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ВЛИЯНИЕ ФОРМАЛЬДЕГИДА *IN UTERO* НА СТРОЕНИЕ ТИМУСА НОВОРОЖДЕННЫХ КРЫС

© И.Ю. Ваш

ГУ ЛНР Луганский государственный медицинский университет им. Святителя Луки, Луганск, Луганская Народная Республика

Цель. Изучение строения тимуса новорожденных крыс, рожденных самками, подвергавшихся ингаляционному влиянию формальдегида (ФА) на протяжении всего периода гестации.

Материалы и методы. Работа проведена на 72 белых беспородных крысах первого дня постнатального развития. Первую группу составили крысята (n=37) – потомство шести крыс, которые в течение всего периода беременности находились в условиях воздействия ФА в концентрации 2,766 мг/м^3. Экспозиции ФА осуществлялись 1 раз в день в течение 60 мин в затравочной камере объемом 1 м^3. Вторую группу составили контрольные животные (n=35) – потомство шести крыс, которые во время проведения эксперимента находились в условиях, аналогичных таковым у экспериментальной группы за исключением влияния ФА. Определяли массу тела новорожденных крыс, абсолютную и относительную массу тимуса. Изучалось строение тимуса на светооптическом уровне. Подсчет количества клеток в корковом и мозговом веществе тимуса осуществлялся на площади 2500 мкм^2.

Результаты. Масса тела и абсолютная масса тимуса новорожденных крыс первой группы были статистически значимо ниже контрольных значений. Отличия между значениями относительной массы тимуса в сравниваемых группах были незначительными. Количество клеток в корковом и мозговом веществе тимуса под действием ФА значительно не изменялось.

Заключение. Ингаляционное влияние ФА на организм беременных крыс в течение всего периода гестации приводит к уменьшению массы тела и абсолютной массы тимуса новорожденных крыс. При этом относительная масса тимуса не претерпевает значительных изменений. Строение тимуса на светооптическом уровне под действием ФА также не претерпевает существенных изменений.

Ключевые слова: *тимус; новорожденная крыса; формальдегид; масса; световая микроскопия.*

THE INFLUENCE OF *IN UTERO* EXPOSURE TO FORMALDEHYDE ON NEWBORN RAT THYMUS STRUCTURE

I.Yu. Vash

St. Luke Lugansk State Medical University, Lugansk, Lugansk People's Republic

Aim. To study the structure of the thymus of newborn rats born from female rats exposed to inhalation of formaldehyde during gestation.

Materials and Methods. The work was carried out on 72 white outbred rats of the first day of postnatal development. The first group consisted of newborn rats (n=37) – the offspring of six rats that were exposed to formaldehyde (FA) in concentration of 2.766 mg/m^3 during the entire period

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of pregnancy. FA exposure was given once a day for 60 minutes in a 1 m^3 exposure chamber. The second group included control animals (n=35), which were kept in conditions similar to those of the experimental groups with the exclusion of the effect of FA. In the newborn rats, the body mass and the absolute and relative mass of the thymus were determined. The structure of thymus was studied in a light optical microscope. The number of cells in the cortex and medulla of the thymus was counted over an area of 2500 μm^2.

Results. The body mass and absolute mass of thymus of the newborn rats of the first group showed a statistically significant reduction against control values. The differences between the values of relative mass of thymus in the compared groups were insignificant. The number of cells in the cortex and medulla of the thymus under the influence of FA did not show any significant changes.

Conclusion. The effect of inhalation of FA on the organism of pregnant rats during the entire gestation period consists in a decrease in the body mass and in the absolute mass of the thymus of newborn rats. With this, the relative mass of the thymus did not undergo significant changes. The thymus structure in the light microscope did not show any significant changes either.

Keywords: *thymus; newborn rat; formaldehyde; mass; light microscopy.*

The structure of thymus of newborn children is described in detail in the works of N.A. Voloshin, et al. [1] and E.A. Grigorieva, et al. [2]. Thymus of a newborn is characterized by lobular structure. Sometimes small areas of adipose tissue in the interlobular septa are determined. The cortico-medullary junction is, as a rule, poorly expressed. With the reduced density of cells in the cortical substance, 'nest-like' loss of lymphocytes may be seen. The most numerous cells of cortex and medulla are small lymphocytes (about 70%). Epithelial reticulocytes make approximately 5% of the total thymic cells. The medulla contains small-size thymic bodies. In the cells that form the latter, destructive changes in the nucleus and cytoplasm are determined. In the thymic tissue, both small and large cystic (with PAS-positive and alcianophilic contents) thymus bodies may be encountered.

