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PRENATAL CHANGES IN THE CONTRACTILE APPARATUS OF RAT VENTRICULAR MYOCARDIUM AFTER CHRONIC ALCOHOL INTOXICATION OF MATERNAL ORGANISM

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The object of research was the hearts of rat embryos and fetuses from the 14th day of prenatal ontogenesis to birth. Quantitative parameters of cardiomyocyte myofibrils in different zones of the ventricular myocardium were determined using transmission electron microscopy. It has been established that chronic alcohol intoxication of the maternal organism leads to inhibition of sarcomerogenesis and general damage of the spatial organization of the contractile apparatus of ventricular cardiomyocytes of embryos and fetuses. On the 14th day of embryogenesis, the absolute particular surface area of myofibrils and the degree of their orientation are significantly lower than normal values in different zones of the myocardium. In the period from the 14th day of embryogenesis to birth, the processes of alteration of cardiomyocyte contractile apparatus are manifested to varying degrees depending on the localization. In newborn rats after intrauterine exposure to alcohol, the absolute particular surface area of myofibrils in cardiomyocytes of the intramural zone exceeds normal values by 36.7% ($p<0.05$) in the left ventricle and by 35.8% ($p<0.05$) in the right ventricle. The values of the degree of myofibril orientation in the composition of all zones of the myocardium of both ventricles are significantly lower than normal values. The greatest damage is observed in the intramural zone of the free wall of both ventricles.

Key words: *prenatal ontogenesis, rats, alcohol intoxication, heart, ventricular myocardium, myofibrils, ultrastructure.*

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Introduction.

The alarming rate of growth in the level of alcohol consumption among women of reproductive age in combination with unplanned pregnancy increases the risk of developing fetal alcohol syndrome and other prenatal and perinatal disorders many times over [1, 2, 3]. It is assumed that high levels of ethanol, even temporary, at a critical stage of embryonic development can be more harmful than the entire duration of maternal alcohol intoxication [4]. Experimental and clinical studies have shown that ethanol freely diffuses through the placenta and quickly accumulates in the amniotic fluid, which leads to numerous fetal injuries [5]. Alcohol and its metabolites are teratogenic and toxic to all fetal organs, including the heart [6, 7]. During prenatal development, they affect a wide range of metabolic pathways – from changes in the activity of DNA methyltransferases, which control the total epigenetics of fetal development [8], to the activation of oxidative stress, which changes the nature of protein synthesis, mitochondrial respiration, and the regulation of cell apoptosis [9]. Previous studies have shown that autophagy may also be a mechanism of ethanol cardiotoxicity due to adenosine monophosphate-activated protein kinase, with subsequent impairment of glucose and lipid metabolism [10].

Morphological and molecular biological studies have proven that long-term ethanol inhibits the synthesis and causes degradation of structural proteins of cardiomyocytes, especially myofibril proteins – actin, myosin, titin, nebulin, troponin, tropomyosin [11, 12, 13]. This leads to damage of myofibrils, their thinning, disorientation, loss of integrity, distortion of the configuration of telophragms and intercalated disks [11, 14]. It has been demonstrated that in cardiomyocytes under the conditions of ethanol action, myofibrils can be de-

termined both in a relaxed and in an excessively constricted state. Significant thinning of myofibrils or their lysis along with the reduction of A- and I-discs are found in the perinuclear zone of the cardiomyocyte [15, 16]. Cardiac myocytes can develop functional and structural compensatory mechanisms capable of minimizing or restoring ethanol-induced damage. In particular, in the early stages of chronic alcoholization, cellular hypertrophy is observed to compensate for contractile dysfunction, however, long-term exposure to ethanol leads to irreversible processes in the structure and functioning of cardiomyocytes, and the intracellular organelles most sensitive to the toxic effects of alcohol are myofibrils and mitochondria [11, 15].

