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Extragenital Pathology and Immunocompetent Cells Relations of Lactating Breast Gland and Offspring Jejunum

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Abstract: Researched the effect of chronic toxic maternal hepatitis on the cytometric features of immunocompetent cells (ICCls) of mammary gland tissues of the female and the jejunum of the offspring during breastfeeding. For morphological researches, pieces of the right inguinal mammary gland of female outbred rats with heliotrine hepatitis and the jejunum of the lean intestine of the offspring on days 1, 3, 7, 15 and 21 of lactation were used. Cytometric researches were carried out on semi-thin sections stained with methylene blue and pyronin G. It was established that in the last stages of pregnancy and in the first week after the onset of lactation, there is an increase in migration to the terminal secretory sections of the mammary gland of the ICCls, which indicates the participation of the mammary glands in the transfer of adoptive immunity to offspring and in maintaining the immune homeostasis of the small intestine, which decreases as the immune apparatus of the small intestine develops. A decrease in the number of ICCls migrating to the lactating mammary gland in case of mother's CTH negatively affects both immune adaptation and the structural and functional development and maturation of the immune apparatus of the jejunum of the offspring during breastfeeding.

Keywords: Hepatitis, Mammary Gland, Lactation, Small Intestine, Offspring, Immunocompetent Cells

1. Introduction

In recent years, significant progress achieved in the study of the structural organization of the immune system as a whole, interorgan and intersystem relationships, led to the creation of the doctrine of the immune system of the mucous membranes, which includes lymphoid formations of the walls of the digestive, respiratory systems, urinary tract, mammary gland, etc. [5, 7, 33, 34]. It has been shown that the mammary glands are the only organ that connects the body of the mother and the newborn child after childbirth and is of exceptional importance in maintaining its immune homeostasis [39, 43]. However, along with this, it should be noted that in human newborns, as well as some other representatives of mammals, almost all organs and systems still remain underdeveloped. This, first of all, refers to the immune system in general, and the immune system of the small intestine, in particular [2, 7, 9]. In this regard, for the growth and development of especially newborn mammals, the mammary gland of the mother is so important, which, together with milk, transfers to the offspring not only nutrients, hormones and biologically active components, but also participates in the transfer of adoptive immunity to the infant [6, 10, 12, 13, 15, 16, 18, 20, 21, 22, 37]. At the same time, the rapid development of industry leads to a change in the environment, unfortunately, not for the better for a person, which in turn contributes to an increase in extragenital pathology among women of childbearing age, as well as high infant mortality from acute intestinal diseases, immunodeficiencies and infectious diseases. diseases [4, 14, 15, 25, 26], which are currently observed and require research in this direction. At the same time, in the literature available to us, it was not possible to find works reflecting the influence of chronic maternal hepatitis on the quantitative parameters of the ICCls of the maternal mammary gland and jejunum of newborns in the dynamics of early postnatal ontogenesis.

The aim of our research was to investigate the effect of chronic toxic maternal hepatitis on the relationship between quantitative changes in the ICCls of the mammary gland of

lactating females and the small intestine of rat pups during lactation.

2. Material and Methods

The work was carried out on 2-3-month-old female white outbred rats weighing 120-130 g (110), which were kept on a standard laboratory diet. As a model of hepatitis, we used chronic heliotrinic intoxication according to the generally accepted method [1]. Experimental females were divided into 2 groups: control and experimental. An experimental group of rats (60) was injected subcutaneously with heliotrin at a dose of 0.05 mg / gram of animal weight weekly for 6 weeks. Control animals (50) were injected with sterile saline. 10 days after the last injection, males were added to the females of both groups. The gestational age was determined by vaginal smears. Animals of both control and experimental groups were sacrificed by decapitation under light ether anesthesia. Pieces of the right inguinal mammary gland were used for morphological studies. The material was examined on the 1st, 3rd, 7th, 14th, and 21st days of lactation with the appropriate control. The study of ICCls of the small intestine in rat pups was carried out during those periods of postnatal ontogenesis (8-10 animals per time point). Semi-thin (1 μm thick) sections were made from small intestine pieces on an LKB-4800 ultra-tome, which were stained with methylene blue — pyronine G. The ratio of different types of them. The number of interepithelial lymphocytes (IELs) was counted per 1000 epithelial cells. The obtained digital data were processed by the parametric method of variation statistics using Fischer's and Styudent's tests. Differences were considered significant at $P < 0.05$.

