DIMETHYL SULFOXIDE AS A CORRECTOR OF DISTURBANCES OF THE CEREBRAL CIRCULATION AND OXYGEN AND CARBOHYDRATE METABOLISM AND OF LIPID PEROXIDATION SOON AFTER INTRACEREBRAL HEMORRHAGE

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Lipid peroxidation (LPO) plays an important role in the pathogenesis of intracerebral hemorrhage (ICH). Within a few hours of ICH the concentrations of LPO products show a definite rise and antiradical activity (ARA) of brain lipids is depressed [9]. This is the basis for the use of antioxidants and, in particular, of dimethylsulfoxide (DMSO), used previously in the treatment of ICH.

The aim of this investigation was to study the effect of DMSO on the state of LPO in the brain and also on the hemodynamics and of integral parameters of the oxygen and carbohydrate metabolism of the brain after experimental ICH.

EXPERIMENTAL METHOD

The state of LPO was studied in 36 noninbred male albino rats weighing 250-300 g. One hour after ICh had been produced [5] in 28 animals, half of them were given an intraperitoneal injection of a 10% solution of DMSO in a dose of 0.7 g/kg body weight, whereas the other half received an equal volume of physiological saline; the control, to study the initial level of LPO, consisted of eight animals undergoing a mock operation. The rats were decapitated 3 h later and brain lipids were extracted as in [9]. The content of diene conjugates (DC) and Schiff's bases (SB) in the lipid fraction was determined [1, 15]. ARA of the lipids was studied by the aid of an α-diphenyl-α-picryl-hydrazyl free radical [10].

After production of ICH [3] in 19 male and female cats weighing 2.5-3 kg, under urethane-chloralose anesthesia (800 and 80 mg/kg respectively) the blood flow was recorded in the right and left maxillaryarteries (MFV-2100 and MFV-1100 blood flowmeters); the systemic blood pressure (SBP) and heart rate also were determined. The following blood parameters were measured: pH, pCO_2, pO_2 (by means of an ABL-4 acid–base laboratory), the glucose concentration (by the orthotoluidine method), and lactate (by the dehydrogenase method). The oxygen, glucose, and lactate consumptions of the brain were calculated as the product of the total cerebral blood flow (TCBF) and the arteriovenous difference in the concentration of the corresponding substance. One hour after production of ICH, a 10% solution of DMSO was infused intravenously into 11 animals for 30 min (total dose 0.3 g/kg, allowing for differences in species sensitivity). In a separate series of experiments (seven animals) the effect of infusion of the 10% solution (0.3 g/kg) was determined on the osmolarity of the blood (OMKA 1Rs-01 osmometers). The results were subjected to statistical analysis by Student's t test and by the Wilcoxon–Mann–Whitney inversions test.

EXPERIMENTAL METHOD

Compared with values obtained in animals undergoing the mock operation, 3 h after production of ICH in the rat brain the concentrations of DC (from 0.052 ± 0.004 to 0.074 ± 0.07 optical density units at 232 nm/mg lipids) and of SB (from 0.090 ±

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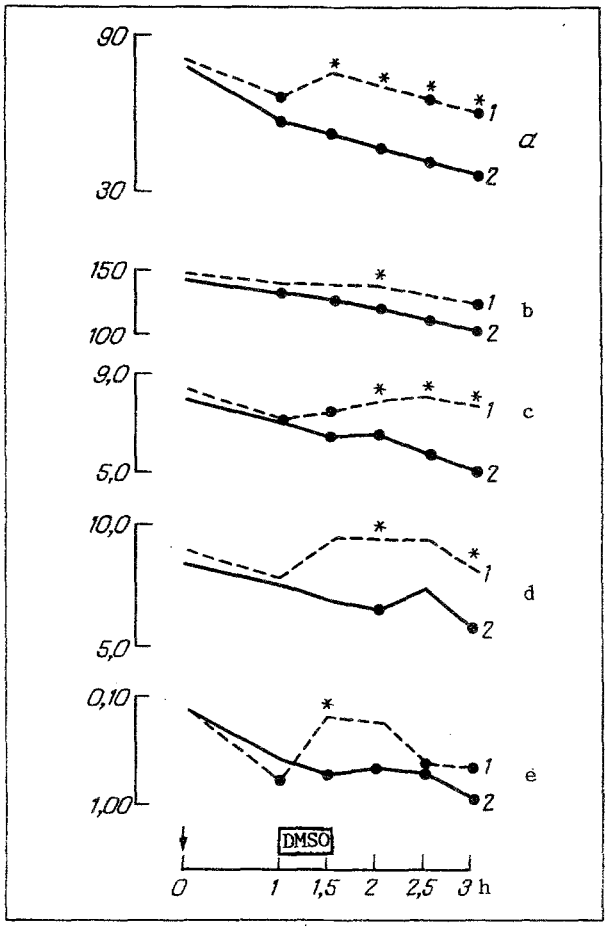

