Effect of Cerebrocrast on Local Cerebral Bloodflow and EEG of Alert Rats with Brain Ischemia

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Cerebrocrast, a 1,4-dihydropyridine derivative, accelerated blood delivery to the brain and normalized the spectrum and total power of the electroencephalogram during brain ischemia; manifestations of interhemispheric asymmetry of the electroencephalogram and cerebral bloodflow were leveled.

Key Words: *cerebrocrast; brain ischemia; local cerebral bloodflow; electroencephalogram power spectrum*

Cerebrocrast (CC), a 1,4-dihydropyridine derivative synthesized at the Institute of Organic Synthesis, Academy of Sciences of Latvia [8], is a selective vasodilating agent. Its protective effect on the brain has been demonstrated in various models of acute cerebrovascular disorders [1,3,6,7,9]. It is noteworthy that, as a rule, the agent has been assessed in experiments on anesthetized animals with a single administration of CC and a limited follow-up period. However, patients with disorders of cerebral circulation develop stable disturbances of cerebral hemodynamics and metabolism and are in need of extended drug therapy [2]. Hence, our purpose was to investigate the effect of a course of CC therapy on cerebral bloodflow and the electroencephalogram (EEG) under conditions approximating the clinical ones on a new model of brain ischemia in alert rats.

MATERIALS AND METHODS

Experiments were carried out in 4 series with 24 male Wistar rats weighing 200 to 250 g. Bipolar platinum electrodes were implanted in the parietal cortex of series I-II to measure the local cerebral bloodflow (LCB) by hydrogen clearance with its electrochemical generation [5] 6-7 days before the experiment, and monopolar Nichrome electrodes for EEG recording were implanted at the same time to animals of series III-IV. LCB was assessed using an FB-01 Pul's device with an N306 automated recorder. The EEG was recorded and spectral analysis carried out for 248 sec using a neurophysiological complex of O.T.E. Biomedica at a time constant of 0.03 sec. The relative total power, power of individual spectral bands (δ 0.5 to 4, θ 4 to 8, α 8 to 12, β_1 12 to 22, and β_2 22 to 32 Hz) and coefficients of asymmetry (the ratio of the relevant band power and total power in the left and right cortex) were estimated. Brain ischemia was induced under ether narcosis by ligation of the left common carotid artery and restriction of the bloodflow in the right common carotid artery to 50% of its initial level, as shown by an MFV-1100 blood flowemeter. CC was given daily per os in a dose of 0.5 mg/kg in starch gel to animals of series II and IV 1 h before the experiment, while animals of the control series (I and III) were given equivalent volumes of starch. The results were statistically processed using Student's *t* test and the nonparametric Wilcoxon test.

RESULTS

In control group I brain ischemia led to a stable decrease of LCB in the left cortex as to low as

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35-40% of its initial level starting from the first hour and up to days 4-5, and it remained low (57-61%) on days 7-10 of the follow-up (Fig. 1). LCB in the right cortex changed similarly but to a lesser degree, with a trend toward normalization on day 10 of ischemia. Clear-cut and stable differences were revealed in the level of blood supply to the parietal cortex of the two hemispheres. In experimental group II, LCB reduction 1 h after ligation of the carotid arteries did not differ from the control, but later the time course of this parameter was quite different (Fig. 1). The tendency toward recovery of LCB in the left cortex of experimental animals was better expressed on days 1-3 than in the control, although the blood supply to the brain at this time was the same, reliably lower than initially. Starting from day 3 the LCB values in the left cortex surpassed the control level and from days 4-5 till the end of the follow-up did not appreciably differ from the initial level. In the right hemisphere the LCB reduction was unreliable as early as on day 1 after ischemia reproduction; later the bloodflow approached the initial level and did not reliably differ from the control. Differences in blood supply to the right and left cerebral cortex were detected only on days 1 and 2 of ischemia. Hence, CC had an evident and rapid normalizing effect on blood supply to the cerebral cortex under conditions of brain ischemia.

