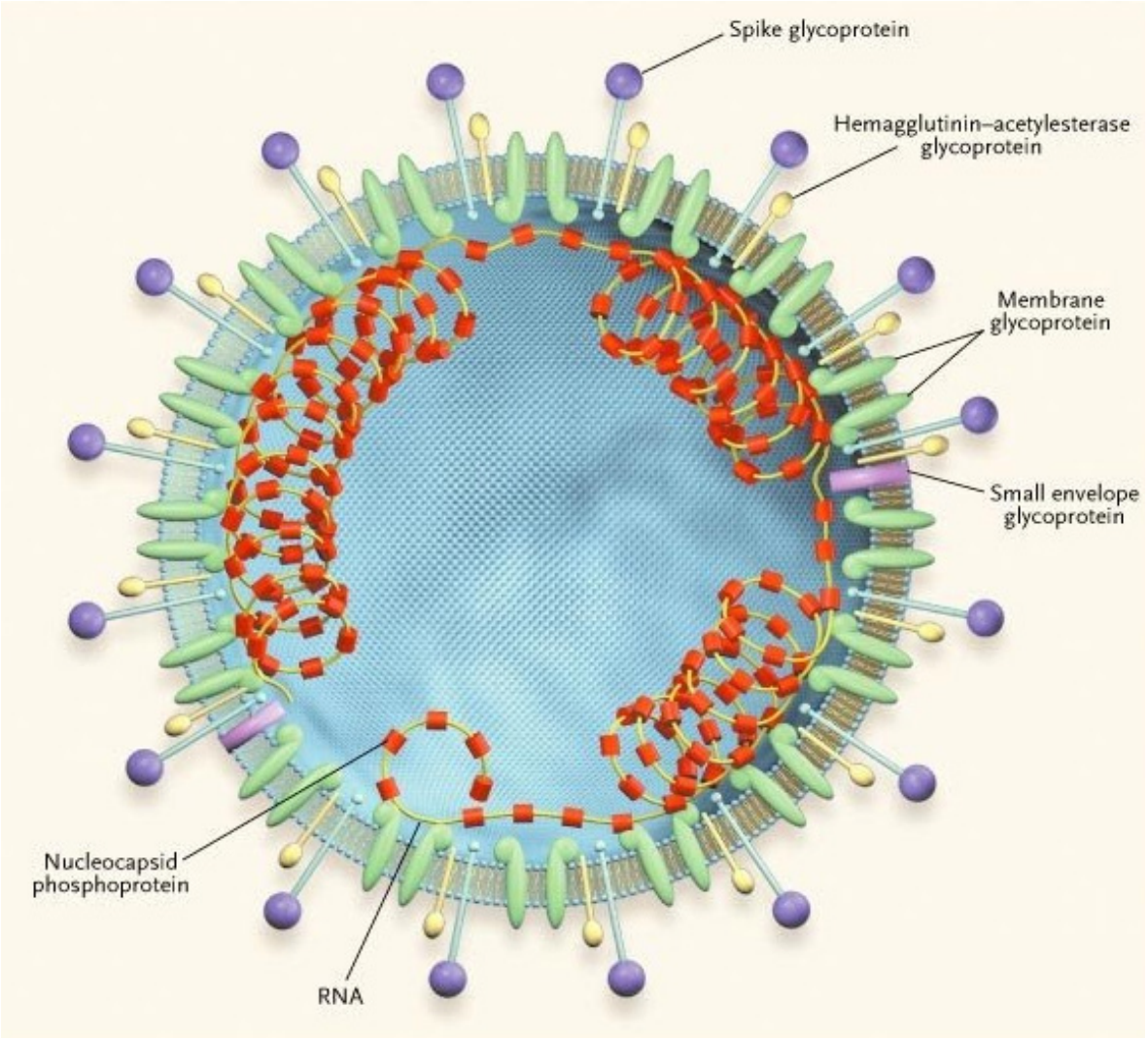

Fig. 2. Coronavirus structure [11]

through the plasmolemma. Before budding, an expressed thickened crescent-shaped layer of the protein appears on the membrane [19, 20]. Results of further studies performed by different researchers demonstrated that the coronaviruses attach to the target cell receptors with their E-2 peplomer termini [21–23]. The virus penetrates into the cell by fusion of the viral envelope with the plasmolemma or by endocytosis [1].

