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MODULATION OF IMMUNITY AND BARRIER FUNCTION IN PRE- AND POSTNATAL ANIMAL ONTOGENESIS. IMMUNOTROPIC CHEMICALS EFFECT ON THE PIGLET POSTNATAL DEVELOPMENT

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INTRODUCTION

Immunoglobulins cannot cross the placenta in pregnant sows. Neonatal pigs are therefore agammaglobulinemic at birth and, although immunocompetent, they cannot mount rapid immune responses at systemic and mucosal sites. Their survival depends directly on the acquisition of maternal immunity via colostrum and milk. Protection by maternal immunity is mediated by a number of factors, including specific systemic humoral immunity, involving mostly maternal IgG transferred from blood to colostrum and typically absorbed within the first 36 h of life. Passive mucosal immunity involves local humoral immunity, including the production of secretory IgA (sIgA), which is transferred principally via milk until weaning. The mammary gland (MG) produces sIgA, which is, then secreted into the milk via the poly-Ig receptor (pIgR) of epithelial cells. These antibodies are produced in response to intestinal and respiratory antigens, including pathogens and commensal organisms. Protection is also mediated by cellular immunity, which is transferred via maternal cells present in mammary secretions. The mechanisms underlying the various immunological links between MG and the mucosal surfaces involve hormonally regulated addressins and chemokines specific to these compartments. The enhancement of colostrogenic immunity depends on the stimulation of systemic immunity, whereas the enhancement of lactogenic immunity depends on appropriate stimulation at induction sites, an increase in cell trafficking from the gut and upper respiratory tract to the MG and, possibly, enhanced immunoglobulin production at the effector site and secretion in milk. In addition, mammary secretions provide factors other than immunoglobulins that protect the neonate and regulate the development of mucosal immunity--a key element of postnatal adaptation to environmental antigens.

Maternal immunity plays a pivotal role in swine health and production because piglets are born agammaglobulinemic and with limited cell-mediated immunity, i.e. few peripheral lymphoid cells, immature lymphoid tissues, and no effector and memory T-lymphocytes. Swine do not become fully immunologically competent until about 4 weeks of age, which means that their compromised ability to respond to infectious agents during the first month of life must be supplemented by maternal immune components:

circulating antibodies derived from colostrum; mucosal antibodies from colostrum and milk; and immune cells provided in mammary secretions. Because maternal immunity is highly effective at protecting piglets against specific pathogens, strengthening sow herd immunity against certain diseases through exposure or vaccination is a useful management tool for ameliorating clinical effects in piglets and delaying infection until the piglets' immune system is better prepared to respond. In this review, we discuss the anatomy and physiology of lactation, the immune functions of components provided to neonatal swine in mammary secretion, the importance of maternal immunity in the prevention and control of significant pathogens.

1. Postnatal developmental physiological processes in mammals modulated with immunotropic chemicals

The immunological state of newborn animals' issue and its changes in the neonatal period have been sufficiently studied. There are certain neonatal developmental periods that are critical in postnatal ontogeny and are associated with the immunodeficiencies development[1][2]. This is indicated by the cortisol level, which changes in the healthy piglets' blood during 7 months of life[3]. Thus, in piglets of 1–3 day old, the level of this hormone is the highest, and ranges from 55.8–78.2 nmol/l. At the end of the first week of life, its concentration decreased to 34.15–46.00 nmol/l, and the lowest level of the hormone was recorded in piglets of 25 day old and in pigs of 2 and 3 months old – 19.9–30.6 nmol/l. This indicates that during the first 2 week of life, piglets are in a constant stress state, which occurs in animals at birth and is associated with changes in environmental conditions, activation of adaptation processes to the environment, etc.[4] Also, an increase in cortisol levels is detected in piglets of 1, 5 and 6 months old, which in the first case is associated

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with the stress development due to weaning and a change in the feeding type, and at an older age – the effect of feed toxins and pathogens[5].