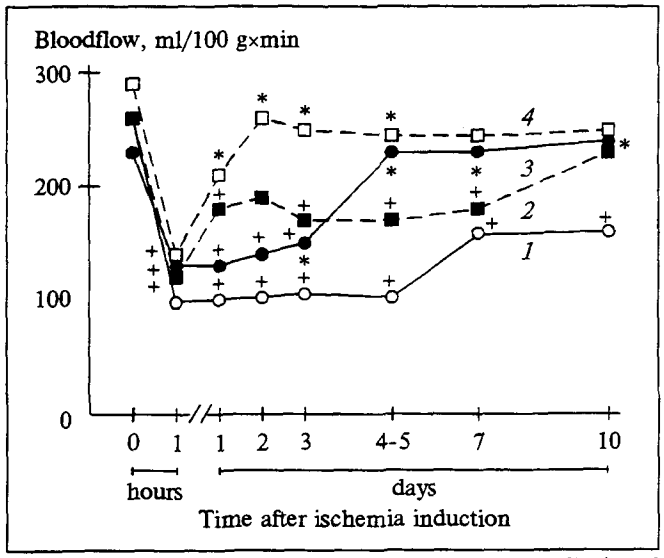

Fig. 1. Time course of LCB in the left (unbroken line) and right (broken line) parietal cortex after brain ischemia in control (*1*, *2*) and CC–treated (*3*, *4*) rats. A plus sign shows statistically reliable changes *vs.* the initial values (0); an asterisk indicates differences from the control.

In control group III brain ischemia was attended by pronounced changes in the EEG and its spectral characteristics (Fig. 2). Regular features were a stable reduction of the total power (37-60% in the left and 28-50% in the right cortex), 21-32% decreased power of the dominant θ-band, a relative increase of the share of the low-frequency

