brane permeability (Table 1). Combination of cordarone with SK (toxic dose) not only prevented SK-induced activation of hydrolytic enzymes in intact rats, but also normalized the functional state of lysosomal membranes. This combination also restored the initial free/total CD activity ratio in rats with CI, which proved the stabilization of lysosomal membranes compared with the control. This was due to opposite effects of cordarone and toxic dose of SK on free and total CD activity. The inhibitory effect of cordarone on CD activity arises from the ability of this α, β, χ-blocker to inhibit lysosomal β-adrenoreceptors [4], which are thought to participate in the regulation of the functional state of lysosomes and the activity of hydrolytic enzymes [4].

Thus, changes in CD activity after administration of the toxic dose of SK in combination with cordarone point to a possible biochemical mechanism of the protective effect of cordarone against glycoside intoxication. This mechanism consists in reducing labilization of lysosomal membranes occurring in CI. Our findings indicate that primary effects of SK can be corrected by directed modulation of the heart lysosomal system, which makes it possible to optimize clinical application of SK.

REFERENCES

1. P. A. Galenko-Yaroshevskii, S. M. Lemkina, and Ya. V. Kostin, *Byull. Eksp. Biol. Med.*, **117**, No. 1, 59-61 (1994).
2. S. M. Lemkina, *Eksp. Klin. Farmakol.*, No. 4, 30-33 (1993).
3. E. V. Montsevichute-Eringene, *Pat. Fizol.*, No. 4, 71-78 (1964).
4. P. V. Sergeev and N. A. Sysolyatina, *Eksp. Klin. Farmakol.*, No. 1, 65-66 (1993).
5. A. J. Barret, in: *Lysosomes. A Laboratory Handbook*, J. T. Dingle (ed.), Amsterdam - London (1977), pp. 40-105.

Antiedematous Effect of the Preparation Polyosm in Brain Ischemia

M. B. Plotnikov, V. I. Smol'yakova, and G. A. Chernysheva

Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 122, No. 10, pp. 410-412, October, 1996
Original article submitted July 27, 1995

The effect of the preparation Polyosm (polyethylene oxide 400) on cerebral edema (impedance measurements) and cerebral circulation is studied in brain ischemia caused by ligation of the left common carotid artery and reduction of blood flow through the right common carotid artery to 25% of the original level. The preparation markedly reduces cerebral edema and induces transient improvements in cerebral circulation.

Key Words: *cerebral edema; brain ischemia; polyethylene oxide*

The preparation "solution of polyethylene oxide 400 30%" is an osmotically active compound used in the therapy of glaucoma [6]. This preparation increases osmotic activity of the blood and decreases intraocular pressure. There is evidence that intravenous administration of polyethylene oxide 400 (PEO 400) is more efficient [6]. It was demonstrated that intravenous administration of PEO 400 in a dose of 6 g/kg markedly decreases the water content in the brain [1]. Based on these findings, we have developed the preparation Polyosm, which is a solution of PEO 400 for intravenous administration. The aim of the present study was to examine the effect of Polyosm on brain ischemia in conscious rats.

MATERIALS AND METHODS

Experiments were performed on male Wistar rats weighing 350-380 g. Cerebral ischemia in conscious

Institute of Pharmacology, Scientific Center of the Russian Academy of Medical Sciences, Tomsk

0007-4888/96/0010-1007$15.00

TABLE 1. Effect of Intravenous Administration of Polyosm on Cerebral Blood Flow (ml×100 g^{-1}×min^{-1}) in Right and Left Cortex of Conscious Rats After Brain Ischemia

Hemisphere		Original value	Day 1		Day 2
			before administration	1 h after administration	
Control	right	221.2±9.3	171.9±12.4*	-	176.2±13.0*
	left	220.4±13.8	162.5±13.0*	-	180.1±15.8*
Experiment	right	238.2±31.2	173.1±17.3*	210.3±20.6**	194.6±16.8*
	left	249.3±19.2	185.1±5.0*	218.3±15.2**	186.4±19.3*

Note. Here and in Table 2: $p<0.05$: *compared with original value; **compared with the value 24 h after brain ischemia.

rats was assessed by the impedance method with our modifications. Six or seven days before experiment, a pair of platinum electrodes was implanted in the left and right parietal cortex at a distance of 5 mm under sodium pentobarbital anesthesia (50 mg/kg intraperitoneally). Experimental and control group consisted of 6 and 5 rats, respectively. Impedance was measured using an I-2 apparatus. Local cerebral blood flow (CBF) was measured in an FB-1 apparatus by the method of hydrogen clearance [3,4] using the platinum electrodes. Chlorine-silver electrode implanted into the nasal bones simultaneously with cerebral electrodes served as an electrode of comparison.

