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MODULATION OF IMMUNITY AND BARRIER FUNCTION IN PRE- AND POSTNATAL ANIMAL ONTOGENESIS. PHYSIOLOGICAL ASPECTS OF NATURAL RESISTANCE IN SOWS

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INTRODUCTION

The main task for the effective breeding of productive animals is obtaining viable offspring and ensuring the appropriate functional status of the organism during all stages of ontogenesis[1]. The most important while of the organism development is a period of early postnatal adaptation[2][3][4]. In Ukrainian pig farms, this adaptation time is one of the main periods during when a high percentage of neonatal piglet mortality is observed[5]. One of the reasons for this problem caused with non-infectious pathology of the digestive and respiratory tracts[6]. This is due to a low level of the innate immunity caused with the increase some technological limitations, the stress induced by various etiologic factors, and the disruptions in the technology of rearing breeding sow. The combined effect of these factors leads to the destruction in the fetal period of organism development, a lack of colostrum quality, and is accompanied by the immunodeficiency changes in newborn piglets[7].

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Therefore, in animal husbandry, it is relevant to enhance the immune status of newborns by using natural immunomodulators that modify the immune response through direct effects on immune competent cells or indirectly through the modulation of various molecular and cellular response of the organism[8][9]. In certain cases, some immunomodulators disrupt the homeostatic balance of the body systems, including the immune and neuroendocrine systems[10]. Therefore, the use of immunomodulators that would not cause side effects, stimulate not only immune reactions but also balance the immune system as a whole with its adaptive capabilities, is a promising direction[11]. The most effective way of immunoreaction in newborn piglets is through indirect influence on the mother's organism. In view of this, studies on the innate immunity of piglets at early stages of postnatal adaptation using immunotropic preparations in the system of mother-colostrum-newborn become particularly relevant[12].

1. Functional status of immune cellular mechanisms

Animals possess two types of immunity: innate (natural) and acquired (adaptive) immunity. The innate immunity is primarily formed by the barrier mechanisms of the organism, such as the skin and mucous membranes, as well as specific proteins such as perforins, agglutinins, the complement system, lysozyme, etc [13][14]. Al of them also involve phagocytosis, which is carried out by leukocytic cells: macrophages, microphages, dendritic cells, and NK lymphocytes. Furthermore, all these factors are dynamic indicators that are

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primarily determined by genetic characteristics of the organism but can also be influenced by various anthropogenic and natural factors[15].

The first barrier that separates the organism from the environmental pathogens constructed with both the skin and mucous membrane mechanisms. In addition to mechanical obstruction, these barriers possess protective components, including lysozyme, fatty acids, and other substances that contribute to the bactericidal properties of skin secretions and mucous membranes. Therefore, studying the skin's microflora reflects the physiological and immunological state of the animal health[16]. Specialized cells of the mucous membrane assist in the removal of foreign particles from the body and cooperate with immune defense mechanisms. Chemical substances present in biological fluids, especially such as hydrochloric acid in the stomach and secretions from respiratory epithelial cells, form specific natural barriers for individual organs[17]. These barriers prevent the penetration of various microorganisms, including conditionally pathogenic ones, which, under certain conditions, can induce pathological processes[18].

In addition to the barrier that separate the internal environment of the organism from the external environment, there are other factors of nonspecific immune defense, represented by the accumulation of lymphoid cells in the form of Peyer's patches, lymph nodes, etc. Lymphocytes have the ability to migrate to the mucous membrane, which is in direct contact with lymphoid formations in which activated B-cells synthesize secretory antibodies, while T-lymphocytes, together with tissue phagocytes, engulf pathogens that enter the thickness of the mucous membranes[19]. Phagocytes are the main immune cells that provide nonspecific defense in mammalian organisms. They are present in almost all tissues of the body, including bone, nerve, and connective tissues. When monocytes enter the tissues, they transform into Kupffer cells in the liver, into alveolar macrophages in the lungs, into osteoblasts in the bones, etc. [20]. In spite of the different names they receive in different organs, macrophages perform their main function of phagocytosis and destruction of

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foreign substances while synthesizing cytokines and growth factors that stimulate the proliferation and differentiation of lymphoid cells[21][22].

