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MECHANISMS OF INFLUENCE OF HYPOXIA ON THE ELECTRICAL ACTIVITY OF THE DEVELOPING BRAIN

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ABSTRACT

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REVELANCE

The nervous system, which consumes 20% of oxygen entering the organism, is the most sensitive to oxygen deficiency. At the same time, the responses of different nervous structures to hypoxia are significantly different. The most sensitive to oxygen deficiency are the hippocampus and the cerebral cortex [1,2]. The most resistant to oxygen deficiency is the peripheral nervous system. In particular, hypoxia is great danger for the developing nervous system. Causing morphofunctional changes in the nervous system, hypoxia delays its development[3].

In early ontogeny, hypoxia often occurs in fetal period and childbirth. Usually, chronic hypoxia develops during pregnancy while acute hypoxia does during childbirth. The frequency of hypoxia occurrence in perinatal pathology reaches 21-45%. Hypoxia/ischemia is considered to be one of the main causes of mortality and various disorders in newborns and older children. According to the opinions of some investigators, 75% of perinatal mortality is associated with oxygen deficiency[4,5].

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Under the effects of hypoxia, the developing nervous and glial cells are damaged or die and the volume of intercellular space changes. The structure of the soma, processes and synapses also change. The damage of the axon of a neuron and its myelin disturbs the nerve conduction. Acute hypoxia can lead to a change in the total brain structure [6,7]. The structural changes in the nervous system under the effects of oxygen deficiency can appear immediately after exposure to hypoxia or can be delayed [6].

Under the conditions of oxygen deprivation, the morphofunctional changes in the developing nervous system, first of all, neuron impairment, are a cause of the development of many of the pathologies. Depending on the severity, perinatal hypoxia can lead to the neurological complications and development of severe diseases [8].

In many ways, the nature of the action of hypoxia on the nervous system depends not only on its type, severity, and duration but also on the period of its influence. It is associated with the fact that during ontogenetic development, the sensitivity of the nervous system and its particular structures to oxygen deficiency changes.

According to the data of electrophysiological studies carried out in the literature, it is assumed that the resistance of the nervous system to oxygen deficiency is high in early ontogenesis and

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decreases with development [9]. At the same time, there are facts that contradict this conventional wisdom appearance [10].

Electrophysiological studies carried out in recent years indicate that the resistance of the nervous system to hypoxia also changes in the course of embryogenesis. It (has been) was revealed that the total electrical activity of different areas of the cerebral cortex of baby rabbits reacts ambiguously to oxygen starvation in different periods of intrauterine life, and this reaction changes in the process of ontogenetic development [11, 12]. However, due to the uncertainty of these changes, it is not possible to determine the prenatal life cycle when the nervous system is most sensitive to oxygen deficiency.

The registration of the EEG along with the clinical and morphological methods is a key technique for studying the effects of hypoxia on the nervous system. This is not only due to the highest sensitivity of the total bioelectrical activity of the cerebral cortex to oxygen deficiency but also to the fact that it better reflects the activity of many of the brain structures[13].

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Studying the effects of hypoxia on the electrical activity of the developing cerebral cortex, it is necessary to have an idea of the formation pattern of the latter in ontogeny. It should be noted that development of the total activity of the cortical areas in ontogeny has not been adequately studied.

One of the main tasks in the study of the effects of hypoxia on the brain is to reveal the mechanisms of the change in the EEG. Identification of the pattern and mechanisms of the change in the total activity of the cerebral cortex during oxygen deficiency increases the diagnostic and prognostic significance of the EEG.

Despite the fact that, in recent years, due to the study of the pattern of the changes [13, 14] , diagnostic and prognostic possibilities of the EEG in treating consequences of hypoxia have increased, its informativity in clinical practice is slightly limited. In particular, the EEG does not give exact information on nature of the damage and in case of prenatal hypoxia it is difficult to determine the time of its action. Life expectancy of both children and adults after oxygen deprivation is not always forecasted either. In many cases of the same pathology of the total activity of the cerebral cortex, some patients recovered, but others do not [14].

Revelation of the mechanisms of the action of hypoxia on the EEG can also have theoretical significance. First and foremost, the mechanisms of the change in the EEG are importance for understanding of its genesis. Such studies resulted in identifying the role of particular structures of the nervous system in the total activity of the cerebral cortex and its particular indicators [15].

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The object and subject of research. Changes in the sensitivity of the nervous system to hypoxia during embryogenesis were studied in rabbit and rabbit fetuse.

The purpose and objectives of the study. The purpose of the work is to determine the sensitivity of the nervous system to hypoxia in the embryonic period, as well as in the early postnatal ontogeny, by recording the general activity of the cerebral cortex.

The objective can be achieved through the following tasks:

1. To study the response of the total electrical activity of the cerebral cortex after hypoxia in different periods of fetal life, as well as its change in early postnatal ontogeny.

2. To study the response of the total electrical activity of the cerebral cortex to oxygen deficiency at the end of prenatal life and at the beginning of postnatal life.

3. To identify the development pattern of the total electrical activity of the cerebral cortex in ontogeny on the basis of findings obtained in the control animals.

4. To study the mechanisms of the action of hypoxia on the EEG and its ontogenetic peculiarities.

Research methods. Electrophysiological studies were performed on the 28-day-old rabbit fetuses and the 10-, 20-, 30-day-old rabbit pups after severe hypoxia (5% of O_2). The first group of fetuses was exposed to hypoxia during the whole embryonic period of prenatal life (1^{st} - 8^{th} days), the second one was done during the prefetal period (8^{th} - 18^{th} days), and the third one was done during the fetal period (18^{th} - 28^{th} days). All the 10-, 20- and most 30-day-old rabbit pups were also exposed to oxygen deprivation during embryonic, prefetal and fetal periods. The rest of 30-day-old rabbit pups were exposed to hypoxia on 24^{th} – 28^{th} days of prenatal life or on 1^{st} – 5^{th} days of postnatal life.

An electrocorticogram (ECoG) of the auditory cortex of both hemispheres was studied. In 28–day-old fetuses, along with the auditory cortex, the total electrical activity of the sensorimotor cortex was also studied. Electrical activity was isolated monopolarly from the surface of the cerebral cortex using nichrome needle electrodes

(thickness 0,3 mm). The reference electrode was fixed in the nasal sinus of the fetus.

The spectral and amplitude analysis of the ECoG was performed using analyzer of Medicor Company and a "Neuron-Spectrum-2" computer. Standard δ–, θ–, α–, β1–, and β2-waves were analyzed. The epochs of analysis for each animal were 30 sec. Reliability of the findings was measured according to Student's t-test.

Main dissertation statements to be defended:

1. In our research, the patterns of development of the total activity of the rabbit auditory cortex in ontogenesis have been established. ECoG by the 30th day of life, during the period when the nervous system is generally formed, acquires definitive indicators.

2. In ontogenesis, differences in the spectral composition of ECoG and its response to hypoxia of different cortical regions appear earlier than is assumed in the literature – even in the embryonic period.

3. In 28–day–old fetuses and 10–, 20-, 30–day-old baby rabbits, hypoxia in different periods of embryogenesis is ambiguously reflected in the total activity of the auditory cortex. In all age groups, after hypoxia in the embryonic period of embryogenesis, the spectral parameters of ECoG deviate slightly from the norm, whereas hypoxia at two later stages of embryogenesis leads to more pronounced, but almost similar changes in spectral parameters. Based on these data, it can be assumed that the nerve structures generating the electrical activity of the rabbit's auditory cortex are more sensitive to lack of oxygen during the prenatal and fetal periods of embryogenesis, compared with the embryonic period of intrauterine life.

4. Oxygen starvation at the end of embryogenesis (days 24-28) and at the beginning of postnatal ontogenesis (days 1-5) in the overall picture and spectrum of the ECoG of the auditory cortex of 30–day–old baby rabbits causes strong and similar changes.

However, after postnatal hypoxia, more fundamental changes are found in the spectrum of electrical activity.

5. Oxygen starvation greatly weakens or eliminates the interhemispheric asymmetry of amplitude–time indicators of ECoG.

6. A new mechanism of susceptibility of the cerebral cortex to hypoxia in early embryogenesis has been proposed. Perhaps the subcortical white matter of the brain plays a significant role in this. Its damage eventually leads to structural changes in the cerebral cortex.

7. It is assumed that one of the main mechanisms of episodic activity of developing neurons is the fluctuation of their membrane potential. 8. The analysis suggests that synaptic inhibition of neurons in the cerebral cortex begins to occur almost simultaneously with the beginning of their generation of background activity. Since the appearance of inhibitory processes, all types of cortical inhibition have been functioning.