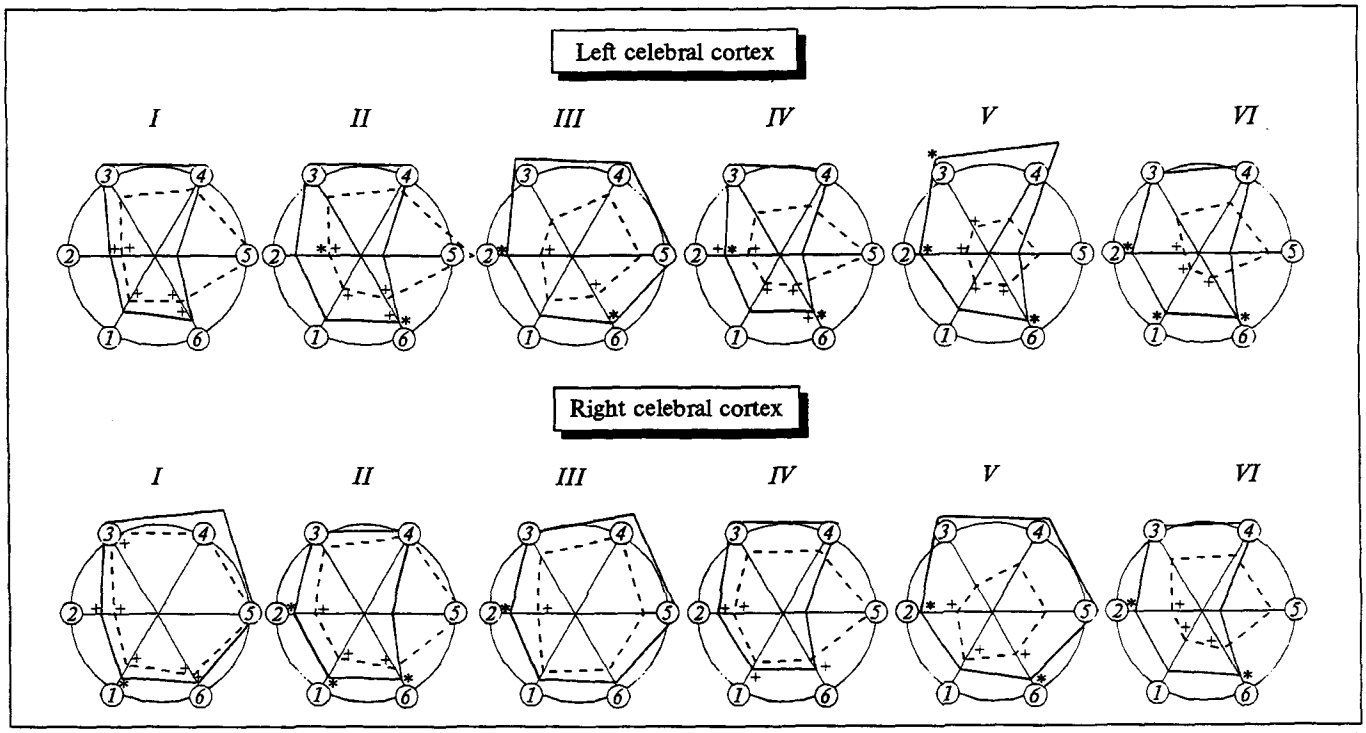

Fig. 2. Changes in the relative power of individual EEG spectral bands (δ, *1*; θ, *2*; α, *3*; β_1, *4*; β_2, *5*) and total EEG power (*6*) in control (broken line) and CC–treated (unbroken line) rats on days 1 (*I*), 2 (*II*), 3 (*III*), 4–5 (*IV*), 7 (*V*), and 10 (*VI*) after ischemia reproduction. A plus sign shows statistically reliable changes in the parameters *vs.* the initial values (100%); an asterisk indicates differences *vs.* the control.

δ-band in the spectrum, and more pronounced pathological shifts in the left cortex, which was involved to a greater measure under conditions of this model (the asymmetry coefficients of all power spectrum parameters were reliably lowered to 0.26-0.33 by days 4-5).

Despite similar values of the tested EEG parameters in groups III and IV before and 1 h after ischemia, a clear-cut tendency toward recovery of the total power and the power of individual frequency bands was observed in CC-treated rats as early as on day 1 (Fig. 2). It is noteworthy that a stable (except on days 4-5) normalization of the power in the dominant θ-rhythm and total EEG power was regularly observed starting from day 2 till the end of the follow-up. Signs of interhemispheric asymmetry leveled out in these rats. Our findings are in line with previously reported data indicating the prevention of depression of the main cerebral rhythms in rats under conditions of 10-min occlusion of the carotid arteries during CC treatment and a clear-cut tendency toward normalization of the EEG power spectrum during intravenous infusion of the drug to cats 1 day after brain stroke [6].

When discussing the mechanism of the protective action of CC one should note, first and foremost, the evident cerebral vasodilating effect, which manifests itself as a selective increase of the cerebral bloodflow [4,8] and leads to improvement of the circulation under conditions of various models of cerebrovascular disorders [1,3,6,7,9]. The positive effect of the drug may also be due to its capacity to prevent microcirculatory and hemorheological disturbances [3]. On the other hand, analysis of the time course and schedule of LCB and EEG normalization and the coefficients of correlation between these parameters over the entire follow-up, which did not surpass 0.48 ($p>0.05$), permit us to postulate a direct neuroprotective effect of the drug (not mediated by the improved blood supply to the brain) participating in the normalization of bioelectrical activity. At the same time, recent reports have demonstrated that the protective and therapeutic effects of CC cannot be explained merely by regulation of Ca^{2+} metabolism in the neurons [10]. Evidently, antihypoxic effects of CC, such as the capacity to prevent lactate accumulation in circulatory hypoxia [9] and to improve oxygen delivery to brain tissue by facilitating oxygen release by hemoglobin [3], as well as the normalization of neurotransmitter metabolism in the brain [10], also contribute to early and stable normalization of the functional activity of the brain.

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