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ЭМБРИОГЕНЕЗ НЕЙРОНАЛЬНЫХ ЭЛЕМЕНТОВ (ГЛИОБЛАСТОВ И ГАМКА-РЕЦЕПТОРОВ) НЕЙРОИММУННОЙ СИСТЕМЫ МОЗГА ЧЕЛОВЕКА ПРИ ПРЕНАТАЛЬНОМ ВЛИЯНИИ АЛКОГОЛЯ

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Резюме. Воздействие алкоголя вызывает дисбаланс нейроиммунной функции и приводит к нарушению развития мозга. Алкоголь активирует сигнальные пути врожденного иммунитета в мозге. Нейроиммунные молекулы, экспрессируемые и секретируемые глиальными клетками головного мозга (микроглия, олигодендроглия), изменяют функцию нейронов и стимулируют в дальнейшем развитие алкогольного поведения. В передаче нейроиммунных сигналов участвуют различные сигнальные пути и клетки мозга. Глиальные клетки являются основными источниками иммунных медиаторов в головном мозге, которые отвечают на иммунные сигналы в центральной нервной системе и выделяют их. Целью настоящего исследования было изучение нейрональных элементов: морфометрических параметров глиобластов, синаптических структур и свойств синаптосомальных ГАМКА-бензодиазепиновых рецепторов нейроиммунной системы в эмбриогенезе мозга человека при перинатальном воздействии алкоголя. Выявлены изменения глиобластов в ткани мозга эмбрионов и плодов человека в условиях хронической пренатальной алкоголизации с увеличением срока беременности по сравнению с контрольными подгруппами: достоверное увеличение среднего количества глиобластов, длины периметров пресинаптических терминальных структур, постсинаптической плотности, пресинаптические терминальные области были значительно меньше ($p < 0,01$) в исследуемой группе, чем в контрольной группе сравнения. Воздействие этанола приводит к снижению аффинности ГАМКА-бензодиазепиновых рецепторов, что влияет на нейрональную пластичность, связанную с развитием и дифференцировкой клеток-предшественников (глиобластов и нейробластов) в период эмбриогенеза головного мозга человека и приводит к подавлению ГАМКергической функции в головном мозге. Это вызывает нарушение взаимосвязей эмбриональных клеток в головном мозге, приводит к чрезмерным явлениям апоптоза из-за активации глиальных клеток нервной ткани, нарушению нейроиммунной

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функции в развивающемся мозге, изменениям нейрональных цепей, а также к изменению баланса возбуждающих и тормозных эффектов, что оказывает влияние на функциональную активность в центральной нервной системе. Активация глии – это компенсаторная реакция, вызванная нейропластическими изменениями, направленная на адаптацию развивающегося мозга эмбриона и плода в условиях нейротоксичности и гипоксии под воздействием пренатальной алкоголизации материнского организма и влияния этанола на плод. Динамика изменений глиальных элементов и рецепторной активности в нервной ткани эмбрионов и плодов человека в условиях пренатального воздействия алкоголя свидетельствует о более выраженном влиянии алкоголя на самые ранние стадии развития эмбриона человека, что имеет большое практическое значение при планировании беременности и недопустимость алкоголизации матери во избежание негативных последствий у потомства.

Ключевые слова: эмбриогенез, нейроиммунная система, головной мозг, алкоголь, глиобласт, ГАМКА-рецептор, синапс

EMBRIOGENESIS OF NEURONAL ELENENTS (GLIOBLASTS AND GABAA RECEPTORS) IN THE HUMAN BRAIN NEUROIMMUNE SYSTEM UNDER PRENATAL ALCOHOL EXPOSURE