9. Under both pathological and normal conditions, the generation of impulse activity of a cortical neuron is regulated by a group of modulating and pacemaker neurons and intracellular mechanisms of the neurons themselves. The neurons included in this association are located in all parts of the nervous system, but are mainly concentrated in phylogenetically ancient subcortical structures. Disruption of the functional group of neurons regulating the level of excitability of cortical neurons is one of the mechanisms for the development of pathological activity on the EEG. Therefore, EEG generation is not a random process, but is partially or completely controlled by the brain itself.

10. It is assumed that the reaction of the total activity of the developing cortex to the effects of hypoxia is realized, both according to mature mechanisms characteristic of early ontogenesis.

Scientific novelty. The registration of the total electrical activity of the cerebral cortex identified the pattern of the change in susceptibility of the nervous system to hypoxia during embryogenesis and early postnatal ontogeny. The novel mechanism

of susceptibility of the cerebral cortex to hypoxia in early embryogenesis was revealed. The studies performed on the control animals identified the development pattern of the total activity of the auditory cortex of the rabbits in ontogeny.

The analysis of the mechanisms of the action of hypoxia on the EEG clarified some issues related to the brain development in ontogeny. As a result, the hypothesis was proposed which explained the episodic nature of the background activity of the developing cortical neurons. The formation patter of the cortical inhibition in ontogeny was identified.

Significant contribution was made to the neurophysiological mechanisms of generation of the total activity of the cerebral cortex. Its generation was proved not to be random and it was regulated by the brain itself under normal and pathological conditions. The novel appearance mechanism of pathological activity in the EEG was proposed. The response of the total activity of the developing cerebral cortex to hypoxia was supposed to realize through the mature and early ontogeny-associated mechanisms.

Scientific and practical significance. The dissertation has theoretical significance for revealing the mechanisms of the action of hypoxia on the EEG and morphofunctional development of the cerebral cortex in ontogeny. The identification of the pattern of the change in the sensitivity of the nervous system to hypoxia during embryogenesis is important for understanding the mechanisms of the brain damage. These findings are of interest for identifying the role of the particular structures of the nervous system in the EEG genesis.

The present work clarified the development mechanisms of the impulse activity of the cortical neurons and identified the pattern of cortical inhibition, which are key issues in the study of the brain development in ontogeny.

Our studies have exclusive importance for understanding the genesis of the electrical activity of the brain. Up to the present moment, it is not known whether the total electrical activity of the cerebral cortex is a random process or has pacemaker characteristics. The performed analysis indicates that under either normal or

pathological conditions, the generation of the EEG is not a random process but partially or completely regulated by the brain.

The present dissertation also has practical significance. The identification of the pattern and the mechanisms of the response of the total electrical activity of the cerebral cortex to hypoxia can significantly increase its informativity in medical practice and, subsequently, increase it prognostic possibilities.

Approbation of the work. The materials of the dissertation were presented at: I Russian Congress of Pathophysiology (Moscow 1996), Scientific-practical conference dedicated to anniversary of T.G.Kadirova (Baku 2003), II Congress of Physiologists of the CIS (Kishinev 2008), and the Azerbaijan Society of Physiologists.

The dissertation materials were set out in 23 scientific articles and 8 theses. The published scientific papers completely reflect the content of the dissertation.

Organization, where the work was performed: Academician Abdulla Garayev Institute of Physiology, Azerbaijan National Academy of Sciences.

The total volume of the dissertation, indicating the volume of the structural divisions of the dissertation separately. The total volume of the dissertation work is 374843 characters (introduction – 20121 characters, results – 92992 characters, discussion – 121725 characters, conclusions – 4912 characters and recommendations – 1008 characters. The work is presented on 307 pages, includes 42 figures and 3 tables. 618 literature sources were used in the dissertation.

MAIN CONTENT OF THE DISSERTATION

The first chapter contains a description of the structural development of the cerebral cortex of rabbit and development of the total activity of the brain in ontogeny. The following parts generalize the data on the action of oxygen deficiency on the morphological development of the nervous system and the EEG development.

The second contains the experimental materials.

1. The effects of hypoxia in different periods of embryogenesis on the amplitude-temporal indices of the ECoG of the auditory cortex of the 28-day-old rabbit fetuses

The performed analysis indicated the presence of all standard waves in the total activity spectrum of the auditory cortex of the control 28-day-old rabbit fetuses. The ECoG was distinguished by stability, and there was no decrease in the amplitude of the waves or appearance of the isoelectric line.

Summarizing the activity indices of the slow δ– и θ–band oscillations and the fast α– and β–waves, we can note the dominance of fast activity in the spectrum. However, the ECoG was distinguished by large slow activity (27.2 %). In the slow spectrum, θ–waves were dominant. The indices of δ– и θ–activity were 11.4±2.1% and 15.8±2.4%, respectively.

In the fast spectrum, β2–band oscillations dominated (33.5±2.6%), which had the highest frequency among the standard waves. β1–waves were slightly less pronounced. The percentage of α–waves among the fast waves was the smallest (15.7±1.8% of the spectrum). (Fig. 1).

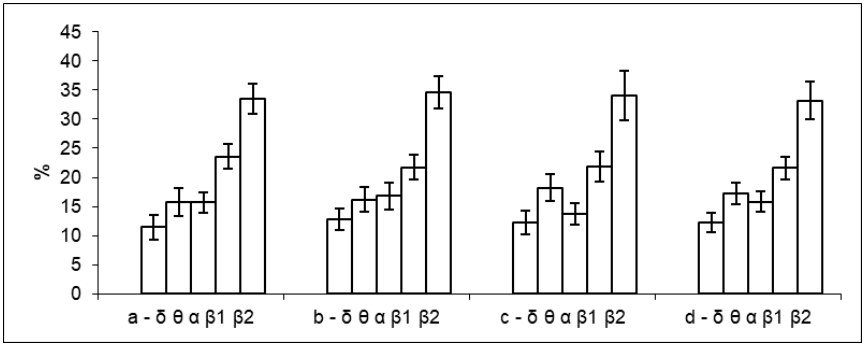

Fig.1. Spectral composition of the ECoG of the auditory cortex of the 28-day-old rabbit fetuses: (a) control, after hypoxia in (b) embryonic, (c) prefetal, (d) fetal periods of embryogenesis. *– ($p<0.05$), **– ($p<0.01$).

The fast waves of the ECoG spectrum of the auditory cortex appeared seldom along the pathway of the potential conduction and mainly superimposed on the slower waves and thereby masked them. Due to that, it was complicated to track the rhythms formed by all standard waves except for α–ones. The dominant rhythm was in δ–band, occupying most of the electrical activity record. Such pattern is specific to the ECoG of the control animals of all age groups.

The ECoG spectrum analysis of the rabbit fetuses exposed to oxygen deprivation in fetal period of embryogenesis did not reveal the significant differences from the control indices. (Fig. 1).

Oxygen deficiency led to minor increase in percentage of the slow waves in the ECoG spectrum. Their percentage (29.0%) was larger than the control by 6.6%. The spectral indices of the waves deviated slightly from the norm (statistical reliability of a change in the indices of the waves of the ECoG spectrum is given in the figures).

Oxygen deprivation during prefetal period of embryogenesis induced more pronounced changes in the spectral composition of the ECoG of the auditory cortex. However, the spectral indices of the standard waves did not deviate significantly from the norm. δ– and, especially θ–waves, got more pronounced. Their percentage being 10.3 % larger than the control made up 30.4% (Fig. 1).

After oxygen deprivation, in fetal period of prenatal life, there were no large changes in the spectral indices of the electrical activity of the auditory cortex. Under the effects of hypoxia, the percentage of the slow spectrum got slightly larger by 7.4%. That increase was associated mainly with θ–activity (Fig. 1).

Regardless of the exposure timing, hypoxia did not affect the pattern and rhythms of the total activity of the cerebral cortex.

It should be noted that in all age groups, the amplitude of the total activity, compared to the spectral composition, weakly responded to oxygen deprivation. Under hypoxia, it deviated slightly

from the norm towards increase or decrease. Those changes were not statistically reliable. The pattern of the amplitude change was not revealed depending on the age or timing of hypoxia exposure. Consequently, the response of the electrical activity of the cerebral cortex could be identified only due to the change in its spectral composition (the amplitude of the ECoG of the control animals is given in the figure 8).

Summarizing the above, we can say that oxygen starvation in the embryonic period of intrauterine life leads to a slight – 2.5% increase in the specific gravity of the slow spectrum. In the subsequent groups, the electrical activity of the auditory cortex of the rabbits reacts more strongly and almost equally to hypoxia. This increase, they have, respectively, is 10.3% and 7.4%. However, the detected spills are not statistically reliable. Consequently, stronger and almost identical changes in the electrical activity of the auditory cortex of 28–day-old rabbit fetuses are detected after hypoxia in the prenatal and fetal periods, and less in the embryonic period of prenatal ontogenesis.