Although research with the introduction of various methodological approaches made it possible to obtain data on the main stages of the development of the contractile apparatus of the myocardium and the mechanisms of its energy resource [17, 18, 19, 20, 21], information on the formation and distribution of myofibrils in cardiomyocytes under the influence of toxic factors, including under the conditions of intrauterine intoxication with ethanol, remain the subject of considerable debate. Difficulties consist, first of all, in the identification of myofibrillogenesis events after the administration of toxic substances to experimental animals. Solving this task, which is related to the study of maternal alcoholization on the heart of embryos and fetuses, can be used as basic knowledge for further study of the spectrum of cardiovascular diseases as a result of prenatal alcohol exposure.

The aim of the study.

To determine the dynamics of prenatal changes in the ultrastructural parameters of the myofibrils of cardiomyocytes of the heart ventricles of rats after chronic alcoholization of the maternal organism.

Object and research methods.

The object of the research was the hearts of offspring of white outbred rats at different periods from birth to adulthood. The model described in the publication of Becker H.C. was used to reproduce the conditions of intrauterine alcohol intoxication [22]. Three stages of chronic alcoholization were carried out using different concentrations of ethanol. The duration of the first stage was two weeks. During this time, the animals were on a normal diet, but instead of water they received a 5% ethanol solution. At the second stage (also 2 weeks), female rats received a 15% ethanol solution. After fertilization, the third stage began, during which pregnant female rats received a 20% ethanol solution for 2 weeks. On the 14th day after fertilization, the females were deprived of access to the ethanol solution and received ordinary drinking water. Time-dated rats (23 intact animals and 26 rats of the experimental group) were euthanized with an overdose of ether anesthesia 14, 16, 18, and 20 days after fertilization, followed by removal of embryos and fetuses for added ultrastructural analysis. Research was carried out in accordance with the principles of the Declaration of Helsinki, adopted by the General Assembly of the World Medical Association (2000), "General Ethical Principles of Experiments on Animals", approved by the First National Congress on Bioethics (Kyiv, 2001) in accordance with the provisions of the "European Convention for the Protection of Vertebrate Animals used for experiments and other educational purposes" [23].

To study the structures of the contractile apparatus of cardiomyocytes, samples of the myocardium of the right (RV) and left ventricles (LV) and the interventricular septum were fixed at a temperature of +2°C for 3-4 hours in a 2.5% glutaraldehyde solution in a 0.2M phosphate buffer (pH =7.4) followed by postfixation for 1 hour in a 1% buffered (pH=7.4) solution of osmium tetroxide ("SPI", USA), dehydration in alcohols of increasing concentration and propylene oxide, and production of epoxy blocks using an epon-araldite composition. Ultrathin sections placed on Mesh Regular Grid 200 ("SPI", USA) copper reference grids. Double contrast was performed according to the Reynolds method [24]. The study was performed using transmission electron microscope PEM-100-01 ("SELMI", Ukraine) at an acceleration voltage of 65-90 kV and primary magnifications from 2000 to 25000 according to the standard scheme [24, 25]. Sections of the preparations were studied according to the original modification of the method [26] and were photo-documented on monochrome "Agfa" film with subsequent digitization with a Canon CanoScan 9000F scanner.

Quantitative assessment of ultrastructural changes was carried out using morphometric determination of the absolute particular surface area of myofibrils and the degree of their orientation using the ImageJ 1.47v software package according to the principles of stereometry [27]. In order to analyze the influence of ethanol on the formation of the contractile apparatus, cardiomyocytes of the subepicardial (SEP), intramural (IMZ) and subendocardial (SEN) zones of the wall of the left (LV) and right ventricle (RV), as well as the left (LVP) and right parts (RVP) of the interventricular septum (IVS).