The number of activated leukocytes in the blood of sows on days 60 and 90 of gestation ranges from 74% to 84%, and the phagocytic index, which characterizes the activity of phagocytes, ranges from 8 to 9 units[23][24]. It is known that the level of phagocytosis depends on the presence of opsonizing substances, such as immunoglobulins, complement components, C-reactive protein, fibronectin, etc. Since the phagocyte plasma membrane contains Fc receptors specific to the Fc fragment of immunoglobulins, the latter, by binding to antigens, provide their adhesion to the macrophage surface and subsequent phagocytosis and lysis of the phagocytosed antigenic structures[25][26]. Macrophages possess a number of fundamentally important functions, including the presentation of antigen to T lymphocyte receptors and synthesis of various biologically active substances (complement proteins C2-C5, lysozyme, interferon, cytokines, etc.)[27]. Another class of leukocytes that perform phagocytic function includes segmented neutrophils. These cells are present in the bloodstream and are capable of penetrating through the endothelium of blood vessels and migrating to the site of pathological processes when necessary[28]. Their main role lies in the phagocytosis of bacterial and fungal antigens. After the formation of a phagosome and its fusion with lysosomes, antigens are degraded by lytic enzymes and active oxygen forms released by neutrophils during the process of phagocytosis[29].

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In addition to that, NK lymphocytes and dendritic cells also possess phagocytic qualities. NK lymphocytes represent a distinct class of lymphocytes that exhibit pronounced activity against viral infections as they destroy cells that have insufficient or no amount of histocompatibility complex proteins on their surface[30][31][32]. Dendritic cells are destroyed or undergo structural changes as a result of the impact of a cell by viruses. It has been shown that NK lymphocytes play a particularly important role in pregnancy immunology[33][34]. During gestation, the level of circulating NK cells significantly decreases, accompanied by a decrease in the production of gamma-interferon by these cells[35]. During pregnancy, placental cells and trophoblasts produce inhibitors of cytotoxic cell activity[36][37]. The high activity of NK lymphocytes and T cytotoxic leukocytes may be associated with infertility and spontaneous abortions[38].

In addition, the development of physiological and immunological deficiencies leads to a range of health problems and complications in both sows and piglets[39]. Immunodeficiency in sows reduces the level of their organism resistance, and in their offspring, it results in significantly lower and shorter-lasting levels of non-specific immune protection, which increases the

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risk of pathogen infection[40,41]. Therefore, changes in the quantity of immune cells exhibiting cytotoxic properties or their activity level in sows during pregnancy, whether increased or decreased, are accompanied by negative consequences in terms of pregnancy progression or the preservation of the health of sows and their offspring[42]. The integral indicator of the humoral branch of non-specific immune defense in the organism of sows is the bactericidal activity of blood serum, which is aimed more against gram-negative microorganisms. It is determined by the combined action of proteinaceous humoral immune factors, such as lysozyme, antibodies, interferon, fibronectin, complement system proteins, properdin, interleukins, fibrinopeptides, and others[43,44,45].

The response against gram-negative microorganisms, immunoglobulins and complement proteins are initially involved in the reaction, followed by the gradual activation of lysins and lysozyme[46,47]. Immunoglobulins IgM and IgA serve as initiators of bactericidal reactions since their role largely depends on complement and lysozyme, respectively[48]. Initially, the destruction of gram-negative bacterial membranes occurs through the action of the complement system, resulting in the destruction of surface molecules of plasmalemma. Afterward, lysozyme, in complex with IgA, joins the process

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of lysis, as it gains access to glycosylic bonds of polyamine sugars, which are structural components of bacterial membranes. After the destruction of bacterial plasmalemma, more sites are available for the contact of their antigenic determinants with the antibodies of the organism, enhancing their lysis[49].

Unlike gram-negative bacteria, the membrane surfaces of gram-positive microorganisms contain molecules of N-muramic acid, the glycosylic bonds of which serve as targets for the enzyme muramidase[50]. This enzyme is present into all living organisms[51] almost. It has been found in mammalian milk, saliva, tears, urine, respiratory, and reproductive systems[52]. In combination with complement proteins and secretory IgA, lysozyme is a critic part of the mechanisms of non-specific local immune defense[53].

