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Antiedematous Activity of Cerebrocrast in Cerebral Ischemia

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The effect of a course of cerebrocrast, a 1,4-dihydropyridine derivative, on brain edema (as shown by impedometry) and cerebral tissue microvascularization in ischemia caused by ligation of the left common carotid artery and 50% restriction of the bloodflow in the right common carotid artery is studied in Wistar rats. Cerebrocrast is found to appreciably limit the development of brain tissue edema and to improve the status of microvessels by reducing the number of sharply constricted nonfunctioning capillaries and increasing the number of capillaries of 4 μ and more in diameter. Pronounced antioxidative effects of cerebrocrast in transitory cerebral ischemia are demonstrated.

Key Words: *cerebrocrast; brain ischemia; brain edema; microcirculation; lipid peroxidation*

Recent experimental and clinical data indicate that the effect of Ca antagonists belonging to the 1,4-dihydropyridines, which is associated with functional protection of the brain, can be manifested irrespective of their influence on the blood supply to the brain [13,14]. For example, a course of treatment with cerebrocrast (CC), a 1,4-dihydropyridine derivative, administered to alert rats after the induction of brain ischemia was associated with a positive impact on the bioelectrical activity of the cerebral cortex which anticipated the recovery of the blood supply to the respective brain areas [2]. Bearing in mind the antiedematous effect of these drugs under conditions of ischemic edema of the brain [9,15], we examined the effect of CC on the time course of edematous swelling of the cerebral cortex in alert rats on a model of cerebral ischemia and studied some mechanisms of this effect.

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MATERIALS AND METHODS

Experiments were carried out on male Wistar rats weighing 220 to 270 g. The degree of edematous swelling of brain tissue in alert rats was assessed by the method of impedance recording in our modification. For this purpose, bipolar platinum electrodes were implanted in 18 animals (6 controls and 12 experimental rats) under narcosis (sodium ethaminal in a dose of 50 mg/kg intraperitoneally) 6-7 days before the experiment. Complete impedance and its constituents were recorded with an I-2 impedometer. The microcirculatory bed was examined in 18 rats (6 sham-operated, 6 controls, and 6 experimental) by the modified calcium adenosine triphosphate method [8]. With reference to the mean diameter of red cells and their deformability [3], capillaries 2±1 μ in diameter were considered as severely constricted and nonfunctioning.

Brain ischemia in control and experimental rats of the above series was reproduced under ether narcosis by complete ligation of the left common carotid artery and restriction of the bloodflow in

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the right common carotid artery to 50% of the initial level, as shown by an MFV-1100 blood flowmeter (Nihon Kohden). CC was administered daily to experimental animals orally in a dose of 500 μg/kg in 1% starch gel; control animals were administered equivalent volumes of gel.

The antioxidative activity of CC was assessed according to previously offered recommendations [10]: the levels of diene conjugates and Schiff's bases in brain tissue were measured at the 30th min of recirculation after 30 min of ischemia (occlusion of both carotid arteries) in rats narcotized with urethan in a dose of 1 g/kg (7 control and 7 experimental rats). CC in a dose of 0.4 μg/kg×min was intravenously infused to experimental animals before ischemia, the solvent (50% dimethylacetamide) being infused to controls.

The results were statistically processed using Student's *t* test and Wilcoxon's nonparametric test.

RESULTS

Cerebral ischemia was attended by the early development of edema: a reliable increase of active resistance reflecting decreased cell-to-cell space was detected as early as by the end of day 1 in the left hemispheric cortex, where a marked reduction of the local bloodflow was observed [2] (Fig. 1). Edematous swelling was maximal by day 3: complete impedance in the left and right hemispheric cortex increased by 133 and 106%, active impedance by 124 and 102%, and reactive impedance by 137 and 98%, respectively. By day 10 gradual involution of brain edema and normalization of the majority of the measured parameters were observed.

In the experimental group the CC course appreciably limited the development of edematous swelling of cerebral tissue (Fig. 1). A reliable increase of impedance and of its active constituent in the left parietal cortex (by 29 and 30%, respectively) was detected only on day 2 of ischemia.

As a result of the antiedematous action of CC, the status of cerebral microvessels improved. In control rats a reliable decrease of the mean capillary diameter due to a drop in the number of capillaries 8±1 μ and 6±1 μ in diameter (three- and twofold, respectively) was observed by days 4-5, the period of maximal decrease of the blood supply to the brain under conditions of this model [4], when edema swelling of brain tissue was still manifest; the number of nonfunctioning capillaries 2±1 μ in diameter sharply (10 times) increased (Table 1). On the other hand, it is possible that, besides compression of the capillaries by edematous brain tissue, such a pronounced reduction of the mean