The literature presents the results of studies showing changes in the structure of thymus of newborn rats, which were *in utero* exposed to various kinds of chemicals. So, in the work of N.V. Yaglova, et al. [3] it was shown that the low-dose exposure to dichlorodiphenyltrichloroethane during pregnancy does not frustrate formation of the thymus of the offspring rats, but leads to changes in its structure consisting in retardation of the lobulation of lobes, formation of an extensive epithelium-free space in the cortex and reduction of formation of thymic bodies in the medulla. Periconceptional alcoholic intoxication of mothers within 1 month in combination with exposure to ethanol during pregnancy also affects the morphogenesis of the thymus of the offspring, which is reflected in its decreased absolute and relative mass, proliferative activity, enhanced cell death, and the appearance of microcirculatory and dysplastic changes [4].

Formaldehyde (FA) is a common organic compound of the aldehyde family [5]. FA is found in low concentrations in food and water and in high concentrations in the environment as a component of: (1) car exhaust gases, (2) tobacco smoke, (3) fume of forest fires, (4) gases formed in the decomposition of plant residues in the soil and in photochemical oxidation of hydrocarbons [6], etc. FA is widely used in the synthesis of phenolic, ureal and melamine resins, as a binder in chipboards, floor coatings and paints, and also in the production of plastic materials, textiles, cosmetics and insecticides [7]. The International Agency for Research on Cancer (IARC) and a number of national agencies have classified FA as a human carcinogen (group 1) [8].

According to some authors, there exists a close connection of the effect of FA with the rate of miscarriage, and with other negative effects – low birth weight, premature birth and disorders in menstrual cycle [9]. In female mice exposed to FA, uterine and ovarian hypo-

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plasia is observed [10]. In addition, in the offspring of female rats and mice exposed to FA, there is an increased incidence of fetal abnormalities, chromosomal aberrations and aneuploidy.

The lack of literature data regarding the effect of FA on the intrauterine formation of the thymus determined the *aim* of the present work – to study the structure of the thymus of the offspring of female rats exposed to FA during the entire gestation period.

Materials and Methods

The work was carried out on 72 white outbred rats of the first day of postnatal development in accordance with the Rules and Recommendations for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes adopted by the European Convention [11] and the Principles of Good Laboratory Practice (National Standard of the Russian Federation GOST 33044-2014). The study was approved at a meeting of the Commission on Bioethics of the SI LPR «St. Luke Lugansk State Medical University» (protocol №5 of 05.11.2018).

The animals were divided into 2 groups. The first group (FA) included newborn rats (n=37), the offspring of six rats exposed to FA inhalation (2.766 mg/m^3) during the entire period of pregnancy. FA exposure was carried out daily for 1 hour in a 1 m^3 exposure chamber. The second group (C) included control animals (n = 35), the offspring of six rats, which during the experiment were kept in conditions similar to those of the FA group excluding the influence of the studied agent. In the time between FA exposures, the rats were kept in standard conditions of the vivarium. Newborn rats were taken weight on a VLR-200 balance, after which they were devitalized by vapors of diethyl ether. After that, the thymus was isolated, its absolute and relative mass was determined, and it was fixed in a 10% solution of neutral formalin.

After paraffin embedding of preparations made in the standard way [12], sections 5-7 μm thick were made and were stained with hematoxylin and eosin. Due to the fact that the division of the thymus of newborn rats into cortical and medullary substance is not clearly expressed, cells were counted on serial sections with the area 2500 μm^2 each that were located: (1) in the immediate vicinity of the thymus capsule or its septa (cortex) and (2) in the center of the lobules (medulla) in six non-crossing fields of view of each section. According to this algorithm, every 10th serial section was examined.

Quantitative data were processed using the parametric (Student's t-test) method for evaluation of the significance of differences and Statistica 10 program. The differences were considered statistically significant at p values <0.05.

Results and Discussion

Table 1 shows the body mass of newborn rats, as well as the absolute and relative mass of the thymus. All these parameters in the offspring of rats exposed to FA are evidently lower than the control parameters.