There was demonstrated that the indicators of bactericidal and lysozyme activities of blood serum in pregnant sows are at a sufficiently high level 2–3 weeks before farrowing. This is indicated by their numbers, which on average are 27% and 48.5%, respectively. On the 3rd day after farrowing, there is a sharp decrease in the level of bactericidal activity to 22%, which occurs due to the use of humoral components for colostrum synthesis and the removal of antigens from the body. This is confirmed by an increase in the amount of circulating immune complexes in the blood serum at this time, reaching nearly 100 mmol/L. At the same time, there is a tendency to decrease the bactericidal activity of blood serum level while the phagocytic activity increases. The difference in the bactericidal activity of blood serum is determined primarily by breed differences and conditions of animal housing and feeding[54]. On the other hand, the decrease in circulating complexes in the blood of pregnant sows, along with an increase in the level of

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immunoglobulins, is due to the enhanced phagocytosis of immune complexes[55].

The non-specific immune defense in animals consists of cellular and humoral components, which are the first to come into contact with foreign substances that have entered the body's internal environment, exhibiting bactericidal or bacteriostatic properties both on their own and during humoral-cellular interactions, enhancing each other's activity under these conditions[56]. Acquired immunity in pigs is provided by two mechanisms: humoral and cellular. The cellular mechanism includes the interaction of the main types of T-lymphocytes – helpers and suppressors, which influence the humoral mechanism by activating and transforming B lymphocytes into plasma cells or, conversely, by suppressing their activity or activation processes. Only the latter are capable of synthesizing immunoglobulins[57][58].

T-lymphocytes are responsible for specific antiviral, antitumor cellular immunity and actively participate in hypersensitivity and autoimmune processes, etc.[59][60]. It is well known fact that T-cells can be differentiated into effector cells: T-killers, helper cells – T-helpers, and immune response blockers – T-suppressors. T-killers possess cytotoxic activity against genetically different or virus-infected target cells, without the involvement of antibodies and complement components. T-helpers, upon activation, interact with B lymphocytes, stimulating their transformation into plasma cells. T suppressors, on the other hand, antagonize T-helpers, blocking their function[61]. The widely recognized classification based on functional activity

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distinguishes three types: T amplifiers, T effectors, and T differentiating lymphocytes. The first group enhances the function of other lymphocytes through the mediators they synthesize. Effector T-lymphocytes can be divided into specific and nonspecific in relation to the antigen. Due to the variety of receptors on their membrane, these cells are characterized by cytotoxicity. Moreover, effector lymphocytes can inactivate bone marrow stem cells. Similarlly to effector cells, the differentiation of T-lymphocytes influence bone marrow stem cells, but they stimulate their proliferation and determine the direction of differentiation[62].

B-lymphocytes are the main cell type involved in the formation of specific humoral immunity since they produce antibodies of various classes after activation and transformation into plasma cells[63]. These cells are extensively involved in the development of accelerated hypersensitivity. In general, the number of T-lymphocytes in the blood of adult pig's ranges from 45–57%, and B-lymphocytes – from 26 to 38% of the total number of lymphocytes[64].

One of the peculiarities of the sow metabolism during the farrowing period is the development of physiological leukocytosis. It is detected from 2–4 weeks after insemination. This is due to the fact that during farrowing, the maternal body is auto-immunized with the fetal antigens, which are genetically different for the fetus. This phenomenon can be explained by the presence of the fetus' hereditary paternal part[65][66].

2. Functional state of the protection with immune humoral mechanisms

As mentioned before, the main function of B-lymphocytes is the production of immunoglobulins[67][68]. As the immune response begins, plasma cells secreting IgM are activated in the body[69]. Later, plasmacytes producing

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IgG, IgA, IgE, and IgD are activated[70]. At the same time, B-lymphocyte's form memory cells[71]. They contain all types of immunoglobulins on their surface, except IgM, which explains its absence in immune reactions in case of repeated contact with antigens[72].

Immunoglobulins are the main factor in the body's specific immune protection against environmental pathogens[73]. Immunoglobulins are protein molecules with a similar structural organization. They can react with antigens[74]. The peculiarity of all immunoglobulins is that their molecules have variable structures – domains that bind to antigens. It should be noted that immunoglobulins are heterogeneous protein structures, as indicated by the different shapes of their different classes[75].

