Forming neuroendocrine apparatus of lung in ontogenesis

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Abstract. Aim of the research is to show the developing legitimacy APUD-system of lungs in pre and post ontogenesis. Condition of neuroendocrine apparatus of lungs on rabbits was studied during the fetal embryogenesis of inner development and after 1-180 days of the birth. Duration of the research on rabbits was chosen according to their changing afterbirth features as physiological function of organism; was selected the periods of newborn stage, enlightenment, complication of locomotion, pre-pubertal and pubertal. Materials were fixed by immersion in liquid of Buena. After suitable wiring, the material was flooded in paraffin. Histologic shears were colored hematoxylin and eosin, stain of Van –Gieson, resorcinol-fuchsinol of Veingeirt. For detecting endocrine cells of shear impregnated by the method of Gremeluise. Luminescent histochemical research was done with the help of V.N. Shvalyova and N.N. Juchkova method with applying glyoxylic acid on fresh-iced shears. For defining, the amount of fluorescent monoamine (serotonin and catecholamine) was used microfluorimetry. However, the intensification of histogenetic processes occurring in the organ after birth due to the expansion of physiological functions is accompanied by an increase in the number of apudocytes and NET. The content of catecholamines and serotonin in neuroendocrine structures depends on the period of growth and differentiation of the lung: during the intensive growth of the respiratory organs in the fetal period and in newborns, the level of catecholamines in apudocytes and NET is increased; with the predominance of differentiation processes in the neuroendocrine apparatus, the serotonin content increases.

1 Introduction

The epithelium of the respiratory tract of the lungs of humans and animals contains highly specialized pulmonary neuroendocrine cells (NEC, apudocytes), distributed as single cells, and in the form of innervated clusters, neuroepithelial bodies (NET). These structures are called neuroendocrine structures, since they are expressed by genes of both neuronal and endocrine cellular phenotypes, including the synthesis and release of amine (serotonin, 5-HT) and various neuropeptides (including bombesin) [17]. They belong to the APUD-system of the body. Installed hyperplasia of apudocytes and NET in chronic diseases in children [2-

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7], as well as in experimental pneumonia [3]. In recent years, intensive research has been carried out on the neuroendocrine cells of the APUD-system of the lungs in many physiological and pathological conditions of the organ [4,8-18]. However, their role in the process of pre- and postnatal ontogenesis has not yet been studied.

The purpose of this study is to reveal the patterns of development of the APUD-system of the lungs in pre- and postnatal ontogenesis.

2 Materials and methods

The state of the APUD-system of the lungs in rabbits during the fetal period of embryogenesis was studied on 15 fetuses obtained on days 20 and 26 of intrauterine development. The study of the APUD-system of the lungs in rabbits in postnatal ontogenesis was carried out at 1,3,7,10,15,21,30,90 and 180 days after birth. The timing of the study in rabbits was chosen in accordance with the characteristics of the physiological functions of the organism changing after birth; the periods of neonatal, enlightenment, complications of locomotion, prepubertal and pubertal are distinguished. In total, 69 rabbits were studied in postnatal ontogenesis, for each period from 5 to 9 animals. The animals were slaughtered under sodium ethaminal anesthesia, followed by transection of the abdominal aorta. The studies were carried out in strict accordance with the bioethical rules for working with laboratory animals adopted in the Republic of Uzbekistan. The material was fixed by immersion in Bouin's liquid. Some of the animals received Bouin's liquid pouring into their lungs. After the appropriate posting, the material was embedded in paraffin. Sections were stained with hematoxylin and eosin, picrofuchsin according to Van Gieson, and resorcinol-fuchsin according to Weigert. To identify endocrine cells, the sections were impregnated according to the Grimelius method. Luminescence-histochemical study was carried out according to the method of V.N.Shvalev and N.N. Zhuchkova using glyoxylic acid. The preparations were studied using a LUMAM-I2 luminescence microscope using an FS-1 filter (4 mm thick), transmitting monochromatic light with a wavelength of 410 nm. Microfluorimetry was used to determine the amount of fluorescent monoamines (serotonin and catecholamines). The analysis was carried out using a luminescent photometric attachment FMEL-1 at an output voltage of 1000 V, with a 0.5 probe and a filter 8 (515 nm) for the determination of serotonin and a filter 6 (418 nm) for the determination of catecholamines. The luminescence intensity was measured in units of the instrument scale with different transmission coefficients. The obtained values were compared with each other after their corresponding reduction to the current strength (conventional units). To obtain whole numbers, the numbers were multiplied by 109. Conventional units are directly proportional to the amount of substance in the structure under study. In this regard, we used the terms “content”, “level”, “concentration” conditionally. For the convenience of presentation, the following verbal designations of the signal for serotonin (in terms of units) will be used: weak - 1-10; medium - 10-30; high - 30-60; very high - 60 and above. Due to the low content of catecholamines in cells, these verbal designations were used with numerical values, respectively: 1-5; 5-10; 10 and up.