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Abstract. Exposure to alcohol causes imbalances in neuroimmune function and impaired brain development. Alcohol activates the innate immune signaling pathways in the brain. Neuroimmune molecules expressed and secreted by glial cells of the brain (microglia, oligodendroglia) alter the function of neurons and further stimulate the development of alcoholic behavior. Various signaling pathways and brain cells are involved in the transmission of neuroimmune signals. Glial cells are the main sources of immune mediators in the brain, which respond to and release immune signals in the central nervous system. The aim of this study was to study neuronal elements: morphometric parameters of glioblasts, synaptic structures and properties of synaptosomal GABAA-benzodiazepine receptors of the neuroimmune system in the embryogenesis of the human brain under perinatal exposure to alcohol. Changes in glioblasts in the brain tissue of human embryos and fetuses were revealed under conditions of chronic prenatal alcoholization with an increase in gestational age compared with control subgroups: a significant increase in the average number of glioblasts, the length of the perimeters of presynaptic terminal structures, postsynaptic density, presynaptic terminal regions were significantly less ($p < 0.01$) in the study group than in the control comparison group. Exposure to ethanol leads to a decrease in the affinity of GABAA-benzodiazepine receptors, which affects neuronal plasticity associated with the development and differentiation of progenitor cells (glioblasts and neuroblasts) during embryogenesis of the human brain and leads to suppression of GABAergic function in the brain. This causes a disruption in the interconnection of embryonic cells in the brain, leads to excessive apoptosis due to the activation of glial cells of the nervous tissue, disruption of neuroimmune function in the developing brain, changes in neuronal circuits, as well as a change in the balance of excitatory and inhibitory effects, which affects the functional activity in the central nervous system. Glial activation is a compensatory reaction caused by neuroplastic changes aimed at adapting the developing brain of the embryo and fetus under conditions of neurotoxicity and hypoxia under the influence of prenatal alcoholization of the maternal organism and the effect of ethanol on the fetus. The dynamics of changes in glial elements and receptor activity in the nervous tissue of human embryos and fetuses

under conditions of prenatal exposure to alcohol indicates a more pronounced effect of alcohol on the earliest stages of human embryo development, which is of great practical importance in planning pregnancy and the inadmissibility of alcoholization of the mother in order to avoid negative consequences in offspring.

Keywords: embryogenesis, neuroimmune system, brain, alcohol, glioblast, GABAA receptor, synapse

Introduction

Exposure to ethanol during pregnancy causes fetal alcohol spectrum disorders (FASD). The most severe form of FASD is fetal alcohol syndrome (FAS), characterized by growth retardation, facial abnormalities, and neurobehavioral changes. In some patients with FASD, only a fraction of the FAS characteristics, such as cognitive and behavioral disorders not associated with facial dysmorphias, are detected. High and moderate prenatal alcohol exposure is associated with behavioral and cognitive problems in childhood and adolescence associated with mood disorders, working memory deficits, attention deficits, increased aggression, and behavior changes [6, 16, 17]. Important brain regions and neuronal circuits involved in the development of alcohol use desorders (AUD) have been identified [10]. Exposure to alcohol causes imbalances in neuroimmune function and leads to impaired brain function. Alcohol activates innate immune signaling pathways in the brain and stimulates alcohol consumption [4, 11]. Neuroimmune molecules expressed and secreted by cerebral glial cells alter neuronal function and stimulate alcoholic behavior [11, 16]. New insights into molecular mechanisms underlying AUD have led to the identification of new therapeutic targets associated with immunity. Various indigenous pathways and brain cells are involved in the transmission of neuroimmune signals [5, 13, 18]. The innate immune system in the central nervous system (CNS) is concentrated in brain cells that are capable of recognizing and responding to changes in the neuronal microenvironment. Microglia and astrocytes are the main immune mediators in the brain that respond to and release immune signals in the central nervous system [11, 12, 13, 14, 15]. Chemokines, cytokines, and pathogen-associated molecular patterns activate various families of cerebral immune receptors. Microglia activation includes morphological transformation into a phagocytic, macrophage-like cell being visualized by increased size of cell bodies, decreased duration of processes and increased immunoreactivity. The investigation of developing disorders of the neuroimmune system shape the basis for designing effective pharmacotherapeutic agents. Alcohol affects the neuronal regulation of innate immunity in brain cells by altering gene expression and molecular pathways regulating neuroinflammation.

The aim of the study consists in examining neuronal elements: glioblast morphometric parameters, synaptic structures and properties of synaptosomal GABAA/benzodiazepine receptors of the neuroimmune system in embryogenesis of the human brain under perinatal alcohol exposure.