For all positive RNA-containing viruses the first stage of the virus cycle after the penetration into the cell involves attachment of the genomic RNA to ribosomes that results in the synthesis of the viral RNA-dependent RNA-polymerase [24].

Nucleocapsid N protein and some non-structural proteins are obviously synthesized on the polysomes in the cytoplasmic matri [25, 26]. Synthesis of E1 and E2 glycoproteins occurs on the polysomes attached to the rough endoplasmic reticulum (RER). Coronavirus spiral nucleocapsid is formed in the cytoplasm of the infected cells due to interactions between the newly synthesized RNA with N protein molecules. Nucleocapsid possesses flexible and rather loose structure, and it is sensitive to RNAse, its density amounts to 1.24–1.29 g/cm^3 [27, 28].

Coronavirus virions are formed by budding from RER membranes and/or Golgi apparatus [18] (Fig. 3).

On RER or Golgi apparatus membranes the host cellular proteins are eliminated from the budding virions and replaced by the viral glycoproteins; nucleocapsid and RER or Golgi apparatus membranes interact through E1 glycoprotein cytoplasmic domain. Coronavirus budding occurs only on the intracellular membranes, where E1 molecules are localized [29–32]. Large amount of E2 can be accumulated on the plasmatic membrane, but virion budding never occurs here, probably due to the lack of free E1. Nucleocapsid-containing budding virions "squeeze" into the RER and Golgi apparatus cavity and move to smooth bulbs (vesicles) and migrate to the edge of the cell, where they fuse with the plasmatic membrane resulting in the release of a large amount of virions in the extracellular space [14, 33, 34].

The virions often release from the cell only after its death, the coronaviruses however can release from the non-destructed cells, evidently, by means of cell secretion mechanism [31, 32, 35, 36]. The ability of the coronaviruses to release from the unlysed cell is the key factor for potential moderate (non-cytopathic) infection. Great number of

