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DYNAMICS OF BRAIN ENZYMES ACTIVITY IN RAT EXPOSED TO HYPOXIA

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The aim of the work was to study the dynamics of lactate dehydrogenase (LDH; EC 1.1.1.27), aconitase (AH; EC 4.2.1.3), NAD-dependent malate dehydrogenase (MDH; EC 1.1.1.37), succinate dehydrogenase (SDH; EC 1.3.99.1) activity in homogenates and sub-fractions of brain structures of rat prenatally endured hypoxia at the organogenesis stage (on 11–15 days of development) and their role in the formation of compensatory — adaptive mechanisms in brain in postnatal ontogenesis. It was revealed that increasing of lactate dehydrogenase and malate dehydrogenase activity ($P < 0.001$; $P < 0.01$, correspondently) in the brain structures of the rats prevented metabolic disturbances in the regulation mechanisms of biosynthetic and bioenergetics processes in the brain. It was shown that prenatal hypoxia upregulates aconitase activity in postnatal development and this process, probably, had a reversible character ($P < 0.01$), the highest indices of succinate dehydrogenase activity were noticed in the hypothalamus and cerebellum of 30-day-old rat as compared to the other structures ($P<0.001$). Based on the data obtained, it can be concluded that hypoxia at the stage of organogenesis leads to a change in the energy supply process of the brain structures and, possibly, is irreversible. Analysis of changes in the enzymatic system in ontogenesis allowed us to identify adaptation mechanisms and to assess the dynamics of changes in enzyme activity when the functional state changed, which made it possible to identify adaptive reserves of enzymes LDH, AH, MDH and SDH in brain exposed to hypoxia.

Key words: enzymes of energy metabolism.

Study in postnatal ontogenesis the consequences of effects of prenatal hypoxia on the dynamics of energy metabolism activity of developing brain is one of the actual problems of physiology and neurochemistry. Short and long term consequences of prenatal hypoxia lead to disturbances in coqnitive functions and behaviour that is connected with disorganization of the processes of proliferation, migration and differentiation of neuroblasts, the formation of neural networks, synaptic plasticity of brain. In these processes, there is a huge role of enzymes of energy metabolism of the brain.

The literature review shows that prenatal hypoxia is most common and one of the important stressful factors leading to physiological, biochemical and morphological changes in postnatal ontogenesis. Pathogenesis effect of prenatal hypoxia depends on prenatal ontogenesis period. During prenatal ontogenesis disturbances caused by hypoxia in structural- functional integrity of cell membrane influences on the central nervous system (CNS) function, as in oxidation of glucose deep changes occur in energy metabolism. That's why the developing brain can be considered, as a very sensitive to hypoxia organ [1, 2]. Oxygen deficiency requires maximal mobilization and intensification of potential adaptive possibilities of the organism [3, 4]. The influence of hypoxia in prenatal period displays by formation of large heterogeneous group of neuropathology [5]. Because of very high level of energy metabolism in the brain a great deal of oxygen entering must be directed for providing the brain's requirements first [6, 7].

To study the dynamics in the activity of some enzymes of the brain's energy metabolism: lactate dehydrogenase (LDH; EC 1.1.1.27) which is a marker of aero- and

anaerobiothic processes, the Krebs cycle's enzymes aconitase (AH; EC 4.2.1.3), NAD-dependent malate dehydrogenase (MDH; EC 1.1.1.37), succinate dehydrogenase (SDH; EC 1.3.99.1) in rat prenatally endured hypoxia at the stage of organogenesis and their role in the formation of compensatory — adaptive mechanisms in brain structures in postnatal ontogenesis have not been fully investigated. Therefore the work proposed by us, in our opinion, can clarify certain aspects of this problem and will be able to help in the decision of some issues of energy supply of the brain in stressful situations in some periods of postnatal ontogenesis. So, the main objective aim of this research is studying the dynamics activity of LDH, AH, MDH and SDH in rat brain structures in postnatal ontogenesis, exposed prenatally to hypoxia.

Materials and Methods

The experiments were conducted in accordance with bioethical principles and guide line documents, recommended by the European Convention for the Protection of Vertebrate Animals used for Experimental and other Scientific Purposes stated by the European Community Directive (86/609/EEC), under the supervision of the local bioethics committee of the National Academy of Sciences of Azerbaijan.