Age-related immunodeficiencies are mainly detected in young pigs during the neonatal period and after weaning. The first immunodeficiency state can develop in piglets in the absence or insufficient colostrum consumption in the first days of life, after a disruption of intestinal absorption mechanisms, or at low immunobiological components of colostrum levels, against the background of stress experienced by the body after birth[6]. Currently, piglets are the most sensitive to environmental influences[7].

The analysis of the piglets' mortality causes from birth to 5 months old shows that the piglets' mortality on the 1st day after birth is 13.5%, including stillbirths, 3% – on the 2nd and 3rd day, 1.9% – on the 4th day[8]. Subsequently, piglet mortality gradually decreases to 0.02% in the period from 4 to 22 weeks after birth. Such mortality rates are directly related to the functioning of piglets' immune defence mechanisms level[9]. Newborns that do not receive colostrum in the first 4–6 hours after birth die within the first few days of life[10]. This is due to a sudden change in the immunoglobulin's concentration in colostrum, which is characterised by a 50% decrease in the immune proteins level in colostrum 4–6 hours after the first piglet is born, since the main piglet immune defence mechanisms are colostral immunoglobulins of two main

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classes – IgG and IgA[11]. In this regard, there are several critical periods in the first month of life: the first day, when newborns should receive colostral antibodies, and the end of the first week of life, when the colostral antibody concentration in the neonatal piglet's blood reaches the lowest concentration[12].

Within 2-3 weeks of birth, another critical neonatal period is identified, which is associated with a decrease in the colostral protective components level, mainly due to immunoglobulins, against the background of an unformed own immune system[1314].

The next critical period associated with the piglet's immunodeficiency state is detected after weaning. At this time, there is a sudden change in the feeding type – a transition from dairy to concentrate feed. Against the background of the feed stress development, piglets have liver function disorders, immune defence mechanisms are depleted, resulting in secretory immunoglobulin synthesis disruption and reduced phagocytic cell activity[151617].

The immune system deficiencies development in mammals necessitates the search for a set of measures that would help prevent the pathology occurrence under such conditions. One of these measures is the use of drugs

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that directly or indirectly affect the body's immune system mechanisms, or selectively, certain components[1819].

There are three groups of immunotropic drugs: immunostimulants, immunosuppressants and immunomodulators. Immunomodulators are drugs that restore the immune system function in therapeutic doses. That is why the immunological effect of immunomodulatory substances depends on the initial body immunity status: these substances reduce elevated and, conversely, increase decreased immunity indicators[20]. Meanwhile, immunostimulants enhance immune responses, bringing reduced indicators to normal values, and immunosuppressants, on the contrary, suppress the body's immune response[2122].

There are 7 main groups of substances that have immunotropic properties: microbial, thymic, bone marrow, cytokine, nucleotide, plant and chemical[23]. Each group is divided into organic and chemical, except for the latter, which is divided into high and low molecular weight substances. Their essence is based on the basic immune system principles, the main activators of which in the mammalian body are foreign organic substances of a protein nature, accordingly, drugs based on this basis are classified as exogenous substances. The immune response development is driven by numerous immunoregulatory

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substances, the use of which also affects the immune response. Drugs based on these substances are classified as endogenous[24][25].

The most pronounced immunomodulatory effect is provided by muramyldipeptide (TIR), a minimal bacterial wall peptidoglycan component[26]. Preparations based on it belong to the immunomodulator's third generation. TIR is found in the peptidoglycan of all known gram-positive and gram-negative bacteria. The main purpose of such drugs is to restore haemopoiesis, leukopoiesis, and immunity. These drugs are widely used in medicine. In the form of a lactobacillus cell wall hydrolysation, they are used to correct the body's resistance and immune system in patients with burns, cancer and respiratory diseases[27][28].

The use of these drugs leads to an increase in haemopoiesis, with a particularly pronounced effect on leukocyte synthesis. Under the TIR effect, phagocytic cells are activated, the number of lymphocytes is normalised, cytokine synthesis is enhanced, etc. Thus, in order to correct the mammalian immune system state during immunosuppressive periods of organism development, it is necessary to use immunotropic drugs that directly or indirectly affect the resistance mechanisms and allow to ensure their optimally high level, and thus reduce the risk of infectious diseases in animals[29].