The valuation of the statistical significance of the differences between the experimental group (after the influence of ethanol on the maternal organism) and the group of intact animals (experiencing normal development) was assessed using Student's t-test. If the empirical distribution obtained in the study did not conform to the normal law, the estimation of differences between samples was evaluated using the non-parametric Wilcoxon test for related samples and Mann-Whitney for unrelated samples, or using the Van der Waerden rank test. During the biostatistical processing of the obtained quantified results, all necessary calculations were performed in the shell of an Excel spreadsheet using the appropriate formulas and using the licensed program STATISTICA (version 6.1; serial number AGAR 909 E415822FA).

Research results and their discussion.

On the 14th day of prenatal development, the values of absolute particular area in cardiomyocytes of both ventricles of intact rats did not differ significantly. The value of this indicator in the SEP of LV exceeded by 51.1% ($p<0.05$) the level of this parameter in RV. The value of the parameter in RVP of the septum was not significantly different from the level of this indicator in LVP. In the animals of the experimental group, the value of this parameter on the 14th day of prenatal ontogeny was statistically significantly lower than normal values: in SEN – by 37.8% in LV and by 38.3% in RV, in IMZ – by 23.6% in LV and by 23.9% in RV, in SEP – by 21.0% in LV and by 21.7% in RV. The difference between the values of the parameter in IVS on the 14th day in comparison

with the norm was 22.8% (p<0.05) in LVP and 24.7% (p<0.05) in RVP.

In intact animals on the 14th day of prenatal ontogenesis, the values of the degree of orientation of myofibrils in different zones of LV and RV significantly differed among themselves. In SEN, the values of the indicator were higher by 110.6% (p<0.05) in LV and by 119.0% (p<0.05) in RV compared to the corresponding values of the SEP parameter of the free wall of the ventricles, as well as by 69 .8% (p<0.05) in LV and 55.9% (p<0.05) in RV in comparison with IMZ. The degree of orientation of myofibrils on the 14th day after ethanol exposure was significantly lower than the value of the indicator during normal development: in SEN – by 39.2% in LV and by 38.0% in RV, in SEP – by 23.0% in LV and on 22.6% in RV, in IMZ – by 22.5% in LV and by 21.1% in RV. The difference between the indicator values of IVS on the 14th day in comparison with the norm was 23.0% (p<0.05) in LVP and 20.8% (p<0.05) in RVP.

On the 15th day of prenatal ontogenesis, the values of the absolute particular surface area of myofibrils in SEP and IMZ had significant differences, while the values of the parameter in SEN of both ventricles did not differ statistically significantly from the indicators of the previous day of development. The value of the parameter in SEP on the 15th day exceeded the level of the indicator on the 14th day by 68.3% (p<0.05) in LV and by 21.4% (p<0.05) in RV; in IMZ – by 18.8% (p<0.05) in LV, and by 34.1% (p<0.05) in RV. The difference between the indicator values of IVS on the 15th day, in comparison with the 14th day, was 37.8% (p<0.05) in LV and 49.4% (p<0.05) in HSH. After alcohol intoxication in the myocardium of embryos on the 15th day of prenatal ontogenesis, the value of the studied parameter in SEP was statistically significantly increased in LV by 68.9% and in RV – by 21.2%, in IMZ – by 21.8% in LV and by 37.5% in RV, in LV SEN – by 23.0% compared to the corresponding values of the parameter established on the 14th day of prenatal ontogenesis. The value of the parameter in SEN of LV and in both parts of IVS was not significantly different from the corresponding values on the 14th day of prenatal development. In the ventricular myocardium of rats of the experimental group on the 15th day of prenatal ontogenesis, in comparison with normal development, the value of the absolute particular surface area of myofibrils in SEN decreased by 35.6% (p<0.05) in LV and by 35.4% (p< 0.05) in RV, in IMZ – by 21.7% (p<0.05) in LV and by 21.9% (p<0.05) in RV, in SEP – by 20.8% (p <0.05) in LV and by 21.9% (p<0.05) in RV. After the effect of alcohol, the value of the parameter was lower by 21.1% (p<0.05) in LVP and by 22.3% (p<0.05) (p<0.05) in RVP compared to the norm.