3. Research Results

It is known that postpartum lactation is the result of the formation of breast tissue in the embryonic, postnatal prepubertal and postpubertal periods, and of course, the final development and preparation of the organ for the active period of functioning occurs during pregnancy [8]. In our previous studies [19, 40], it was shown that in the prenatal period, namely, on the 21st day of pregnancy, the number of ICCs infiltrating the mammary gland reaches its maximum. During this period, intraepithelially located macrophages, small lymphocytes and plasma cells appear in the alveoli of the mammary gland. In the connective tissue stroma, the number of ICCls is somewhat reduced, which is probably due to their migration into the epithelium. Attention is drawn to the high content of plasma cells.

An interesting picture of structural and functional changes, accompanied by a peculiar dynamics of quantitative changes in ICCls, as shown by the results of our research, is observed on the 1st day after delivery. During this period, the total number of intraepithelially located immunocompetent cells (IEICCls) of the mammary gland reaches 6.6%, the bulk of which are monocyte-like cells (2.4%) and large lymphocytes (1.4%), followed by macrophages, medium and small lymphocytes, also among the epithelial cells of the terminal secretory sections of the gland, plasma cells are found (0.7%). At the same time, the number of ICC in the perialveolar connective tissue increases due to its infiltration by monocyte-like, plasma cells and small lymphocytes.

On the 3rd day of lactation, the total number of IEICCls in the alveoli reaches its maximum values (11.2%) (see Table 1), mainly due to an increase in the number of small lymphocytes, plasma cells and monocyte-like cells. It should be noted that plasmacytes are still found among intraepithelial immunocytes. The amount of ICCls in the perialveolar connective tissue also increases and reaches its maximum. At the same time, a significant increase in the number of monocyte-like cells was found, with a moderate decrease in the number of small lymphocytes and plasma cells.

Subsequently, on the 14th-21st day of lactation in the mammary gland, against the background of a decrease in the secretory activity of lactocytes, the number of ICCls in the alveoli gradually decreases in the alveoli, which pass with mother's milk to the offspring.

Table 1. *Cytometric features of terminal intraepithelial cells secretory parts of the mammary gland of primiparous rats during lactation in females with heliotrinic hepatitis ($X \pm xm$).*

Intraepithelial cells	Group of animals	Lactation terms (in days)				
		1	3	7	15	21
Total amount	Control	65,9±1,55	134,1±3,87	55,5±2,27	36,9±1,57	29,8±1,55
	Experim	60,5±2,31	112,5±2,43	37,7±1,73	22,1±1,58	16,7±1,41
Large lymphocytes	Control	14,2±0,81	20,6±0,87	10,4±0,52	5,6±0,0,37	4,0±0,26
	Experim	11,2±0,77	13,1±0,71	4,1±0,53	3,0±0,40	2,30±0,37
Average lymphocytes	Control	7,0±0,40	15,9±0,72	13,1±0,53	12,6±0,70	10,6±0,64
	Experim	15,1±0,97	26,4±1,22	19,6±0,93	10,9±0,86	8,9±0,57
Small lymphocytes	Control	5,8±0,33	33,0±0,87	6,4±0,56	6,8±0,39	5,2±0,36
	Experim	5,4±0,43	20,4±0,76	4,5±0,34	3,9±0,53	3,3±0,52
Cells like monocyte	Control	23,8±0,77	49,6±1,07	15,8±0,68	7,4±0,31	6,0±0,36
	Experim	16,6±1,11	40,7±1,73	13,4±0,66	5,1±0,46	3,0±0,16
Macrophages	Control	8,3±0,37	8,6±0,92	9,8±0,97	4,5±0,40	4,0±0,26
	Experim	4,6±0,43	4,7±0,48	6,1±0,68	1,2±0,33	1,0±0,26
Plasmacytes	Control	6,8±0,42	6,4±0,43	–	–	–
	Experim	4,6±0,40	3,5±0,33	–	–	–

Note: The values where the differences are significant relative to the control at $P < 0.05$ are highlighted in bold.

Table 2. *Dynamics of the average number of interepithelial lymphocytes (IEL) of the mucous membrane the jejunum of the small intestine of offspring born to females with chronic heliotrine intoxication (X ± xm).*

Investigated parameters	A group of animals	Terms of postnatal development (in days)				
		1	3	7	15	21
IEL villi	Control	1,7±0,14	3,4±0,2	5,8±0,20	8,1±0,30	10,8±0,6
	Experim	1,4±0,10	2,2±0,15	3,1±0,12	4,3±0,16	8,6±0,4
IEL crypt	Control	1,0±0,12	2,1±0,12	2,7±0,12	3,7±0,16	6,0±0,5
	Experim	0,7±0,10	1,2±0,10	1,5±0,10	2,0±0,11	4,2±0,2