Materials and methods

The study involved women aged 25 to 41 years (mean – 37 years), divided into two groups. The first group included participants, without somatic or mental pathology, who did not drink alcohol before (within the 1 month before conception) and during pregnancy. The second group consisted of women who suffered from I-II degree alcoholism for 3 to 13 years. All participants in the study had previously undergone treatment for alcoholism, but in the period preceding collection of biomaterial for the study, none of them received disulfiram. The material was obtained during operations for the artificial termination of pregnancy in maternity hospitals and gynecological departments of hospitals in the city of Tomsk. All procedures were carried out in accordance with the conditions and instructions of the ethics committee and do not contradict to the Declaration of Helsinki 1975 or the provisions of the 2000 revision. During the operations, samples of embryonic material were obtained ranging from 8 to 15 weeks of intrauterine development. Based on the gestational age and confirmed alcohol consumption by mothers, 2 groups were formed, divided into subgroups. Group Alcohol (A) was formed by collecting biomaterial obtained from women suffering from alcohol dependence and included 2 subgroups: A1 – embryos at the age of 8-9 weeks of gestation and A2 – at the age of 10-11 weeks of gestation. Both subgroups included 6 samples. The Control group (K) was formed in a similar way from apparently healthy women: K1 – 9 weeks and K2 – 10-11 weeks, 7 samples per each group.

Microscopic and morphometric assay

The study of the samples was carried out by using light microscope Axio Scope A1 (Carl Zeiss, Germany) with sample preparation: preliminary fixation in 0.5%- glutaraldehyde solution in 0.1 M sodium phosphate buffer (pH 7.3-7.4) and additional fixation in 1%-osmium oxide solution. Subsequent processing included dehydration in alcohols of ascending concentrations and embedding in epoxy

resins (Araldite). Next, the obtained samples were cut by using an Ultracut-E ultratome (Reichert, Austria) into semi-thin sections (0.5-1 μm) and stained with toluidine blue (Nissl's dye) according to the standard technique. In this study, we used slice cut at the level of the intermediate layer. During the subsequent photography, a Canon G10 digital camera was used. Sections were also stained by hand using saturated aqueous solution of uranyl acetate (1.5 h at 56 °C) and a 2% solution of lead citrate (30 min at room temperature) and viewed under a JEM 100CX electron microscope (Jeol). The cells of the intermediate layer of the GM cortex, which were isolated by focusing on the ventricular layer, were examined electronically-microscopically.

The analysis of changes in morphometric parameters was used to identify quantitative changes among glioblasts of the human cerebral cortex at different stages of intrauterine development, as well as to reveal a correlation between the degree of differentiation of the listed tissue components and degree of the pathological factor (alcohol) impact on the process of tissue development. For this, the AxioVision 4.8 software was used, in which the diameter and area of each individual element, as well as the average number of units of cellular or vascular structures per unit of cut area, were determined.

Electron microscopy examined in the intermediate layer of the forebrain wall, neuro- and glioblasts (including microglia cells). Morphometric analysis was carried out by using photographs of negatives obtained under electron microscope. Images were scanned at 300 dpi and saved in TIFF format, processed with ScionImage for Windows developed at the National Institutes of Health (Scion Corporation), used to assess the regions of presynaptic terminals, their perimeters and the length of postsynaptic densities. In each case, 15-20 photomicrographs of the intermediate layer were analyzed. The measurement results are presented in relative units: the number of pixels to estimate the length and the number of image pixels squared to estimate the areas of synaptic structures.

Radioreceptor assay

Parameters of GABAA / benzodiazepine receptors were studied by the radio-receptor assay of [^{3}H]-flunitrazepam (Amersham) to the synaptosomal membranes of the brain samples tested at concentration range of 0.2-10 nM. The protein concentration in the synaptosomal membranes was 0.3 mg/ml. Non-specific binding was determined in the presence of a non-radioactive ligand at a concentration of 10 μM. Radioactive assay of the amount of bound ligand was performed in a scintillation beta-counter "Rack-beta" ("LKB"). The constant of dissociation of the radio-ligand complex (Kd) and the maximum number of specific binding sites (Bmax) were determined by studying kinetic binding in Scatchard coordinates. To determine the statistical significance, the Statistica 10 program was used with the analysis of the Mann–Whitney test (significant differences at ($p < 0.05$), Student's t-test ($p < 0.01$), correlational relationships were assessed by Spearman analysis.

Results and discussion

The study of the patterns of developing glial cells in the embryonic brain revealed that the numerical indicator of the average area of glioblasts after prenatal alcohol exposure (in the main studied subgroup A1) was significantly lowered compared to control study group (in group K1) (table). The average perimeter of cells significantly differed between groups A1 and K1, where the perimeter of glioblasts in the control group at this time of development (K1) also exceeded that in the main group (A1). The number of cells in the studied samples of the embryonic brain tissue in the main group (A1) significantly exceeded the number of cells in the samples of the control group (K1) (table). Thus, we found that under prenatal alcoholization, the growth of glioblasts in the brain tissue of human embryos at the gestational age of 8-9 weeks was retarded, whereas the number of cells increases, which we consider as a compensatory reaction due to decreased size of glioblasts in the brain tissue of embryos after prenatal alcohol exposure.

