at midday in summer and at 18:00 h in the fall; for the right ventricle in the fall at either time).

In the winter period, verapamil reliably increased the contractility reserves of both ventricles when administered at 12:00 h, whereas only a tendency to an increase was observed when the drug was administered at 18:00 h.

Analysis of the correlation between different functional indices of the cardiovascular system has revealed that in hypertensive rabbits in spring, summer, and winter the interrelation between IVR_{real} l.v. and AP_{min} becomes less marked; in other words, cardiac output is not adequate to the peripheral vascular resistance. In both cases, administration of verapamil has a negative effect on the above correlation as well as on the interrelation between AP_{max} and AP_{min}. The average absolute values of the correlation coefficients upon verapamil administration or without treatment are compared in Table 4.

As follows from Table 4, administration of the drug at 18:00 h proved to have a higher normalizing effect on hypertension-induced disturbances in the correlations compared to administration at 12:00 h.

Thus, the hypotensive effect of verapamil is much more pronounced when the drug is administered at midday than at 18:00 h. However, in winter a hypertensive effect of the drug was registered at any time of its administration. The action of verapamil on the myocardium was also time-dependent: the heard muscle functioned in a more "sparing" regime when the drug was administered at 12:00 h compared to 18:00 h. But in winter myocardial hyperfunction was recorded in both cases.

The results obtained allow us to conclude that in terms of the intensity of the hypotensive effect and extent of myocardium involvement, administration of verapamil to animals with vasorenal arterial hypertension at 12:00 h yields better results than administration at 18:00 h. This conclusion is valid for spring, summer, and fall. As for the winter period, verapamil does not exert a hypotensive effect but even provokes a drastic overloading of the myocardium.

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Disturbed Behavior of Rats Suffering Intrauterine Hypoxia is Corrected by Postnatal Treatment with Piracetam

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Fetal hypoxia is one of the most widespread causes of disturbances in brain development exhibited at later dates in neuropsychic disorders [8,9]. In the treatment of such disorders nootropic drugs can be assumed to be effective. In pediatrics nootropics are used in the therapy of mental disturbances of diverse origin in the presence of obvious symptoms of illness [10, 15]). At the same time, the consequences of oxygen deficiency

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displayed in brain function disturbances are often found not immediately after birth, but later on, when intellectual and neuropsychic loads appear [9], and when the possibility of therapeutic correction is already lost or reduced. The possibility of correcting fetal hypoxia behavioral sequelae by nootropics applied in the early postnatal period has not been elucidated. In the investigation of this question, modeling the pathology of the developing brain and evaluation of the effect of nootropics in this model acquire paramount significance.

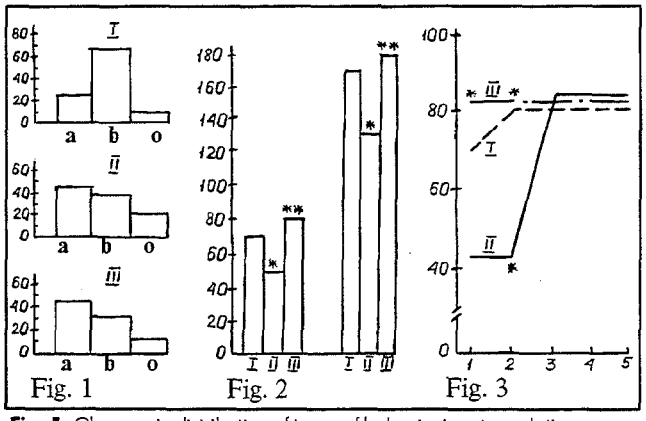

Fig. 1 Fig. 2 Fig. 3

Fig. 1. Changes in distribution of types of behavior in extrapolative escape test in mature rats subjected to intrauterine hypoxia and treated with piracetam. I) control rats not subjected to hypoxia; II) untreated rats subjected to hypoxia; III) animals subjected to hypoxia and treated with piracetam. A, B and 0) subgroups of animals isolated in EET by type of behavior. Ordinate: number of animals (in %) in the subgroup.

Fig. 2. CRPA reproduction improvement by piracetam 1 (left) and 14 (right) days after its reproduction in mature rats subjected to intrauterine hypoxia. Ordinate: latent time (sec) of first run into "dangerous" compartment of the box, in which rats received electropain reinforcement during conditioning. Other designations as in Fig. 1. One asterisk - $p<0.01$ in comparison to group I, two asterisks - $p<0.05$ in comparison to group II according to Wilcoxson-Mann-Whitney test.

Fig. 3. CRAA reproduction improvement by piracetam 14 days after mature rats subjected to intrauterine hypoxia passed conditioning test. Abscissa: days of reproduction, ordinate: number of animals (in %) passing test during habit reproduction. One asterisk $p<0.05$ in comparison to group I, two asterisks - $p<0.05$ in comparison to group II by χ^2. Other designations as in Fig. 1.

The purpose of the present study was to investigate the effect of piracetam on the behavior, training abilities, and memory of adult rats subjected to prenatal hypoxia.

