# PERMEABILITY OF THE BLOOD-BRAIN BARRIER IN AN ALTERED FUNCTIONAL STATE OF THE CENTRAL NERVOUS SYSTEM

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M. Ya. Maizelis

Scientific Research Institute of Psychiatry (Director—Professor D. D. Fedotov)
RSFSR Ministry of Health, Moscow
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In studying the effect of the central nervous system on the permeability of the blood-brain barrier (BBB) a number of authors have concluded that there exists a definite dependence of permeability of the BBB on the state of the central nervous system. However, all data mainly reflects either the ratio of electrolytes in the blood and spinal fluid [7, 8, 14, 15] or the distribution of exogenous, injected substances between the blood and the spinal fluid in animals which have been anesthetized and given stimulants [1, 3, 9] or put under conditions of experimental neurosis [10]. These data do not give a fair representation of the penetration of substances into the brain during the altered functional state of the central nervous system. Only in isolated works is there indication of the change in permeability of $P^{32}$ into the brain under the influence of caffeine [5, 6]; however, the data obtained by the authors are contradictory. In our work on rabbits and rats we studied the penetration of radioactive indicators into the spinal fluid, into different sections of the brain, and into the ocular media (aqueous humor) during different functional states of the central nervous system.

## EXPERIMENTAL

For indicators we used radioactive isotopes of phosphorus ($P^{32}$) and iodine ($I^{131}$). In experiments on rabbits we studied the dynamics of isotope penetration into the spinal fluid. At 1, 2, 3, and 24 h after intravenous injection of the isotopes in a total activity of 8 μCi, samples of spinal fluid (0.2 ml) were taken by cisternal puncture. In rats we studied the isotope penetration into different sections of the brain and ocular media at 1 h after intravenous or intraabdominal injection. The radioactivity of the structures was measured on an B-2 apparatus in a lead-housed counter BFL-25. The ratio of radioactivity in brain tissue, spinal fluid, and ocular media to that in the blood, as well as the amount of injected isotope per unit of body weight were calculated as the indices of permeability.

The studies were carried out on control animals and on animals which had been subjected to the action of pharmacological substances which alter the functional state of the central nervous system: sodium amytal (70-80 mg/kg), ethyl ether, caffeine (40 mg/kg), phenamine (6-8 mg/kg), and stimulation by loud noise. Twenty-two rabbits and 72 white mice were used in the experiments.

## RESULTS

During sleep produced by sodium amytal we observed a significant decrease (in comparison to the control) in the penetration of $P^{32}$ into all areas of the brain. The largest changes in $P^{32}$ permeability were observed in the cerebellum, brain stem, corpora quadrigemina, and parietal cortex. In the white matter and hippocampus major these changes were statistically insignificant (Fig. 1).

The permeability of $P^{32}$ into the cerebrospinal fluid in rabbits during sleep was decreased in comparison to the control. In addition the isotope content in the aqueous humor was significantly increased.

Similar data were obtained in experiments with $I^{131}$, the content of which (insignificant in comparison with $P^{32}$) was still further diminished during sleep in almost all areas of the brain.

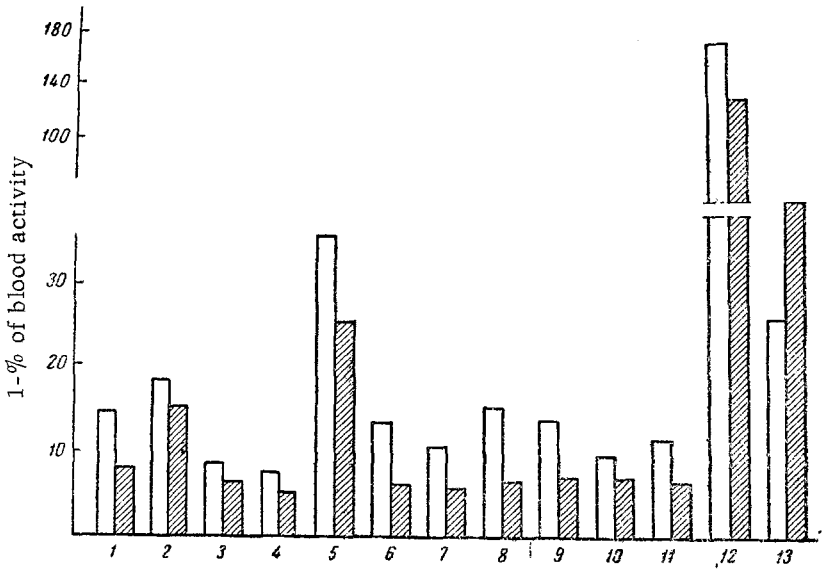


Fig. 1. Penetration of $P^{32}$ into areas of the brain and the aqueous humor in rats during sleep produced by sodium amytal. Clear bars) control; striped) experimental. 1) Parietal cortex; 2) olfactory cortex; 3) white matter; 4) hippocampus major; 5) hypothalamus; 6) pons Varolii; 7) medulla oblongata; 8) cerebellum; 9) corpora quadrigemina; 10) subcortical bundles; 11) homogenate; 12) hypophysis; 13) aqueous humor.