Table 1

Parameters of Body and Thymus Mass of Newborn Rats

Group	Parameter	Mean	SD	min	max	t	p
C	BM, g	6.03	0.39	5.27	6.71	–	–
	Abs, mg	12.01	0.36	11.20	12.60	–	–
	Rel, mg/g	2.00	0.15	1.74	2.37	–	–
FA	BM, g	4.75	0.37	4.12	5.35	14.42	<0.001
	Abs, mg	9.31	0.36	8.40	9.80	31.97	<0.001
	Rel, mg/g	1.97	0.17	1.72	2.35	0.78	>0.05

Note: BM – body mass of small rats, Abs – absolute mass of the thymus; C – control; Rel – relative mass of thymus; FA – formaldehyde

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Histological examination under low magnification shows oval shape of the thymus lobes. The number of septa is low. Within the latter, as well as between the lobes of the thymus, vessels and some amount of adipose tissue are well defined. Examination of the thy-mus of both groups of the rats in a light optical microscope shows a poorly expressed boundary between the cortex and medulla. Nevertheless, it is seen that the center of the lobules is less intensely stained as compared to their peripheral sections (Figures 1, 2).

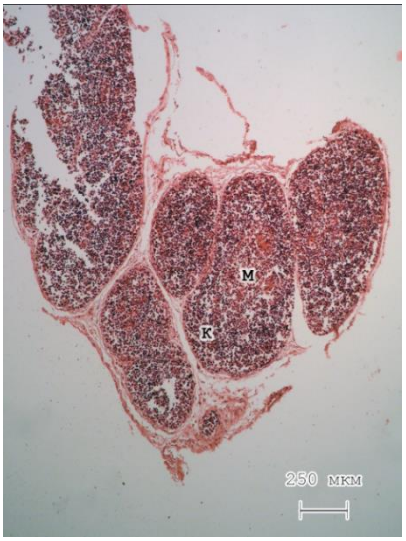

Fig. 1. Thymus of a newborn rat of the control group.
The objective x4. Hematoxylin and eosin

Note: the boundary between the cortex and medulla is not clearly defined. C – cortex; M – medulla

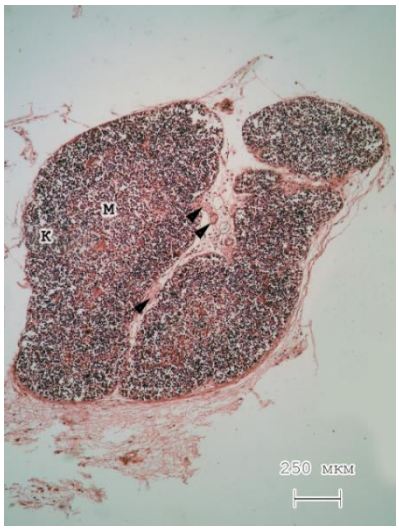

Fig. 2. Thymus of a newborn rat of the FA group
The objective x4. Hematoxylin and eosin

Note: the boundary between cortex and medulla is more clearly defined in comparison with the control. C – cortex; M – medulla

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The structure of the thymus of rats in the light optical microscope in both groups does not practically differ from each other. The karyolemma of large lymphocytes due to a less intense staining of their nucleus is visualized surrounded by oxyphilic cytoplasm and is often determined as a thin strip of different thickness. Besides, in the cortex there are also found epithelioreticulocytes of irregular shape in a small amount. In some preparations their processes are quite clearly visible (Figures 3, 4).

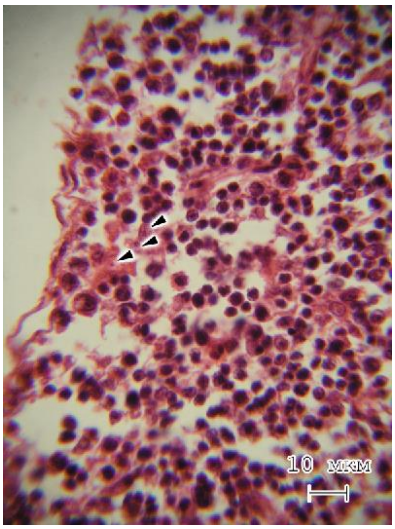

Fig. 3. Thymus cortex of a newborn rat of the FA group
The objective x100. Hematoxylin and eosin

Note: Lymphoblasts in the subcapsular zone are visible; arrows point to epithelial reticulocytes

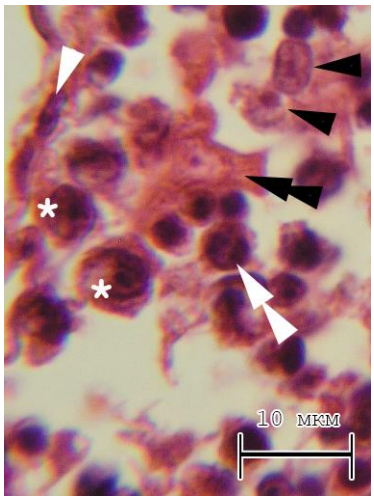

Fig. 4. Subcapsular zone of thymus cortex of a newborn rat of the FA group
(enlarged section of Figure 3)
The objective x100. Hematoxylin and eosin