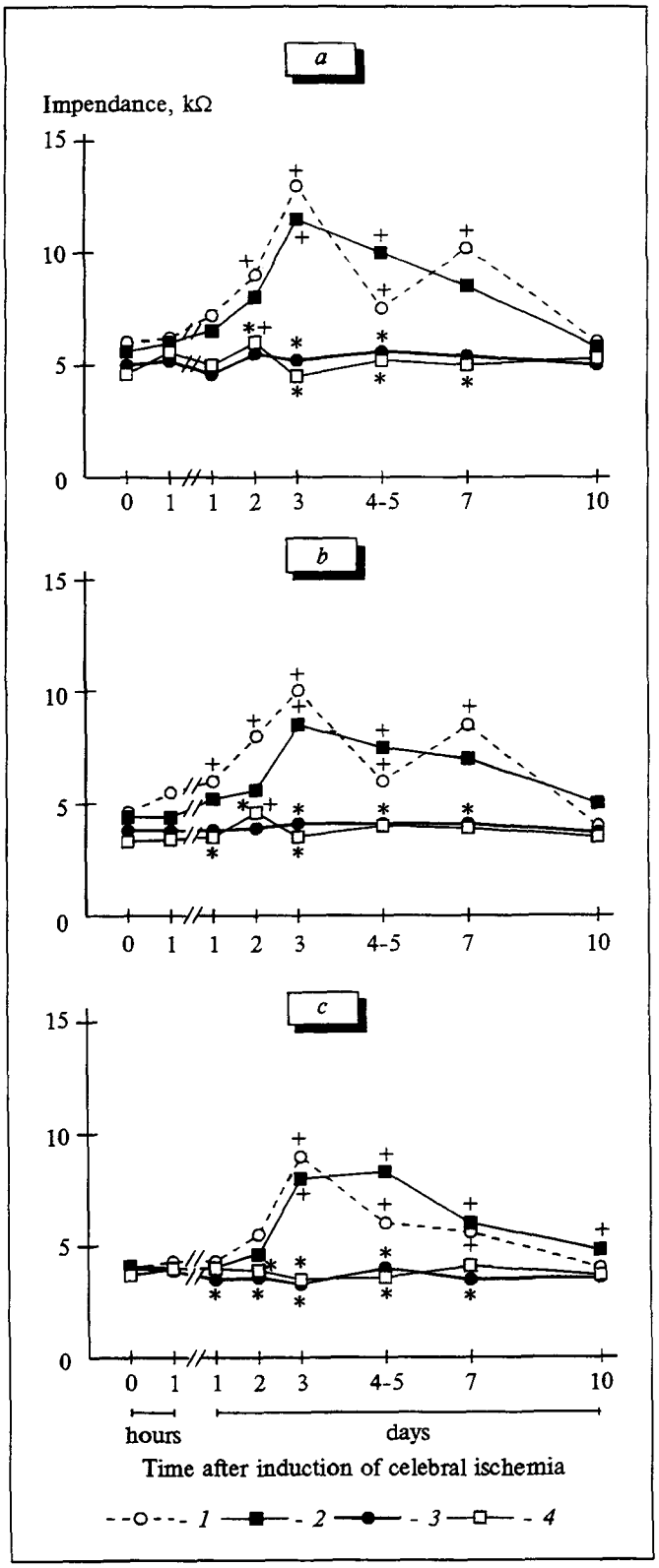

Fig. 1. Time course of complete impedance of brain tissue (*a*) and of its active (*b*) and reactive (*c*) constituents in the left (unbroken line) and right (broken line) parietal cortex after cerebral ischemia in control (*1*, *2*) and CC-treated (*3*, *4*) rats. A plus sign shows statistically reliable changes *vs.* the initial values (0); an asterisk shows changes *vs.* the control.

TABLE 1. Effect of CC on the Mean Capillary Diameter and Size Distribution of Capillaries in Rat Cerebral Cortex (% of Total Number)

Animal group	Mean diameter, μ	Share of capillaries of diameter, μ				
		2±1	4±1	6±1	8±1	10±1
Sham-operated	5.6±0.9	3.9±0.9	42.5±5.4	33.9±2.0	15.2±2.3	5.8±1.8
With brain ischemia (control)	4.0±0.2*	37.0±1.5*	38.3±1.5	17.6±4.6*	4.7±1.1*	2.3±0.5
Treated with CC	5.1±0.1+	11.4±1.8*+	45.4±2.5+	27.0±1.4*+	9.8±1.1*+	5.6±1.7

Note. Asterisk shows $p<0.05$ *vs.* sham-operated animals, a plus sign $p<0.05$ *vs.* control.

diameter of cerebrocortical capillaries and increase in the number of nonfunctioning capillaries may be due to a lower intracapillary pressure caused both by ligation of the carotid arteries and by the development of arteriolar spasm in response to brain ischemia [16].

The course of CC appreciably alleviated the microcirculatory disorders. By days 4-5 of ischemia the mean capillary diameter increased, the number of severely constricted capillaries fell 3.5 times, and the number of capillaries 6±1 and 8±1 μ in diameter increased 2.5 and 2 times, respectively (Table 1). The inability of CC to completely repair the lumen of cerebrocortical capillaries and restore their diameters, despite the almost complete recovery of the blood supply to the cortex of both hemispheres in this period [2], and the absence of signs of brain edema may be due to the reaction of distal vessels to persisting occlusion of the carotid arteries [16].

One of the mechanisms possibly underlying the antiedematous effect may be the antioxidative activity of 1,4-dihydropyridine derivatives [11]; the manifestation of this CC property was studied under conditions of transitory ischemia of the brain. A drastic increase of the content of diene conjugates (from 56±4 to 142±12 rel. units) and Schiff's bases (from 36±3 to 108±6 rel. units) in brain tissue was observed by the 30th min of recirculation. In animals protected by CC the levels of diene conjugates and Schiff's bases in the brain increased to only 64±6 and 42±10 rel. units, respectively ($p>0.05$). Bearing in mind the role of lipid peroxidation processes in neuronal membrane damage during ischemia and the development of brain edema [6], one should note in particular the suppressive effect of CC on the development of edematous swelling of cerebral tissue related to inhibition of lipid peroxidation. Moreover, the antioxidative activity of CC may be partially related to its capacity to limit lactate accumulation in the brain, as was demonstrated under conditions of acute transitory ischemia [1] and hypoxia [12], since lactacidosis is known to intensify the development of lipid peroxidation in brain tissue [7].

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