MATERIAL AND METHODS

The offspring of 10 mongrel albino rats were used in the experiments. Fetal hypoxia was created by a modified method of M.Ya.Maizelis et al. [5], by placing the rats on the 15th day of hypoxia in a pressure chamber with rarefied air corresponding to an altitude of 8500 m for 2 hours. At a velocity of 500 m/min the animals were "raised" to an altitude of 5000 m, where they were kept for 15 min, and then "raised" at the same velocity to an altitude of 8500 m. The "descent" velocity was 3000 m/min. The young rats whose mothers had suffered hypobaric hypoxia during pregnancy, were injected hypodermically on the 8th - 20th day of life with a 0.9% solution of NaCl or piracetam in a dose of 200 mg/kg a day. The progeny of "intact" females were injected with 0.9% NaCl. The following investigations were carried out only on the male progeny. The physical development of the young rats was evaluated from the 8th - 20th day of life by body weight gain and times of eye opening. At the age of 2 months during 5 successive days the behavior of the offspring was investigated in an open field. At the age of 2.5 months their behavior was studied in an extrapolative escape test (EET) [1]. For this purpose the rats were placed in a cylinder immersed 1 cm vertically into water. The latent time of the first attempt at escape and the time of escape from the stress situation (an attempt of diving under and successful diving under the edge of the cylinder) were examined. In 3-months rats the conditioned reflex of passive avoidance (CRPA) was elaborated in a device of the Lafayette Instrument Co (USA). The preservation of the habit was monitored 24 hours and 2 weeks after its formation. At the age of 3.5 months the conditioned reflex of active avoidance (CRAA) [4] was developed in the animals in a Ugo Basile shuttle box (Italy). Fifty pairings of conditioned sound stimulus and electropain reinforcement were presented daily. The conditioning was performed up to the training test (8 escapes for 10 presentations) but no longer than 5 days. Two weeks after achievement of the training test the preservation of CRAA was checked by repeating the conditioning. Learning and memory were evaluated by the number of animals passing the training test.

RESULTS

Weight gain in the progeny exposed to prenatal hypoxia was delayed. While in the control group body weight on the 20th day of life vis-a-vis to the 8th day accounted for 53.3%, in the group of "hypoxic" animals it was just 37.1%. The times of eye opening in the control group and in the animals subjected to intrauterine hypoxia did not differ.

No changes of activity in the open field were observed in the "hypoxic" animals. In EET experiments we identified the rats whose time of the first attempt at escape and the successful diving under the edge of the cylinder was less than 15 sec (subgroup A), and the animals whose time of the first attempt at escape was less than 15 sec, and the time of the successful escape was more than 15 sec (sub-group B). A separate group comprised rats, which were not able to solve the task of escape during 120 sec and which never dived under the edge of the cylinder (subgroup 0). Intrauterine hypoxia changed the population structure in EET: the number of animals in subgroup B decreased, while their number in subgroup A increased (Fig. 1).

Oxygen deficiency during the prenatal period of development destroyed reproduction of CRPA 14 hours as well as 2 weeks after its elaboration (Fig. 2).

Taking into account the decrease of the number of animals isolated into subgroup B and usually reproducing CRPA most successfully [11], we can assume that a short-term oxygen deficiency during intrauterine development lowers the number of animals capable of optimum reproduction of CRPA. It is necessary to mention that, during the repeated testing of CRPA 2 weeks after training the latent period of the first run in intact animals is significantly longer than during the first check-up after 24 hours. Such an improvement in CRPA reproduction during the repeated testing in intact rats was observed earlier both by us [6] and by other researchers [13]. It can be conditioned by the "remembering" which is initiated not only by a stimulus identical to the reinforcement, but by other influences causing emotionally similar states [3]. These stimuli can be such stressors taking place during the first testing of the habit as taking the animal in the hands, fear of height, or of a bright light on the platform. Prenatal hypoxia worsened the cognitive processes involved in "rememberring".

Prenatal oxygen deficiency delayed CRAA reproduction after 2 weeks of its elaboration, *i.e.*, it strengthened forgetting (Fig. 3).

Piracetam applied in the early postnatal period normalized physical development of the progeny. The body weight gain of these animals on the 2nd day of life in comparison to the 8th day accounted for 62.2%.

Piracetam corrected the disturbances in cognitive functions of offspring subjected to intrauterine hypoxia. In nootropic-treated "hypoxic" rats during CRPA reproduction 24 hours and 2 weeks after training the latent period of the first run into the "dangerous" compartment of the box was significantly longer than in untreated "hypoxic" animals and practically did not differ from that in intact rats (see Fig. 2).

In the animals subjected to prenatal hypoxia and treated with piracetam, as well as in control rats the phenomenon of "remembering" was observed: CRPA reproduction 2 weeks after its elaboration was significantly better than on the next day after training. This also gives evidence of rehabilitation of the cognitive processes.

Piracetam did not normalize the structure of the population in EET indications (see Fig. 1). Consequently, while improving learning and memory, piracetam did not restore the animals' initial state determining the distribution of the intact rats in EET.

Improvement of memory, but not of learning, was also observed in the CRAE model. The rats into which piracetam was injected postnatally reproduced the habit 2 weeks after passing the training test no worse than did intact animals (see Fig. 3).

Thus, in our experiments, as well as in those of other workers [7, 14], prenatal hypoxia was accompanied by subsequent disturbances in brain functioning, manifested in disturbances in cognitive processes, in the models of passive and active avoidance, and in changes of the nature of behavior in EET. One of the possible reasons can be a postnatal suppression of protein metabolism after intrauterine hypobaric hypoxia [2], increasing with age [5]. Piracetam [12] activates the protein and nucleic synthesis, necessary for learning and memory, which can provide for compensatory processes when this preparation is given in the critical period of postnatal development.

On the whole the results attest to the effectiveness of piracetam applied in the early postnatal period as a corrector of brain functional disturbances in rats.

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