In the lungs fixed with pouring, the airways were sketched using the RA-2 apparatus, measured by a cartographer, and after appropriate recalculation, the true length of the bronchi was determined in millimeters. Then, under a microscope, argyrophilicapudocytes and NETs located in the sketched bronchi were determined and the number of these elements per 1 mm of epithelial lining was calculated. In the respiratory department, the number of argyrophilic elements was counted in 100 fields of view with magnification of the objective 40 and the eyepiece 10. For mathematical processing of the data, the Student's method was used with the determination of the arithmetic mean M, the average error of the relative values m and the coefficient of reliability of the difference t. In some cases, the nonparametric Wilcoxon-

Mann-Whitney U test was used, suitable for any distribution of the trait. Differences were established as significant at $P < 0.05$.

Histological preparations were examined and photographed using a LeicaGME microscope (Leica, India) coupled with a LeicaEC3 digital camera (Leica, Singapore) and a Pentium IV computer.

3 Results

On the 20th day of the fetal period of embryogenesis, the lungs of the rabbit are at the tubular stage of development. Apudocytes and NETs are found in the epithelium of all developing bronchi, up to terminal and respiratory bronchioles. Lung apudocytes in rabbit fetuses are predominantly oval in shape and belong to closed cells. Neuroepithelial bodies occupy the entire thickness of the epithelial layer, slightly rising above the bronchial mucosa. The largest number of apudocytes and NETs was determined by us in the middle and small bronchi (Table 1).

Table 1. The number of apudocytes and NET in bronchuses(for 1mm) and in respirator unit (for 100 area eyestrain of lungs on fetus of rabbits(M±m)

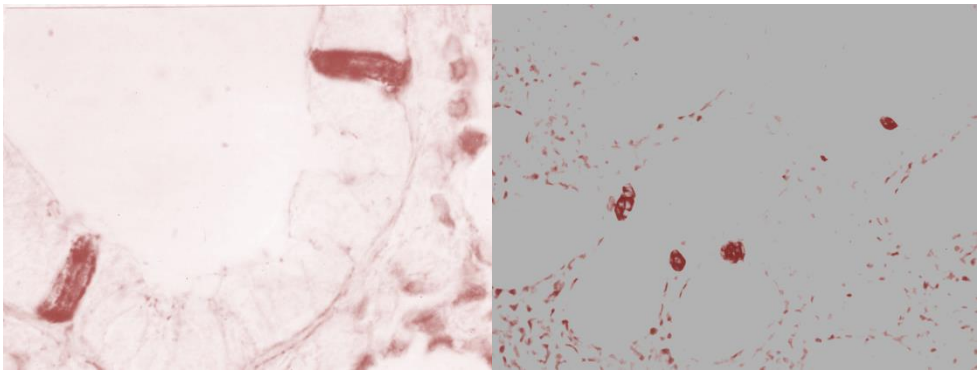
Age of fetus (days)	Structure	Bronchuses			Respirator unit
		Big	Average	Small	
20	A	1.4±0.15	1.5±0.57	1.8±0.63	4.7±1.34
	B	0.6±0.39 (3)	1.6±0.26 (8)	2.6±0.67 (9)	9.7±0.67 (6)
	C	7.0±0.55 (3)	7.2±0.50 (8)	6.5±1.33 (9)	4.2±0.53 (6)
26	A	1.0±0.36	0.9±0.17	0.7±0.04*	4.0±1.24
	B	1.1±0.19 (5)	1.3±0.28 (14)	0.5±0.12*(15)	5.1±0.79*(7)
	C	8.0±0.77 (6)	6.5±0.96 (11)	5.9±0.83 (14)	5.0±0.86 (5)