Note: Asterisks point to lymphoblasts. Single black arrows show epithelial reticulocytes having an oval-shaped nucleus. In the center of a poorly stained nucleus, a nucleolus is visible. A double black arrow points to an irregularly shaped epithelial reticulocyte. The processes of the cell are visible. The poorly colored nucleus in the center contains a nucleolus. A single white arrow points to the nucleus of the fibroblast capsule. The double white arrow shows mitosis of a thymocyte

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The nuclei of these cells look lighter in comparison with those of lymphocytes. Their shape varies from oval to irregular. As a rule, in the nucleus of these cells, more often in the center, one nucleolus is present. The number of lymphocytes in the medulla decreases and therefore epithelial cells are visualized better. In the medulla, thymocytes are represented mainly by medium and small- size cells. Their nuclei have an intense basophilic staining. The cytoplasm stains oxyphilic and the cytolemma sometimes forms clearly visible protrusions. The nuclei of the medullary epithelial reticulocytes are weakly granular and are of a pale basophilic color. Mitoses of thymocytes and epithelial cells are observed both in the cortical and, to a lesser extent, in the medullary substance. Small foci of pycnotic lymphocytes are detected in the inner zones of the thymus cortex of rats of both groups. Hassal bodies were not determined either in the control or in the experimental group.

The number of cells in the cortical and medullary substance of the thymus of rats of the FA group was below the control values by 1.39% (t=1.37; p=0.174), 0.78% (t=0.92; p=0.361), respectively (Figure 5).

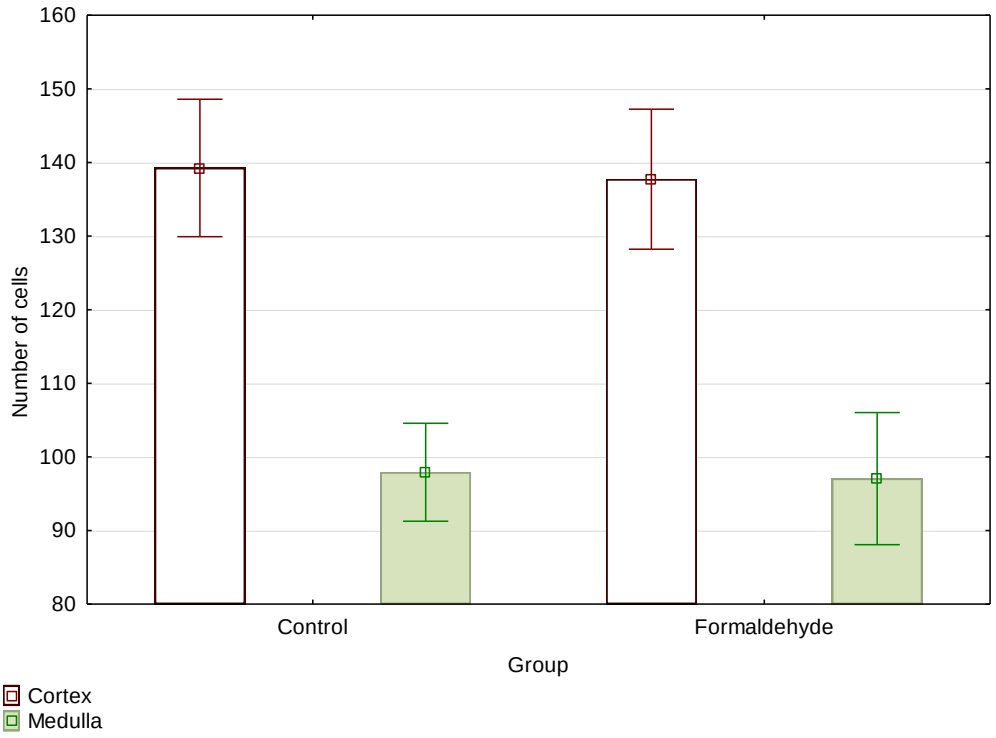

Fig. 5. The number of cells of the cortex and medulla of the thymus of a newborn rats on an area 2500 μm^2 (segment – ± 2 standard deviations)

Discussion

Epidemiological studies link the effect of FA with a high rate of miscarriages, menstrual irregularities, congenital malformations, decreased birth weight, and infertility in both humans and animals [13]. However, other authors criticized such results that were obtained in studying of small samples or due to their incorrect interpretation [14]. A recent histomorphological study showed that FA induces toxic changes in the structure of the placenta in mice leading to dysfunction of the latter and to a decrease in fetal weight [15]. An increase in the level of FA in the atmosphere and in residential premises has become a serious toxicological public health problem.

