Increasing the Efficacy of Antiepileptic Effect of Diazepam by Cerebellar Cortex Electrostimulation

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Diazepam effects on epileptic foci induced by benzylpenicillin application to the posterior sigmoid gyrus were studied in acute experiments on cats. Diazepam more effectively decreased the activity of the foci after preliminary electrostimulation of the IX and X lobules of the vermis than without such a pretreatment.

Key Words: diazepam; cerebellum; electrostimulation; epileptic activity

Electrical stimulation (ES) of caudate portions of the vermis during regular use of the benzodiazepines diazepam or phenazepam potentiates the anticonvulsive effect of the drugs both during and after ES and eliminates the factors promoting epileptogenesis [1,4].

Our purpose was to assess the opposite effect: stimulation of antiepileptic action of diazepam by preliminary ES of the cerebellar cortex.

MATERIALS AND METHODS

The study was performed on 27 cats of both sexes weighing 2.5-3.5 kg. Tracheostomy, trephination, implantation of constantan bipolar electrodes (0.12-0.15 μ, distance between the electrodes 0.25 mm) in the cerebellar cortex (IX-X lobules of the vermis according to [5]), and catheterization of the femoral vein were carried out under ether rausch narcosis. Electrodes were fixed to the skull bones by rapidly hardened Noracryl. The animals were transferred to forced respiration after intraperitoneal injection of 0.25 mg/kg d-tubocurarine (Orion). Follow-up started from 22.5 h after the end of ether narcosis. Twenty sessions of ES of cerebellar cortex (rectangular pulses, 100-300 Hz, 300-400 μA, pulse duration 0.25 msec, ES duration 5-7 sec) were performed every 3 min with an ESU-2 electrostimulator. To control animals, electrodes were similarly implanted, but no ES was performed.

After opening the dura mater, a focus of epileptic activity (EpA) was created by applying a filter paper (2x2 mm) moistened with fresh-prepared benzylpenicillin sodium solution (10,000 U/ml) onto the posterior sigmoid gyrus. Activity of EpA was recorded through monopolar electrodes by an electroencephalograph (Medicor) with indifferent electrodes fixed in the nasal bones.

EpA of the foci was expressed in arbitrary units: a mean amplitude of 1 mV at 1 charge/min generation was taken for one unit. A 1-min Bpoque of charge generation was taken for estimating the level of EpA, and the life span of foci was determined as the period from the first to the last spike [3]. Diazepam (Gedeon Richter) was injected intravenously in doses 0.5 and 1.5 mg/kg during generation of stable activity in the foci. Controls were injected with 0.5 ml normal saline.

Results were statistically processed using ANOVA tests with subsequent processing by the Neumann-Keuls test. Differences were considered significant at p<0.05.

RESULTS

After application of benzylpenicillin (in 3-7 min), the first spike charges were generated in the focus. The amplitude and frequency of these charges in-
Fig. 1. Effects of diazepam on the foci of epileptic activity created by application of penicillin (10,000 U/ml) to the cerebral cortex of cats. 
a) time course of power of foci in the control (0.5 ml normal saline); b) effects of diazepam in doses 0.5 (light bars) and 1.5 mg/kg (dark bars). Here and in Fig. 2: abscissa: time since generation of first epileptic charges in focus, min; ordinate: power of foci; *p<0.05 vs. the control (100%).

cresed during subsequent 10-15 min (with the
application on-going), reaching 1.2-1.9 mV and 25-43
charge/min, respectively. Twenty minutes after ap-
plication of the epileptogen, the power of foci was
47.5±9.6 arb. units (Fig. 1, a). Stable EpA was
observed during the next 10-15 min, after which the
frequency and amplitude of charges gradually sub-
sided during 20-35 min. Total life span of foci was
65.7±10.7 min.

Injection of 0.5 mg/kg diazepam 15 min after
the potentials had been evoked in the focus was
associated with a decrease in the frequency and am-
plitude of charges 5 min after the injection (Fig. 1,
b). After 15 min, the power of foci was 20.29±5.8
arb. units, which was significantly lower than in the
control (normal saline, p<0.05, Fig. 1, b). The differ-
ences persisted until the end of observation, and total life span of foci was the same as in the control.

Application of benzylpenicillin to the cerebral
cortex of cats exposed to 20 sessions of ES of the
cerebellar cortex was associated with appearance of
the first spike potentials 5-15 min after the epilepto-
gen was applied. During subsequent 10-15 min, EpA
power gradually increased, and 15 min after genera-
tion of the first potentials it was 37.2±7.2 arb. units
(Fig. 2, a). Stable EpA was observed for 10-15 min,
after which the frequency and amplitude of spike
potentials decreased (Fig. 2, a). The total life span of
EpA foci under these conditions was 52.7±9.8
min, which was virtually the same as in the group
without ES of cerebellum (65.7±10.7 min, p<0.05).

Injection of 0.5 mg/kg diazepam 15 min after
generation of the first spike charges decreased in 5
min the power of foci, which was 57.3% lower than
the control (cerebellar ES without diazepam, p<0.05,
Fig. 2, b). These differences remained significant
until the end of observation (Fig. 2, b). On the other

Fig. 2. Effects of diazepam on foci of epileptic activity created by application of penicillin (10,000 U/ml) to the cerebral cortex of cats after preliminary electrostimulation of cerebellar cortex. a) time course of power of foci during 20 sessions of preliminary electric stimulation of cerebellar cortex and injection of 0.5 ml normal saline; b) effect of diazepam in a dose of 0.5 (light bars) and 1.5 mg/kg (dark bars) after 20 sessions of electric stimulation of the cerebellar cortex.