Note: * 0,05>P<0,001 in the comparison with the previous deadline of research. A,B, C- the number of audocytes, NET and cells of NET. In bracket – number of bronchus, 100 areas of eyestrain respirator unit and NET of researched 3-5 animals.

A large number of apudocytes and NETs are found in the epithelial tubules. NETs are mainly localized at the border of the transition of bronchioles into epithelial tubes. Apudocytes and NET, as a rule, fluoresce very weakly; the color of their luminescence is greenish-yellow.

On the 26th day of embryogenesis, the lungs of rabbits pass into the alveolar stage of development. Endocrine elements in the lungs of these fetuses are determined both in the bronchi and in the respiratory region (Fig. 1). By this time of the fetal period, we did not observe significant changes in the number of apudocytes and NETs in large and medium bronchi, compared with the previous study group (Table 1). At the same time, a significant decrease in both apudocytes and NETs is observed in small bronchi, and the number of NETs in the endocrine apparatus of the respiratory part of the lungs sharply decreases. Apudocytes and NET of the lungs have a more intense luminescence than the endocrine elements of the previous period.

On histological sections in 1-day-old rabbits, the air-conducting part of the lungs occupies a larger area than the respiratory one. The acini of the respiratory section are short, the alveolar sacs are formed by 7-10 wide alveoli. Apudocytes acquire a predominantly columnar shape and reach the airway lumen (Fig. 1).



A B

Fig. 1. Apudocytescolumnial form open type in epithelia of bronchus(A). NET in bronchus and in the place where transferred to alveolar bag (B). Lung of one-day rabbit. Impregnation of Grimelius

In terms of quality of relationship, in comparison with 26-days fetus of lungs, was being observed statistically reliable decrease on number of NET and/or cell in their all of the bronchuses and in respirator unit, the number of apudocytes decreased only in small bronchuses

Table 2.The number of apudocytes and NET in bronchuses(for 1mm) and in respirator unit (for 100 area eyestrain of lungs after birth (M±m)

Age (days)	Structure	Bronchuses			Respirator unit
		Big	Avarage	Small	
1	A	1,0±0,18	0,7±0,12	0,3±0,06*	3,9±0,41
	B	0,6±0,07*(24)	0,8±0,07 (25)	0,5±0,07 (25)	2,9±0,53*(11)
	C	3,9±0,35* (29)	5,0±0,34(30)	4,5±0,29*(29)	4,4±0,72(11)
2	A	1,3±0,15	0,5±0,08	0,4±0,05	1,8±0,42*
	B	0,5±0,09 (26)	0,5±0,06*(23)	0,4±0,05*(23)	2,8±0,5 (11)
	C	4,2±0,35 (17)	4,8±0,36 (20)	3,3±0,32*(23)	4,8±0,42 (11)
3	A	1,3±0,24	0,8±0,1	0,6±0,09*	1,0±0,35
	B	0,3±0,08 (19)	0,5±0,12 (17)	0,4±0,12 (23)	1,8±0,56 (14)
	C	2,9±0,11 (7)	4,1±0,6 (15)	4,4±0,53 (15)	4,3±0,62 (11)
10	A	1,0±0,11	0,8±0,09	0,4±0,06*	2,9±0,87*
	B	0,4±0,08 (24)	0,9±0,09* (20)	0,3±0,05 (23)	3,3±0,86 (12)
	C	3,5±0,31 (14)	4,5±0,4 (18)	3,7±0,41(16)	3,8±0,32 (12)
15	A	0,6±0,12*	0,4±0,03*	0,3±0,05*	1,4±0,49
	B	0,3±0,09 (12)	0,5±0,08*(14)	0,2±0,05(20)	1,0±0,5* (8)
	C	4,3±0,91(8)	6,3±1,0 (12)	3,4±0,35(18)	4,1±0,83(3)
21	A	0,4±0,11	0,4±0,13	0,4±0,06	0,4±0,14*
	B	0,4±0,15 (12)	0,3±0,07 (14)	0,3±0,09 (20)	0,9±0,32 (13)
	C	4,6±0,96 (8)	4,1±0,51*(12)	3,3±0,41 (18)	3,7±0,56 (13)
30	A	0,7±0,13	0,3±0,06	0,5±0,2	0,6±0,18

