grounds that after injection, exogenous heparin can combine with several blood proteins to form complexes which create an increase in NEFA in the plasma. However, unlike the experimental animals of group 4, the degree of NEFA in rats of group 3 after injection of heparin rose briefly but then began to fall, and 30 min after injection this parameter was much lower in value than in the animals after injection of the complex.

The results are evidence that intravenous injection of the H–AT III complex considerably enhances the anticoagulant background and potentiates the nonenzymic fibrinolytic activity of the animals' plasma. According to our data, intravenous injection of this complex may largely neutralize activity of the enzyme thrombin, unlike injection of AT III alone into the blood stream [5]. These data are evidence that AT III is one of the components of the anticlotting system of the body responsible for controlling the liquid state of the blood through limitation of thrombin production and lysis of unstabilized fibrin clots which have formed in the blood stream.

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MECHANISM OF THE CEREBROVASCULAR EFFECT OF PYRACETAM

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According to data in the literature [2, 7] pyracetam increases the blood supply to the brain both in intact cats and in animals with mild hypoxia. The increase in the cerebral blood flow produced by pyracetam is also found in patients with chronic cerebrovascular insufficiency [6]. However, the mechanism of the effect of the drug on the cerebral circulation has not yet been established. In particular, we have no information on the effect of pyracetam on nervous control of the cerebral blood supply. At the same time, it has been found that GABA, the natural analog of pyracetam, takes part in the realization of the cerebrovascular effects of GABA-ergic substances [3, 5]. For the reasons given above it was decided to study the effect of pyracetam on nervous control of the cerebral circulation with an analysis of the role of GABA in its cerebrovascular effects. Another aim of the investigation was to study the effect of pyracetam on the cerebral hemodynamics under conditions of hemorrhagic shock.

EXPERIMENTAL METHOD

Experiments were carried out on 31 cats weighing 3-4 kg under general anesthesia (urethane, chloralose) with artificial ventilation of the lungs, and on 10 unanesthetized rabbits

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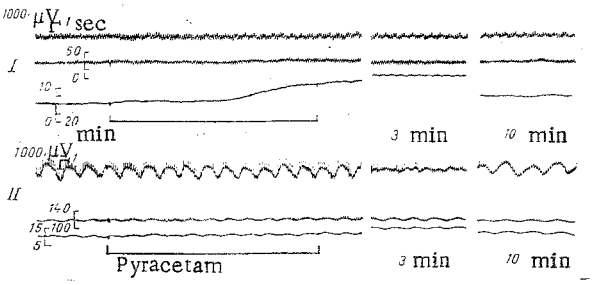

Fig. 1. Effect of pyracetam (300 mg/kg, intravenously) on cerebral circulation of unanesthetized rabbits. I) Hemorrhagic shock, II) intact animals. From top to bottom: ECG in lead II, BP in carotid artery (in mm Hg), cerbral blood flow (in ml/min).