Cerebral ischemia was modeled under ether anesthesia by ligating the left common carotid artery and reducing blood flow through the right common carotid artery to 25% of the original level under the control of an MFV-1100 electromagnetic flowmeter (Nihon Kohden).

Polyosm was administered to conscious rats 24 h after occlusion of carotid arteries. The preparation was slowly infused in the tail vein in a volume containing 1 g/kg PEO 400. An equal volume of normal saline was injected into control rats. The results were analyzed using the Wilcoxon's nonparametric test.

RESULTS

Ligation of one carotid artery and reduction of blood flow through the other led to a noticeable decrease in CBF on days 1 and 2 of the experiment (Table 1). Cerebral edema was revealed in the cortex: 24 h after ligation of carotid arteries, inductive and capacitative components of impedance increased, indicating that the distance between cells decreased and the stability of the plasma membranes impaired. Twenty-four hours after modeled ischemia, the inductive component in the left cortex of control animals increased by 60% and in the right cortex by 40%, while the capacitative component increased by 52 and 29%, respectively; these value did not change considerably on day 2 after brain ischemia (Table 2).

Intravenous administration of Polyosm markedly reduced cerebral edema. As soon as 1 h after ad-

TABLE 2. Effect of Intravenous Administration of Polyosm on Inductive and Capacitative Components of Impedance (kOhm) in Left and Right Brain Cortex of Conscious Rats After Brain Ischemia

Hemisphere		Original value	Day 1			Day 2
			before administration	after administration		
				1 h	2 h	
Inductive component						
Control	left	8.9±1.9	12.2±1.6*	-	-	12.3±1.9*
	right	9.4±1.5	15.1±1.3*	-	-	14.8±1.2*
Experiment	left	8.1±1.2	12.4±1.1*	8.4±1.2**	8.5±1.7**	8.2±0.9**
	right	9.4±1.2	13.2±1.8*	10.4±1.4**	10.5±1.2**	10.6±1.5**
Capacitative component						
Control	left	15.9±0.1	24.4±1.7*	-	-	21.8±1.1*
	right	12.7±2.1	19.5±1.1*	-	-	19.8±1.8*
Experiment	left	11.3±1.9	15.6±1.7*	13.0±1.9**	13.5±1.7**	13.9±1.2**
	right	11.1±1.6	15.4±1.9*	13.4±0.8**	13.5±0.8**	13.6±0.9**

ministration of the preparation, the inductive component in the left and right cortex significantly decreased by 33 and 27%, respectively. Changes in the capacitative component were significant, although less pronounced (Table 2). These parameters did not change significantly 2 h after administration of Polyosm. The effect of the preparation was retained on day 2, judging from the dynamics of impedance. The rapid development of the effect of PEO 400 after its intravenous administration in a dose of 1 g/kg is probably determined by the dynamics of plasma osmolarity: it was increased during several minutes after administration of Polyosm, reached the maximum by the 30th min (14 mmol/kg above the baseline level), and slowly decreased during subsequent 150 min [5]. Thus, the substantial decrease in the inductive component of the impedance and the maintenance of impedance at a close to baseline level for 24 h indicates a rapid decrease in cerebral edema.

After 1 h, local CBF in the right and left cortex increased 88 and 87% of the original level, respectively (Table 1). Reduction in cerebral edema was accompanied by an observable tendency toward restoration of blood flow probably due to a decreased compression of blood vessels by edematous tissue; however, this effect was not observed on day 2.

The following findings indicate that Polyosm is an effective and prospective preparation. First, Polyosm exerted an antiedematous effect in a model of cerebral edema that has a clinical analog (stroke). Second, the studied dose of the preparation (1 g/kg PEO 400) is within the dose range for osmotic diuretics used to decrease cerebral ischemia [2], being 6-fold lower than the dose inducing cerebral dehydration in intact animals.

REFERENCES

1. G. B. Vainshtein and L. E. Pinegin, *Fiziol. Zh. SSSR*, **65**, No. 9, 1369-1375 (1980).
2. M. D. Mashkovskii, in: *Drugs* [in Russian], Vol. 1, Moscow (1993), pp. 586-589.
3. V. V. Natochin and E. I. Shakhmatov, *Byull. Eksp. Biol. Med.*, **69**, No. 4, 79-81 (1970).
4. *Methodological Recommendations on the Unification of Examination of Cerebral Circulation* [in Russian], Leningrad (1986).
5. V. I. Smol'yakova, in: *Proceedings of the Investigations Carried Out by Young Scientists at the Institute of Pharmacology of the Tomsk Scientific Center* [in Russian], Tomsk (1995), pp. 36-38.
6. V. M. Cherednichenko and N. S. Pushkar', *Oftalmol. Zh.*, No. 3, 157-159 (1983).