	B	0,2±0,05 (26)	0,3±0,04(12)	0,5±0,2 (16)	0,7±0,43(14)
	C	4,5±0,68 (17)	4,7±0,07(11)	6,1±0,8* (9)	4,1±0,61 (10)
90	A	0,4±0,12	0,5±0,17	0,3±0,13	1,3±0,13
	B	0,4±0,11 (11)	0,3±0,11(14)	0,1±0,05(13)	0,5±0,16*(12)
	C	3,7±0,4 (8)	3,7±0,52 (8)	5,2±2,3(4)	3,7±0,54 (6)
180	A	0,9±0,21	0,1±0,03*	0,1±0,02	0,4±0,15
	B	0,01±0,009(20)	0,1±0,06(19)	- (n=20)	0,6±0,18(18)
	C	3,3±0,3 (3)	5,3±0,3 (3)	-	3,6±0,77 (8)

Certainly, according to this the general number of all endocrine structures in bronchus comparing with their fetus decreased. However, like this condition is more characteristic for large and middle bronchus than small ones.

In cutting of three-day rabbit, the area of breathing ways were still bigger than respirator unit. Pulmonary acini expanded, they were produced in large and not deep alveolar. In this duration of research big bronchuses endocrine apparatus in the comparison with one-day rabbits did not changed a lot.

In middle and small bronchus, the number of NET decreases, in small one- the number of cells in NET decreases too. At the same time in respirator unit, the number of apudocytes becomes twice smaller than one-day rabbits. After a week of birth, during the study it was revealed an increase of apudocytes in histolysis. Statistically reliable differences, as before for only the average and small bronchus. In big bronchuses the size of NET decrease significantly. During the fluorescence microscopy of drugs, it was observed yellow luminescence of apudocytes and NET. Histostructure of lungs in ten-day rabbit do not differ with seven-day one. However, the amount and morph functional condition of endocrine apparatus the deadline of research continuously changing. Moreover, the change is not unidirectional in bronchial tree and respirator unit. The number of apudocytes and NET in big bronchuses of this group do not change, the amount of NET significantly increase in average bronchuses, the number of apudocytes decrease in small ones. The amount of apudocytes significantly increase in respirator unit. (Table 2)

In histolic research of rabbit lungs after 15 days of birth, we detected that the respirator unit occupied more territory than internal bronchuses. In epithelia all, the bronchuses were observed rapid decrease in number of apudocyte.Besides, number of NET in average bronchuses and respirator unit became less than previous series of experiments. After 21 days of birth, in rabbits' lungs revealed high level of bronchial tree cytodifferntiation: in big bronchuses identified plate of matured gristle, in average one – well-expressed folding of mucous membrane. The respirator unit occupied more territory than airline ways. Many apudocytes as usual were in columnar form.Most of the cells achieved the light of airline ways. In bronchus with different diametric were available approximately the same number of apudocytes and NET. However, in the comparison with 15-day rabbits' reliably decreased number of cells in NET, which were situated in average bronchuses. Significantly lower became the number of apudocytes in respirator unit. These animals have greenish yellow and yellow luminescence of apudocytes and NET.

