PERMEABILITY OF THE BLOOD–BRAIN BARRIER FOR INTRAVASCULAR FORMALDEHYDE

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The study of the mechanisms of the protective action of formaldehyde on brain tissue in ischemia [4, 5] requires prior investigation of the ability of formaldehyde to pass through the blood–brain barrier (BBB) when the cerebral blood flow is preserved. Although we know that ischemia causes changes in permeability and functions of the BBB [1, 3], information of this kind would enable the localization of the protective action of formaldehyde in ischemia to be postulated, for its protective effect is observed if it is administered before ischemia [4, 5].

To study the permeability of the BBB for formaldehyde, the time course of changes in the formaldehyde concentration in brain tissue, in the CSF, and in the arterial and venous blood of dogs was studied after intra-arterial injection.

EXPERIMENTAL METHOD

Mongrel dogs of both sexes were anesthetized with hexobartital. Formaldehyde was injected into the animal's right carotid artery in a dose of 1.5 mmole/kg body weight as a 0.2% solution in 0.9% NaCl solution at the rate of 10 ml/min. Brain tissue was removed for analysis through a burr-hole in the parietal region of the skull, and CSF was obtained by cisternal puncture. Arterial blood was taken from the right carotid artery and venous blood from the right jugular vein.

Samples were taken before the beginning and at the end of formaldehyde injection, and again, 5, 20, 40, and 60 min later. Parameters of intact animals were used as the control.

Brain tissue samples were washed free from blood in 0.9% NaCl solution cooled to 0°C, before precipitation of the protein, and the washing solution was removed with filter paper. Proteins were precipitated by homogenization of the test material with 1% HCl solution in absolute ethanol. The formaldehyde concentration was determined by the color test with tryptophan in a sulfuric acid medium, in the presence of ferric chloride [6] in the supernatant fraction obtained by centrifugation of the homogenate at 8000g for 10 min.

EXPERIMENTAL RESULTS

The results of determination of formaldehyde levels in the brain, CSF, and arterial and venous blood of intact animals are given in Table 1.

Intra-arterial injection of formaldehyde led to changes in its concentration in the tissues. The formaldehyde concentration in the brain and arterial blood was virtually identical and significant, and it exceeded its concentration in venous blood ($P < 0.05$). Starting from the 5th minute after injection of formaldehyde a tendency was noted for the arteriovenous difference of the formaldehyde concentration to decrease, and this tendency was most marked at the 20th minute (Table 1).

The formaldehyde level in the tissues, starting with the 5th minute after injection and until the end of the period of observation, did not differ significantly from that in intact animals.

The ratio of the formaldehyde concentration in arterial blood of intact animals to its concentration in venous blood was 1.5. The formaldehyde concentration in brain tissue occu-

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TABLE 1. Time Course of Changes in Formaldehyde Concentration in Body Tissues (nmoles/g) and Fluid (nmoles/ml) after Intra-Arterial Injection (M ± m) (M ± σ)

Material studied	Control	End of injection	Time after injection, min			
			5	20	40	60
Brain	378±127	920±214*	—	—	—	—
CSF	34±11	91±32*	39±14	40±10	38±58	34±11
Arterial blood	505±107	993±320*	508±149	396±135	370±137	335±158
Venous blood	342±118	533±77*	354±54	389±48	317±158	288±67

Note. No fear than 3 determinations. *P < 0.01, compared with control.

pied an intermediate position between its concentration in arterial and venous blood, but these differences were not significant. The ratio of the formaldehyde concentration in brain tissue to its level in arterial blood was 0.75, and to its concentration in venous blood 1.1.

The formaldehyde concentration in the CSF was an order of magnitude lower than in brain tissue and blood. The ratio of the formaldehyde concentration in the CSF to its level in arterial blood was 0.068, and in venous blood 0.1. Considering that CSF contains only traces of protein (20 mg/100 ml [2]), and also the results of model experiments on the ability of formaldehyde to bind reversibly with proteins [8], the fact that the formaldehyde concentration in the CSF is considerably lower than in brain tissue and blood can evidently be explained by absorption of formaldehyde by proteins and by its existence in the body in a system of dynamic phase equilibrium: formaldehyde — protein and formaldehyde + protein. In that case, a higher protein concentration in the tissue ought to correspond to a higher formaldehyde level in its aqueous medium.

Injection of formaldehyde caused an almost twofold increase in its concentration in the brain tissue by the end of injection, a threefold increase in the CSF, and twofold in arterial blood. The ratio between formaldehyde concentrations in arterial and venous blood under these circumstances increased to 1.9.

An increase in the formaldehyde concentration in brain tissue and in the CSF in response to its injection can be regarded as evidence that the BBB is permeable for formaldehyde. The increase and decrease in the arteriovenous difference for formaldehyde, and the synchronized rise and fall of its concentration in arterial blood are evidently the result of changes in the rate of its consumption, due to changes in its concentration in arterial blood.

The calculated change in the formaldehyde concentration after injection of the dose used corresponds to a fourfold increase in its concentration in the body tissues. According to data in the literature, the half-elimination time of formaldehyde from the blood is 1.5 min [7]. The effect of such a rapid fall in the formaldehyde concentration is probably the result of activation of the simultaneous processes of its binding with protein and metabolic conversion of formaldehyde in the body.

LITERATURE CITED

1. T. V. Birich and S. A. Eremenko, Dokl. Akad. Nauk BSSR, 24, No. 6, 568 (1980).
2. M. M. Bradbury, The Concept of the Blood–Brain Barrier [Russian translation], Moscow (1983), pp. 11-76.
3. Yu. Yu. Keerig and G. A. Kuzovkov, Abstracts of Proceedings of the 5th Conference on Tissue–Blood Barriers [in Russian], Moscow (1978), pp. 177-178.
4. A. D. Rozvadovskii, S. O. Trenin, and V. I. Tel'pukhov, Patol. Fiziol., No. 1, 12 (1985).
5. V. I. Tel'pukhov, S. O. Trenin, G. D. Knyazeva, and T. I. Lapkina, Vest. Akad. Med. Nauk SSSR, No. 4, 65 (1985).
6. J. Chrastil and J. T. Wilson, Anal. Biochem., 63, 202 (1975).
7. K. E. McMartin, G. Martin-Amat, P. E. Noker, and T. R. Tephly, Biochem. Pharmacol., 28, 645 (1979).
8. E. Schauenstein et al., Aldehyde in Biological Systems, London (1977), pp. 9-24.