2. The effects of hypoxia in different periods of embryogenesis on the amplitude-temporal indices of the ECoG of the auditory cortex of the 10-day-old rabbit pups

The performed analysis indicated that, in the spectrum of the total electrical activity of the auditory cortex of the 10-day-old rabbit pups, the ratio of slow and fast waves was strongly shifted towards the latter. However, the ECoG was distinguished by high content of low-frequency δ– and θ–waves whose percentage was 25.6%. In the slow spectrum, θ–activity (14.4±2.2%) was dominant and the percentage of δ–waves was slightly less (11.2±1.2%).

Large percentage of α–band oscillations (index: 15.0±1.6%) was also specific to the spectrum of the ECoG. The largest percentage (almost 60 %) of the total activity spectrum was made up by β–waves. Moreover, the percentage of β2-activity was twice as large as β1-activity in the spectrum (41.3±3.6% and 18.1±2.1%, respectively) (Fig. 2).

In embryonic period, oxygen deficiency induced minor changes in the spectrum of the ECoG of the auditory cortex. Only the indices of α– and β2– waves deviated slightly from the norm. The ratio of slow and fast waves in the spectrum remained almost unchanged. The overall percentage (24.6%) of slow δ– and θ–waves was smaller than that in the normal rabbit pups by 3.9% (Fig. 2).

After exposure to hypoxia, the significant changes in the spectrum of the total activity of the auditory cortex were identified in prefetal period of embryogenesis. In particular, the percentage of the slow spectrum got larger by 9.4 % and reached a value of 28.0%. That increase was associated only with δ–activity; θ–activity compared to the other waves did not respond to hypoxia.

This increase was associated only with δ–activity; θ–activity did not respond to hypoxia compared to other waves.

In the fast spectrum, the spectral indices of α– and β1–band oscillations changed significantly. If α–activity decreased by 25.3 %, then β1–activity increased by 22% (Fig. 2).

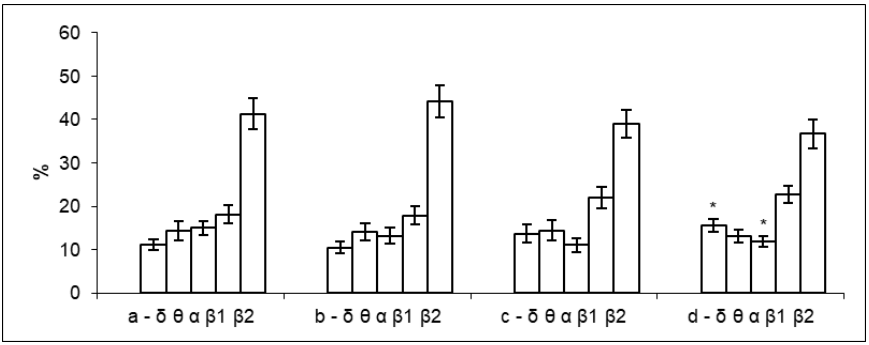

Fig. 2. The spectral composition of the ECoG of the auditory cortex of the 10-day-old rabbit pups: (a) control, after hypoxia in (b) embryonic, (c) prefetal and (d) fetal periods of embryogenesis. *– ($p<0.05$), **– ($p<0.01$).

Oxygen deprivation in fetal period induced significant changes in the spectral composition of the ECoG of the auditory cortex. Under hypoxia, the percentage of the slow waves in the ECoG

spectrum increased up to 28.7 %. There were more significant changes in the composition of the slow spectrum compared to its percentage. Under the effects of oxygen deficiency, the activity index of δ–waves significantly increased by 39 % ($p<0,05$); as for θ–waves, this index was lower by 9 %. Such changes led to the dominance of δ–activity in the slow spectrum compared to the control (Fig. 2).

There were the ambiguous changes also in the fast spectrum. The percentage of α–band oscillations got smaller by almost 20% in the background activity ($p<0,05$). Weakening of β2–activity was less pronounced in contrast to the control indices (precisely by 11%). However, the percentage of β1–waves increased by 25% (Fig. 2).

Oxygen deprivation was slightly reflected in the overall pattern and rhythmical activity of the ECoG only during last 2 periods of fetal life. It induced only increase in δ–rhythms.

Making a comparison, we can say that the lack of oxygen in the last two periods of embryonic life, compared with the previous period, has a stronger and similar effect on the spectral indicators of the total activity of the auditory cortex.

3. The effects of hypoxia in different periods of embryogenesis on the amplitude-temporal indices of the ECoG of the auditory cortex of the 20-day-old rabbit pups

The performed analysis showed that in the spectrum of the ECoG of the 20-day-old rabbit pups, the fast waves were dominant, and the percentage of the slow ones was 25.4%. In the slow spectrum, the index of δ–activity made up 11.3±1.5% which was smaller than the index of the dominant θ–activity (14.1±1.3%). The fast β1– and β2–waves had the largest indices in the spectrum of the electrical activity – 19.5±2.2% and 40.7±4.2%, respectfully. The percentage of α–activity was 14.4± 1.7% of the spectrum (Fig. 3).

Under the effects of hypoxia in embryonic period of embryogenesis, slow-wave activity increased in the ECoG spectrum. The increase in the δ– and θ–waves was 21–23% and their spectral indices were 13.9±1.9% and 17.0±1.4%. The overall percentage of

those waves made up 30.9% of the spectrum, which was 21% larger that the norm. Hypoxia also reduced the fast waves (Fig. 3).

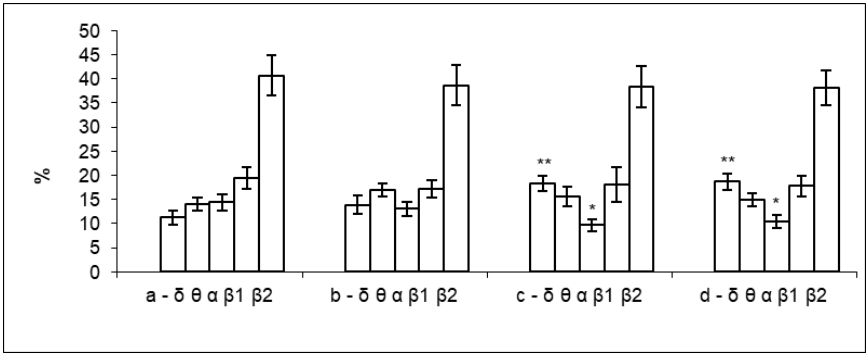

Fig. 3. The spectral composition of the ECoG of the auditory cortex of the 20-day-old rabbit pups: (a) control, after hypoxia in (b) embryonic, (c) prefetal and (d) fetal periods of embryogenesis. *– ($p<0.05$), **– ($p<0.01$).

The analysis of the ECoG of the auditory cortex of the rabbit pups exposed to oxygen deficiency in prefetal period of embryogenesis demonstrated that the percentage of the slow δ– and θ–waves in the spectrum increased by 33% and eventually got 33.9%. In addition, that increase was mainly associated with δ–activity, which became dominant in the slow spectrum ($p<0,001$).

Under the effects of hypoxia, the percentage of the slow α–waves decreased by 1.5 times ($p<0.05$). β–activity was decreasing more moderately. If the index of the β2–waves was lower by 12% in comparison to the control, then the decrease of β1–activity was minor (Fig. 3).

The effects of hypoxia in fetal period of embryonic life induced large changes in the spectral composition of the total electrical activity of the cerebral cortex. In its spectrum, the percentage of low-frequency δ– and θ–waves increased dramatically by 32% and reached 33.6%. The increase in the percentage of the slow spectrum was mainly associated with δ–activity ($p<0,001$). The

index of θ–waves was almost identical to the control. Thus, δ–frequency band became dominant in the slow spectrum.

The decrease in the percentage of all fast waves was identified. If α–activity decreased by 40% ($p<0,001$), then the changes in the spectral indices of β1– and β2–waves were less pronounced (Fig. 3).

The change in the spectral composition of the ECoG under the effects of hypoxia was reflected in the pattern of the latter. In the rabbit pups exposed to oxygen deprivation in embryonic period of embryogenesis, the changes in the electrical activity was manifested only in increase in δ–rhythm. After hypoxia in prefetal and fetal periods of prenatal life with reducing activity of the fast waves in the spectrum, the slow waves, as well as their rhythms became clearer. The dominant δ–rhythm intensified and became continuous. Pathological δ– and θ–rhythms consisting mainly from one frequency were reported in most rabbit pups. Simultaneously there was decrease in activity of the fast rhythms.

Summarizing the presented findings, we can assert that oxygen deficiency in last 2 periods of embryonic life, compared to the first one, induced larger and equal changes in the spectral composition of the total activity.