The albino nonlinear female rat was exposed to hypoxia in 11–15 days of organogenesis stage of prenatal development. Model of hypoxia was conducted for 20 min every day during 5 days in a special hyperbaric chamber with a volume of 0.012 m^3 into with gas mixture of 5% O_2 and 95% N_2, was supplied from gas cylinders, which measured with a gas meter. Enzyme's activity was assayed on 17- (period of maturation), 30- (period of weaning, completion of earlier period of postnatal ontogenesis) and 90- (reproductive period) old- days of postnatal ontogenesis. The first two periods are considered critical in postnatal ontogenesis.

After each series of experiments the animals were sacrificed and the whole brain carefully dissected on ice under hypothermia and identified by Pellegrino L.T.et al. atlas (1979). Orbital (OC), sensorimotoric (SMC), limbic cortices (LC), hypothalamus (H) and cerebellum (C) were isolated and the tissues were frozen immediately prior to homogenization [8]. Tissues were homogenized by using a homogenizer with a Teflon pestle in a solution of 0.2 M Tris-HCl (pH 7.4); 1 mM EDTA; 0.25 M sucrose at a ratio of 1:9. Tissue homogenates were centrifuged at a refrigerated centrifuge K-24 (Germany) at 900 g for 10 min [9]. After removing tissue scraps and nuclei the supernatant was dissolved at a ratio of 1:10 with 0.32 M sucrose for further procedures. The supernatant was centrifuged within 20 min at a speed of 11000–14000 g. Cytosolic fraction (CF) was obtained from supernatant by differential centrifugation at a speed of 100000 g within 1.5–2.0 hours in Beckman coulter Optimal L-100XP Ultracetrifuge. The mitochondrial fraction (MF) was centrifuged at the regime of 14000 g and then it was decomposed with 0.1% solution of Triton X-100 [10]. All the procedures were carried out under 0–4 °C. To obtain the appropriate control group of animals the intact rats of the same age were placed into the same chamber under normal oxygen content. This allowed us to eliminate the effect of handling stress.

LDH — and MDH — activity were determined by the method of H.U.Bergmeyer (1975) [11], AH was determined by the method of G.C. Guilbault (1976) [12], SDH-activity was determined by M.I.Prokhorov (1982) [13]. The protein contents of the samples were determined according to the method of Bradford with bovine serum albumin used as a standard [14]. Data processing was carried out in program Origin Pro 7.0. The assessment of the significance of data differences between the groups was carried out using Student's t-test at P values <0.01.

Results and Discussion

The results of the experiments show, that in the homogenate of OC on 17th and 30th days of postnatal ontogenesis LDH activity was closer to the control level ($P > 0.05$; $P < 0.01$) (Fig. 1, *a*). But in 90-day-old rat the enzyme activity rose by over 2.4 times compared to their controls. In CF another dynamics was observed: despite the fact that in early ontogenesis LDH–activity was higher by over 58% as compared to the control level, its activity rose with time by 6.8 (on 30 day) and 3.3 (on 90 day) times as compared to the controls. The highest enzyme activity was registered on 30th day of postnatal development ($P < 0.001$) (Fig. 1, *c*). In the MF the enzyme's activity decreased with the course of postnatal development, but it did not reach the control level. Though there was a tendency to recover, it does not reach the control level and this difference is considered to be reliable ($P < 0.01$) (Fig. 1, *b*).

The activity of LDH in the homogenate of SMC rose with increasing the age and was 2.5 times higher in comparison to the control level (Fig. 1, *a*). The highest enzyme activity in this structure was fixed in CF on 30th day of postnatal ontogenesis ($P < 0.001$) (Fig. 1, *c*). The enzyme activity in the CF of SMC rose many times. In MF the picture of opposite type is revealed, i.e. the activity of enzyme falls with the elongation of postnatal period (Fig. 1, *b*). However, the lowest index was 2.0 times higher than the control level.