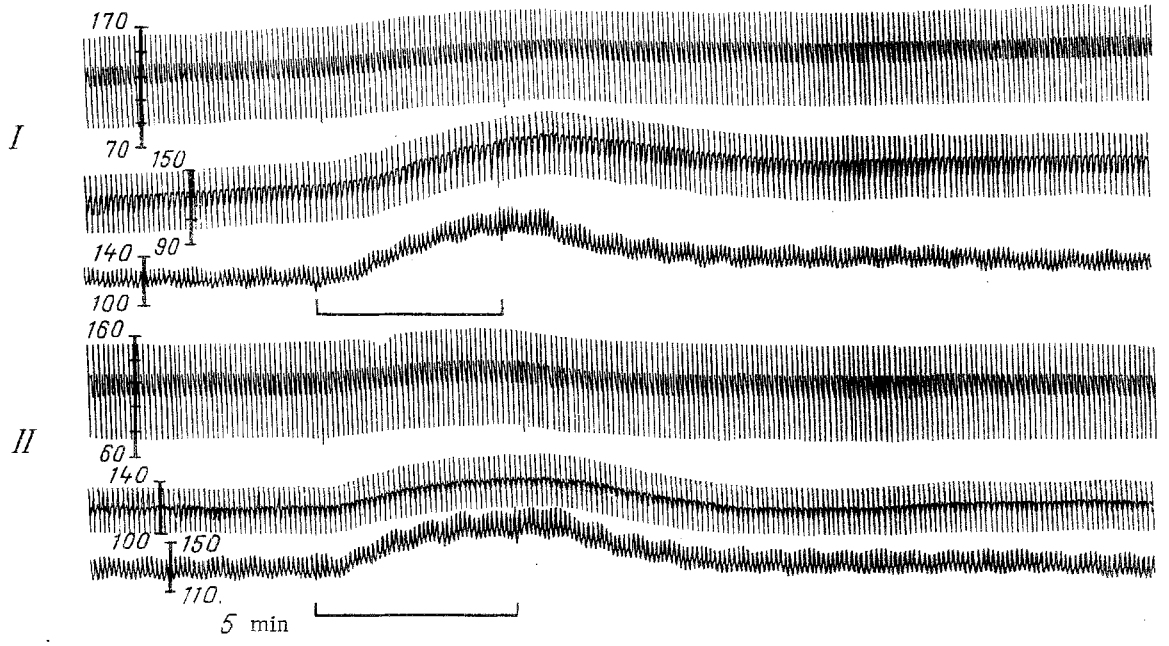

Fig. 2. Effect of pyracetam (300 mg/kg, intravenously) on reflex constrictor responses of cerebral vessels. I) Control response, II) 5 min after injection of pyracetam. From top to bottom: perfusion pressure in carotid territory, in vertebrobasilar system, BP (in mm Hg), marker of stimulation (20 V, 20 stimuli/sec, 20 msec, 15 sec).

weighing 2-3 kg. The inflow of blood into the brain through the carotid arteries, after careful ligation of their extracranial branches, was measured by means of an electromagnetic flowmeter (Nihon Kohden, Japan). The EEG in the parietal region, the ECG in lead II, and the arterial pressure (BP) in the femoral artery were recorded simultaneously. Tonic activity and reflex discharges in the sympathetic nerves of the renal plexus were recorded [1]. The vascular component of the action of the substances on the cerebral hemodynamics was differentiated by the method of separate perfusion of the carotid and vertebral arteries bilaterally [4].

The effect of pyracetam on the cerebral hemodynamics, BP, and ECG also was studied under conditions of hemorrhagic shock (bleeding from the femoral artery) in unanesthetized rabbits. Bleeding was stopped when BP had fallen to 40 mm Hg. This level of Bp was maintained for 20 min, after which the effect of pyracetam on the cerebral circulation and BP was investigated.

The partial pressure of CO_2 (pCO_2) was determined in the cats' arterial blood and maintained within the limits of the control values (35-40 mm Hg).

The substances for testing were injected intravenously: pyracetam in doses of 100-300 mg/kg, bicuculline in a dose of 0.15-0.2 mg/kg. The animals were killed with a mixture of urethane and chloralose.

EXPERIMENTAL RESULTS

Pyracetam in doses of 100-300 mg/kg increased the inflow of blood into the brain. When pyracetam was given in a dose of 300 mg/kg the increase in the blood supply to the brain was 39 ± 5.6% and the effect lasted 20-40 min. Pyracetam depressed vascular tone in the carotid and vertebrobasilar systems of the brain equally (by 22-23%). In intact rabbits pyracetam (300 mg/kg) increased the inflow of blood into the brain by the same degree as in anesthetized cats (Fig. 1). However, the cerebrovascular effect of pyracetam was manifested to a much greater degree in rabbits with hemorrhagic shock. In the animals of this series of experiments pyracetam increased the blood supply to the brain on average by 80 ± 16.4% (Fig. 1). In most experiments the cerebrovascular effect of pyracetam was observed immediately after its injection. In other experiments the increase in the cerebral blood flow under the influence of pyracetam developed gradually and reached a peak after 30-45 min. The increase in the cerebral blood flow, incidentally, was not accompanied by any significant elevation of BP.

The study of the effect of pyracetam on nervous control of the cerebral circulation showed that in a dose of 300 mg/kg the drug can inhibit reflex vasoconstrictor responses in the carotid and vertebrobasilar systems by 33 ± 3.4 and 34 ± 5.0%, respectively (Fig. 2). A series of experiments in which the cerebral blood flow was recorded showed that the drug considerably increases the inflow of blood into the brain during formation of the vasomotor reflex. Pyracetam has a varied action on pressor reflex responsnes of BP. Mainly the drug inhibited the vasomotor reflex. In some experiments initial depression of the pressor reflex was following by enhancement. Tonic and reflex activity in the sympathetic nerves was depressed somewhat by pyracetam in most experiments.

If GABA-receptors were blocked by bicuculline, pyracetam increased the cerebral blood flow by 53 ± 10% (39 ± 5.6% in the control, difference not statistically significant). Changes in vascular tone in the carotid and vertebrobasilar systems under the influence of pyracetam under these conditions likewise did not differ from the control.

After administration of bicuculline pyracetam inhibited reflex vasoconstrictor responses in the carotid and vertebrobasilar systems. The depressant effect of the drug on the cerebrovascular reflexes was manifested under these conditions to the same degree as in intact animals. The results are evidence that the ability of pyracetam to increase the blood supply to the brain and to weaken reflex vasoconstrictor responses of the cerebral vessels is not mediated through bicuculline-sensitive GABA receptors.

Pyracetam thus has a marked effect on the cerebral blood supply when the cerebral hemodynamics is disturbed by hemorrhagic shock. Pyracetam was shown to have a depressant effect on nervous control of the cerebral circulation and to inhibit reflex vasoconstrictor responses in the two arterial systems of the brain.

The cerebrovascular effects of pyracetam are not mediated through bicuculline-sensitive GABA-ergic mechanisms, for the effects of the drug are exhibited when GABA-receptors are blocked.

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