4. The effects of hypoxia in different periods of embryogenesis on the amplitude-temporal indices of the ECoG of the auditory cortex of the 30-day-old rabbit pups

The analysis showed that, in the spectrum of the ECoG of the 30-day-old rabbit pups, the fast waves were dominant while the percentage of the high amplitude slow waves was only 26.9% of the spectrum. In the slow spectrum, δ– and θ–waves were represented irregularly with dominance of little difference in the latter. The indices of δ– and θ–activities were 12.2±1.8% and 14.7±1.5%, respectfully. In the fast spectrum, the percentage of α–waves was the smallest (15.1±1.7%). The spectral index of β2–waves was twice as high as the index of β1–ones and made up 38.4±4.1% and 19.6±2.1%, respectfully, of the ECoG spectrum. (Fig. 4).

The spectral composition of the ECoG of the rabbit pups exposed to oxygen deprivation in embryonic period of embryogenesis deviated slightly from the norm. First of all, the ratio of the fast and slow waves in the spectrum shifted towards the latter. The percentage of the slow waves being 15% larger than the control made up 31.1% of the spectrum. The increase in the index of the slow waves was associated with both δ– and θ–activities. As it was in norm, the percentage of θ–activity was higher than that of δ–activity (Fig. 4).

Hypoxia slightly affected the indices of α– and β1–waves of the fast spectrum. The percentage of the first ones decreased and of the second ones increased. The β2–activity also reduced slightly.

The analysis revealed the significant changes in the spectral composition of the electrical activity of the auditory cortex under the effects of oxygen deprivation in prefetal period. The total percentage of slow δ– and θ–waves compared to the control increased by 27% and made up 34.2% The increase in activity of slow oscillations was due to δ–waves ($p<0.01$), while the index of θ–waves remained almost unchanged. α–activity reduced by 50% ($p<0.01$), the change in the indices of the other fast waves was less pronounced. The activity index of β1–waves decreased while β2–waves increased. (Fig. 4).

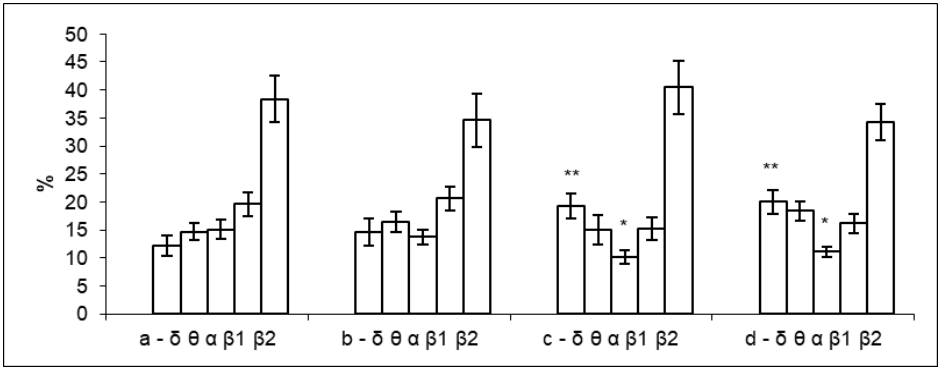

Fig. 4. The spectral composition of the ECoG of the auditory cortex of the 30-day-old rabbit pups: (a) control, after hypoxia in (b) embryonic, (c) prefetal and (d) fetal periods of embryogenesis. *– ($p<0.05$), **– ($p<0.01$).

Hypoxia in fetal period of prenatal life led to large change in the spectral composition of the ECoG in the 30-day-old rabbit pups. The percentage of the slow waves significantly increased up to 38.4% in the spectrum ($p<0.01$). That index was 42.5% larger than the control. The increase in the slow spectrum was associated with both δ– and θ–waves. In addition, δ–activity, whose increase was twice as high as θ–activity ($p<0.001$), became dominant frequency in in the slow spectrum.

Simultaneously, the percentage of all fast waves decreased in the spectrum. The largest changes (by about 30%) occurred in the percentage of α–waves ($p<0.01$), while the smallest ones occurred in β1– and β2-activitis (Fig. 4).

The change in the spectral composition of the ECoG under the effects of hypoxia affected the overall pattern and rhythmic activity of the latter. The overall pattern of the electrical activity in the rabbit pups exposed to oxygen deprivation in embryonic period of embryogenesis was almost identical to the control. However, the dominant δ–rhythms compared to the control became almost continuous. After oxygen deprivation in prefetal and fetal periods of embryonic life, the overall pattern and rhythmic activity of the ECoG changed significantly. Because of the decrease in the percentage of the fast waves in the spectrum, the slow waves and their rhythms became more pronounced. The index of the increasing δ–rhythm equaled 100%. In most animals, δ– and θ–rhythms consisting mainly of one frequency appeared. Simultaneously, β1– and β2–rhythms became less pronounced.

In 30–day-old baby rabbits, the spectral parameters of the ECoG auditory cortex after oxygen starvation in the prenatal and fetal periods of prenatal development, compared with the embryonic period, deviate more from the norm. Accordingly, in the three experimental groups, the slow waves of the spectrum increase by 15%, 27% and 42.5%. In the last experimental groups, the specific

gravity of the slow ECoG spectrum, respectively, is 34.2% and 38.4%. However, the differences between them are statistically unreliable.

Summarizing these data, we can say that the lack of oxygen in the embryonic period of prenatal development leads to minimal changes, while hypoxia at later stages of embryogenesis causes more noticeable and almost identical changes in the spectral parameters of ECoG 30.day rabbits.

5.The effects of hypoxia in different periods of embryogenesis on the amplitude-temporal indices of the ECoG of the sensorimotor cortex of the 28-day-old rabbit fetuses.

The total electrical activity of the sensorimotor cortex of the 28-day-old rabbit fetuses contained all standard waves of the spectrum (Fig. 5). The electrical activity was distinguished by stability and there were no cases of appearance of isoelectric lines.

In the spectrum of the total activity of the cerebral cortex, the fast waves were dominant, while the percentage of the slow waves was the lowest and made up 14.9%. θ–activity was twice as high as δ–activity in the low-frequency spectrum. Their indices were 5.2±0.9% and 9.7±1.2%.

Among all standard waves, the percentage of β-band oscillations was the largest in the electrical activity of the cerebral cortex and made up 64% of the spectrum. In addition, the indices of β1– and β2–waves were almost the same (32.4±3.1% and 31.5±2.9%, respectfully) The large percentage of α–waves was specific to the total electrical activity of the cerebral cortex. Those waves made up 1/5 of all waves of the background activity – 21.2± 2.2% (Fig. 5).

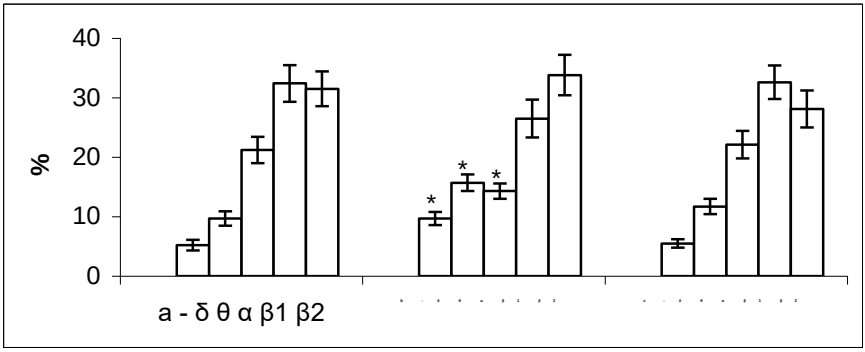

Fig. 5. The spectral composition of the ECoG of the sensorimotor cortex of the 28-day-old rabbit fetuses: (a) control, after hypoxia in (b) prefetal and (c) fetal periods of embryogenesis. *– ($p<0.05$), **– ($p<0.01$).

The analysis revealed the significant changes in the spectral composition of the ECoG of the fetuses exposed to hypoxia in prefetal period of embryonic life. (Fig. 5). First of all, there was a shift towards the slow waves in the ECoG and their percentage increased from 14.9% to 25.4% ($P < 0.01$). The percentage of δ– and θ–waves also increased significantly ($P < 0.05$ and $P < 0.01$, respectfully) (Fig. 5). However, there was more dramatic increase in δ–waves: their index was almost twice as high as that of the control.

Ambiguous changes were also identified in the spectral indices of the fast waves. Under the effects of hypoxia, α–activity was suppressed very much ($P < 0.05$). Statistically unreliable changes were identified in the indices of β1– and β2–waves. The first ones significantly decreased, while the second ones slightly increased. Consequently, the shift towards the slow waves in the spectrum was due to decrease in α– and β1–waves.

The frequency analysis revealed the minor changes in the ECoG of the sensorimotor cortex of the fetuses exposed to hypoxia in fetal period of prenatal life. The percentage of the slow waves in the spectrum increased by 15% and made up 17.2%. It should be noted that, in the previous experimental group, that index increased

by 70%. The percentages of δ–, α– и β1–waves were almost identical to the norm. (Fig. 5).

Oxygen deprivation in prefetal period compared to fetal period of embryogenesis was greatly reflected in the overall pattern and rhythms of the total activity of the sensorimotor cortex. The slow waves and rhythms became clearer.