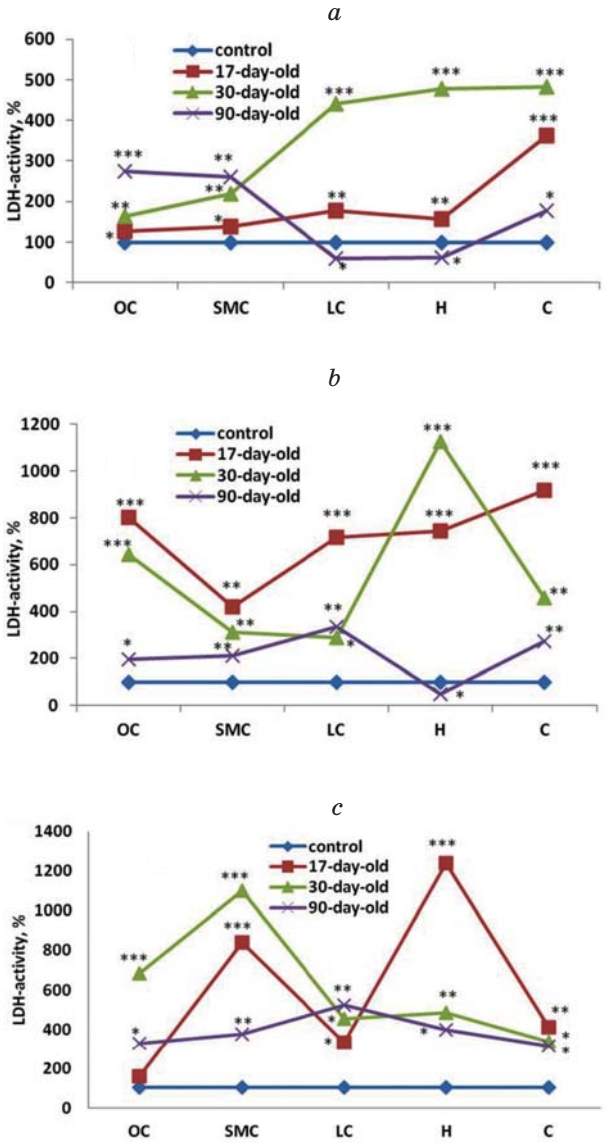

Fig. 1. **Postnatal developmental dynamics of LDH- activity in:** homogenate (*a*), mitochondrial (*b*) and cytosolic (*c*) fractions of the rat brain structures, exposed to hypoxia ($M \pm m$; $n = 6$). *Hereinafter:* 1) OC- orbital cortex; SMC- sensorimotoric cortex; LC- limbic cortex; H — hypothalamus; C — cerebellum. 2) * — $P < 0.05$; ** — $P < 0.01$; *** — $P < 0.001$ with compared to control

There was high LDH activity in the LC from homogenate of tissue on 30-day of postnatal ontogenesis ($P < 0.001$), while on the 17th and 90th days of the experiment its activity was closer to the control level, even its decreased activity was observed (Fig. 1, *a*). In the MF and CF of the LC the activity of LDH was significantly different in all age groups of rat as compared to the control (Fig. 1, *b*, *c*). In the CF the activity of enzyme increased with the elongation of postnatal development. In spite of being reliably high ($P < 0.01$) as compared to the control ones, there were small difference between the age groups (Fig. 1, *c*). In MF on 17th day the activity of enzyme rose by 7.6 times, on 30th and 90th days its activity rose by 2,9 and 3,4 times, correspondently ($P < 0,001$) (Fig. 1, *b*). This may indicate associated activation of protective and adaptive brain functions [15].

In the H the activity of LDH was characterized with uneven distribution in age-related manner. On the tissue and MF levels an identical pattern was apparent in the dynamics of LDH-activity: the highest activity was observed on 30th day (Fig. 1, *a*, *b*). In CF of this structure the peak of LDH activity was observed on the 17th day of postnatal development ($P < 0.001$). But for 30th and 90th days the activity of the enzyme sharply decreased, but its level did not recover to the control indicators (Fig. 1, *c*). While at the age row of 17→30→90-day-old the enzyme's activity had a decreasing tendency. It should be noticed, that on 90th day LDH-activity decreased in the tissue and MF by 39% and 51%, correspondently as compared to the control.