30 days after the birth big bronchuses of lungs sent to multi-bank epithelia, at the same time the average ones one-bank cylindrical, the small ones to cubical. The respiratory section is formed by branched acini, in the wall of which there are wide alveoli. In the endocrine apparatus, there are some changes in the number of apudocytes and NETs, both in the bronchial tree and in the respiratory section, but the differences are insignificant. In small bronchi, the number of apudocytes and NET increases and becomes larger than in the middle ones. The number of cells in the NET, located in the small bronchi, sharply increases (Table 2). The endocrine structures of the lungs are characterized by a greenish-yellow glow.

90 days after birth, pulmonary acini are long, branched, many deep alveoli are located in the wall. The bronchial wall is completely differentiated. The quantitative content of apudocytes and NET in the epithelium of the bronchi does not change, compared with 30-day-old rabbits. In the respiratory department, we observed a significant decrease in the number of NETs, compared with the previous study period. The luminescence-histochemical study revealed that in 90-day-old apudocytes and NETs are distinguished by a yellow glow, characteristic of the serotonin content. The luminescence of NET is more intense than that of apudocytes.

In adult animals, the endocrine apparatus of the APUD system is represented mainly by apudocytes, which are located mainly in the small bronchi. The apudocytes are oval and racquet-shaped. Some apudocytes have long processes extending from the base of the cell. NET occurs occasionally in large and medium-sized bronchi; they are absent in small bronchi. NETs are usually located deep in the epithelial layer of the bronchi. Compared with 90-day-old animals, we found a sharp decrease in either the number of apudocytes or NET in the bronchi (Table 2).

Comparative analysis of the content of serotonin and catecholamines in neuroendocrine structures showed the following. The serotonin content in lung apudocytes in rabbits at the age of 1,3,7,10 days is approximately at the same level, and on the 15th day its amount increases sharply. During this period, the concentration of serotonin in apudocytes is the highest.

Then its level gradually decreases and by the 30th day, it turns out to be the lowest. Further, we registered an increase in serotonin levels by 180 days after birth. The frequency of accumulation of catecholamines in apudocytes is different from that of serotonin. Their highest level is determined 1 day after birth. Starting from this day of the experiment, a decrease for catecholamines occurs in apudocytes, and to a minimum level. However, by the 15th day, the level of catecholamines increases sharply. After this, there is an alternation of periods of decrease and increase in the content of catecholamines in apudocytes.

The level of serotonin in NET decreases from 1 to 3 days of the experiment, and increases from 7 to 10. By this time, it reaches the highest value in comparison with all other days of the study. Then the serotonin level decreases again from 15 to 30 days. At the same time, the lowest indicators of the amount of serotonin were found by us in 30-day-old animals. This period of decline is then replaced by a slight rise in serotonin levels by day 90, and its decline is noted again by day 180 after birth. In contrast to changes in serotonin levels, the content of catecholamines in NET first increases (from day 1 to day 7) and then decreases (by day 10). The peak concentration of catecholamines is determined by the 15th day of the study. From that moment on, their content gradually decreases and on the 180th day after birth, the level of catecholamines is the lowest. Consequently, on the first day of postnatal development, histogenesis of the lungs occurs at a higher level in the APUD-system of light catecholamines than in the following days. Then, on the 10-15th day, the level of serotonin increases sharply. Subsequently, the serotonin content decreases, and especially significantly on the 30th day after birth.

4 Discussion

Summarizing the data presented on the study of the endocrine apparatus of the lungs in the bronchial tree and in the respiratory section, we found that during the fetal period of embryogenesis, many neuroendocrine structures are located in the distal sections of the bronchial tree and in the developing respiratory section. After the beginning of the formation of alveolar structures, the largest number of them is determined already in the middle, and not in the small bronchi. During postnatal development, the number of endocrine structures decreases. Against the background of this process, periods are noted that are distinguished