Under conditions of normal development, on the 15th day of prenatal ontogenesis, compared to the 14th day, the values of the degree of orientation of myofibrils in SEP and IMZ had significant differences, while the value of the parameter in SEN was not statistically significantly different from the previous period of the study. The value of the parameter in SEP on the 15th day exceeded the level of the indicator on the 14th day by 84.0% (p<0.05) in LV and by 107.1% (p<0.05) in RV, in the IMZ – by 56.2% (p<0.05) in LV and 59.9% (p<0.05) in RV, by 89.7% (p<0.05) in LVP and 75.8% (p< 0.05) in the RVP of the septum. The value of the parameter on the 15th day after the effect of ethanol significantly exceeded the value of the indicator of the previous day of development: in IMZ – by 50.2% in LV and by 54.8% in RV, in SEP – by 81.6% in LV and by 113.0% in RV. However, the level of the parameter in the SEN of both ventricles did not change statistically significantly compared to the 14th day. The degree of orientation of myofibrils in cardiomyocytes of LVP of the septum increased by 91.6% and in RVP by 78.8% compared to the previous day of prenatal development. The values of the degree of orientation of myofibrils in almost all zones of the ventricular myocardium changed significantly compared to the norm. In particular, the value of the parameter decreased significantly: in SEN – by 40.2% in LV and by 38.8% in RV, in IMZ – by 23.9% in LV and by 23.4% in RV, in SEP – by 21, 0% in LV and by 20.1% in RV. As part of the IVS, the values of the parameter changed statistically significantly by 22.1% (p<0.05) in LVP and by 20.6% (p<0.05) in RVP compared to the norm.

On the 16th day of prenatal ontogenesis, compared to the 15th day, the values of the absolute particular surface area of myofibrils in SEN did not change significantly, while the value of the parameter in SEP increased statistically significantly by 140.2% in LV and by 119.0 % in RV, in IMZ – by 64.7% in LV and by 41.8% in RV. The value of the indicator on the 16th day increased by 37.8% (p<0.05) in LVP and by 49.4% (p<0.05) in RVP compared to the 15th day. In the rats of the experimental group, during the 16th day, the values of the absolute particular surface area of myofibrils changed significantly relative to the level of the indicator of the previous day of development. The value of the indicator increased sharply in SEP by 145.2% in LV and by 124.5% in RV, in IMZ – by 64.1% in LV and by 51.9% in RV, in SEN – by 26.0% in RV, in IVS – by 69.8% in LVP and by 33.3% in RVP. The values of the parameter in the SEN of RV did not differ significantly from the value of this indicator in the previous period of development. During the 16th day of prenatal ontogenesis after the influence of alcohol on the maternal organism, the level of the absolute particular surface area of myofibrils changed significantly compared to the norm: the values of the indicator were statistically significantly reduced in SEN by 35.6% in LV and by 35.0% in RV, in IMZ – by 21.9% in LV, and by 20.7% in RV, in SEP – by 21.6% in LV, and by 20.0% in RV. The values of the parameter in the IVS were statistically significantly reduced by 20.2% in the LVP and by 20.0% in the RVP of the septum.

Compared with the 15th day of prenatal ontogenesis, the degree of orientation of myofibrils on the 16th day with normal development increased in SEP of LV by 57.2% (p<0.05), in IMZ of LV by 33.8% (p< 0.05), in SEN of LV by 37.5% (p<0.05) and in ventricular septal LVP by 35.8% (p<0.05). On the contrary, the values of the parameter in RV did not change statistically significantly in all studied zones of the myocardium. In the experimental group of animals the level of the degree of orientation of myofibrils on the 16th day of prenatal ontogenesis, in comparison with the values of the previous day of development, after the effect of ethanol increased statistically significantly in SEP of LV – by 36.9%, in IMZ of LV – by 39.8%, in SEN of LV – by 40.0%, in LVP of septum – by 39.1%. However, the value of the parameter in cardiomyocytes of all zones of the right ventricle did not change statistically significantly compared to the data of the previous day of prenatal ontogenesis. On the 16th