FA is known to react with many biomolecules such as proteins, nucleic acids and amino acids. This can lead to DNA crosslinking with proteins with formation of

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complexes that can accumulate in the tissues of placenta and fetus [16]. These formations accumulated in the placenta can produce an adverse effect on trophoblast and thus lead to syncytiotrophoblastic hormonal dysfunction.

The experimental conditions of the presented study led to a significant decrease in the body mass of newborn rats, which agrees with the results of the previous studies [15] and can be explained by disorders of the hormonal activity of the placenta [3]. It is known that gonadotropin acting in the paracrine and autocrine way, causes differentiation of the villous trophoblast throughout pregnancy, and human placental lactogen and placental growth hormone are involved in the adaptation of the mother to pregnancy and are involved in controlling fetal growth [17].

Reduction of the absolute mass of the thymus in the offspring of females exposed to FA was quite natural due to the fact that the body mass of the newborn rats was below the control parameters. The absence of statistically significant differences between the relative mass of the thymus in the control and experimental groups of the animals testifies in favor of a proportional reduction of both the body weight of newborn rats and the weight of the organ. According to J.D. Thrasher, et al. [18], FA adversely affects zygotes/embryos and bone marrow cells. The results of this study showed embryonic cell damage and a high mortality rate, while bone marrow cells showed increased parameters of chromosomal aberrations and aneuploidy. Similar observations of the chromosomes of peripheral blood lymphocytes were recorded in students of medical educational institutions exposed to FA. It was found that exposure to FA in concentration of 1.5-3.17 mg/m^3 causes an increase in the frequency of exchange with sister chromatids, aberrations, and formation of micronuclei. Formaldehyde concentrations less than 1 mg/m^3 do not affect lymphocyte chromosomes, but cause an increase in CD19 and a decrease in CD4, CD5. In their work, J.D. Thrasher, et al. [18] showed the involution of lymphoid tissue and the appearance of numerous centers of extramedullary hematopoiesis in the offspring of females exposed to FA in concentration of 0.012 and 1.0 mg/m^3. These data do not agree with the results of the present study, in which no pronounced changes in the thymus were detected in the light microscope, probably, due to the different concentration of FA used in these studies.

FA causes abnormalities in the buffer capacity of blood leading to metabolic acidosis. Blood pH in the fetus decreases, while hypercapnia, combined with iron deficiency, increases in both the fetus and the mother. In addition, there is a deficiency of iron in the fetus and in the mother. Such changes, as a rule, lead to increased mortality of embryos [18]. FA probably affects embryos and fetuses also through a detrimental effect on mitochondria. Oxygen stress caused by the generation of free radicals is associated with apoptotic cell death and fragmentation of the mitochondrial genome [19]. In addition, FA can initiate apoptosis through the formaldehyde generators (for example, alkylating agents) [20]. Thus, such congenital defects as low birth weight, are probably best explained by intrauterine oxidative stress and mitochondrial damage resulting from exposure of maternal organism to FA.

Conclusion

The obtained data show that the effect of FA inhalation on female rats during the entire period of pregnancy leads to a significant reduction of body mass and the absolute mass of thymus of newborn rats. Here, the relative mass of the thymus did not show any significant changes. Examination of the structure of thymus in the light optical microscope did not reveal significant deviations in the morphology of the organ in the offspring of animals exposed to FA.

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Информация об авторе [Author Info]

Ваш Ирина Юрьевна – соискатель кафедры анатомии человека, оперативной хирургии и топографической анатомии, ГУ ЛНР Луганский государственный медицинский университет им. Святителя Луки, Луганск, Луганская Народная Республика. [**Irina Yu. Vash** – Degree Seeker of the Department of Human Anatomy, Operative Surgery and Topographic Anatomy, St. Luke Lugansk State Medical University, Lugansk, Lugansk People's Republic.]
SPIN: 4171-5115, ORCID ID: 0000-0001-9289-6788, Researcher ID: AAB-4877-2020. E-mail: IrinaVash1988@mail.ru

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