TABLE 1. DYNAMICS OF THE NUMERICAL INDICATORS OF GLIOBLASTS IN THE STUDIED GROUPS

Analyzed parameter	Average area, μm²	Average perimeter, μm	Number of cells per 1 mm², pcs
Control 1 (C1)	32.1	23.9	75
Control 2 (C2)	13.3*	15.0*	160
Alcohol 1 (A1)	21.3*	19.1*	121
Alcohol 2 (A2)	12.9**	14.8**	263

Note. *, significant differences compared to Control 1 ($p < 0.05$). **, significant differences compared to Alcohol 1 ($p < 0.05$).

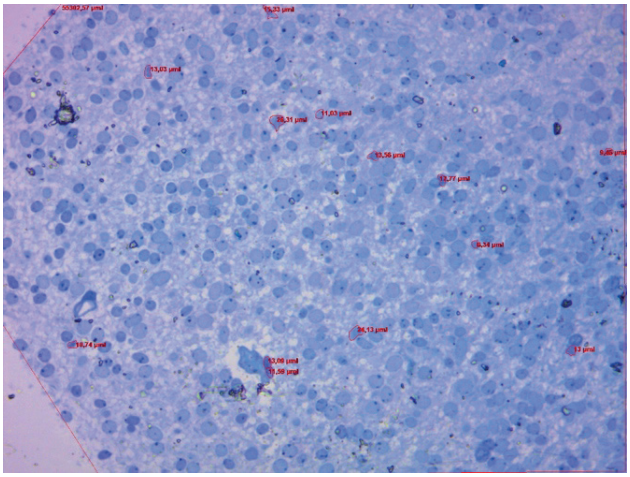

Figure 1. Photo shows a section of the brain tissue of a human embryo at 8-9 weeks of intrauterine development in the process of visualization and obtaining digital indicators of the perimeter of glioblasts and the total perimeter of the section in the AxioVision 4.8 program

Note. Glioblasts, which are asymmetric hyperchromic cells, are highlighted in red. The photo also shows rounded normochromic neuroblasts. Staining with toluidine blue, magnification ×400.

Regarding human fetal development at 10-11 weeks of gestation, we revealed no significant differences in the size of glioblasts (average area and perimeter of cells) in the control (K2) and main (A2) study groups; however, the tendency to an increase in the average number of glioblasts per unit area in tissue the embryonic and fetal brain exposed to the prenatal alcohol (in the main subgroups (A1 and A2)) was preserved at all examined stages of development (Table 1, Figure 1). These changes may indicate at retarded development of cellular components with a compensatory increase in their number that might be regarded as a protective, compensatory reaction of glia to prenatal ethanol exposure.

The results obtained indicate at morphometric changes in the human embryonic and fetal brain tissue under conditions of chronic prenatal alcoholization: along with increasing gestational age, a significant increase in the average number of the studied structures vs. control subgroups was observed. The dynamics of changes in glial elements in the nervous tissue of human embryos and fetuses exposed to prenatal alcohol indicates a more pronounced effect of alcohol at the earliest stages of human embryonic development, which is of great practical importance in planning pregnancy and the inadmissibility of maternal alcoholization in order to avoid negative consequences in offspring.

