THE ROLE OF THE HEMATOENCEPHALIC BARRIER IN THE PATHOGENESIS AND THERAPY OF ACUTE CEREBROSPINAL TRAUMA

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Clinical observations show that acute cerebrospinal trauma, like certain diseases of the central nervous system, is accompanied by disturbance of the functional state of the hematoencephalic barrier [1, 2].

In the present investigation* we attempted to clarify the physiological mechanisms bringing about an increase in the permeability of the hematoencephalic barrier in cerebrospinal trauma, and also to seek methods of reducing it. Since in cerebrospinal trauma there is an accumulation of acetylcholine in the tissues of the brain and the cerebrospinal fluid [4, 5, 6] which may cause increased permeability of the hematoencephalic barrier because of increase in the activity of the tissue hyaluronidases [3]; concurrently with the study of the permeability we determined the acetylcholine content and the hyaluronidase activity of the cerebrospinal fluid.

EXPERIMENTAL METHOD

In order to determine the permeability of the hematoencephalic barrier we used radiophosphorus (P^{32}), which was given orally to the subjects of the investigation in a dose of 80-100 mC. From 45-60 min after administration of the P^{32}, lumbar puncture was performed, and then over a period of time repeated examinations of the cerebrospinal fluid and blood were made (in patients in whom lumbar puncture was indicated for diagnostic or therapeutic purposes).

The radioactivity of the test fluids was determined by means of a counter with a type B apparatus. The results were expressed as percentages of the content of P^{32} in the blood.

The acetylcholine was investigated by a biological method in the dorsal muscle of a leech against a standard acetylcholine solution.

Hyaluronidase was estimated by McClean's method of mucin precipitation.

EXPERIMENTAL RESULTS

Our observations were made on 100 patients with acute cerebrospinal trauma. The patients were admitted to the hospital within a few days of the injury.

Two clinical groups were distinguished in accordance with the severity of the trauma and the findings of the permeability of the hematoencephalic barrier: patients with moderately severe and those with severe forms of injury.

We also distinguished a group of patients with slight head injuries without signs of concussion of the brain, and on investigation of the permeability of the hematoencephalic barrier in this case the findings were taken to be normal.

In addition we investigated the distribution of P^{32} in the brain of 8 patients who were given the isotope previously and who died as a result of severe cerebrospinal trauma two days before examination.

The results obtained showed that the permeability of the hematoencephalic barrier in slight injuries without signs of concussion of the brain is 1.5-3%, which evidently represents the normal permeability to P^{32}; in trauma of moderate severity the permeability is raised to 7.5-9%; in severe trauma it amounts to 11-12% and sometimes reaches 25-30%, which agrees completely with the findings of A. M. Vein [1].

* The work was carried out under the guidance of Prof. G. N. Kassil'.

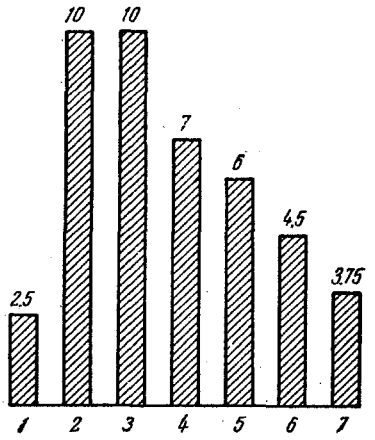

Fig. 1. Content of P^{32} in the cerebrospinal fluid (in percentages of its content in the blood; average data of all the investigations made). 1)Normal; 2) in closed trauma of the skull; 3) in closed trauma of the skull after administration of atropine; 4) in closed trauma of the skull after administration of phenylephrine; 5) in closed trauma of the skull after administration of prostigmin (moderate and severe forms); 6) in closed trauma of the skull after administration of pentamine; 7) in closed trauma of the skull after administration of benadryl.

