EFFECT OF ETHOMERSOL ON BLOOD SUPPLY AND OXYGEN METABOLISM OF THE BRAIN DURING ACUTE TRANSIENT ISCHEMIA AND RECIRCULATION

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Reducing the oxygen demand of brain tissue by antihypoxic drugs combined with increasing the blood supply to the brain without any substantial changes in parameters of the systemic hemodynamics [1, 8, 9, 13] creates favorable opportunities for the use of preparations of this group as correctors of disturbances of the cerebral circulation and lays the foundations for further research in this direction. Among mercaptobenzimidazole derivatives the preparation ethomersol has been found: it exhibits marked antihypoxic properties on various models of hypoxia and its activity under conditions of circulatory hypoxia is superior to that of sodium hydroxybutyrate and gutimin [5, 6].

The aim of this investigation was to study the effect of ethomersol on the cerebral hemodynamics and oxygen supply of the brain in acute transient cerebral ischemia and to elucidate the mechanisms of the antihypoxic action of the drug under these conditions.

EXPERIMENTAL METHOD

Experiments were carried out on 14 male and female cats weighing 2.5-3.5 kg, anesthetized with urethane and chloralose (800 and 80 mg/kg respectively). Cerebral ischemia was induced by occlusion of the internal maxillary arteries for 30 min after preliminary compression of the vertebral arteries. The systemic blood pressure (SBP) and the total cerebral blood flow (TCBF) were estimated in the experiments by measuring the inflow of blood to the brain along both internal maxillary arteries by means of MFV-2100 and MFV-1100 flow meters; pO_2 in the parietal cortex (polarographically), and pO_2, pCO_2, and pH of the cerebral arterial and venous blood were determined on an ABL-4 gas analyzer. Animals of the experimental group were given ethomersol in a dose of 50 mg/kg by intravenous infusion over a period of 60 min, 30 min before occlusion of the internal maxillary arteries. The effect of the drug on the affinity of hemoglobin for oxygen was estimated in 11 noninbred rats, anesthetized with urethane (1 g/kg, intraperitoneally), by the method suggested by ourselves [10], involving calculation of p_{50} [3]. Ethomersol was injected intraperitoneally in a dose of 50 mg/kg 1 h before the blood sample was taken. The results were subjected to statistical analysis by Student's t test and by Wilcoxon's nonparametric test [4].

EXPERIMENTAL RESULTS

Occlusion of the internal maxillary arteries (after preliminary compression of the vertebral arteries) was accompanied by acute hypoxia of the brain tissue: pO_2 in the cortex fell quickly and stabilized at a level of 56-48% of the initial value. During the recirculation period after a short phase of an increase, pO_2 fell again and did not exceed 60% before the end of the period of observation (Table 1). The method used to record the blood supply of the brain did not enable us to estimate its level in the period of ischemia, but values of pO_2 of the brain tissue during this period reflects maintenance of a reduced cerebral blood

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TABLE 1. Effect of Ethomersol on TCBF (in ml/100 min), SBP (in mm Hg), pO_2 of the Parietal Cerebral Cortex (bpO_2, in per cent of initial value), pO_2 in Venous Blood (vpO_2, in mm Hg), and Arteriovenous Oxygen Difference ($AVpO_2$, in mM), and OC (in mg/100 g/min) during Cerebral Ischemia and Recirculation