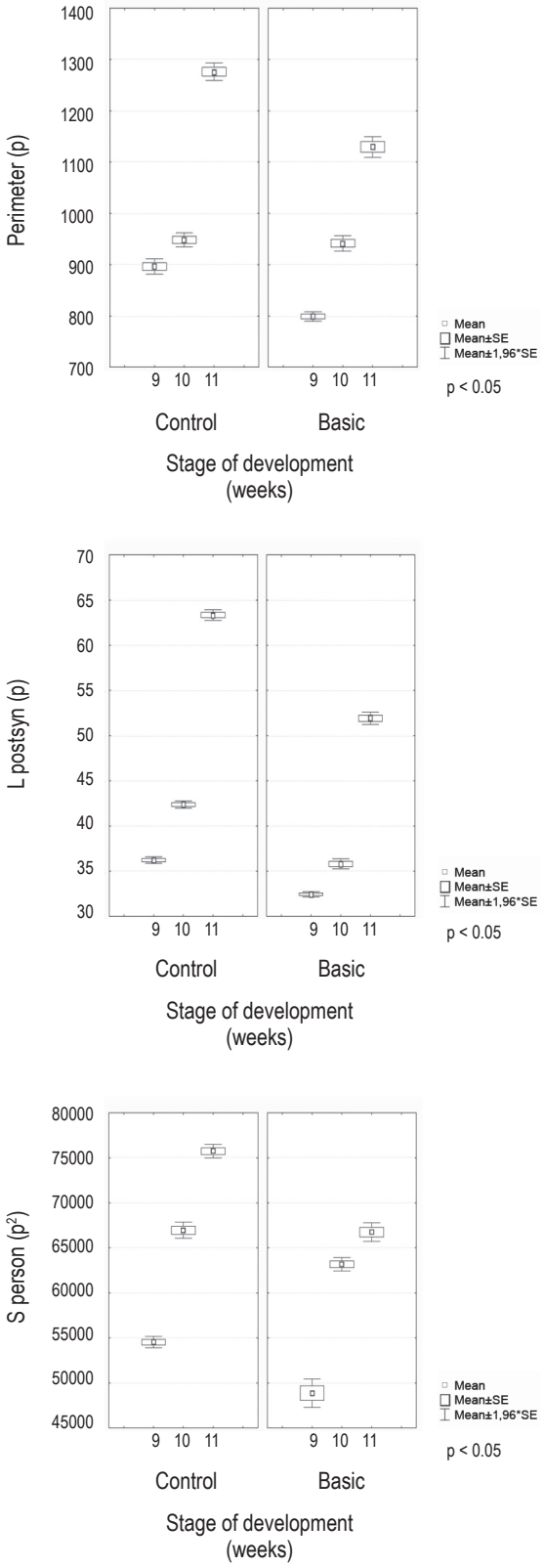

Figure 2. Statistical analysis of morphometric indices of presynaptic terminals (S, presynaptic terminal area; L, postsynaptic density length; P, presynaptic terminal perimeter) in the human embryonic brain at various stages of development in the control and main (prenatal alcoholization) groups

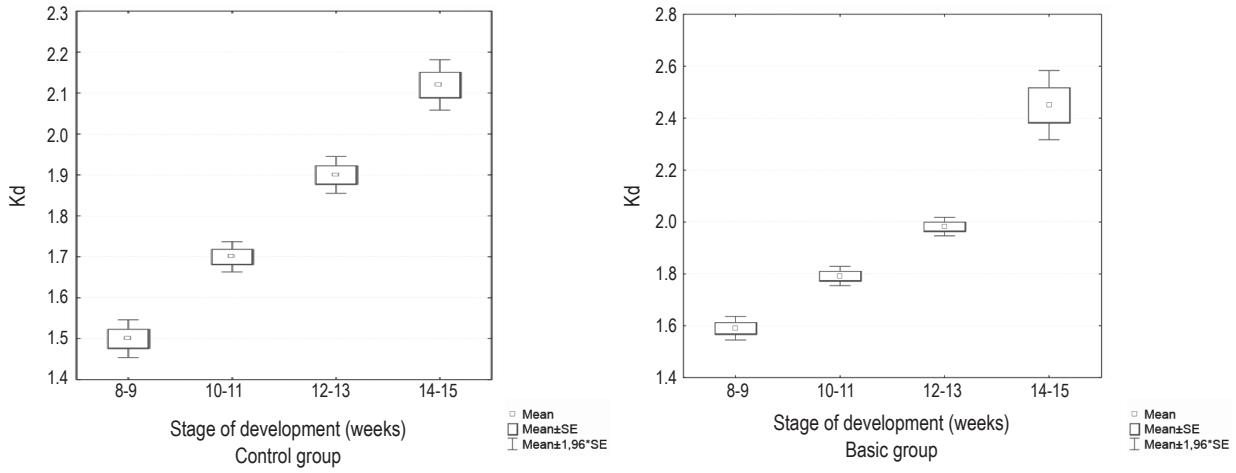

Figure 3. Statistical analysis of the binding parameter (Kd) of [^{3}H] flunitrazepam with membranes of synaptosomes of the human embryonic brain in the control and experimental groups