day of prenatal development after exposure to ethanol, the value of the parameter was significantly lower than the corresponding normal level: in SEN – by 38.0% in LV and 38.2% in RV, in SEP – by 20.2% in LV and on 21.0% in RV, in SEP – by 20.2% in LV and by 21.1% in RV. The difference between the indicators of IVS on the 15th day in comparison with the norm was 20.3% ($p<0.05$) in LVP and 20.4% ($p<0.05$) in RVP. A significant decrease in indicators in the subendocardial zone on the 16th day of prenatal ontogenesis testified to a more intensive effect of alcoholization of the maternal organism on the development of this particular part of the ventricle.

On the 18th day of prenatal development, the values of the absolute particular surface area of myofibrils in all zones of the ventricular myocardium of rats differed significantly from the values of the 16th day of the embryonic development. The value of this parameter on the 18th day exceeded the value of the indicator on the 16th day: in SEN – by 24.1% ($p<0.05$) in LV and 26.7% ($p<0.05$) in RV, in IMZ – by 40.4% ($p<0.05$) in LV and by 27.8% ($p<0.05$) in RV, in SEP – by 29.8% ($p<0.05$) in LV and by 18.1% ($p<0.05$) in RV. The value of the parameter in the IVS of the heart of the animals during the studied period of normal development increased statistically significantly by 26.7% in LVP and by 25.5% in RVP compared to the value of the parameter on the 16th day. After alcohol intoxication the level of the absolute particular surface area of myofibrils in SEP and IMZ significantly differed compared to the 16th day of development. The value of the indicator increased in SEP of LV by 20.6%, in IMZ – by 36.3% in LV and by 27.9% in RV, in SEN – by 42.3% in LV and by 30.0% in RV, in IVS – by 26.5% in LVP and by 25.0% in RVP. The value of the parameter in the SEP of RV did not significantly differ from the indicator of the 16th day of embryogenesis. The value of the parameter in SEN cardiomyocytes decreased by 30.4% ($p<0.05$) in LV and by 30.1% ($p<0.05$) in RV, in IMZ – by 24.2% ($p<0.05$) in LV and by 20.6% ($p<0.05$) in RV, in SEP – by 25.3% ($p<0, 05$) in LS, and by 20.6% ($p<0.05$) in RV.

With normal development, the level of the degree of orientation of myofibrils on the 18th day of prenatal ontogenesis in all zones of the ventricular myocardium, except for the SEN and IVS, did not statistically significantly differ from the indicators on the 20th day. The difference between the values of IVS on the 18th day was 38.3% in LV and 24.4% in RV ($p<0.05$), as well as 26.5% ($p<0.05$) in SEN in LV and in RV – 25.5% ($p<0.05$), in comparison with the indicators of the previous period of the study. On the 18th day of rat embryogenesis after exposure to ethanol, the degree of orientation of myofibrils in SEN cardiomyocytes was statistically significantly increased in LV by 22.9% and in RV by 22.0%, compared to the indicators of the previous day of development. At the same time, the values of the parameter in IMZ and SEP, as well as in the left and right parts of the IVS did not reliably differ from the corresponding indicators on the 16th day of embryogenesis. In the animals of the experimental group, on the 18th day of prenatal development, the values of the degree of orientation of myofibrils were significantly lower than the normal level in all zones of the myocardium: in SEN – by 40.7% in LV and by 40.0% in LV, in IMZ – by 30.3 % in LV and by 21.0% in RV, in SEP – by 32.5% in LV and by 20.7% in RV, in IVS – by 30.5% in LVP and by 24.5% in RVP of the septum.