Summarizing the findings, we can assert that the electrical activity of the sensorimotor cortex of the 28-day-old rabbit fetuses was affected by hypoxia more in prefetal period than in fetal one.

Oxygen deprivation in the prenatal period, in contrast to the fetal period of embryogenesis, is significantly reflected in the overall picture and rhythms of the total activity of the sensorimotor cortex. Slow waves and rhythms get a clearer look. The electrical activity of the sensorimotor cortex of 28–day-old rabbit fetuses reacts more sharply to hypoxia during the pre-fetal period of embryogenesis than the fetal period.

6. The effects of hypoxia in late embryogenesis (24^{th} – 28^{th} days) and early postnatal ontogeny (1^{st} – 5^{th} days) on the amplitude-temporal indices of the ECoG of the auditory cortex of the 30-day old rabbit pups

Oxygen deprivation on 24^{th} - 28^{th} days of embryogenesis significantly changed the spectral composition of the total activity of the auditory cortex of the 30-day old rabbit pups. First of all, the ratio of the slow and fast waves in the spectrum shifted dramatically towards the first ones. Their percentage significantly ($p<0.05$) increased from 26.9% to 32.4%. There was increase in both δ– and θ–activities. If the index of the first one increased slightly up to 14.2±2.4%, then the second one increased twofold. So, θ–frequency continued to be dominant in the slow spectrum – 18.2±1.9% ($p<0.05$) (Fig. 6).

Hypoxia did not affect the spectral index of α–activity – 14.9±1.6% and induced ambiguous changes in the spectral indices of β–activity. The percentage of β1-waves increased slightly in the spectrum and reached 21.4±2.5%. The decrease in activity of the fast

waves of the spectrum was directly associated with β2–activity and the index of the latter compared to the control decreased by 20% and made up 31.3±4.2%. ($p<0.05$) (Fig. 6).

The analysis of the ECoG registered in the auditory cortex of the 30-day-old rabbit pups exposed to hypoxia on 1st – 5th days of postnatal life revealed large increase in the percentage of the slow spectrum. That increase occurred due to both δ– and θ–waves. Consequently, θ–activity, like in the control, continued to be dominant. Their percentages were 17.9±2.1% и 20.3±1.9% of the spectrum (overall – 38.2%). That index was 42% larger than that in the control (Fig. 6).

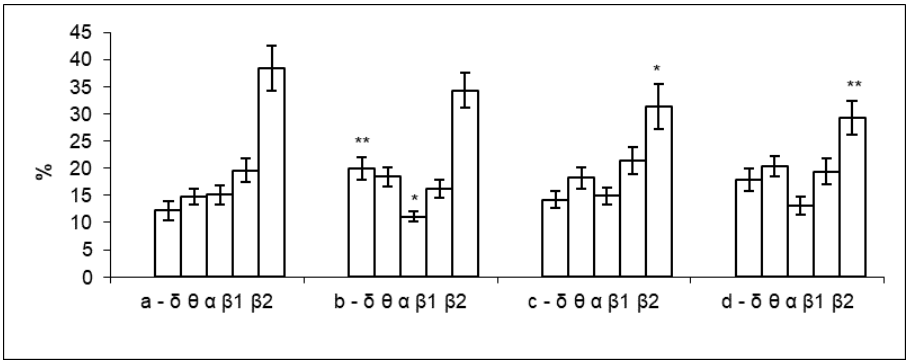

Fig. 6. The spectral composition of the ECoG of the auditory cortex of the 30-day-old rabbit pups: (a) control, after hypoxia in (b) fetal, (c) 24th – 28th days of embryogenesis and (d) 1st – 5th days of postnatal ontogeny. *– ($p<0.05$), **– ($p<0.01$).

The index of α–waves was 13.1±1.6% (slightly less that the norm). The spectral indices of β1–activity remained almost unchanged – 19.4±2.3%. At the same time, the percentage of β2–waves dramatically decreased by 28% and made up 29.3±3.1% ($p<0.01$). Thus, the decrease in the fast spectrum was associated with β2–activity.

Both prenatal and postnatal hypoxia were equally reflected in the overall pattern and rhythms of the ECoG. Those changes were similar to those in the previous experimental groups.

We can assert that hypoxia on 24^{th} – 28^{th} days of prenatal life and 1^{st} – 5^{th} days of postnatal one induced large and similar in nature changes in both the spectrum and the overall pattern of the ECoG of the auditory cortex of the 30-day-old rabbit pups. Under the effects of hypoxia there was increase in the slow waves, and in the slow spectrum, the ratio of δ– and θ–waves, specific to the control, remained unchanged. The peculiarity of the effects of oxygen deprivation in the period mentioned above on the total activity of the cerebral cortex was dramatic decrease in β2–activity of the spectrum. In addition, the indices of the other fast waves did not change. However, hypoxia during the first day of life compared to embryonic period induced larger changes in the spectrum of the ECoG of the auditory cortex. If under the effects of hypoxia, the percentage of the slow waves increased by 42%, then after the prenatal hypoxia it increased by only 20%.

7. Development of the ECoG of the auditory cortex of rabbit in ontogeny

Studies performed on the control 28-day-old rabbit fetuses and 10-, 20-, 30-day-old rabbit pups make it possible to get an idea of the development of the ECoG of the auditory cortex and auditory analyzer in ontogeny.

As mentioned above, the fast waves were dominant in the electrical activity of the auditory cortex of the control 28-day-old rabbit fetuses. Nevertheless, the spectrum of the ECoG was distinguished by the large percentage of slow waves (fig. 7). The amplitude indices of the electrical activity are given in the fig. 8.

To the 10^{th} day of postnatal ontogeny, there were not any changes in the overall pattern and rhythmic activity of the ECoG of the auditory cortex. However, the changes in ontogeny were reflected in the spectral composition of the total activity of the cerebral cortex. They were associated with β–activity. While the percentage of β–

activity remained unchanged, there were decrease in β1–waves and increase in β2–waves. At the same time, the indices of δ–, θ– and α–waves did not change (fig. 7).

Simultaneously with the spectral composition, the amplitude indices of the electrical activity changed as well. They were 30% larger than those in the previous period. There was increase in the amplitudes of all standard waves of the spectrum (fig. 8). However, the changes in the amplitude-temporal indices of the ECoG were statistically unreliable.

The spectral composition of the total activity of the cerebral cortex of the 20-day-old rabbit pups did not differ from that of the 10-day-old ones. There were no differences in the overall pattern and rhythmic activity in the ECoG either (fig. 7). In addition, the amplitude indices of the electrical potentials dramatically changed. They significantly increased by 40% ($p<0.5$) (fig. 8).

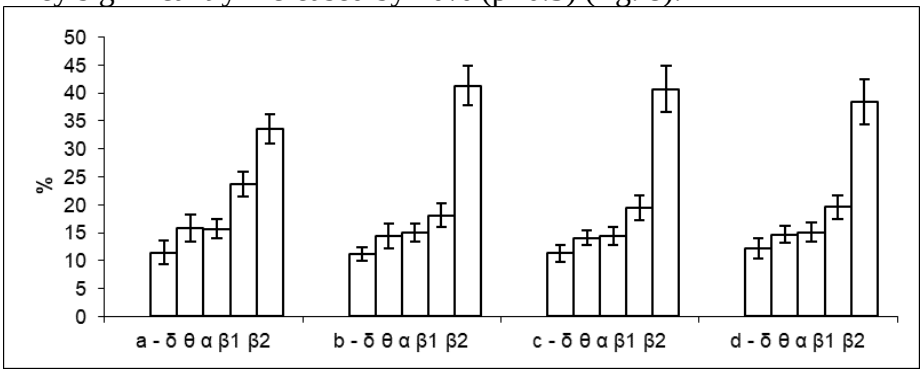

Fig. 7. The spectral composition of the ECoG of the auditory cortex of the (a) 28-day-old rabbit fetuses, (b) 10-, (c) 20-, (d) 30-day old rabbit pups. *– ($p<0.05$), **– ($p<0.01$).

To the 30th day of postnatal life, the pattern and rhythms of the total activity of the auditory cortex of the brain resembled those of the previous age. There were not any changes in the spectral composition either (fig. 7). The changes were associated only with the amplitude indices of the electrical potentials which were 20% larger than those in the previous age. In particular, the average

amplitude of δ–waves increased from 115 uV to 141 uV. However, that increase was statistically unreliable (fig. 8).