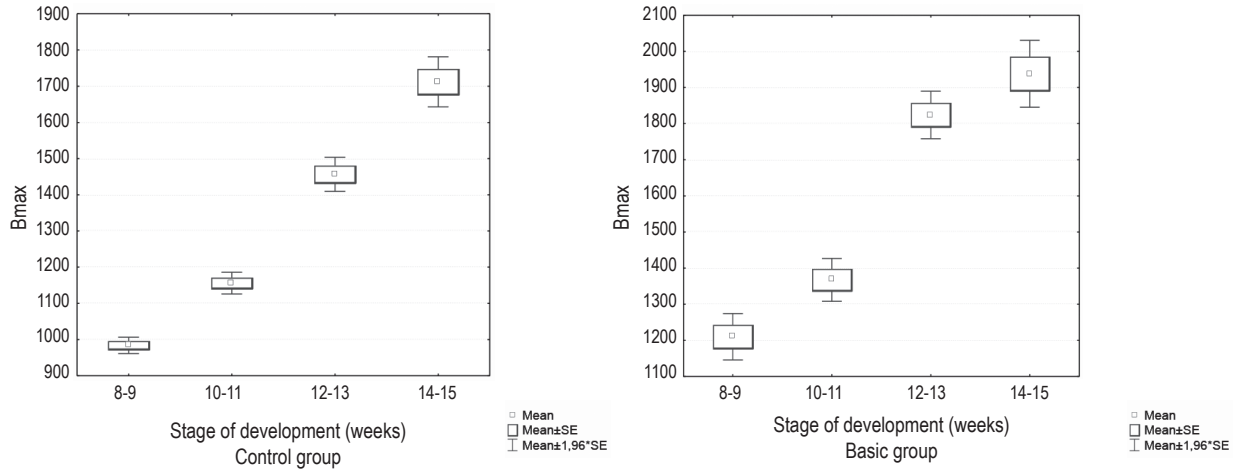

Figure 4. Statistical analysis of the binding parameter (Bmax) of [^{3}H] flunitrazepam with membranes of synaptosomes of the human embryonic brain in the control and experimental groups

Electron microscopic examination with the assessment of morphometric parameters of cerebral tissue synaptic structures

The quantitative morphometric parameters of synaptic contacts of the developing human brain in the main and control groups were significantly differed. Alcohol has a modulating effect on the formation of intercellular contacts.

We observed that the length of presynaptic terminal perimeters, postsynaptic densities, presynaptic terminal areas were significantly shortened ($p < 0.01$) in the study group vs. controls group (Figure 2).

Radioreceptor assay of GABAA / benzodiazepine receptors of synaptic structures of the brain tissue

Radioreceptor analysis of binding the selective ligand 3H flunitrashpam with the fraction of the brain tissue sample membranes from human embryos and fetuses in normal conditions and after prenatal alcohol exposure showed that the properties of benzodiazepine receptors (BDR) in synaptosomal membranes of GM embryos and human fetuses were distinct at different developmental periods (Figure 3, 4).

In the control group, the affinity of receptors in the brain of human embryos and fetuses decreased during the development period of 8-9-12-13 weeks: dissociation constant (Kd) increased from 1.5 to 2.12 nM was noted. In the experimental group, the affinity of benzodiazepine receptors in the brain of embryos and fetuses was lower at all studied developmental stages compared to the control group, which was expressed as increased absolute values of Kd from 1.59 to 2.45 nM. The dynamics of changes was not linear in the experimental group. The number of receptors in the human embryonic and fetal brain

from the control group during developmental period of 8-9-12-13 weeks increased with some deceleration at the age of 10 weeks of gestation. The number of receptors in the experimental group was significantly higher than in the control at all studied stages of development of embryos and fetuses, which can be compensatory in nature with decreased receptor affinity. The dynamics of changes in the number of receptors was not linear, which was more prominent in the experimental group.

The data obtained indicate about a structural and functional relationship between the development of receptors and the synaptogenesis of young cellular elements of the human cerebral cortex upon maternal pregnancy-related alcoholism, which is expressed in the simultaneous appearance of structural synaptic and benzodiazepine receptor components overlapped with maturation delay at the week 10 of development. Consequently, the ability of normal functioning and allosteric modulation of the GABAA/benzodiazepine receptor complex in synaptic membranes, regulating the general processes of inhibition in the central nervous system вусдштуы. We have found that alcohol consumption by mothers during pregnancy affects the properties of GABAA/benzodiazepine receptors and may subsequently affect the development of the embryonic and fetal central nervous system.