The values of the absolute particular surface area of myofibrils on the 20th day of normal development increased statistically significantly, in comparison with the indicators of the 18th day, in SEP – by 33% in LV and by 30.6% in RV, in IMZ – by 20.7 % in LV and 26.8% in RV, in SEN – by 26.1% in LV and by 33.1% in RV, in IVS – by 31.8% in LVP, and by 33.1% in RVP of the septum. After exposure to ethanol in rats of the experimental group on the 20th day of prenatal ontogenesis, in comparison with the 18th day of embryogenesis, the values of the absolute particular surface area of myofibrils in SEP increased statistically significantly by 46.7% in LV and by 33.3% in RV, in IMZ – by 46.6% in LV and by 59.8% in RV, in SEN – by 126.0% in LV and by 140.2% in RV. The value of the indicator in this period of development increased significantly in LVP by 60.0% and in RVP by 60.5% compared to the 18th day of embryogenesis. The destructive effect of alcohol intoxication of the mother's organism was manifested in a significant increase in the values of the absolute particular surface area of myofibrils: in SEN – by 25.1% in LV and by 22.3% in RV. However, the level of this parameter in SEP of both ventricles, in other studied zones of the ventricular myocardium, did not change significantly compared to the norm.

Under conditions of normal development, on the 20th day of prenatal ontogenesis, the degree of orientation of myofibrils increased by 38.2% ($p<0.05$) in SEN in LV and by 29.3% ($p<0.05$) in RV in comparison with the 18th day. Also, the indicators reliably increased in the IMZ in LV by 58.3% and in RV by 68.9%. The values of the degree of orientation of the myofibrils of the IVS increased by 33.1% ($p<0.05$) in LVP and 35.7% ($p<0.05$) in RVP compared to the indicators of the previous period of the study. In the experimental group of animals during the 20th day, the values of the degree of orientation of myofibrils were statistically significantly different from the indicators of the 18th day. The values of the parameter increased in IMZ – by 51.9% in LV and by 70.6% in RV, in SEN – by 34.4% in LV and by 34.5% in RV, in IVS – by 24, 0% in LVP and by 42.0% in RVP. Compared with normal cardiogenesis, the value of the cardiomyocyte parameter in SEN was significantly reduced by 41.5% in LV and by 40.2% in RV, in IMZ – by 31.1% in LV and by 20.2% in RV, in SEP – by 32.7% in LV and by 21.8% in RV. The degree of orientation in LVP of IVS was lower than the normal value by 32.4% ($p<0.05$) and in RVP of IVS – by 21.0% ($p<0.05$).

The values of the absolute particular surface area of myofibrils of newborn rats, compared to the 20th day of prenatal ontogenesis, in SEN were statistically significantly increased by 57.2% in LV and by 56.9% in RV, in SEP – by 75.8% in LV and by 59.1% in RV, in IMZ – by 94.1% in LV and by 67.8% in RV. In IVS the level of the parameter in newborn intact rats exceeded the value of the indicator on the 20th day of development by 27.7% in LVP and by 19.9% in RVP. In newborn rats of the experimental group, compared to the 20th day of embryonic development, the values of the absolute particular surface area of myofibrils in the SEP increased statistically significantly by 109.0% in LV and by 90.0% in RV, in the IMZ – by 204.0 % in LV and by 133.0% in RV, in SEN – by 27.2% in LV and by 27.1% in RV. The value of the indicator of newborn rats significantly increased in the LVP by 34.4% and in the RVP – by 31.4% compared to the 20th day of embryogenesis. The level of the abso-

lute particular surface area of myofibrils in cardiomyocytes of newborn rats of the experimental group was not significantly different from the corresponding values of the indicator during normal development in SEN, SEP of both ventricles and in IVS. However, the value of the parameter in IMZ exceeded normal values by 36.7% ($p<0.05$) in LV and by 35.8% ($p<0.05$) in RV.