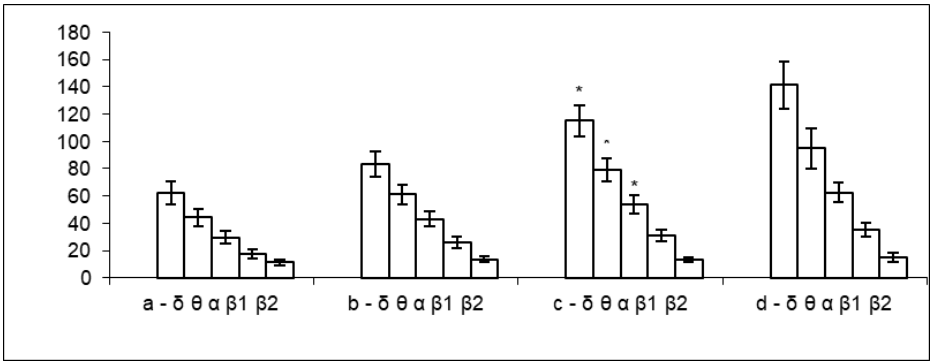

Fig. 8. The amplitude of the waves of the ECoG of the auditory cortex of the (a) 28-day-old rabbit fetuses, (b) 10-, (c) 20-, (d) 30-day old rabbit pups. *– ($p<0.05$), **– ($p<0.01$).

Summarizing the obtained findings, we can assert that the spectral indices and the pattern of the total activity of the auditory cortex of rabbit was developed very early – on the 10th day of postnatal life. As it developed, only the amplitude of the waves of the ECoG increased. On the 30th day of life, there also developed the amplitude indices of the ECoG of the auditory cortex.

The electrical activity of the auditory cortex acquired slight asymmetry in the spectral composition from the 10th day of postnatal life and in both the spectral and amplitude indices from the 20th day. There were slightly more fast waves in the electrical activity of the left auditory cortex compared to the right. The former had higher amplitude as well.

8. The effects of hypoxia on the interhemispheric asymmetry in the amplitude-temporal indices of the ECoG

In most cases, hypoxia reduced or eliminated the interhemispheric asymmetry in the amplitude-temporal indices of the

total activity of the cerebral cortex. So, the central interaction of the brain got impaired.

9. The effects of prenatal hypoxia on the development of the rabbit fetus

Oxygen deprivation during fetal period disturbed the development of the rabbit fetus. In 43 female rabbits exposed to hypoxia in embryonic and prefetal periods of embryogenesis, the gestational age exceeded 30-31 days. In one of the female rabbits after oxygen deprivation in prefetal period, the gestational age made up 37 days. After hypoxia in embryonic period of prenatal life, it was significantly difficult to obtain offspring. Oxygen deficiency in fetal period of embryogenesis almost did not affect the gestational age.

The fourth chapter discusses the data obtained.

First of all, for understanding the effects of hypoxia on the electrical activity of the developing cerebral cortex, it is necessary to identify the pattern of its development in ontogeny. Our research has established that even before the completion of the formation of the nervous system, on the 10th day of postnatal life, the spectral composition of the ECoG auditory cortex acquires definitive indicators. By the end of the 1st month, during the period when the rabbit's nervous system is generally formed, the development of amplitude-time indicators of ECoG is completed.

Comparing the amplitude–time indicators of the electrical activity of the sensorimotor and auditory cortex of 28–day-old rabbit embryos, it can be argued that the total electrical activity of the projection areas of the cerebral cortex even before birth acquires a characteristic feature. The ECoG of the sensorimotor cortex, in comparison with the auditory cortex, contains fewer slow waves, has a slightly larger amplitude and reacts more strongly to hypoxia. Hypoxia in the prenatal period, compared to the fetal period of

embryogenesis, causes more changes in the spectral composition of the ECoG auditory cortex.

With the registration of the total activity of the auditory cortex, a pattern of changes in the sensitivity of the nervous system to hypoxia during intrauterine life was revealed. It was found that hypoxia in later periods, compared with the embryonic period of prenatal development, leads to more noticeable and almost identical changes in the spectral parameters of ECoG. These data indicate that the nerve structures generating the electrical activity of the rabbit's auditory cortex in the last two periods of intrauterine life exhibit a higher sensitivity to oxygen deficiency [16, 17].

In recent years, it has been found that during embryogenesis, the sensitivity to hypoxia of the cerebral cortex, subcortical white and gray matter of the brain and a number of other structures of the nervous system changes [6, 18]. Given the role of subcortical white and gray matter of the brain in the genesis of EEG [19], it can be assumed that oxygen deficiency in different periods of embryogenesis affects the morphofunctional state differently not only the cortex, but also the subcortical structures of the brain, which is expressed in differences in the spectral characteristics of ECoG recorded in different periods of postnatal development.

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[16] Гусейнов, А.Г. Формирование суммарной электрической активности слуховой коры кролика в онтогенезе // Известия БДУ. Серия естественных наук, – 2018, – 4, – с. 27–33.

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Hypoxia in relatively early periods of embryonic life leads to significant changes in the cerebral cortex and subcortical white matter in the postnatal period[6,18]. This period is critical for the cerebral cortex, since its basic elements are laid at this time 6. The main reason for the high susceptibility of subcortical white matter to hypoxia is the appearance of young oligodendrocytes[18]. By the end of embryonic life, these structures acquire relative resistance to lack of oxygen, and subcortical gray matter, on the contrary, becomes susceptible to its action [6,18].

An increase in the sensitivity of gray matter, or rather subcortical nuclei, to hypoxia by the end of embryogenesis is attributed by some authors to a lack of energy due to an increase in their activity[20]. However, in studies conducted on sheep fetuses, it was found that in late embryogenesis, compared with its early periods, with a weakening of the ability to maintain blood pressure and membrane functions of neurons, subcortical nuclei become more susceptible to hypoxia [21].

Ours studies revealed a new mechanism of susceptibility of the cerebral cortex to hypoxia in early embryogenesis. It can be supposed that damage of the immature subcortical white matter of the brain also plays the role in high susceptibility of the cortical neurons and the entire cerebral cortex to hypoxia in relatively early periods of embryogenesis[12].

It was found, the neurons migrating from the matrix layer to the cortical plate and subplate in the developing white matter are more susceptible to pathological factors. Due to that cause, in early ontogeny, the structural changes in white matter of the brain are

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[20] Billiards, S. Is the late preterm infant more vulnerable to gray matter injury than the term infant? / S. Billiards, C. Pierson, R. Haynes [et al] // Clin Perinatol., – 2006, – 33, – p. 915–933.

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accompanied with death of the cortical neurons migrating in it, including GABAergic ones [22].

The consequences of damage of immature subcortical white matter of the brain for the developing cortical neurons are not probably limited to that. The findings in recent years have shown that one of the major causes of damage or death of the brain neurons under the effects of hypoxia or other pathological factors is their deafferentation as a result of disturbance of the neural nets[22]. Consequently, the destructive changes in the developing subcortical white matter of the brain, disturbing the formation of the afferent connections of the cerebral cortex, lead to damage or death of the cortical neurons after the end of migration [12].

According to the studies performed on rodents, two critical periods were identified in early embryogenesis when the developing organism was more susceptible to pathological factors. The first one is prior to the attachment (implantation) of the embryo to the uterine wall, when the most common cases of death of embryos under various impacts occur. The second one is the period when the primordial organs form and the adverse factors can contribute into formation of various defects [23].

In rabbits, both the preimplantation and implantation periods correspond to embryonic period of fetal life[24]. As mentioned in our studies, after hypoxia in embryonic period compared to the other periods it is very difficult to obtain offspring. Mortality of newborns compared to the other experimental groups is also higher.

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Nevertheless, in our studies, the nervous system of the rabbit pups is less susceptible to oxygen deprivation in embryonic period of embryogenesis. Perhaps, the relative tolerance of the nervous system to oxygen deficiency during embryonic period of prenatal life is associated with little needs of the embryo in oxygen in the mentioned period [25].

It is supposed that the synaptic signals also play the role in damage of the nervous system under the effects of hypoxia[26]. Consequently, it cannot be ruled out that in early periods of embryogenesis, the absence of the synaptic connection in neurons is one the causes of their relative tolerance to the effects of hypoxia.

In rabbits, prefetal period of embryonic life is characterized by the intensive processes of organogenesis [24]. Impairment of these processes under the effects of hypoxia, undoubtedly, are reflected in the structures of the nervous system. In the mentioned period, the cerebral cortex and subcortical white matter are still sensitive to oxygen deficiency [6,18]. It can be supposed that these structural impairments are the key causes of large change in the ECoG under the effects of hypoxia during prefetal period of fetal life.

At the beginning of fetal period of prenatal life of rabbit, the cerebral cortex and subcortical white matter are still susceptible to hypoxia and only at the end of embryogenesis, they become relatively tolerant to oxygen deficiency[6,18]. The studies performed on rabbit revealed that when young oligodendrocytes appear, subcortical white matter of the brain of rabbit can again become susceptible to hypoxia by the end of embryonic life [18].

Presumably, damage of the grey matter of the subcortical structures of the brain under oxygen deficiency in fetal period of prenatal life[18] can also play the significant role in change in the ECoG spectrum. ЭКоГ. Высокую чувствительность нервной

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системы к гипоксии в плодный период эмбриогенеза также можно объяснить усилением ее функциональной активности, что приводит к повышенным энергетическим затратам.