Despite the fact that the use of immunotropic, probiotic and biologically active substance-based drugs to prevent the immunodeficiency development in animals has been sufficiently studied, a number of unresolved issues remain regarding their effect on newborn animals in the first days of life[30]. One of the

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effective schemes for the use of immunotropic substances to address these issues is the use of corrective substances in the mother-fetus-newborn organism complex. This complex should be considered as a single system, which components are closely interconnected, and functional changes in each component affect the others[3132].

Influencing the newborn immune system indirectly, through the mother's colostrum, by stimulating the sows' immunity is an extremely effective way of using immunocorrective drugs. In most cases, these are substances that are introduced into the sow's body with feed or parenterally[333435].

Correction of the sows' and piglets' adaptive capacity is possible with the use of ascorbic acid. Feeding the latter to sows 10 day before farrowing can increase the newborn piglets' stress resistance during critical neonatal development periods[3637]. Biological metal compounds also affect the sows' immunity. For example, feeding inorganic chromium compounds to sows a week before farrowing results in a change in antioxidant defence during piglet development's critical periods, which contributes to the prooxidant processes inhibition in their body[38]. All these feeding various substances to gestating

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sows schemes determine the antioxidants effect on preventing the stress and immunosuppression development in piglets, against which an increase in animal productivity is established[39][40].

The use of immunotropic substances in the mother-fetus-newborn chain leads not only to an improvement in piglets and their mothers natural resistance, but also improves their productive performance by increasing young animal safety, increasing average daily weight gain and reducing biological costs of adaptation and immunoreactivity[41][42]. A good example is the use of Echinacea purpurea extract in gestating sows. This helps to increase immunity in piglets born from them. Such changes occur due to the intake of biologically active substances in the mother's milk and colostrum[43].

Feed additives are also used to correct the immunosuppressive state of piglets after weaning. For this purpose, starting from 3–5 day after birth, piglets are fed a peat-based biologically active feed additive. As a result, the piglets' safety has increased and their weight has increased during the suckling period. This contributes to increased stress resistance during weaning. Such changes are associated with the hematopoiesis processes activation against the background of a decrease in the immunosuppressive compounds functional load on the liver[44]. These compounds are formed in the intestine during stress due to their absorption[45].

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There are reports of parenteral drugs administered to piglets in the first days of life for immunobiological correction of their body's defensive reactions to influence critical periods that may occur in postnatal ontogeny. One of the most common substance groups used for this purpose is tissue drugs[46]. It has been established that biologically active substances contained in thymus tissues can stimulate the T-cell component of piglet immunity[47]. A much more significant effect was observed after using an extract of thymic tissues in piglets at 20 day old[48].

The biogenic substances positive effect on the pig's immune system is accompanied by an increase in haemopoiesis, which was marked by a significant increase in the number of red blood cells, T- and B-lymphocytes and an increase in the phagocytic activity of leukocytes in piglets' blood[49]. It should be noted that cellular immunity in newborn piglets can also be stimulated with fat-soluble vitamins and interferon, which promotes the reorganisation of the lymphocyte membrane receptor part and leads to increased plasma membrane receptor expression[50].

The combination of tissue preparations from the thymus and bone marrow used in piglets of the first days of life promotes an increase in bactericidal and lysozyme activity in the animal serum on day 5[51]. Studies have shown that strengthening the immune system in piglets is also possible with the use of a porcine immunoglobulins injectable solution. Their parenteral injection a

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week before weaning stimulates the level of nonspecific resistance in piglets by activating factors[52].