In the C, as in the other structures of the brain, the same pattern was apparent, i.e., with the elongation of the postnatal development the activity of enzyme in homogenate, CF and MF of the C did not return to the control level, but was even several times higher (Fig. 1, *a*, *b*, *c*).

AH is a polyfunctional enzyme complex and takes part in the providing of constructive and energy metabolism. The increased activity AH from MF and SF of brain structures had reversible character ($P < 0.01$).The increasing in substrate amount results in activation of both mitochondrial and cytosolic AH [16]. The activation of glycolysis causes the increase in the amount of acetyl-coenzyme A which is necessary for the synthesis of citric acid — the substrate of AH. Prenatal hypoxia leads to the changes in the activity of AH-enzyme in CF and MF from brain structures of the all studied ages of postnatal ontogenesis too (Fig. 2, *a*, *b*).

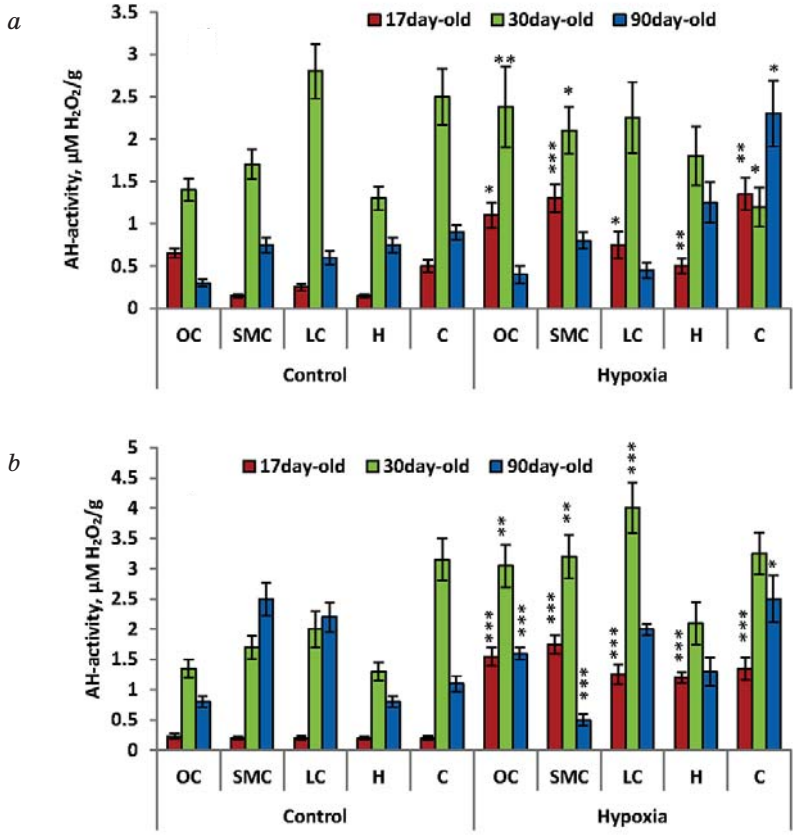

Fig. 2. **Postnatal developmental dynamics of AH-activity in: mitochondrial (*a*) and cytosolic (*b*) fractions of the rat brain structures, exposed to hypoxia**

As the results of the experiments show, in the CF of brain structures of the 17-day-old rat sharp increase of AH-activity was observed (2–5 times; $P < 0.001$). These results prove that prenatal hypoxia in the tested brain tissues of 17-day-old rat intensifies biosynthetic processes. The activity of cytosolic AH in the most tissues of the hypoxized 30-day-old animal is increased. Only in the C its activity is 2.0–2.5 times lesser than the control level ($P < 0.001$). In the LC unreliable decrease in the activity of enzyme was revealed ($P > 0.05$).While in the others insignificant changes occurred, in the CF of the C of 90-day-old hypoxized animal was revealed threefold increase in the AH-activity ($P < 0.001$).

In the CF the activity of AH rises of the 17-day-old and 30-day-old albino ratis explained by maintaining the normal energy supply. While in the CF of the analyzed brain structures (with the exception of the C) of 90-day-old rat restoration of the normal functioning takes place.