The observed decrease in the formation of synaptic structures in the fetal and embryonic brain at different stages of development influenced by maternal alcoholism vs. normal and decreased affinity of GABAA/benzodiazepine receptors with increased receptor density can be considered as a compensatory reaction aimed at adaptation of the embryonic and fetal nervous system to conditions of functional insufficiency in GABAergic neurotransmission (Table 2).

TABLE 2. CORRELATION ANALYSIS OF MORPHOMETRIC PARAMETERS OF SYNAPTIC STRUCTURES AND THE NUMBER OF BENZODIAZEPINE RECEPTORS IN THE BRAIN TISSUE OF EMBRYOS (BDR) AT DIFFERENT DEVELOPMENTAL STAGES, M±m

Develop ment period (weeks)	Control group				
	The number of sites of specific binding of [^{3}H]-flunitrazepam with BDR (Bmax), fmol/mg protein	Perimeter of the presynaptic terminal region (P), M±m Pixel	Area of the presynaptic terminal region (S), M±m Pixel^2	Presynaptic length terminal area (L), M±m Pixel	Number of samples (n), pcs Pixel
8-9	984.22±34.92	896.28±63.7 r = 0.80 p = 0.0006	54521±2673 r = 0.79 p = 0.0003	36.21±1.56 r = 0.89 p = 0.0004	9
10-11	1156.00±43.06	948.19±58.2 r = 0.77 p = 0.0004	66964±3833 r = 0.62 p = 0.0002	42.37±1.70 r = 0.87 p = 0.0008	8
12-13	1456.29±63.93	1276.02±73.08 r = 0.83 p = 0.0008	75742±3207 r = 0.76 p = 0.0001	63.33±2.51 r = 0.91 p = 0.0003	7
	Experimental group				
8-9	1210.00±98.36	798.90±40.09 r = 0.78 p = 0.0004	48861±6773 r = 0.64 p = 0.0002	32.45±1.23 r = 0.85 p = 0.0007	9
10-11	1367.40±96.08	941.56±64.44 r = 0.82 p = 0.0006	63178±3168 r = 0.71 p = 0.0001	35.80±2.37 r = 0.88 p = 0.0005	10
12-13	1824.13±94.79	1129.00±86.87 r = 0.79 p = 0.0004	66750±4436 r = 0.70 p = 0.0003	51.90±2.88 r = 0.83 p = 0.0008	8

Our data show that exposure to ethanol reduces the GABAA / benzodiazepine receptor affinity, which affects neuroplasticity associated with the grous (не понятно), differentiation and development of glioblasts and neuroblasts (progenitor cells) during embryogenesis, which causes disruption of the brain embryonic cell interconnections leading to excessive apoptosis phenomena due to activated glial cells, impaired neuroimmune function, changes in neural circuits, altered balance of excitatory / inhibitory effects. Glial activation is a compensatory response caused by neuroplastic changes aimed at adapting the developing embryonic and fetal brain under conditions of neurotoxicity and hypoxia due to ethanol exposure. Microglia provide a fundamental basis for development of normal processes in the nervous system, including neurogenesis [1, 2, 9, 19], as well as the formation, growth and functioning of neuronal elements, such as synapses and receptors [12, 20]. Brain functions are coordinated by the interaction of the main elements in neural circuits: glial elements, receptors and synapses. Cerebral glial cells execute an immune function, contact with synaptic neuronal cell elements, expanding and contracting their processes.

Conclusion

Glia plays a significant role in the developing brain, synapse pruning and regulating the function of nerve circuits. Disturbing glial homeostatic role can lead to neuronal dysfunction and developing pathology. The activation of glial cells during the period of toxic effects or other pathology is a necessary cerebral protective function. Glial cells control neuronal excitation, regulation of synaptic plasticity and release of neurotrophic factors [2, 3, 7]. They surround the somas of highly active neurons in order to reduce excitation, as well as migrate and displace synapses with inhibitory function in neurons of the cerebral cortex to increase the expression of neuroprotective molecules. Thus, changes in microglial activity cause disruption of the normal neuronal activity and increased neurotoxicity caused by ethanol acting on various neuroimmune molecules.

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