With normal development, the value of the degree of orientation of myofibrils of cardiomyocytes in newborn rats, compared to the 20th day of prenatal ontogenesis, did not change significantly in both parts of the IVS. The degree of orientation of myofibrils in the SEN significantly increased by 20.8% in LV and by 28.7% in RV, in SEP – by 26.9% in LV and by 35.8% in RV, in IMZ – by 25.0% in LV and by 27.7% in RV. The values of the parameter in newborn rats of the experimental group increased significantly in comparison with the values of the indicator on the 20th day of development: in SEN – by 61.6% in LV and 59.6% in RV, in SEP – by 44.9% in LV and on 21.0% in RV. The difference between the values of the parameter of the cardiomyocytes of the IVS in comparison with the 20th day of embryonic development was 36.0% ($p<0.05$) in LVP and 25.0% ($p<0.05$) in RVP, however, the value of the parameter in the IMZ was statistically weight did not change relative to the 20th forehead of prenatal ontogeny. After the effect of ethanol on the maternal organism in newborn rats, the values of the degree of orientation of myofibrils in the all zones of the myocardium of both ventricles differed significantly from normal values. In particular, the value of the parameter was significantly lower than the norm: in SEN – by 21.8% in LV and by 22.6% in RV, in IMZ – by 36.4% in LV and by 36.5% in RV, in SEP – by 20.7% in LV and 24.2% in RV. Also, the values of the parameter in IVS were statistically significantly lower than the equivalent values of intact rats by 20.4% in LVP and by 23.4% in RVP.

Thus, the nature of myofibril damage after prenatal exposure to alcohol is consistent with the ideas about the toxic effect of this factor on the structure and function of cardiomyocytes, and the quantitative characteristics of prenatal changes obtained in this study significantly clarify the pathological rearrangements of the contractile apparatus as the leading consequences of damaged cardiogenesis. The fact that the dynamics of inhibition of sarcomerogenesis and a general decrease in the content of myofibrils after the influence of alcohol is strictly related to damage to the architecture of the contractile apparatus of cardiomyocytes and to data on the destruction of mitochondria, as was proved by the results on models of hypoxic situations and under other conditions, draws attention toxic effects. The results obtained in this work confirm and detail the general model of myofibrillogenesis, in particular with regard to those leading ultrastructures that are most sensitive to the long-term toxic effects of alcohol in the prenatal period.

Conclusions.

1. Chronic alcohol intoxication of the maternal organism leads to suppression of sarcomerogenesis and general damage to the spatial organization of the contractile apparatus of cardiomyocytes of the ventricles of the heart of embryos and fetuses. On the 14th day of embryogenesis, the absolute particular surface area of myofibrils is lower than normal values in SEN – by 37.8% in LV and by 38.3% in RV, in IMZ – by 23.6% in LV and by 23.9% in RV, in SEP – by 21.0% in LV and by 21.7% in RV. The degree of orientation of myofibrils is also significantly lower than the indicators of intact rats in the corresponding zones of the myocardium.

2. In the period from the 14th day of embryogenesis to birth, the processes of alteration of the contractile apparatus of cardiomyocytes are manifested to varying degrees depending on the localization in the zones of the ventricular wall and interventricular septum.

3. In newborn rats after intrauterine exposure to alcohol, the absolute particular surface area of myofibrils in cardiomyocytes of the IMZ exceeds normal values by 36.7% ($p<0.05$) in LV and by 35.8% ($p<0.05$) in RV. The values of the degree of orientation of myofibrils in the composition of all zones of the myocardium of both ventricles are significantly lower than normal values. The greatest damage is observed in the intramural zone of the free wall of both ventricles.

Prospects for further research.

Electron microscopic analysis of intracellular structures involved in the energy supply of the contractile function of cardiomyocytes after exposure to alcohol intoxication is expected.

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ПРЕНАТАЛЬНІ ЗМІНИ СКОРОТЛИВОГО АПАРАТУ МІОКАРДА ШЛУНОЧКІВ ЩУРІВ ПІСЛЯ ХРОНІЧНОЇ АЛКОГОЛЬНОЇ ІНТОКСИКАЦІЇ МАТЕРИНСЬКОГО ОРГАНІЗМУ

Твердохліб І. В., Марченко Д. Г.

