CORRELATION BETWEEN RESISTANCE OF RATS AT DIFFERENT STAGES OF ONTOGENY TO SEIZURES AND HYPOXIA

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The possibility of the practical use of hypoxic stimulation to increase nonspecific resistance and, in particular, to increase the resistance to the action of epileptogens, is being widely studied at the present time. It has been shown on adult animals that correlation exists between resistance to hypoxia and resistance of the brain to seizures [1, 3]. Considering that two-thirds of all cases of epilepsy occur in children [8], the resistance of experimental animals to seizures declines during postnatal ontogeny [10, 11], but resistance to hypoxia is significantly higher in the early stages of ontogeny than in adults [2, 5, 7, 9], it is interesting to study the period in which resistance to hypoxia begins to correlate with resistance to seizures.

The aim of this investigation was to determine resistance to hypoxia and to seizures at different stages of ontogeny.

EXPERIMENTAL METHOD

Experiments were carried out on noninbred albino rats at different times of postnatal development: on the 3rd, 7th, 14th, 21st, and 40th days after birth, and also in adult male rats (weighing 270 g). At each period two groups (each consisting of 20 animals) were formed, one of which was subjected to acute hypoxia, whereas resistance to seizures was recorded in the animals of the other group. Individual resistance to hypoxia was determined in a pressure chamber in an "altitude" of 12,000 m (rate of rise 200 m/sec), as reflected in the duration of the period from the time of elevation to this "altitude" until reversible respiratory arrest (survival time — ST). The resistance of young rats aged 3-7 days to hypoxia was also determined at an "altitude" of 13,000 m, for the ST of animals of both groups at 12,000 m was more than 30 min. To discover the resistance of the rats' brain to seizures, metrazol was injected intraperitoneally in a dose of 80 mg/kg. During the 60 min after injection the animals were kept under observation and behavioral changes were assessed: the latent period of seizure development was determined and the percentage of animals with developed epileptic fits and the percentage dying during seizures were calculated.

EXPERIMENTAL RESULTS

The results are given in Table 1. Their analysis shows that newborn rats aged 3-7 days were the most resistant to hypoxia. No significant differences could be found between them ($p > 0.05$). With age, resistance to hypoxia decreased. The survival time of the 14-day-old rats under these conditions approximated to 9.8 min, compared with 2.8 min for rats aged 21 days and 1.4 min for rats aged 40 days. Some increase of resistance to hypoxia was observed in the adult rats compared with rats aged 40 days (their ST was 2.9 min). Significant differences were found between animals of all age groups, starting with the 7th day after birth, in their resistance to altitudes ($p_{7\text{-}14} < 0.01$; $p_{14\text{-}21} < 0.01$; $p_{21\text{-}40} < 0.01$; $p_{40\text{-adult}} < 0.01$).

The resistance of the brain to seizures induced by metrazol, like resistance to hypoxia, was maximal during the first days (3rd-7th) after birth. After injection of metrazol, animals of all age groups exhibited hyperactivity and alternate myoclonic movements first of one, then of the other limb, flexion of the spine, thrusting forward of the head, and in rare cases, falling on the side. The latent period of development of this state in the young rats aged 3 days was 28.7 min, compared with 21.9 min for rats aged 7 days. No significant differences could be found in the results between animals of these two age groups ($p > 0.05$).

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TABLE 1. Changes in Resistance of Rats to Hypoxia and Seizures during Postnatal Development ($M \pm m$)

Age, days	Survival time, sec	Latent period of epileptic fit development, sec	Number of animals with developed epileptic fit, %	Number of animals dying, %
3	1898,3±318,4	1724,0±232,5	37,5	0
7	1607,5±133,5	1314,8±143,6	65,0	2,5
p_{3-7}	>0,05	>0,05		
14	588,1±31,2	952,5±109,8	96,8	38,7
p_{7-14}	<0,01	>0,05		
21	169,2±10,0	440,3±49,7	77,1	5,7
p_{14-21}	<0,01	<0,01		
40	86,7±7,3	642,9±69,6	80,0	16,0
p_{21-40}	<0,01	<0,05		
Adult	176,7±3,75	628,7±61,5	96,3	29,6
P_{40}-adult	<0,01	>0,05		

The number of animals developing an epileptic fit was 37.5% at the age of 3 days and 65% at the age of 7 days. At the age of 3 days all animals survived after injection of the convulsant, whereas at 7 days, 2.5% of the animals died.

During postnatal ontogeny the severity of the seizure disturbances increased. On the 14th-21st day marked generalized seizures affecting the whole body, with frequent falls on the side, were observed (in 96.8% at 14 days, in 77.1% of cases at 21 days), terminating in death of 38.7% of the animals at 14 days and 5.7% at 21 days. The latent period of seizure development was 15.9 min at 14 days and 7.3 min at 21 days ($p_{7\text{-}14} > 0.05$; $p_{14\text{-}21} < 0.01$).

The increasing sensitivity to the action of the convulsant, observed at the age of 21 days, showed a small decrease by the 40th day. Although epileptic fits developed in 80% of cases, and mortality was 16%, nevertheless the latent period of seizure development increased until 10.7 min ($p_{21\text{-}40} < 0.05$). Approximately the same values for the latent period of development of seizures (10.5 min) also were found in adult animals ($p_{40\text{-adult}} > 0.05$). The development of an epileptic fit was observed in 96.3% of cases and 29.6% of the animals died.