Parameter	Initial value	Infusion of ethomerol		Recirculation time, min					
		30 min before ischemia	30 min of ischemia	1	5	30	60	90	120
				Ethomersol (n = 7)					
TCBF	17,8±2,4	21,5±3,4	—	28,2±4,4[a]	19,4±4,7	13,6±2,5	13,5±2,7	13,7±2,4[b]	14,6±2,8[b]
SBP	156±6	171±5[a]	192±9[a, b]	145±6	147±5	162±5[b]	167±6[b]	165±7[b]	158±9[b]
bpO_2	100	115±7	62±20	139±16[a, b]	130±13[a, b]	118±15[b]	119±18[b]	115±18[b]	111±17[b]
vpO_2	41,5±4,4	43,6±3,9	33,0±6,5	—	—	37,7±5,0	36,9±4,0[b]	38,0±4,3	36,9±4,5[b]
$AVpO_2$	2,9±0,6	2,4±0,5	4,1±0,7	—	—	3,3±0,8	3,5±0,7	3,3±0,8	3,6±0,7
OC	+4,0±0,6	+4,3±0,7	—	—	—	+3,5±0,7	+3,6±0,5	3,4±0,6	+4,2±0,7
				Control (n = 7)					
TCBF	17,1±0,8	—	—	14,7±1,3	11,2±0,8[a]	11,1±0,9[a]	9,5±0,9[a]	8,0±1,2[a]	8,2±0,8[a]
SBP	147±4	—	162±5[a]	121±6[a]	129±5[a]	132±6[a]	124±8[a]	118±6[a]	108±6[a]
bpO_2	100	—	44±6[a]	68±17	62±14[a]	60±10[a]	60±10[a]	54±11[a]	47±11[a]
vpO_2	41,4±3,3	—	29,0±3,6[a]			33,9±3,2	26,4±3,5[a]	28,3±3,3[a]	23,6±4,7[a]
$AVpO_2$	2,7±0,3	—	4,7±0,6[a]	—	—	3,2±0,4	4,8±0,4[a]	4,7±0,4[a]	5,2±0,4[a]
OC	+4,8±0,5	—	—	—	—	+3,9±0,5	+4,7±0,3	+4,7±0,3	+4,7±0,4

Legend. a) $p < 0.05$ compared with initial background, b) $p < 0.05$ compared with control.

flow, probably due to the well developed collateral circulation in cats through branches of the ophthalmic artery [7]. Maintenance of perfusion of the brain via the collateral circulation is partly assisted by elevation of the systemic blood pressure (Table 1). In the postischemic period the blood flow briefly (for 1 min) rose, but then fell again and stabilized toward 1-2 h after the beginning of reperfusion at 50% of the initial level. The fall in pO_2 of the cerebral venous blood from 41.4 ± 3.3 to 29.0 ± 3.6 mm Hg by the end of ischemia and to 23.6 ± 4.7 mm Hg toward the end of recirculation reflects the critical level of brain tissue hypoxia [11]. Correlation of TCBF and pO_2 of the brain in the postischemic period ($r = +0.54$) is evidence that hypoxia of the brain tissues during this period is due mainly to the state of postischemic hypoperfusion. A factor contributing to disturbance of the cerebral hemodynamics may be lowering of the perfusion pressure, developing as the result of the long-lasting hypotensive reaction of the systemic blood pressure (Table 1).

Despite the marked disturbances of the systemic and cerebral hemodynamics the brain oxygen consumption (OC) remained close to its initial level, confirming the characteristics of this parameter as the most stable value [15]. Stability of OC against the background of a depressed TCBF was preserved on account of an almost twofold increase in the arteriovenous oxygen difference toward the end of the postocclusion period (Table 1). In turn, the rise in the value of this parameter may be connected with increased extraction of oxygen from the blood because of a sharp fall in pO_2 of the brain tissue and an increase in the blood/tissue oxygen ratio, caused by tissue hypoxia.

Prophylactic administration of ethomersol to the cats caused a significant increase in pO_2 of the parietal cortex against the background of very small changes (not significant) in the oxygen consumption of the brain tissue, blood gasses, and TCBF. The last parameter increased but not significantly, despite the hypertensive response to injection of the drug. Compression of the internal maxillary arteries for 30 min against the background of ethomersol infusion caused a smaller decrease in pO_2 of the brain tissue and venous blood than in the control animals. In the postischemic period a short phase of hyperperfusion was observed followed by stabilization of TCBF at a level somewhat lower than initially, but significantly higher than in the control group (Table 1). Throughout the postocclusion period pO_2 of the brain tissue was higher than initially and also significantly higher than in the control group. Judging by the values of pO_2 of the venous blood in the experimental series, during ischemia the hypoxia did not reach the critical level, and in the postocclusion period it virtually did not arise (Table 1).