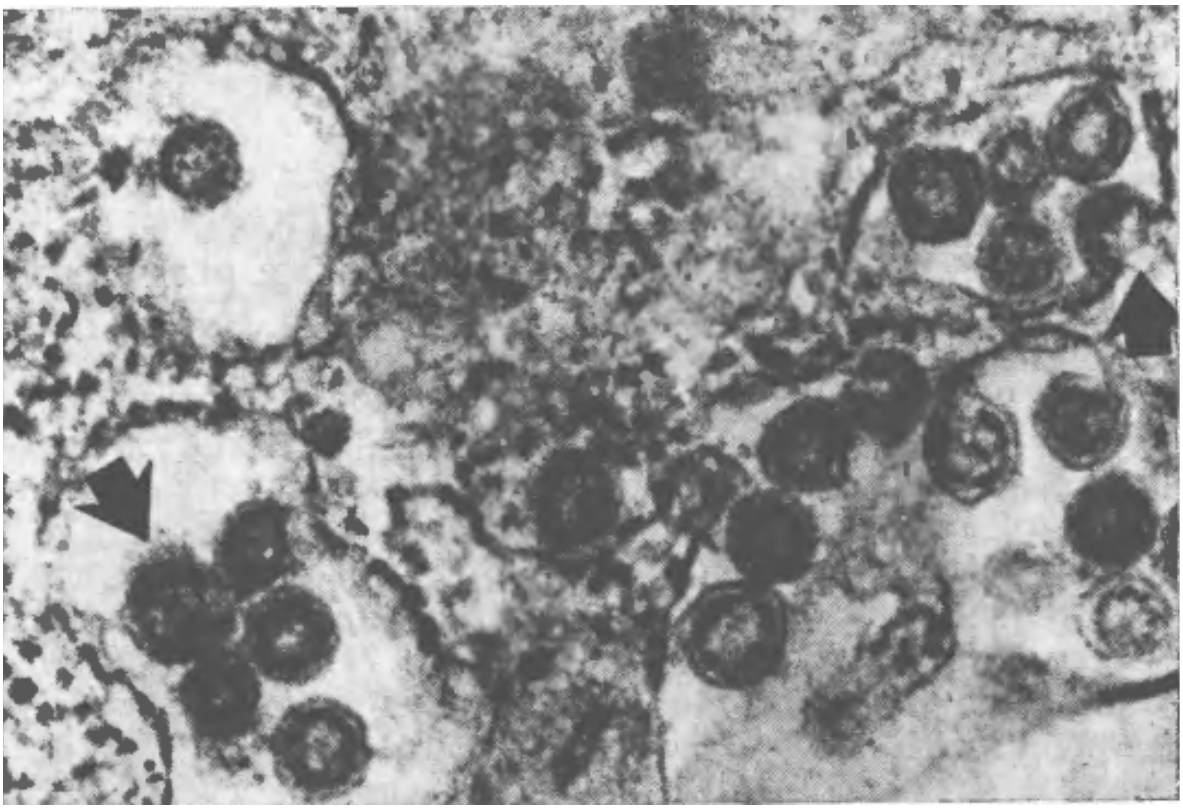

Fig. 3. A cell infected with the human respiratory coronavirus HCoV-229E. Budding of the coronavirus spherical virions (arrows) is observed on the membranes of RER and smooth vesicles. Inside the virions, electron-dense nucleocapsids are visible. Before leaving the cell due to exocytosis or cell lysis, the virions enter the RER cavity or pass through the Golgi apparatus (magnification 60,000×) [21]

virions were observed on the plasmatic membrane of the infected cells and they did not bud from it but most likely adsorbed to it after the release from the infected cells [37].

IMMUNOLOGICAL ASPECTS OF CORONAVIRUS INFECTION

The coronaviruses as well as other enveloped viruses have a complex antigenic composition. Studies of humans and animals recovered from the natural coronavirus infection or artificially infected with the coronaviruses attest to the fact that the antigens are capable of inducing virus neutralizing, complement-fixing, precipitating, lytic and antihemagglutinating antibodies. Immune response develops quite rapidly: relatively high antibody titers can be reported in blood by day 10–15 post infection or immunization. Antibody action mechanism was studied by direct electronic microscopy. Thus it was demonstrated that sera of convalescent or immunized birds not only had virus-neutralizing properties but they were also capable of inducing clearly microscopically visible agglutination of the coronavirus virions [4]. Moreover, different effects of the homologous and heterologous sera were established thus being indicative of the uneven structure of the coronavirus membranes and presence of definite loci, where the most active antigens are accumulated. Virus-encoded specific whole antigens are localized on the distal termini of the spikes. This data obtained from IBV examination were supported in other avian coronavirus model – turkey enteritis virus [38].

General knowledge of the antigenic properties of different coronavirus species are based on comparative studies of the relationship between various strains performed using neutralization test, complement fixation test and less frequently by hemagglutination inhibition test as well as by observation of cross-resistance effect *in vivo* [4, 14].

According to some reports, the coronaviruses causing porcine encephalomyelitis, transmissible gastroenteritis of swine (TGE) and porcine epidemic diarrhea (PED) are antigenically independent species, but according to other reports they contain common antigens [39–48]. Comparative studies of PHEV strains isolated in different countries including USA, England and Japan, demonstrated their antigenic structure similarity, and they were ranged in the same serotype [39, 40]. No antigenic variability was determined for TGE virus: strains isolated from animals in different countries were serologically identical [41]. In 1986, TGE-like porcine respiratory coronavirus (PRCV) was isolated and identified, which was antigenically related to TGE virus and induced TGEV-neutralizing antibodies. The key difference of the new coronavirus included its extraordinary pneumotropism with lack of enteropathogenicity [42, 47]. Both viruses are antigenically similar and have neutralizing epitopes in the basic virion proteins (N, S and M) [47].

Among the mammalian coronaviruses TGEV demonstrates relatedness to canine enteric coronavirus, feline infectious peritonitis virus and strain 229E-associated respiratory coronavirus in humans [43, 44]. The antibodies induced in the blood of dogs following the coronavirus infection are capable of TGEV neutralization [45].

Knowledge of antigenic and genomic homology of *Coronaviridae* family members are based on comparative studies involving different up-to-date methods. As a result, type-specific (within the same species), group-specific (within a group of antigenically related viruses: TGEV and PRCV) and interspecies (canine, feline, porcine coronaviruses) antigenic relatedness was determined.