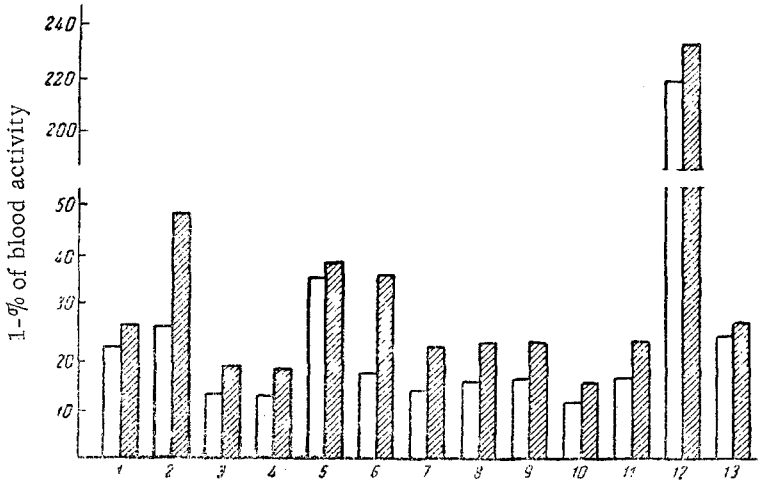


Fig. 2. Penetration of $P^{32}$ into brain and aqueous humor in rats under the influence of caffeine. Designations same as in Fig. 1.

As in the experiments with $P^{32}$, the concentration of $I^{131}$ in the aqueous humor during sleep was significantly increased.

A study of the permeability of the BBB for $P^{32}$ in rabbits during ether anesthesia continued for 1 h showed that the isotope concentration in the cerebrospinal fluid was decreased. However, the accumulation of $P^{32}$ in the brain of rats was increased, especially in the olfactory portions of the cortex, the pons Varolii, the medulla oblongata, corpora quadrigemina, and also in homogenates of brain and hypophysis. In the aqueous humor the isotope was not significantly increased.

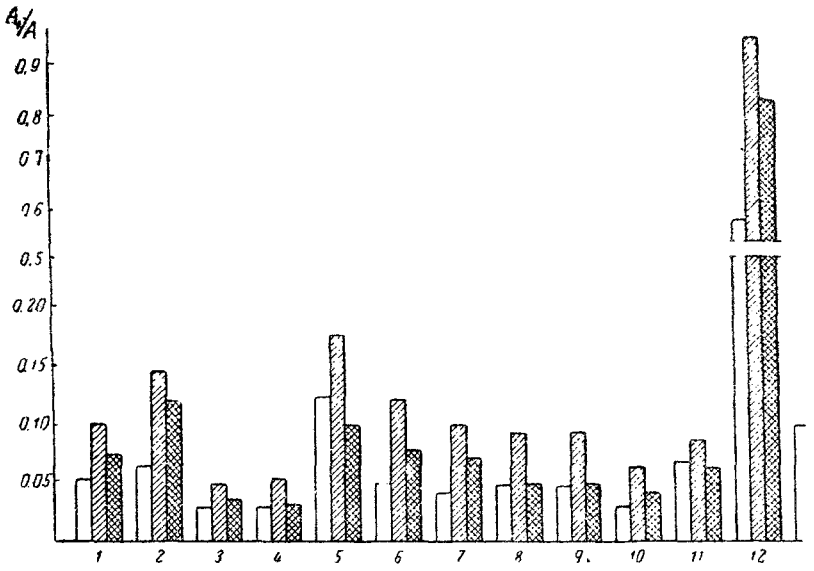


Fig. 3. Penetration of $P^{32}$ into brain and aqueous humor in rats after noise stimulation. Open bars) control; doubly striped) after motor stimulation; striped) after epileptiform seizures. $A_1/A$) Ratio of activity per gram of tissue ($A_1$) to injected activity per gram of weight (A). Remaining designations same as in Fig. 1.

Under conditions of stimulation of the central nervous system by subcutaneous injection of the sodium benzoin salt of caffeine (caffein sodium benzoate) the $P^{32}$ content in the cerebrospinal fluid of rabbits did not change significantly. At this level the isotope was increased both in the brain homogenate and in a number of brain areas (medulla oblongata, pons Varolii, olfactory cortex, white matter). The isotope concentration in the aqueous humor did not change (Fig. 2).

The increased penetration of $P^{32}$ under the influence of phenamine was noted only in the subcortical bundles and medulla. The isotope concentration in the aqueous humor did not change in comparison with the control.

A considerable increase in the blood-brain barrier permeability was obtained in rats after acute stimulation of the central nervous system by a loud noise. In rats which reacted to the sound by motor excitation, 5 sound stimuli in 1 h produced an increase in the penetration of $P^{32}$ only into certain areas of the brain: the parietal regions and the olfactory lobes, the medulla and pons Varolii. In the other regions of the brain and in the aqueous humor no significant changes in $P^{32}$ penetration occurred.

In animals in which motor stimulation by sound was accompanied by epileptiform seizures, a significant (2-3 times) rise in $P^{32}$ penetration into all brain areas and into the aqeuous humor was found in comparison with the control (Fig. 3).

The results of the investigations show characteristic changes in the penetration of radioactive indicators into the brain after disruption of the functional state of the central nervous system. Single pharmacologic substances produce an increase or decrease in the isotope permeability only into certain brain structures, while other influences (sleep as a result of sodium amytal administration, convulsions produced by noise) initiate generalized permeability changes. Evidently, the influence of the central nervous system on the penetration of substances into the brain proceeds with participation of the lower subdivisions, in particular the vegetative nervous system. This is indicated by data from a number of authors [4, 14, 15, 16], as well as by studies carried out in our laboratory [11]. Such an effect should not be considered isolated. Its mechanism may be supposed to involve the participation of humoral mechanisms and alteration in tissue metabolism in the brain [2, 12, 13, etc].

After different stimuli the changes in indicator permeability into areas of the brain, the cerebrospinal fluid, and the aqueous humor are not always concurrent. This may indicate the different physiological mechanisms for regulation of the permeability barrier structures of the eye and brain. The different changes in isotope penetration

into different sections of the brain after certain stimuli, which we observed, are of great interest. This fact may be explained not only by local peculiarities in metabolic processes but also by the various barrier formations in the central nervous system in its different portions.

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