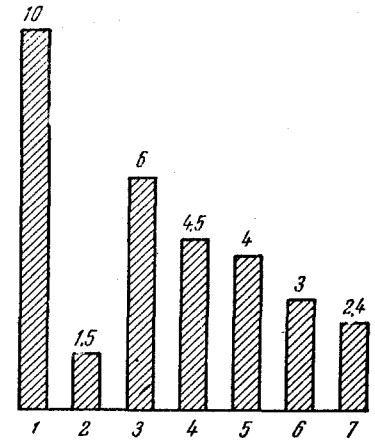

Fig. 2. Content of acetylcholine in the cerebrospinal fluid in γ% (average results of all investigations). 1) Standard solution of acetylcholine – 10%; 2) normal; 3) in closed trauma of the skull; 4) in closed trauma of the skull after administration of atropine; 5) in closed trauma of the skull after administration of phenylephrine; 6) in closed trauma of the skull after administration of prostigmin; 7) in closed trauma of the skull after administration of pentamine.

The acetylcholine concentration in the cerebrospinal fluid does not normally exceed 1-1.5 γ%. In severe head injury its content was raised to 6-7 γ%.

In severe trauma, in addition to increased permeability of the hematoencephalic barrier, increased activity of hyaluronidase in the cerebrospinal fluid was observed.

When the brain of patients dying from the sequelae of trauma was investigated rapid penetration of P^{32} into the brain was found: even 30 min after the administration of P^{32} to the patients it could be found in the brain tissue in considerable quantity.

The intensity of accumulation of P^{32} depends on the period elapsing from the time of its administration until death. P^{32} is distributed in the brain tissue as follows: hypophysis > vascular plexi > diencephalic region > > cerebral cortex > brain stem > white matter.

It was found by examination of symmetrical areas of the brain that in regions in which pinpoint hemorrhages were present without mechanical damage to the vessel walls, there was a considerably larger accumulation of P^{32} in comparison with macroscopically unchanged areas of the brain.

In contused areas of the cerebral cortex the accumulation of P^{32} was considerably greater than in the undamaged cortex or in the cortex where small subpial hemorrhages were present. If the high content of P^{32} in the contused areas is connected with mechanical damage to the walls of the vessels, in the region of the subpial and pinpoint hemorrhages, as shown by control histological investigations, no mechanical damage to the vessel walls could as a rule be detected, and for this reason it must be considered that the high content of P^{32} in these regions is due to a sharp increase in the permeability of the vascular walls, through which may pass not only plasma but also the blood cells.

In view of the functional disturbances established, in the second part of the work we tested the activity of anticholinergic (atropine), adrenergic (phenylephrine), anticholinesterase (prostigmin) antihistamine (benadryl) and ganglion-blocking (pentamine) drugs on the altered permeability of the hematoencephalic barrier.

On subcutaneous injection of atropine in a dose of 1.5-2 ml of a 0.1% solution, in 12 out of the 15 patients under observation a fall in the permeability of the hematoencephalic barrier was found. The percentage content of P^{32} in the cerebrospinal fluid fell from 10-11 to 4-5%, remaining at this level for almost the whole of the rest of the investigation.

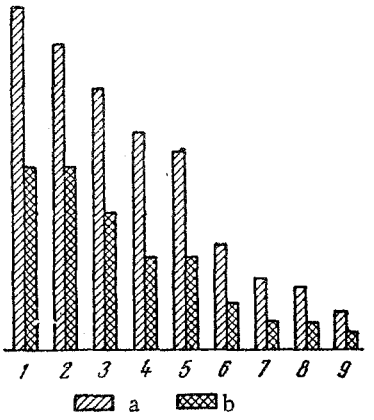

Fig. 3. Distribution of P^{32} in various areas of the brain. a) In cerebrospinal trauma; b) in cerebrospinal trauma after treatment with pentamine. 1) Hypophysis; 2) the ventricular plexi of the brain; 3) contused areas of the cerebral cortex; 4) areas of the cerebral cortex in which there were small hemorrhages with no damage to the vessel walls; 5) diencephalic region; 6) cerebral cortex (intact); 7) subcortical ganglia; 8) brain stem; 9) white matter.

When the patients were injected with phenylephrine (metasympatol) in a dose of 1.5-2 ml of a 1% solution, 9 of the 12 patients under observation showed a fall in the permeability to P^{32}, but it was shorter in duration and less pronounced, while in 2 patients the permeability was unaffected and in one it was increased to 5-7%. The action of atropine and phenylephrine also lowered the acetylcholine content of the cerebrospinal fluid, which evidently led to a fall in the permeability of the hematoencephalic barrier on account of the reduced activity of the tissue hyaluronidases.