The analysis of the data of the dynamics of activities of SDH and MDH under hypoxia showed the most prominent indexes in the 30-day-old animal (Fig. 3 and 4).

The most intensive increase in the activities of the brain SDH and MDH of the 30-day-old animal as compared to other studied age groups is explained by that particularly 2^{nd}–4^{th} weeks of development for the rat are related to the process of intensive myelination, completing the neuronal development, appearance of electrical activity in the brain cortex and motive reactions during electro-stimulation of the brain, i.e. particularly this time activation of the biosynthetic reactions is observed [17].

Reduction of oxygen concentration in the medium to 10 μM sets in difficulties in the NADN-oxidase way of oxidation in the Krebs cycle that activates the compensatory metabolic flow in the cells with the intensification of succinate oxidase oxidation.

For the first time the adaptive role of transition to primary use of succinic acid as a substrate for oxidation in the mitochondria

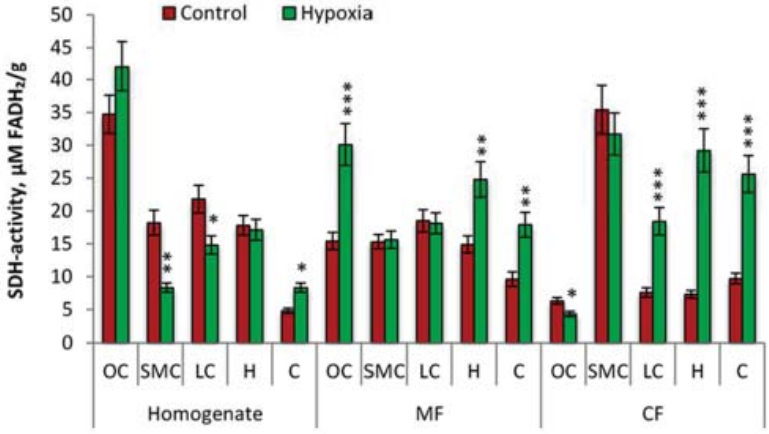

Fig. 3. **Dynamics of SDH-activity in the brain structures of the 30-day-old albino rat, exposed to hypoxia**

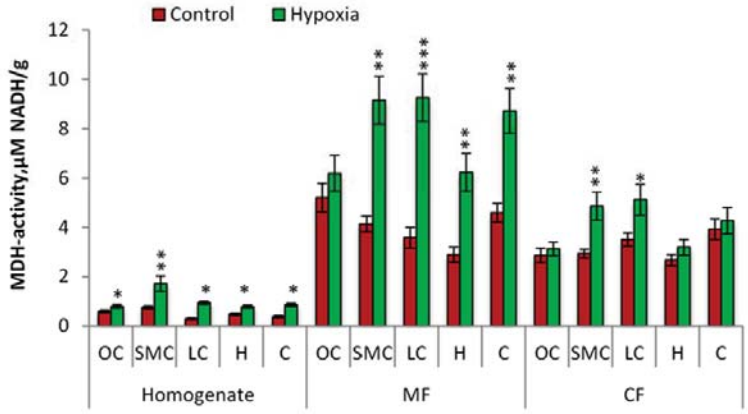

Fig. 4. **Dynamics of MDH-activity in the brain structures of the 30-day-old albino rat, exposed to hypoxia**

under hypoxic states is proposed, provided by revealed increase in these states of the SDH activity. Rather high and practically stable indexes of MDH in 30-day-old rat under hypoxia in the all age groups points to the stability of the animals to the stress-factor. The highest indexes of SDH activity are shown by H and C of the 30-day-old rats as compared to the other structures ($P < 0.001$).

Results and Discussion

So, it should be noticed that the change in the dynamics of LDH-activity after exposure to hypoxia was peculiar, depending on the brain structure being studied and the level of research (homogenate, mitochondrial and cytosolic fractions). It has been revealed that increasing of LDH activity ($P < 0.001$) in the different brain structures of albino rat may prevents metabolic disturbances in the regulatory mechanisms of biosynthetic and bioenergetics' processes in the neuronal cells of the brain structures. It should be noticed that glycolytic processes in the brain proceed in aerobic conditions, whereas LDH is the only enzyme involved in glycolysis under anaerobic conditions. Elevation in LDH activity in the brain in extreme conditions can be explained by its anaerobization due to the increase in anaerobic fractions in the isoenzyme of the LDH spectrum [6, 15, 18, 199].