The research of the jejunum of rat pups during the period of breastfeeding showed a peculiar dynamic of the distribution of ICCls in the mucosa. It has been established that by the time of birth, the immune apparatus of the small intestine (IASI) is still far from complete formation. In the process of postnatal development, the gradual formation of immune structures occurs. In this, the intake of antigens with food seems to be essential. Indeed, up to the 3rd day after birth, in rat pups, IELs are found in very small amounts in the composition of the integumentary epithelium of the jejunum. Whereas, on the 7th day of postnatal ontogenesis, IELs make up 4–6% of all cells of the integumentary epithelium of the intestine. Even by the 21st day, this indicator has not yet reached that in adult animals (Table 2). It should also be noted that in the dynamics of postnatal ontogenesis, the proximal-distal gradient of the number of IELs is preserved, the number of which in the wall of the ileum is 55-62% higher than that in the duodenum. The largest leap in the number of IEL in all IELs in all the jejunum was noted on the 14th day after birth, when the pups switched to a mixed diet. In the future, after the complete cessation of milk nutrition, the number of IELs increases slightly and subsequently stabilizes.

A slightly different dynamics of cytometric changes in ICCls in the mammary gland is observed in the experimental group of animals, that is, in females with CTH, where there is a lag in the development of the glandular tree, as well as a decrease in the migration of ICCls into the glandular epithelium of the terminal secretory sections of the mammary gland in the dynamics of lactation, and a decrease in the total the number of IEICCls is noted from the first day after birth and progresses up to 21 days of lactation (Table 1). The decrease in IEICCls occurs mainly due to a decrease in the number of macrophages, plasma cells, small and large lymphocytes, monocyte-like cells, while it should be noted that against this background, up to 7 days of lactation, there is an increase in migration to the terminal secretory sections of medium lymphocytes, which in the subsequent periods of lactation are also decreasing (see Figure 1 and Figure 2).

The results of the research of the jejunum of the offspring showed that during breastfeeding, a significant decrease in the number of IELs could be noted (Table 2), and a decrease in cell density, as well as a lag in cell differentiation and migration of immunocompetent cells into the lamina propria up to 21 days of postnatal ontogenesis. It should also be noted that in subsequent periods of development, these indicators reach the lower limits of control indicators.

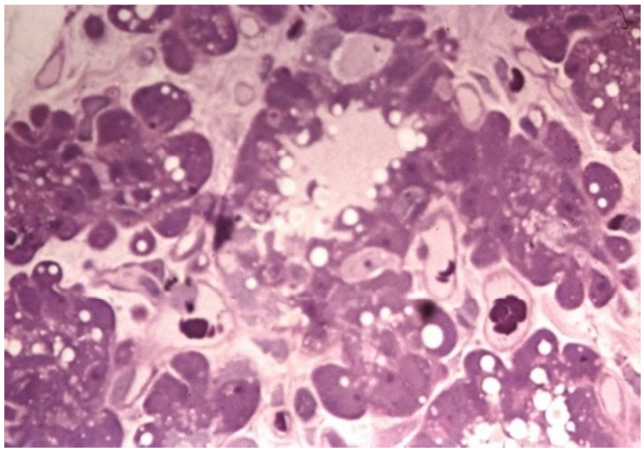

Figure 1. *Semi-thin section stained with methylene blue fuchsin basic. Mammary gland of the control group of animals on the 3st day of lactation, shows the migration of immunocompetent cells from the vessels through the perialveolar connective tissue stroma to the terminal secretory sections. Magnification x 200.*

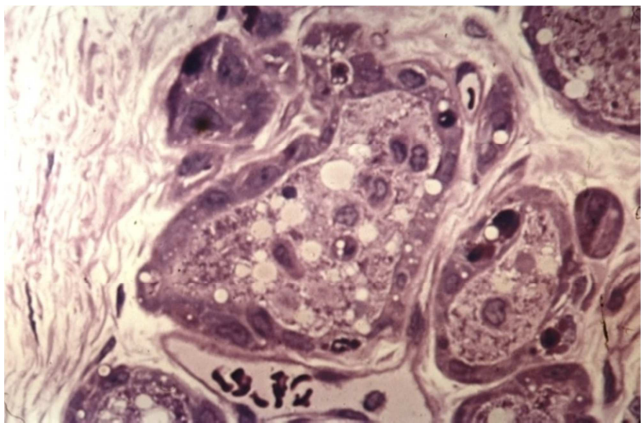

Figure 2. *Semi-thin section stained with methylene blue fuchsin basic. H-semithin section, the mammary gland on the 3rd day of lactation, the presence of immunocompetent cells in the alveoli. Magnification x 200.*