Behavioral responses in adult animals after injection of metrazol differed only a little from those in rats aged 14 and 21 days.

These investigations thus confirmed the results of our previous experiments on adult animals, in which correlation was found between resistance to hypoxia and to seizures. Correlation between these values was observed from the first days after birth. During this period, their values reached a maximum. Later, with an increase in the age of the rats, there was a synchronized decrease in resistance to both hypoxia and seizures. A sharper decrease in resistance to hypoxia was observed, which reached a minimum after the 40th day of birth. Resistance of adult animals to hypoxia was higher than in 40-day-old rats.

During growth of the animals, the resistance of their brain to seizures also decreased. Whereas the shortest latent period of development of the epileptic fit was recorded on the 21st day of life, the fits themselves developed more readily on the 14th day after birth (in 96.8% of cases), and mortality also was highest at this time, namely 38.7%. The subsequent increase in resistance of the rats to seizures can be explained by cell differentiation in the outer granular layer of the cerebellum, which takes place at the end of the 2nd week of postnatal development, by maturation of neurons of the cerebral cerebellar nuclei (by the 18th day), and by cell differentiation in the caudate nucleus, one of the antiepileptic structures of the brain [6], in the 2nd week of postnatal life [4].

It can be tentatively suggested that resistance to hypoxia and to seizures is based on common mechanisms, which explain the correlation between them. This correlation is found in the first days after birth and persists in the adult state.

LITERATURE CITED

1. N. A. Agadzhanyan and V. I. Torshin, "Action of convulsants on animals differing in individual resistance to hypoxic hypoxia," Byull. Éksp. Biol. Med., **95**, No. 6, 20 (1983).
2. A. A. Bashkirov and O. B. Shakhanova, "Physiological principles of postnatal ontogeny and acute hypoxia," in: Current Problems in Perinatology [in Russian], Moscow (1978), pp. 129-132.
3. V. A. Berezovskii, Hypoxia and Individual Differences in Reactivity [in Russian], Kiev (1978), p. 215.
4. N. I. Dmitrieva, "On periods of development of brain structures in ontogeny of the rat," Zh. Évol. Biokhim. Fiziol., **17**, No. 3, 287 (1981).
5. A. Z. Kolchinskaya, Oxygen Deficiency and Age [in Russian], Kiev (1964), p. 335.
6. G. N. Kryzhanovskii, Determinant Structures in Pathology of the Nervous System [in Russian], Moscow (1980).

7. L. A. Orbeli, "The nervous system at low pressure," Sov. Nauka, No. 10, 66 (1940).
8. Yu. A. Yakunin, "Epilepsy," in: Neurology and Pathology of Early Childhood [in Russian], Leningrad (1981), pp. 299-315.
9. P. D. Altland and B. A. Rattner, "Age and altitude tolerance in rats: temperature, plasma, enzymes and corticosterone," J. Appl. Physiol., **50**, No. 2, 367 (1981).
10. E. A. Cavalheiro, "The susceptibility of rats to pilocarpine-induced seizures is age-dependent." Develop. Brain Res., **37**, 43 (1987).
11. D. Marcsova and P. Mares, "Ontogenetic development of wet dog shakes accompanying hippocampal epileptic after-discharges in rats," Active Nerv. Sup. (Prague), No. 4, 254 (1988).

ABOLITION OF DISTURBANCES OF ELECTRICAL STABILITY OF THE HEART AND ARRHYTHMIAS A SYNTHETIC ACETYLCHOLINE ANALOG

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The cholinergic regulation of the heart limits excessive adrenergic (stressor) effects on that organ, helps to maintain a sufficiently high resting potential (RP) of the myocardial cells, and thus possesses a stress-limiting, antiarrhythmic action [4]. In many cases, however, strong negative chronotropic effects of the vagus nerve are linked with suppression of automatism of the sinus node and may lead to the realization of foci of ectopic excitation at a lower level, and the appearance of cardiac arrhythmias [1, 5]. Accordingly, the search for new antiarrhythmic factors, which would completely possess the adrenolytic and hyperpolarizing actions of acetylcholine, but which would not have the excessive negative chronotropic effect, characteristic of acetylcholine, and would thus prove to be optimal antiarrhythmics, has become particularly urgent.

The aim of this investigation was to study the effect of ethyl-3/2-ethyl-2,2-dimethylhydrazinium propionate· iodide (EDHPI) (approved invention No. 4217356/31-04) on the disturbance of electrical stability of the heart and arrhythmias associated with acute myocardial infarction and postinfarction cardiosclerosis, and also with acute ischemia and subsequent reperfusion.

EXPERIMENTAL METHOD

Experiments were carried out on male Wistar rats weighing 250-400 g. The first stage in the investigation envisaged assessment of the effect of EDHPI on the disturbance of electrical stability of the heart associated with acute myocardial infarction and postinfarction cardiosclerosis, and consisted of the six following series: I) control animals; II) animals receiving EDHPI; III) animals with experimental myocardial infarction; IV) animals with experimental myocardial infarction and receiving EDHPI; V) animals with postinfarction cardiosclerosis; VI) animals with postinfarction cardiosclerosis and receiving EDHPI. In the second stage the effect of EDHPI, atropine, and their combinations were studied on ischemic and reperfusion arrhythmias,

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