Pigs have three main classes of antibodies – IgG, IgA, and IgM, which are part of the total γ-globulin fraction. It has been shown that the IgG fraction is the largest part. It accounts for about 80 % of all immunoglobulins. The amount of these antibodies in sows' blood ranges from 28-36 mg/ml. The second largest fraction is IgM, which makes up about 15%. Their absolute amount in sows' blood ranges from 4-7 mg/ml. IgA in pigs' blood is the smallest amount – about 5%, which in absolute quantities is 1-2 mg/ml. In sows' blood 20 days before farrowing, the second highest protein fraction is immunoglobulins. The main proportion of them is IgA and IgG. Their total amount fluctuated around 26 mg/ml[76].

The blood serum of sows contains 24 mg/ml of immunoglobulins. It is three times less than their concentration in the sow colostrum a few hours before farrowing (61.8 mg/ml IgG). During lactogenesis, the number of

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immunoglobulins in the mammary gland's secretion decreases more than thirty times during the first 7 days of lactation[77].

The downward dynamics of immunoglobulin levels in colostrum has been reported by several authors[78][79]. Throughout the colostrum feeding, the maximum level of antibodies is detected only at the beginning of lactation[80].

3. Neurohumoral regulation and interaction between soluble factors and immune functions

The neuroendocrine system plays a significant role in the immune system regulation and the immune protection level in mammals[81]. It is known that lymphoid organs contain a large number of the autonomic nervous system's sympathetic division's nerve endings. They produce catecholamines. The catecholamines affect the proliferation and differentiation of immunocompetent cells through specific receptor proteins located on their plasma membrane. Catecholamines affect mainly the proliferation of T cells, accelerating their differentiation[82]. Also, a significant impact on the immune system of pregnant sows is made by the trophoblast and biologically active substances (they regulate the immunological relationship between the fetus and the mother's body)[83]. During pregnancy, there is a humoral restructuring in the animals' body at the level of the mother's defence mechanisms. It begins at the beginning of farrowing. At this time, there is a decrease in the estrogenic hormones effect, and, due to the influence of luteinising releasing factor, the

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pregnancy corpus luteum and the placenta are formed. This leads to an increase in the progesterone and estradiol synthesis, which plays an important role in embryo formation[84]. The corpus luteum reaches its maximum development stage at the beginning of the 60–70th day of pregnancy. As a result, the maximum progesterone level is recorded in the blood[85].

It is a well-known fact that progesterone stimulates T-suppressor lymphocytes to synthesise immunosuppressive factors while suppressing the production of IL-1, IL-6 and IL-8 and γ-interferon. There is a decrease in the lymphocyte's reactivity in response to myogens and alloantigens on the background of general immunosuppression. This leads to the development of the mother's body immunological tolerance. Progesterone also stimulates the progesterone-induced blocking factor in lymphocytes. This changes the cytokine synthesis mechanism and reduces the activity of immunocompetent cells[86]. It should be noted that the immunosuppressive effect of progesterone is mainly expressed locally on the immunocompetent structures of the reproductive tract of uterus. It has been established that phagocytic and cytotoxic cells of the uterine mucosa have a significantly lower antigenic activity level than peripheral blood cells[87]. This indicates that progesterone has no suppressive effect on the global resistance mechanisms of the sow's organism barriers.

There was established important data in respect with the ratio between T-helper and T-suppressor forms of lymphocytes during pregnancy is about 2 to1. It decreases over time due to the predominance of theophylline-sensitive lymphocytes. Adding a mineral preparation to the sow's diet for 30 days, an increase in the total number of T lymphocytes is recorded while the fraction of theophylline-resistant lymphocytes increases and theophylline-sensitive forms and B-lymphocytes decrease[88]. Luteotropic hormone not only affects the formation and the corpus luteum maintenance, but also regulates the thymus functional activity and its dependent cells. Luteotropic releasing factor

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has its own specific receptors on the surface of lymphocytes. It confirms the regulatory function of this hormone in relation to lymphoid leukocytes[89]. Hence, luteotropic hormone has the ability to directly and indirectly affect the activity of immune cells. Whereas the progesterone mechanism of action is associated with progesterone-induced blocking factor, but nevertheless, both have regulatory properties in relation to immunocompetent cells.