Also, the use of organic acid preparations during critical periods showed a positive effect on the state of natural piglet resistance[53]. It was confirmed by an increase in the animal viability and productivity against the background of a decrease in piglet mortality by 2.5–3 times. An increase in immune defence was found in piglets fed sodium humate in combination with succinic acid and trace elements after weaning. This was reflected in an increase in the number of T-lymphocytes in the blood, which is associated with the succinic acid's ability to activate the phagocytic cells' oxygenation, which promotes their proliferation. Also, under the peat preparations influence, there is an increase in the T– and B-lymphocyte differentiation against the background of an increase in the number of red blood cells and a decrease in the lymphocyte index[54].

2. Modern concepts and application of promising strategies for modulating the immune response in newborn piglets

Natural resistance in pigs is provided by a number of cellular and humoral mechanisms that are closely interconnected. All of them are dynamic indicators that are determined by both the pigs' genetic characteristics and adaptive changes to the various anthropogenic and natural factors[55].

Sows are particularly sensitive to environmental changes, as the pregnancy period causes a decrease in the level of their immune defence mechanisms both at the general and local levels, which affects the physiological adaptation reactions of both their organism and newborn young animals, and correlates with the animal safety and productivity level[56].

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At the same time, newborn piglets, due to a number of biological characteristics, are prone to the immunodeficiency states development during the neonatal period of life, which contribute to the occurrence of infectious diseases and economic losses[57].

Due to the mechanisms of neonatal pathology development in piglets and the sow's immune system peculiarities, the use of immunotropic substances has become widespread. They are used according to various schemes both for sows during the farrowing period and directly to newborn piglets[58]. The latter option does not allow to influence the newborn period immunodeficiency, so it is more effective to correct the piglets' natural resistance mechanisms indirectly, through the mother's body. The sows' immunobiological natural resistance mechanisms are in close contact and, owing to the factors of humoral and cellular defence mechanisms, provide immunotolerance to fetal antigens. Therefore, an active immunosuppressive or immunostimulatory effect on sows' resistance mechanisms can lead to fetal developmental disorders or fetal rejection[59].

CONCLUSIONS

Thus, the critical piglet developmental periods during the suckling period are based on immunodeficiency states, which are caused by a decrease in the natural resistance level and an increase in the animals' susceptibility to environmental pathogens. These conditions contribute to the piglets' death in the first days of life. To prevent the occurrence of immunosuppression in piglets, it is effective to use immunotropic substances in the mother-colustrum-newborn system, which purposefully or selectively affect the defence mechanisms of both mother and fetus, minimising the risk of developing an immunodeficiency state of the newborn or, if it occurs, reducing its degree, increasing the piglets' resistance capacity during postnatal ontogeny.

Prevent the immunodeficiency states development and correct the immune defence mechanisms of both newborns and their mothers, it is necessary to use drugs with immunomodulatory effects. Their use does not cause an imbalance in the mother-colostrum-newborn immune system and provides a less expressed but more effective impact on their body. However, the literature does not reveal data on the state of sows' natural resistance during the second

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half of pregnancy, the colostrum immunobiological parameters level and the quantitative and functional parameters of the piglets' main immune system links against the background of age-related immunodeficiencies occurring during the neonatal period, under the peptidoglycan-based immunotropic drugs indirect action in the mother-colostrum-newborn biological chain.

SUMMARY

The integrative analysis of the cellular and humoral immunity in piglets during early ontogenesis carried out to clarify the exact mechanisms of the immune response modulation. Effectiveness and selectivity of the immunotropic chemicals application to regulate immune cell populations in piglets is presented. The progress in immune cell populations is regulated by the various cytokines production in the universal concentration-dependent manner. Furthermore, the development of the immune functions cross reacts with innate immunity mechanisms including anti-bacterial enzymes, epithelial barrier integrity in the both skin and intestine. The interaction between multiple components of innate immunity is a critic initiator of the dynamic changes in adaptive immunity. The natural resistance targets to the establishment of infection root and delays disease progression. The duration of the exposure to infectious agents plays an important role in the dynamics of immune response as well as its efficacy. The chapter discusses the plural mechanisms so far proposed to be responsible for the modulation natural resistance.

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