by an increase in the number of endocrine structures. This happens on the 7th, 10th and 30th days after birth. Such a change in the number of endocrine structures precedes intensive histogenetic processes, which, according to our data, intensively occur in the lungs of rabbits after 7 and 30 days in the distal parts of the bronchial tree and in the respiratory part. They are associated with the expansion of the connections of the developing animal organism with the environment, due to enlightenment, the complication of locomotion, and a change in the nature of nutrition. All this has an increasing effect on the histogenetic processes in the lungs. In the prepubertal period in the intrapulmonary bronchi of rabbits, the same localization of APUD-system cells is observed as in adult animals, but their number was greater than in sexually mature animals. This is due to the ongoing development of the lungs during puberty. The content of monoamines in apudocytes and NET of the lungs in rabbits in postnatal ontogenesis is characterized by the fact that in the first stages of postnatal development, a higher level of catecholamines is determined in the endocrine structures than in the subsequent ones. On days 10-15, a particularly high level of serotonin was found in them. In the future, low levels of monoamines are determined, and especially, on the 30th day after birth. The noted dates, in general, coincide with those indicated earlier. This indicates morphofunctional transformations of the endocrine apparatus of the APUD-system at these stages of histogenesis.

In the course of postnatal ontogenesis, the ratio of the components of the APUD-system of the bronchial tree changes. During prenatal development, the most frequent structure is NET. After birth, the number of NETs gradually decreases, but nevertheless they are common, starting from the 7th day, the proportion of apudocytes in the endocrine apparatus gradually increases. In adult animals, these cells become the predominant part of the APUD system. Comparing one-day old and adult rabbits in terms of the content of endocrine structures in the lungs, we are convinced of a significant decrease in the number of NETs. So, in large bronchi the number of apudocytes for 6 months of development almost did not change, and NET decreased 60 times, in the middle bronchi the number of apudocytes decreased 7 times, and NET - 8 times. In small bronchi in adult animals, apudocytes became 3 times less, and NETs were not detected at all. These data point to the decisive role of NET in lung development compared to apudocytes. Only in the respiratory department is the number of NETs in all age periods, as a rule, higher than that of apudocytes.

During the last decade, studies using modern methods of cell and molecular biology have revealed the complex functional role of the APUD system, starting from the early stages of lung development as modulators of growth and differentiation of fetal lungs and during childbirth as oxygen sensors of the respiratory tract involved in neonatal adaptation. ... Postnatally, the APUD-system cells are suppliers of the lung stem cell niche, which is important for the regeneration of the airway epithelium and lung carcinogenesis. The possible role of the APUD system components in the pathogenesis and pathobiology of childhood lung diseases is discussed, which includes congenital pulmonary disorders, bronchopulmonary dysplasia, respiratory control disorders, childhood neuroendocrine hyperplasia, cystic fibrosis, bronchial asthma and pulmonary hypertension [9,11,12,17]. Patients with neuroendocrine cell hyperplasia had the highest mean percentage of bombesin-positive NEC in the airways compared with other children. An increase in the number of NEC occurs in pathologies associated with immaturity of the lungs, such as impaired synthesis of surface-active protein and pulmonary interstitial glycogenosis. Therefore, NEC may, to some extent, be a marker of airway immaturity, and not a direct cause of neuroendocrine cell hyperplasia [15,19,20]. Classical in vitro studies have shown that pulmonary neuroendocrine cells can respond to a variety of aerosol stimuli such as hypoxia, hypercapnia, and nicotine. Recent in vivo data indicate their significant role in neuroimmunomodulatory foci of action, releasing neuropeptides, neurotransmitters and accelerating asthmatic reactions to the allergen. In addition, there is evidence that pulmonary

neuroendocrine cells can function both as progenitor cells and as precursor niches after damage to the airway epithelium [13, 14, 16].

5 Conclusion

There are high differential endocrine apparatus of APUD- system during the fetus period of embryogenesis in rabbit lungs. In postnatal period of ontogenesis, the number of neuroendocrine structures decreases. However, strengthening histolic processes which are appearing in organs after the birth follow the increase of apudocytes and NET. The content of catecholamines and serotonin in neuroendocrine structures depend on the period of rise and lungcytodifferentiation : During the intensive growth of breathing organs in fetus period and in case of newborns apudocytes and NET the level of catecholamine increased; during the predominating the process of cytodifferentiation in neuroendocrine apparatus increase the content of serotonin.

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