Резюме. Відомості про формування скоротливого апарату серця і розподіл міофібрил у кардіоміоцитах після внутрішньоутробної інтоксикації етанолом залишаються предметом значних дискусій.

Мета цієї роботи – визначення динаміки постнатальних змін ультраструктурних параметрів міофібрил кардіоміоцитів шлуночків серця щурів після хронічної алкоголізації материнського організму.

Об'єктом дослідження слугували серця ембріонів і плодів щурів у терміни від 14-ї доби пренатального онтогенезу до народження. За допомогою трансмісійної електронної мікроскопії визначені кількісні параметри міофібрил кардіоміоцитів різних зон міокарда шлуночків.

Встановлено, що хронічна алкогольна інтоксикація материнського організму призводить до пригнічення саркомерогенезу та загального ушкодження просторової організації скоротливого апарату кардіоміоцитів шлуночків серця ембріонів і плодів. На 14-у добу ембріогенезу абсолютна питома площа поверхні міофібрил і ступінь їх орієнтації значно поступаються нормальним значенням у різних зонах міокарда. У період від 14-ї доби ембріогенезу до народження процеси альтерації скоротливого апарату кардіоміоцитів виявляються в різному ступені в залежності від локалізації.

У новонароджених щурів після внутрішньоутробної дії алкоголю абсолютна питома площа поверхні міофібрил у кардіоміоцитах інтрамуральної зони перевершує нормальні величини на 36,7% ($p<0,05$) у лівому шлуночку та на 35,8% ($p<0,05$) у правому шлуночку. Значення ступеня орієнтації міофібрил у складі всіх зон міокарда обох шлуночків суттєво поступаються нормальним значенням.

Найбільше ушкодження спостерігається в інтрамуральній зоні вільної стінки обох шлуночків.

Ключові слова: пренатальний онтогенез, щури, алкогольна інтоксикація, серце, міокард шлуночків, міофібрили, ультраструктура.

PRENATAL CHANGES IN THE CONTRACTILE APPARATUS OF RAT VENTRICULAR MYOCARDIUM AFTER CHRONIC ALCOHOL INTOXICATION OF MATERNAL ORGANISM

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Abstract. Information on the formation of the heart contractile apparatus and the distribution of myofibrils in cardiomyocytes after intrauterine ethanol intoxication remain a subject of considerable debate.

The aim of this work is to determine the dynamics of prenatal changes in the ultrastructural parameters of the myofibrils of ventricular cardiomyocytes in the rat heart after chronic alcoholization of the maternal organism.

The object of research was the hearts of rat embryos and fetuses from the 14th day of prenatal ontogenesis to birth. Quantitative parameters of cardiomyocyte myofibrils in different zones of the ventricular myocardium were determined using transmission electron microscopy.

It has been established that chronic alcohol intoxication of the maternal organism leads to inhibition of sarcomerogenesis and general damage of the spatial organization of the contractile apparatus of ventricular cardiomyocytes of embryos and fetuses. On the 14th day of embryogenesis, the absolute particular surface area of myofibrils and the degree of their orientation are significantly lower than normal values in different zones of the myocardium. In the period from the 14th day of embryogenesis to birth, the processes of alteration of cardiomyocyte contractile apparatus are manifested to varying degrees depending on the localization.

In newborn rats after intrauterine exposure to alcohol, the absolute particular surface area of myofibrils in cardiomyocytes of the intramural zone exceeds normal values by 36.7% ($p<0.05$) in the left ventricle and by 35.8%

(p<0.05) in the right ventricle. The values of the degree of myofibril orientation in the composition of all zones of the myocardium of both ventricles are significantly lower than normal values.

The greatest damage is observed in the intramural zone of the free wall of both ventricles.

Key words: prenatal ontogenesis, rats, alcohol intoxication, heart, ventricular myocardium, myofibrils, ultrastructure.

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