The molecular transformation of LDH tetramer as a result of changes in the H- and M-subunits is coupled with anaerobization of glycolytic cycle and therefore LDH-related reactions can be used as a marker of the changes occurring in aerobic and anaerobic ratio in hypoxia. So, the rate and direction of LDH reactions are regarded as a most valid expression of glycolysis intensity and the rate of pyruvate utilization ratio in the Krebs cycle, glyconeogenesis and other reactions. Particularly, molecular transformation of LDH tetramer as a result of changes in the H- and M-subunits is coupled with anaerobization

of glycolytic cycle and therefore LDH-related reactions can be used as a marker of the changes occurring in aerobic and anaerobic ratio in hypoxia [18].

The obtained data indicate that hypoxia of developing brain realizes its specific effect by means of activation of HIF-1 signaling way which is an important stage in the formation of physiological systems in prenatal period of development [19–22]. Hence, the increase in LDH-activity in brain in extreme conditions can be explained by its anaerobization as a result of development of adaptation-compensatory response of the brain. Changes in the LDH-activity of the brain structures with increase of age can be regarded as an important determinant of cell reaction to the prenatal hypoxia in postnatal ontogenesis [22].

The comparison AH-activity from CF and MF is of great interest. These enzymes in the cell are designed for realization of different functions. As seen from Fig. 2, *a*, *b* the activity of enzyme in the both fractions of 17-day-old and 30-day-old control animals is almost similar. Only in the tissues of 90-day-old animal, in which the enzyme's activity changes considerably in the mitochondria relatively to the control, the correlation between the enzymes drastically changes ($P < 0.05$). These results are explained by running the synthetic processes of lipids going in the brain of 17-day-old and 30-day-old rat. NADPH necessary for this process is provided by cytoplasmic AH. In the tissues of the 90-day-old albino rat the process of intensified biosynthesis is completed and brain goes over to the way of obtaining energy in the Krebs cycle. It is, may be, results in the activation of the enzymes of the Krebs cycle, including AH from MF (Fig. 2, *a*, *b*).

The only difference is that in the MF of SMC of the hypoxized rat the activity of enzyme decreases by over 5 times, whereas in the CF it does not undergo any changes. On the basis of the obtained data one can conclude that prenatal hypoxia of fetus during organogenesis increases the activity both in activity AH from MF and CF in postnatal development and this process is being reversible by character.

Fig. 2, *a*, *b* shows the results of the impact of prenatal hypoxia on activity AH from MF. Repeated increasing of enzyme activity in the MF of the 17-day-old animals is practically identical with the enzyme activity in the CF as compared to the controls ($P < 0.01$). In the MF of the 30-day-old hypoxized albino rats the activity of the enzyme is higher than in other age groups and in average by over 2 times exceeds the control indexes with the exception of the C, in which enzyme activity does not change. The reasons causing these changes in the mitochondria are the same to the cytoplasmic AH. In the mitochondria of the 90-day-old rats one can notice more complex picture. In the C up regulation of its activity occurs, while in the SMC it decreases. In the LC, OC and H the activity of AH are closer to the control level. It is obvious that changes in the activity of enzyme from MF are identical to its changes in the CF [20].

Thus, the presented study will be able to help in the decision of some matters of energy supply of the brain in stress situations [6, 18]. Free radical theory occupies a definite role in this matter [23]. So, increasing in LDH and MDH activities in the brain structures can be related with metabolic disturbances in the regulatory mechanisms of biosynthetic and bioenergetics' processes in the brain [18, 22]. Increase in AH-activity bore reversible character. The highest indexes of SDH activity showed H and C of the 30-day-old rat as compared to the other structures. The changes revealed in the activity of the enzymes can be explained by the activation of biosynthetic reactions in these brain structures. At the same time, different purposefulness in the changes of these enzymes in brain structures can be related to structural organization of the brain structures under study on this stage of development. Prenatally hypoxia at the stage of organogenesis has a multidirectional effect on the activity of enzymes of energy metabolism of the brain and prolongs the periods of full-fledged postnatal development of the animal. Analysis of the changes in the enzyme system during ontogenesis allows adaptive mechanisms, formed in this period, to be revealed and study of the dynamics of their activity under changed functional state in hypoxia will give an opportunity to reveal adaptive resources of LDH, AH, MDH and SDH in the organism.