It is known that cortical areas differ in sensitivity to hypoxia. This is primarily due to the fact that in different cortical egions, neurons, nerve fibers and the subcortical white matter adjacent to it react differently to lack of oxygen. An important role in this is also played by the ability to maintain blood circulation in the structures of the nervous system [2]. However, presumably, the main reason for these differences is that these cortical areas are at different stages of development. The sensorimotor analyzer is characterized by high rates of development in ontogenesis, while the auditory analyzer is formed in the late periods of ontogenesis. Neurons of the sensorimotor cortex, developing at an accelerated pace, are more susceptible to hypoxia during the pre-fetal period of embryogenesis. It is known that differentiated neurons, compared with undifferentiated ones, are more sensitive to oxygen deficiency.[26]

The electrical activity of the sensorimotor cortex, in contrast to the auditory cortex, also reacts more sharply to hypoxia in the prenatal than fetal period of embryogenesis. As already mentioned, by the end of embryogenesis, the sensitivity of the cerebral cortex and subcortical white matter to hypoxia decreases, and subcortical gray matter, on the contrary, increases [6,18]. Consequently, in a rabbit at the beginning of the fetal period of prenatal life, the cerebral cortex and subcortical white matter, and at the end of this period, subcortical gray matter are susceptible to lack of oxygen. Damage to these structures under the influence of oxygen deficiency can change the electrical activity of the sensorimotor cortex. It can be assumed that due to accelerated development, the sensorimotor cortex and the subcortical white matter adjacent to it acquire immunity to hypoxia at an earlier period. As a result, oxygen deficiency in the late period of embryogenesis in these structures causes minor changes, which is reflected in the ECoG.

As the rabbit pups develop in ontogeny, the changes in responses of their nervous systems to hypoxia in different periods of

embryogenesis reflect the delayed morphofunctional changes in the nervous systems themselves. The structural changes can occur in all structures of the nervous system immediately or delayed after a certain time after exposure to hypoxia. In most cases, they occur after a long time. After the first ones are followed by the second waves of damage or death of the nervous structures[6,27].

Hypoxia at the beginning of postnatal ontogeny (1^{st} – 5^{th} days) compared to embryonic period (24^{th} – 28^{th} days) induces larger changes in the ECoG of the auditory cortex of the 30-day-old rabbit pups. These findings indicate that after birth, sensitivity of the nervous system to hypoxia increases. However, it is difficult to objectively evaluate it, because the rabbit pups of both groups were exposed to hypoxia under different conditions. Perhaps, higher sensitivity of the nervous system to oxygen deficiency is associated with deficiency of energy due to its increasing activity. In case of prenatal hypoxia, maternal organism can compensate oxygen deficiency to a certain extent.

In addition, the nature of changes in the indices of the ECoG of the 30-day-old rabbit pups is largely similar. These findings indicate that the mechanism of changes of the total activity under the effects of hypoxia have a lot in common at the end of prenatal and at the beginning of postnatal period and differ from those in the rabbit pups of the same age, exposed to oxygen deprivation in fetal period of embryogenesis [28].

During the analysis of the mechanisms of the influence of hypoxia on the EEG, some key issues related to the development of the brain in ontogenesis were clarified.

As a result of the analysis of the mechanisms of formation of impulsive activity of neurons, it can be concluded that not in all cases

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it is possible to detect a correlation between obstructing factors and the episodic nature of background impulses of developing cortical neurons. On this basis, it can be assumed that in different types of cortical neurons, individual obstructing factors have different values, and the episodicity of background activity is carried out by different mechanisms [29].

The results of the analysis of impulse activity development mechanisms of neurons allow to conclude that there is no correlation between hindering factors and episodic character of the background impulse activity of the developing cortical neurons. On this basis, it can be supposed that particular hindering factors of different kinds of the cortical neurons have unlike values, and episodicity of the background activity is implemented through various mechanism[29].

Fluctuation of the level of membrane potential, specific to the immature cortical neurons in early periods of development, is supposed to be one of the causes of their episodic activity. Significant decrease in the level of membrane potential, at which generation of action potential become impossible, can lead to long-term periods of neuronal inactivity. Long-term periods of inactivity, sometimes measured in minutes, are hardy associated only with low lability of the cell membrane [29].

To understand the process of the development of the cerebral cortex and the brain in ontogeny, it is necessary to the identify the range of key issues, one of which is development of cortical inhibition. It is impossible to reveal the mechanisms of electrical activity of the developing cerebral cortex, as well as its responses to hypoxia without determining the start time of the functioning of cortical inhibition and the functional peculiarities of the cortex on early stages of ontogeny. To date, the timing of appearance of synaptic inhibition in the cerebral cortex is not fully determined. The

[29] Гусейнов А.Г. Механизмы формирования фоновой активности нейронов коры головного мозга в онтогенезе // Журн. эвол. биох. и физиол., 2007, 43 (6), – с. 451–459.

functional peculiarities of cortical inhibition on early stages of ontogeny are still unclear.

We have brought some clarity to the issues mentioned above based on the analysis of morphological, neurochemical and electrophysiological findings on cortical inhibition development. As a result of the performed analysis, the synaptic inhabitation of the neurons of the cerebral cortex is supposed to develop simultaneously with generation of background activity by them. Since the appearance of inhibitory processes, all types of cortical inhibition start to function. Thus, the key mechanisms involved in cortical inhibition in the mature cerebral cortex begin to function since the activation of the latter in ontogeny [30].

Revealing the mechanisms of the action of hypoxia on the total activity of the cerebral cortex, one of the key issues is identifying the relationship between activity of the cortical neurons and the EEG pattern. At present, little was known about the neuronal mechanisms of the EEG, and the EEG pattern is not an indicator of the activity of cortical neurons in all cases. Alpha-rhythms are supposed to be possibly generated by both the activated and inhibited cerebral cortex [31].

However, some investigators consider that decrease in discharge activity of cortical neurons leads to increase in slow waves in the EEG [32]. That opinion is corroborated by the results of a lot of studies. In rats exposed to hypoxia, the initial activation of the EEG coincides with enhanced background impulsation of cortical neurons,

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and as that impulsation is being suppressed, the percentage of the slow waves increases[33]. Postsynaptic depression of the impulse activity od cortical neurons are reflected in the EEG by reduction of the high frequencies of the spectrum [34].

It has been found that upon activation of thalamocortical neurons, higher frequencies are generated as a result of depolarization of their membranes[31]. In sheep's fetuses, disappearance of high-frequency waves in the EEG during asphyxia is associated with acute damage of cortical neurons [35]. On the basis of these findings, we can suppose that increase in the slow waves in the EEG during hypoxia is associated with decrease in the impulse activity of cortical neurons and vice versa.

In case of hypoxia, the morphofunctional changes in the nervous system can activate or inhibit its impulse activity through the changes in membrane potential of cortical neurons. In turn, this can lead to increase or decrease in the EGG activity. However, during oxygen deprivation, as usual, the percentage of the slow waves increase in the EGG, which is supposed to be associated with suppression of discharge activity of cortical neurons. This suggests that those changes are not random but focused and carried out by intracellular mechanism of the neurons themselves and maybe under the effects of certain brain structures.

It is known that intracellular mechanisms can control generation of the nerve impulse of neuron, as well as the rhythmic activity of neurons through the regulation of synaptic activity and

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non-synaptic signals. Thus, they can play a significant role in the generation of different EEG waves and rhythms [36,37].

There are findings indicating the role of the intracellular mechanism in the change in the electrical activity of both subcortical, and central neurons under oxygen deficiency. The change in the permeability of the membrane channels of neurons can occur immediately after the effects of hypoxia, when their energy supply is not disturbed so far. It was found that in case of anoxia of the neurons of the vagus, activation of K^+–channels of the membranes is not associated with the level of ATP[32,38]. Based on the findings mentioned above, it cannot be ruled out that during oxygen deprivation, hyperpolarization or strong depolarization of the membranes of neurons, which lead to reduction or termination of their impulse activity, can also be induced by the effects of the intracellular mechanisms.

It is known that some cortical neurons, in comparison with others, play a more significant role in the genesis of the EEG. In the rat cerebral cortex, a small number of neurons provide the appearance of θ–rhythm, spindles and arousal waves and strongly affect the acuity of the EEG [38].

Some investigators consider that individual cortical neurons play a more significant role in the development of both normal and pathological EEG. In the cerebral cortex of rat, joint activity of a relatively small number of neurons can produce theta-rhythms,

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36 Karameh, F. Modeling the contribution of lamina 5 neuronal and network dynamics to low frequency EEG phenomena / F. Karameh, M. Dahleh, E. Brown [et al] // Biol. Cybern., – 2006, – 95, – p. 289–310.