Antigenic relatedness of human and animal coronaviruses are of particular interest. Human coronaviruses were determined to be serologically related to bovine and murine coronaviruses as well as to PHEV [1].

Coronaviruses of rodents (murine hepatitis virus and rat coronavirus) are antigenically related to each other and to the human coronavirus [49].

Enteropathogenic coronaviruses of turkeys and bovines also demonstrate antigenic relatedness. Bilateral antigenic relatedness was determined for turkey coronavirus and chicken and murine coronaviruses.

Genetic recombination was reported to be the most frequent between the genomes of different but related coronaviruses. This can be an important mechanism for the natural occurrence of genetically-modified viruses [47].

ROLE OF CORONAVIRUSES IN ANIMAL AND AVIAN PATHOLOGY

The major coronavirus-induced disease in pigs is *transmissible gastroenteritis* manifested with vomiting, profuse diarrhea, systemic dehydration and high lethality, particularly in piglets during the first 10 days of life. During primary outbreaks, the morbidity and mortality of newborn piglets can reach 100%, in such case the farm remains nearly without litter [33, 44].

TGE pathogenesis is featured by its ability to reproduce in the respiratory tract of the pigs as well, i.e. in the epithelial cells of the nasal and pulmonary mucosa [50, 51]. *In vitro* experiments demonstrated that TGEV replicates in porcine macrophage alveolar cell culture. This supports the fact that the virus infects not only intestines [44, 52–54].

Fattening pigs are considered to be the most probable TGEV reservoir in inter-epidemic period, who maintain the disease in enzootic and asymptomatic forms [44]. Reservoirs of the infection agents can be the herds, where weekly farrowing system is practiced [55].

Another porcine coronavirus with hemagglutinating activity induces severe disease, and it is currently known as *porcine encephalomyelitis* virus [34, 49, 56]. The outbreak of the disease with encephalomyelitis clinical manifestation was first described in 4–7-day-old pigs in Ontario (Canada) by A. S. Greig et al. [57].

Porcine hemagglutinating encephalomyelitis virus was isolated from the diseased newborn piglets in Poland in 1971 as well as from nasal conchae of pigs demonstrating atrophic catarrh in the USA in 1972. This coronavirus infection is specified by high contagiousness (nearly 100%), and it is manifested with vomiting, anorexia, constipation and progressive cachexia in animals. The disease mostly affects pigs of over 2 weeks of age [57]. According to C. K. Roe and T. J. Alexander, mortality in pigs of such age reaches 100% [58], and results of the studies performed by other researchers indicate that this parameter somewhat varies [59]. The disease incubation period generally lasts for 5–6 days. Sometimes, vomiting and anorexia are the key symptoms during the first 2–3 days, however, later on signs of severe CNS lesions come to the fore.

The virus replicates in the porcine thyroid cell culture, porcine embryo lung cells, in the continuous neonatal porcine testis cell culture and in porcine kidney cell line PK-15. During reproduction in the porcine kidney cell culture giant cells are formed [60].

Coronavirus enteritis in calves. In 1972 the American researcher C. A. Mebus et al. for the first time established possible coronavirus origin of dyspepsia in newborn calves [61, 62]. Primary etiologic role of the agent was proven during the experimental infection of calves with coronavirus in the natural environment as well as during the experimental infection of newborn, colostrum deprived calves and gnotobionts [63].

Whereas the most typical clinical sign of coronavirus enteritis in calves involves diarrhea, the virus infects not only the intestines but also the respiratory tract of the animals. The agent mostly replicates in distal part of the small intestine and colon, epithelial cells of nasal, tracheal and lung mucosa. Bovine coronaviruses can induce latent infections. Clinically healthy animal can be chronic virus carrier and it can shed the virus with the feces for seven months [64].

Mebus C. A. et al. described pathological and anatomical lesions in gnotobiotic calves infected with coronavirus enteritis agent [61]. The disease progression was supported by immunofluorescence tests and electronic microscopy of ultra-thin sections of intestinal walls of calve demonstrating acute diarrhea signs, which were emergently slaughtered in different periods post infection including those slaughtered at the peak of clinical manifestation. Specific fluorescence was reported in the epithelial cells of the small intestinal villi already in 4 hours post infection and reached its maximum by 44 hours post infection. Electronic microscopy of small intestine mucosal cells demonstrated virus particles in cytoplasmic vacuoles, large cisterns and pericellular space in the reticuloendothelial cells of the mesenteric lymph nodes [65, 66].