Observance with ethical standards

All applicable international, national important and / or institutional principles of care and animal use have been observed.

This article does not contain any investigations involving people as objects of studying.

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ДИНАМІКА АКТИВНОСТІ ЕНЗИМІВ У МОЗКУ ЩУРІВ, ЯКІ ЗАЗНАЛИ ГІПОКСІЇ

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Метою роботи було вивчити динаміку активності лактатдегідрогенази (ЛДГ; КФ 1.1.1.27), аконітази (АК; КФ 4.2.1.3), НАД-залежної малатдегідрогенази (МДГ; КФ 1.1.1.37) та сукцинатдегідрогенази (СДГ; КФ 1.3.99.1) в гомогенатах і субфракціх структур мозку щурів, які зазнали гіпоксії в 11–15-й дні пренатального розвитку, та їхню роль у формуванні компенсаторно-адаптивних механізмів структур мозку в постнатальному онтогенезі. Виявлено, що підвищення активності ЛДГ і МДГ ($P < 0.001$; $P < 0.01$, відповідно) в структурах мозку щурів запобігає метаболічним порушенням у механізмах регуляції біосинтетичних і біоенергетичних процесів у мозку. Пренатальна гіпоксія підвищує активність АК в постнатальному розвиткові, і цей процес має оборотний характер ($P < 0.01$). Найвищі показники активності СДГ було відзначено в гіпоталамусі й мозочку 30-денних щурів порівняно з іншими структурами ($P < 0.001$). На підставі отриманих даних можна зробити висновок, що гіпоксія на стадії органогенезу призводить до зміни процесу енергозабезпечення структур мозку і, можливо, є незворотною. Аналіз змін в ензиматичній системі в онтогенезі дає змогу ідентифікувати механізми адаптації й оцінити динаміку активності досліджуваних ензимів за зміни функціонального стану, що уможливлює виявлення адаптаційних резервів ензимів ЛДГ, АК, МДГ і СДГ в мозку після впливу гіпоксії.

Ключові слова: ензими енергетичного обміну.

ДИНАМИКА АКТИВНОСТИ ЭНЗИМОВ В МОЗГЕ КРЫС, ПОДВЕРГШИХСЯ ГИПОКСИИ

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Целью работы было изучить динамику активности лактатдегидрогеназы (ЛДГ; КФ 1.1.1.27), аконитазы (АК; КФ 4.2.1.3), НАД-зависимой малатдегидрогеназы (МДГ; КФ 1.1.1.37) и сукцинатдегидрогеназы (СДГ; КФ 1.3.99.1) в гомогенатах и субфракциях структур мозга крыс, перенесших гипоксию в 11–15-й дни пренатального развития и их роль в формировании компенсаторно-адаптивных механизмов структур мозга в постнатальном онтогенезе. Выявлено, что повышение активности ЛДГ и МДГ ($P < 0.001$; $P < 0.01$, соответственно) в структурах мозга крыс предотвращает метаболические нарушения в механизмах регуляции биосинтетических и биоэнергетических процессов в мозге. Пренатальная гипоксия повышает активность АК в постнатальном развитии, и этот процесс носит обратимый характер ($P < 0.01$). Самые высокие показатели активности СДГ были отмечены в гипоталамусе и мозжечке 30-дневных крыс по сравнению с другими структурами ($P < 0.001$). На основании полученных данных можно сделать заключение о том, что гипоксия на стадии органогенеза приводит к изменению процесса энергообеспечения структур мозга и, возможно, необратима. Анализ изменений в энзиматической системе в онтогенезе позволяет идентифицировать механизмы адаптации и оценить динамику активности исследованных энзимов при изменении функционального состояния, что дает возможность выявить выявить адаптационные резервы энзимов ЛДГ, АК, МДГ и СДГ в мозге после воздействия гипоксии.

Ключевые слова: энзимы энергетического обмена.