4. Discussion of the Obtained Data

As we indicated earlier, in our previous researches, pregnancy is characterized by an increase in infiltration of the connective tissue stroma and an increase in the migration of ICCls to the terminal secretory sections of the mammary gland, associated with the morphogenesis of the mammary gland and the preparation of the afterbirth for lactation. With the onset of lactation in the terminal secretory sections of the mammary gland, there is a decrease in the number of intraepithelial and an increase in the number of stromal ICCls. This is most likely due to their transfer into milk after the

start of breastfeeding, which is consistent with the data indicating the positive chemotactic properties of colostrum in relation to leukocytes [17, 23, 24, 35, 36]. In addition, during this period, intensive processes of immunogenesis begin in the mammary gland, aimed at the synthesis and secretion of the necessary immunoglobulin components of milk. It should also be noted that leukocytes entering milk create in it a high concentration of biologically active substances, such as lysozyme, lactoferrin, enzymes, etc. These milk components are necessary for a newborn, since IASI remains completely unformed by the time of birth, and its postnatal development is closely related to the nature of nutrition. Considering that during the period of milk feeding, the restructuring of the IASI proceeds relatively slowly and the immune system of newborns remains insufficiently developed on the 1st day after birth, it becomes obvious that during this period adaptive immunity, provided by the transmission of immunoglobulins and ICC from mother to child. The transition to a mixed diet is, probably, a triggering factor in the differentiation and migration of ICC. It should also be emphasized that the postnatal formation of the immune components of the small intestine in its parameters clearly correlates with the formation of the crypt-villus system and the structural and functional formation of the small intestine as a whole [2, 7, 27, 28, 44].

However, this completely harmonious system of genetically determined processes fails in extra genital pathology of the mother. Namely, CTG in female rats leads to a decrease in the number of IEICCls of the terminal secretory parts of the mammary gland, and, consequently, the cellular components supplied to the rat, which, most likely, is one of the factors characterizing the decrease in the immunomodulatory function of milk. Along with this, a decrease in the number of macrophages, monocytes and lymphocytes, on the one hand, contributes to a violation of the transfer of adoptive immunity, on the other hand, as indicated in our previous researches, the intake of lysosomes, lipid droplets present in these cells is significantly reduced, the trophic effect is significantly reduced and immunobiological properties of breast milk [17, 24, 39]. Along with the above, with hepatitis, profound changes in metabolic processes occur, including a violation of protein metabolism, which, naturally, affects the hormonal balance, and, consequently, the development of the placenta and mammary gland, as well as the developing offspring. It was found that in the offspring of rats with chronic hepatitis, there is a steady decrease in body weight gain, and a lag in the structural and functional development of the small intestine [2, 19, 30, 31, 38]. Perhaps one of the reasons for these changes during the period of lactotrophic nutrition is the previously discovered decrease in the amount of protein, carbohydrates and enzymatic activity of milk [2, 23, 26]. A decrease in cellular components, apparently, is one of the factors characterizing a decrease in the immunomodulatory function of milk. If we also take into account the immunodeficiency condition of the mother with hepatitis, it becomes clear what is the reason for the lag in the development of the digestive and immune systems of the offspring, established by many researchers [2, 11, 30, 36]. In addition, it has been shown that the process of chronic heliotrinic hepatitis is accompanied by profound morphological changes in the body's immune system. These changes lead to an imbalance between the T and B systems of the immune system and the development of an autoimmune process [3, 33, 37, 40, 42].

As it was established in our previous researches, CTH in female rats leads to a significant lag in the formation of the crypt-villus system [19], the present work is, as it were, a continuation of those studies, here we show the lag in the development of the components of the immune system of the small intestine of the offspring. It is also necessary to point out that a certain dynamic of the level of hormones in milk is revealed, associated with their participation in the process of metabolic adaptation of newborns to extrauterine existence and causing the restructuring of protein, carbohydrate and fat metabolism in the postnatal period. Violation of the processes of formation of the small intestine in offspring with experimental chronic hepatitis of the mother is most likely due to the toxic effect transplacentally on the developing fetus and through the mother's milk on the body of the newborn [2, 29, 40, 41, 45]. Summarizing all the above causal relationships, we can assume that they could contribute to morphological changes in the small intestine of the offspring of mothers with chronic toxic hepatitis.

5. Conclusion

Thereby, the established dynamics of the ICCls of the breast and small intestine indicates that there are certain cellular-tissue relationships between the ICCls of the mother's mammary gland and the ICCls of the small intestine of the offspring, which, in the early periods of lactation, the mammary gland provides immune homeostasis of the small intestine, and this is its function. As the immune system of the small intestine develops, it gradually regresses. CTH in female rats leads to a decrease in the flow of ICCls through mother's milk to offspring and a slow development of structural formations of the immune system and a decrease in IEL migration into the small intestine of offspring. Therefore, therapeutic and prophylactic measures aimed at correcting the lag in the development and formation of the immune apparatus of the small intestine of the offspring born from mothers with chronic toxic hepatitis, most likely, would be more appropriate to carry out immediately after birth and further in the dynamics of breastfeeding.

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