The much more marked prevention of hypo-oxygenation of the brain than of hypoperfusion in the recirculation and also the significant increase in pO_2 during the first 30 min of infusion of the preparation against the background of a small but not significant increase in TCBF, must be noted. Evidently, the antihypoxic action of ethomersol is realized mainly on account of the direct effect of the drug on oxygen metabolism, and only partly as the result of improvement of the blood supply to the brain. This is confirmed by the low degree of correlation ($r = -0.13$) between TCBF and pO_2 in the postischemic period in animals of the experimental series. The antihypoxic action of ethomersol is probably partly due to a decrease in oxygen consumption of the brain. To study other possible aspects of this effect, the effect of ethomersol on binding of hemoglobin with oxygen was investigated.

The value of p_{50} in the rats' blood 1 h after intraperitoneal injection of ethomersol in a dose of 50 mg/kg increased from 28.0 ± 0.3 to 30.7 ± 0.3, evidence of a marked decrease in affinity of hemoglobin for oxygen; in the control p_{50} changes from 28.7 ± 0.4 to 28.3 ± 0.4. Consequently, an important component of the antihypoxic effect of ethomersol is intensification of the giving up of oxygen by the hemoglobin, as shown by improvement of oxygenation of the brain during recirculation and weakening of hypoxia during ischemia. The decrease in the affinity of hemoglobin for oxygen is an effective method of correcting the disturbances of the oxygen supply of organs. It has been shown that increasing p_{50} by 2 mm Hg is equivalent to increasing the oxygen supply to the tissues by 30% [14]. The rationality of administering drugs with this property in cerebral ischemia rests on a sound theoretical basis [2, 12], but there are as yet no antiischemic agents with this type of mechanism of antihypoxic action yet available.

Thus ethomersol is an effective corrector of ischemic and reperfusion disturbances of the cerebral circulation. Reduction of the cerebral hypoxia by the drug at a time of ischemia and in the recirculation period is the result of an increase in blood supply to the brain and also a decrease in the affinity of hemoglobin for oxygen. The moderate depressant effect of ethomersol on the brain oxygen supply in the realization of the antihypoxic action of the drug cannot be ruled out, but the real contribution of this effect requires further study.

LITERATURE CITED

1. E. A. Bendikov, T. S. Gan'shina, and R. S. Mirzoyan, Byull. Éksp. Biol. Med., No. 11, 555 (1979).
2. V. M. Vinogradov and Yu. Yu. Uryupov, Farmakol. Toksikol., No. 4, 9 (1985).
3. I. L. Vinogradova, S. Yu. Bryantseva, and G. D. Derviz, Probl. Gematol., No. 6, 26 (1981).
4. E. V. Gubler and A. A. Genkin, The Use of Nonparametric Statistical Tests in Medical and Biological Research [in Russian], Leningrad (1973).
5. I. A. Ivanova, Yu. G. Bobkov, and M. D. Mashkovskii, Pharmacologic Regulation of States of Disadaptation [in Russian], Moscow (1986), p. 82.
6. A. S. Losev, A. M. Alybaev, and T. D. Karpova, Pharmacologic Regulation of States of Disadaptation [in Russian], Moscow (1986), p. 54.
7. A. D. Nozdrachev, Anatomy of the Cat [in Russian], Leningrad (1973).
8. M. B. Plotnikov, T. M. Plotnikova, T. V. Yakimova, et al., Farmakol. Toksikol., No. 4, 38 (1988).
9. M. B. Plotnikova, A. S. Saratikov, T. M. Plotnikova, et al., Byull. Éksp. Biol. Med., No. 5, 583 (1989).
10. M. B. Plotnikov, B. I. Laptev, and T. M. Plotnikova, Farmakol. Toksikol., No. 6, 83 (1989).
11. G. A. Ryabov, Hypoxia of Critical States [in Russian], Moscow (1988).
12. H. Aberman, Acute Care, **11**, 216 (1987).
13. G. Johnson and F.W. Marcoux, Ann. Rep. Med. Chem., **21**, 109 (1980).
14. M. Osava and S. Maruyama, Veng. Farmakoter., No. 3, 91 (1984).
15. B. K. Siesjö, Brain Energy Metabolism, Chichester (1978).