37 Lytton, W. Control of slow oscillations in the thalamocortical neuron: a computer model / W. Lytton, A. Destexhe, T. Sejnowski // J. Neurosci., – 1996, – 70, – p. 673–684.

38 Fujimura, N. Contribution of ATP–sensitive potassium channels to hypoxic hyperpolarization in rat hippocampal CA1 neurons in vitro / N. Fujimura, E. Tanaka, S. Yamamoto [et al] // J. Neurophysiol., – 1997, – 77, – p. 378–385.

spindles and arousal waves through modulation of activity of the other neurons and has a great effect on the severity of the EEG [39].

According to some of investigators, in the subcortical structures, there are hypothetic pacemaker neurons that can affect the activity of the cortical neurons. It was found, the decrease in the pacemaker effects on the neurons of the cerebral cortex during hypoxia is one of the causes of disorganization of the standard slow complex of the EEG [40]. The cortical and subcortical neurons, functioning of which is regul ated by endogenic mechanism is believed to form descending pathways modulating activity of the sensory pathways and receptors [41].

Based on the performed analysis, it is supposed that modulating and pacemaker neurons, the functioning of which are mainly controlled by the intracellular mechanisms, form a functional group that can affect the activity of neurons of the cerebral cortex and other brain structures during hypoxia. Neurons, both excitatory and inhibitory, forming the system, are located in all parts of the nervous system, but are mainly concentrated in phylogenetically ancient subcortical structures. They have connections with all structures of the nervous system, from the center to periphery, through direct ascending and descending or indirect pathways.

Under the effects of hypoxia, the group of modulating and pacemaker neurons, together with the intracellular mechanisms of cortical neurons, is able to regulate their activity, thereby determining the nature of the EEG. The regulation of activity of cortical neurons can be carried out by synaptic contacts and non-

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synaptic signals, as well as activation of the endogenic mechanisms of the neurons themselves. The control of excitability of cortical neurons can be carried out indirectly – by the regulation of functioning of those structures of the nervous system, that can affect the cortical activity.

The signals for activation of the system can come from its neurons. They, like some neurons of the medulla oblongata, can indirectly respond to the beginning of hypoxia [42]. Perhaps, some of the neurons are activated by oxygen deficiency. As hypoxia develops, because of the action of the system's neurons and endogenic mechanisms, the discharge activity of the neurons is depressed so that their damage or death are prevented. This process is reflected in the EEG by the increase in the slow waves and generation of the slow rhythms.

It is difficult to determine which neurons form the system. It can be assumed that gabaergic neurons of the RAT, which exert pacemaker effects on cortical neurons and play an exceptional role in the generation of EEG [43], are its key element. This may also apply to Cajal–Retzius neurons, which are resistant to hypoxia, are able to generate ectotopic action potentials and have synaptic connections with a large number of cortical neurons [44].

One of the candidates for the constituent elements of the system are the principle neurons. In studies conducted on slices of

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the rat cerebral cortex, it was found that during reperfusion, their activity increases more compared to other neurons.[45]

Studies show that in the first days of newborns, EEG acuity is associated with damage to the basal ganglia, thalamus, subcortical white matter, internal capsule, but not with the cerebral cortex[46]. Undoubtedly, this fact indicates the important role of subcortical structures in the regulation of excitability of cortical neurons. Based on this, it cannot be ruled out that the weakening or cessation of the effects of modulating and pacemaker neurons of subcortical structures on central neurons in violation of subcortical–cortical relationships is one of the reasons for their increased excitability, underlying the pathological activity of the EEG.

A lot of investigators consider that the overall pattern and most parameters of both the normal and pathological EEG are genetically determined [47]. It can be supposed, that the system of modulating and pacemaker neurons is one of the mechanisms of realization of genetic condition of the electrical activity of the cerebral cortex.

Presumably, the regulation of EEG generation by modulating and pacemaker neurons is carried out under both pathological and normal conditions. Consequently, EEG generation is not a random process, but is partially or completely controlled by the brain itself[48].

As a result of the analysis, it is supposed that the response of the total activity of the developing cortex to the effect of hypoxia is

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realized through mature mechanisms, as well as the ones specific to early ontogeny [48].

CONCLUSION

1. In our studies, it was found that spectral indicators and the overall picture of the total electrical activity of the rabbit's auditory cortex are formed on the 10th day, and amplitude indicators – on the 30th day of postnatal life. From the 10th day of life, the ECoG acquires an interhemispheric asymmetry in spectral composition, and from the 20th day in amplitude. The total activity of the left auditory cortex, compared with the right, contains more fast waves and has a higher amplitude.

2. In ontogenesis, differences in the electrical activity of different cortical regions appear even in embryogenesis. During this period, the ECoG of the auditory and sensorimotor regions of the cerebral cortex differ sharply in spectral composition and amplitude, and they react differently to hypoxia.

3. As a result of our research, a pattern of changes in the sensitivity of the nervous system to oxygen deficiency during embryogenesis has been revealed. It was found that hypoxia in the embryonic, prenatal and fetal periods of prenatal development has a different effect on the formation of the ECoG spectrum of the auditory cortex of baby rabbits. In the ECoG spectrum of the auditory cortex of 28–day–old fetuses, 10–, 20– and 30-day-old baby rabbits, lack of oxygen in late periods of prenatal development, compared with embryonic, leads to more noticeable and almost identical changes in the spectral parameters of ECoG. With age, oxygen starvation in all periods of prenatal ontogenesis has a more intense effect on the electrical activity of the cerebral cortex. Based

[48] Гусейнов А.Г. Механизмы влияния гипоксии на суммарную активность коры головного мозга // Росс. физиол. журн., – 2017, 103 (11), – с. 1209–1224.

on these data, it can be assumed that the nerve structures generating the electrical activity of the rabbit's auditory cortex in the last two periods of intrauterine life show a higher sensitivity to lack of oxygen.

4. Oxygen starvation at the end of embryogenesis (days 24-28) and at the beginning of postnatal ontogenesis (days 1-5) causes strong and similar changes in the overall picture and spectrum of the ECoG of the auditory cortex of 30–day–old baby rabbits. However, after postnatal hypoxia, stronger changes are detected in the spectrum of electrical activity.

5. Under the influence of hypoxia, asymmetry in the amplitude–time indices of ECoG is weakened or eliminated, and the interhemispheric interaction of the brain is disrupted.

6. A new mechanism of susceptibility of the cerebral cortex to hypoxia in early embryogenesis has been proposed. Damage to the subcortical white matter of the brain with a lack of oxygen eventually leads to structural changes in the cerebral cortex.

7. A hypothesis has been put forward that the fluctuation in the level of membrane potential of developing cortical neurons is one of the reasons for their episodic activity.

8. The regularities of the formation of cortical inhibition in ontogenesis have been established; As a result of the analysis, it is assumed that synaptic inhibition of neurons of the cerebral cortex begins to occur almost simultaneously with the beginning of their generation of background activity. The main mechanisms that carry out cortical inhibition in the mature cerebral cortex begin to function from the moment it is included in ontogenesis.

9. Under conditions of hypoxia, the generation of impulse activity of a cortical neuron is regulated by a group of modulating and pacemaker neurons and intracellular mechanisms of the neurons themselves. With oxygen starvation, the weakening of the impulse activity of cortical neurons is reflected in the EEG by an increase in the severity of slow waves of the spectrum and the generation of slow rhythms. Disruption of the functional group of neurons regulating the level of excitability of cortical neurons is one of the mechanisms for the development of pathological activity on the

EEG. Such regulation of EEG generation takes place under both pathological and normal conditions. Therefore, the generation of EEG is not a random process, but is partially or completely controlled by the brain itself.

10. It is assumed that the reaction of the total activity of the developing cortex to the effects of hypoxia is realized, as well as by mature mechanisms characteristic of early ontogenesis.

THEORETICAL RECOMMENDATIONS

1. The description of the morphological development of the rabbit cerebral cortex in embryogenesis has theoretical significance for understanding the development of the brain as a whole. This work gives an idea of the development of the mammalian cerebral cortex in the prenatal period and can be recommended for inclusion in works on brain development in ontogenesis.
2. The study of the mechanisms of formation of the impulse activity of cortical neurons and the establishment of patterns of formation of cortical inhibition are very important for understanding the functional development of the brain in ontogenesis. The results of the research can be recommended for inclusion in textbooks on age physiology.
3. The results of studies on changes in the sensitivity of the nervous system to hypoxia in embryogenesis and the mechanisms of the effect of hypoxia on the EEG can be recommended to doctors for the treatment of children who have undergone prenatal hypoxia.
4. The results of research on the mechanisms of the effect of hypoxia on the EEG have very important theoretical significance for understanding the generation of electrical activity of the brain. These data can be recommended for inclusion in books on electrophysiology.

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LIST OF ABBREVIATIONS

ATP	– adenisine triphosphate
GABA	– gamma–amino butyric acid
EEG	– electroencephalogram

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