Infectious bronchitis (IB) virus is the best studied representative of avian coronaviruses. The basic clinical signs of the disease include air sac inflammation, rhinitis, mucous sputum producing cough, sneezing, conjunctivitis, dyspnea, depression. The disease incubation period is short: it averages between 18 and 36 hours. Birds of different ages have different disease: mortality of 1–5-week-old chicks reaches 25–40%. The disease is highly contagious and already on the first days post outbreak onset, 70–90% of chicks develop expressed clinical signs. In adult layers the disease is specified by less expressed respiratory signs and general low mortality. The birds demonstrate apathy, loss of appetite, sneezing, nasal discharge and egg drop [19, 67, 68]. It is egg drop that is considered to be the most harmful effect of the coronavirus infection.

Coronavirus enteritis (blue comb) of turkeys. The disease was first reported in the USA in 1951. In 1953 the virus was isolated, which was ranged in coronavirus family in 1974.

In all cases the disease was reported as highly contagious and it affected 90–100% of chicks and adult birds [70]. The outbreaks as a rule occur spontaneously and already in 3–5 days all susceptible population becomes infected. The incubation period lasts for 48–72 hours. The disease starts with the temperature rise and the turkeys refuse from feed and water; gastrointestinal disorder (diarrhea), weakness, cyanosis of the comb and body weight loss are reported [71].

Feline infectious peritonitis is a highly contagious disease, which was first described by American researchers L. G. Wolfe and R. A. Griesemer in 1966 [72]. Its most typical signs include ascites, anorexia, body weight loss, temperature fluctuations accompanied with depression. Some animals demonstrate vomiting, diarrhea, anemia and jaundice. The disease generally develops slowly and lasts for 3–4 months. The mortality of the diseased cats is pretty high. Using electron microscopy of tissues of the euthanized cats B. C. Zook et al. demonstrated virus particles morphologically similar to the coronaviruses in the cells of the liver, spleen and intestines [73]. J. M. Ward proved etiological relation between these agents and feline infectious peritonitis virus [74].

Etiological agent of *canine coronavirus enteritis* was for the first time isolated in USA in 1971. The virus is well replicated in the canine kidney cell culture. Experimental infection of puppies resulted in diarrhea due to the destruction of mature cells of the villi of the small intestines. Canine coronavirus is antigenically related to the porcine transmissible gastroenteritis virus, porcine respiratory coronavirus and feline infectious peritonitis virus [75].

CONCLUSION

While summing up the data presented in the paper, one should mention that typical feature of coronaviruses is a wide variety of their natural hosts along with the pronounced species-limited pathogenicity. Due to the capacity of infecting various organs the coronaviruses can be classified as pantropic viruses [1]. The diseases induced by them are mostly acute, but can transform to chronic and latent forms. All coronavirus species are specified by clear dependence of the disease severity on the age of the susceptible animal and intensity of the pathological processes. Thus, severe bronchitis was reported only in chicks (IBV), lethal hepatitis – in newborn mice (murine hepatitis virus), lethal pneumonia – in newborn rats (coronavirus of rats), severe lethal gastroenteritis and encephalomyelitis – only in piglets (TGEV and PHEV), lethal diarrhea – only in newborn calves (agent of coronavirus enteritis in calves). In adult animals of the same species the infection was subclinical and inapperant.

All described cases of the diseases induced by different coronaviruses have one thing in common – acute disorder of capillary circulation in the affected organ, which is the base of the pathological process caused by the agent. This results in the edematous organ, profuse serous exudate, and in the most pronounced cases – to necrosis and lining detachment. Similar signs were reported in case of "blue comb" disease in turkeys, when cyanosis of the comb and general asthenia were associated with severe enteritis and profuse diarrhea [14].

There is a definite amount of data on each species of coronaviruses described in the paper and these data allow for the comparative analysis of their properties, structure, antigenic relations as well as for getting an idea of their role in the pathology of farm and domestic animals and birds. However, even those pathological syndromes, which are currently reliably associated with the coronaviruses, are indicative of major damage to agriculture caused by these pathogens.

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