In patients with closed head injuries a series of investigations was performed in which 1.5-2 ml of a 0.05% solution of prostigmin was injected. In moderate and severe trauma to the skull, prostigmin lowered the permeability and reduced the acetylcholine content of the cerebrospinal fluid; in slight trauma to the skull, when a low acetylcholine content was observed in the cerebrospinal fluid, prostigmin had no effect, or in some cases even increased the permeability of the hematoencephalic barrier.

Considering that in cerebrospinal trauma there is damage to brain tissue, accompanied by liberation of histamine (I. L. Vaisfel'd), we injected benadryl into patients with acute head injuries, but no noticeable effect was found on the permeability of the hematoencephalic barrier.

The most obvious action on the permeability of the hematoencephalic barrier in patients with cerebrospinal trauma was shown by intramuscular injection of the ganglion-blocking drug pentamine in a dose of 50 mg. In 25 of the 30 patients under observation a fall in the P^{32} content of the cerebrospinal fluid was observed, from 10-20 to 2-5%. In 3 patients the permeability was unchanged and in 2 patients a small rise in the permeability of the hematoencephalic barrier was detected.

After administration of pentamine there was also a considerable fall in the acetylcholine content and the hyaluronidase activity of the cerebrospinal fluid. We obtained analogous results also in experiments on rats.

A brain examination was made on two groups of patients who died two days after severe skull injury; the first group had received P^{32} and repeated injections of pentamine, the second had not. The P^{32} content in various areas of the brain was 2-3 times smaller in the group that had not received pentamine.

We considered it possible to compare these findings, since the results obtained after the injection of pentamine considerably exceeded the limits of variation in patients not treated with pentamine (Fig. 3).

Systematic treatment of patients with cerebrospinal trauma with pentamine gave good clinical results and the electroencephalogram was more rapidly restored to normal than with other forms of therapy.

SUMMARY

The permeability of hematoencephalic barrier was investigated in 100 patients with acute craniocerebral trauma by comparison of the content of P^{32} in the blood and in the cerebrospinal fluid. The content of acetylcholine and the activity of hyaluronidase in cerebrospinal fluid was also studied. These examinations were carried out prior to and after the action of anticholinergic (atropine), adrenergic (phenylephrine), anticholinesterasic (prostigmin), ganglion-blocking (pentamine) and antihistaminic (benadryl) substances. All the substances except benadryl decreased the permeability of the hematoencephalic barrier and the content of acetylcholine in the cerebrospinal fluid. Pentamine produced the most pronounced effect.

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THE EFFECT OF PARTIAL AND TOTAL EXTIRPATION OF THE CEREBRAL CORTEX ON THE "MECHANICAL SECRETION" OF GASTRIC JUICE

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As can be seen from the correspondence of I. P. Pavlov with S. I. Chechulin, I. P. Pavlov not only agreed with the stimulatory role of a mechanical factor (which he had earlier denied) [6] in gastric secretion, but also indicated ways of future investigation of this problem: "Because your fact was hidden from me so well and for so long, more and more tests of all kinds now need to be performed, for example, is not standing in the apparatus a conditioned stimulus that slowly develops its action; is the reflex not concerned with time, and so on . . . ."***

Thus in I. P. Pavlov's view, in order to accept finally the intrinsic importance of the mechanical factor as a stimulus of gastric secretion, the most important consideration was to exclude all the purely conditioned reflex factors which could in some way hide the other mechanisms lying at the basis of this phenomenon.

Pavlov's view was particularly clearly and succintly expressed in the following letter to S. I. Chechulin. "Well," asked Pavlov, "haven't you received your dogs without cerebral hemispheres yet to solve your elusive problem of the mechanical stimulation of gastric juice? Best of luck! Yours, I. Pavlov."****

However, the experiments were not carried out, for Prof. S. I. Chechulin died.

Our aim was to continue these investigations along the lines suggested by I. P. Pavlov [7, 8, 9, 10].

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* In Russian.

** Original Russian pagination. See C. B. translation.

*** Letter of September 7, 1933.

**** Letter dated January 21, 1934. Published in Fiziol. Zhur. SSSR No. 5, 626-627 (1954).