In the second half of pregnancy, the pig placenta begins to synthesize its own estrogenic hormones and chorionic gonadotropin. The chorionic gonadotropin is the main hormone secreted by the placenta during pregnancy. Due to its ability to bind to the receptors of monocyte and lymphocyte leukocytes, it affects their activity[90]. Estrogens, which are synthesized in small amounts by both the ovaries and the placenta during farrowing, have immunomodulatory properties by increasing the level of immunoglobulin synthesis. Estrogens during pregnancy also stimulate the T-helper cells synthesis, reduce the T-killers activity and increase the phagocytes activity[91]. It is known that estrogens indirectly, through estrogen-dependent enzymes, affect lipid peroxidation and the amount of reactive oxygen species[92]. This is due to the fact that sows in the second half of pregnancy are in a state of oxidative stress. This is indicated by the accumulation of free radicals in the body against the background of low activity of the enzyme's superoxide dismutase and catalase. Active forms of oxygen, including free radicals and peroxides, contribute to the bactericidal activity of blood and the phagocytic ability of leukocytes. They are considered an essential part of the mechanism of nonspecific immune protection. At the same time, these substances play an important role in the alternative, immunosuppressive and autoimmune reactions development[93].

Increased immunobiological local protective mechanisms activity is detected before farrowing, starting from 105-110 day of farrowing. It

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coincides with corpus luteum involution. These processes in the sows' bodies are accompanied by a reverse humoral reconstruction. This humoral modulation is characterized by an increase in cortisol and estrogen contents in the animal blood in spite of the stable decrease in progesterone level. Aforementioned changes accompanied by the increase in prolactin level. This stimulates the lactose synthesis in the mammary gland. Further, it encourages the water ingress into the udder, resulting in the synthesis of colostrum and, subsequently, milk[94][95]. Thus, the natural resistance local and general mechanisms of sows during the farrowing period are functionally different, depending on the level and intensity of metabolic processes and hormonal state of the organism.

CONCLUSIONS

During the second half of pregnancy, changes in morpho-biochemical parameters observed in the sow blood and present as developmental modulation of sow immune system. These changes are an anaemic state characteristic. This occurs against the background of increased fetal weight and increased circulatory blood volume and total blood volume. During pregnancy, sows have a pronounced effect of immunological tolerance. It is formed against the background of hormones' action on immune cells. This is accompanied by the suppression of interleukins and γ-interferon production, decreased lymphocyte reactivity due to the immune response inhibition as well as immunosuppression pathway stimulation. Together abovementioned changes contribute to the decrease in the immunocompetent cell activity. Before farrowing, sows increase the immunobiological mechanisms of local defense activity, accompanied by humoral restructuring. This is characterized by an increase in cortisol and estrogen in the animals' blood, the effect of which causes immunomodulatory changes in the animal protective systems. All of these mechanisms have a balanced effect on the sow. It allows to ensure its adaptation to gestation and fetal delivery against the background of maintaining resistance and internal homeostasis.

SUMMARY

The regulation of innate immunity in piglet is extremely complex process in which involved various cellular types and multiple humoral factors. The production, excretion and redistribution all of them affect the targeting and the power of innate immunity in all mammalian. Recent data is evidence that

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the phenomenon of natural resistance depends on great number of different factors with affect both innate and adaptive immunity. However, several aspects of the immune response regulation remain unknown. Particularly, several natural compounds that is potent activate cell resistance against various infectious agents through the stimulation intracellular pathogen recognizing receptors belong to Nucleotide Ologimerization Domen family (NOD-receptors). Muramyl peptide family is derived from bacterial wall and is a natural ligand for NOD-receptors to induce cell response against various pathogens. The study of muramyl peptides effect on cell response initiation could be a prospective way to construct natural nontoxic immunomodulators. Similar immunomodulators may ameliorate cellular activity via more universal mechanisms of resistance. The chapter discusses the different mechanisms so far proposed to be responsible for the modulation natural resistance. In particular, this chapter focuses on determining the mechanisms involved in the protection of piglets during early ontogenesis.

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