Fig. 1. Effect of intravenous infusion of DMSO (1) and physiological saline on total cerebral blood flow (a), systemic blood pressure (b), and oxygen (c), glucose (d), and lactate (e) consumption of the brain after intracerebral hemorrhage in cats. Dots indicate significant changes ($p < 0.05$) compared with initial background level; asterisks — compared with control. Abscissa, time (in h); ordinate: a) in ml/100 g/min, b) in mm Hg, c, d, and e) in mg/100 g/min. Arrow indicates time of hemorrhage.

0.005 to 0.133 ± 0.02 relative units/mg lipids) rose, whereas ARA of the lipids fell from 0.86 ± 0.04 to 0.6 ± 0.04 μeq hydroquinone/g lipids ($p < 0.05$). Injection of DMSO 1 h after hemorrhage prevented activation of lipid peroxidation and the DC and BS levels in the group of animals treated with DMSO did not differ from those in animals undergoing the mock operation (0.052 ± 0.003 optical density unit at 232 nm/mg lipids and 0.083 ± 0.005 relative units/mg lipids respectively); ARA of the lipids was 0.74 ± 0.04 μeq hydroquinone/g lipids ($p > 0.05$).

The mechanism of the antioxidative action of DMSO consists of scavenging hydroxyl radicals and activating superoxide dismutase [2, 11]. The compound exhibits an antioxidative effect in a concentration as low as $0.5 \cdot 10^{-3}$ M. Allowing for the high permeability of the tissue-blood barriers for DMSO [7] the concentration of the compound created in brain tissue when injected into rats in a dose of 0.7 g/kg, according to our calculations, is at least an order of magnitude higher. The antiradical effect of DMSO is manifested as a membrane-stabilizing action: the compound increases the resistance of glial cells to destruction and stabilizes lysosomal membranes [12, 16]. Considering the ability of the compound, with its membrane-stabilizing action, to prevent disturbances of the circulation and metabolism of the brain during the first hours after ICH [6], it was decided to evaluate DMSO as a corrector of early disturbances of the hemodynamics and oxygen and carbohydrate metabolism of brain tissue.

In cats ICH was accompanied by a progressive decline of TCBF and the oxygen consumption of the brain throughout the period of observation, and by increased lactate production; glucose consumption by the brain tissue began to fall after the 2nd hour. Under the influence of DMSO the utilization of oxygen and glucose by the brain remained close to its initial level. DMSO, by inhibiting the oxygenase pathway of oxygen utilization by the brain and increasing oxygen diffusion into the tissues [7], can preserve the level of normal oxidase reactions, as reflected in its ability to prevent excessive accumulation of lactate and its release into cerebral venous blood. A definite contribution to the formation of these metabolic effects is made by the normalizing influence of DMSO on the cerebral hemodynamics (Fig. 1).

The mechanism of action of DMSO on TBCF, in our view, is quite complicated. The increase in TCBF toward the end of DMSO infusion and its preservation at a higher level than in the control may be due both to the action of the compound on SBP and to its direct action on the cerebral hemodynamics. The writers showed previously that in ICH the autoregulation response of the cerebral blood flow is disturbed [4] and, for that reason, a higher TCBF level toward the 2nd-3rd hour in the treated cats compared with the control may be partly attributed to a raised value of SBP. Meanwhile TCBF rose toward the end of infusion of DMSO, while SBP remained stable. This was not due to the direct myotropic action of DMSO, because the compound has vasodilator activity only in concentrations of 1% or higher [13], which are not created in the blood by infusion of DMSO in a dose of 0.3 g/kg. The effect was probably due to the antiedematous properties of the compound. For instance, toward the end of infusion the osmolarity of the blood rose from 335 ± 2 to 352 ± 3 milliosmoles/liter ($p < 0.05$). Such an increase in osmolarity of the blood following intravenous injection of glycerol is accompanied by a distinct antiedematous effect [14]. The reduction of the lactacidosis of the brain tissue, reflected in reduced lactate release by the brain, may facilitate this antiedematous action of DMSO. Absence of mortality during the first few hours after ICH in the group of treated cats was a manifestation of the beneficial effect of DMSO on brain activity (in the control, death of 25% of the animals was observed by 3 h).

The earlier administration of DMSO after ICH thus prevents activation of lipid peroxidation in the brain tissue, improves the cerebral hemodynamics, and restored normal oxygen and carbohydrate metabolism of the brain.

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