THE GABA-ergic SYSTEM AND CEREBRAL EDEMA

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KEY WORDS: cerebral edema; GABA-ergic system; pharmacologic correction; antiedema effect.

The mechanism of development of cerebral edema has not been finally explained. This is largely responsible for the absence of effective remedies for its prevention and treatment.

The writers showed previously that diazepam, phenazepam, and fenibut (β-phenyl-GABA) have a marked antiedema action experimentally [4, 7]. These preparations are known to be GABA-positive [5, 6].

This paper describes an attempt to study the role of GABA-ergic structures in the formation and pharmacologic correction of cerebral edema.

EXPERIMENTAL METHOD

Experiments were carried out on 157 noninbred albino rats of both sexes weighing 150-220 g. Toxic cerebral edema was induced by intraperitoneal injection of nicotine in a dose of 40 μg/kg, and traumatic cerebral edema by epidural compression with polyethylene tubes [8]. The criteria of development of edema were the content of total water in the tissue and the density of the brain structures. The water content was determined by the usual method of weighing the dry residue, the tissue being dried to constant weight at 110°C. Density was determined in solutions of copper sulfate of varied concentration [9]. The increase in water content and decrease in density were interpreted as the development of edema.

The GABA-ergic blocker picrotoxin (0.5-1-2 mg/kg), the GABA derivative fenibut (50 mg/kg), the benzodiazepine tranquilizers diazepam (0.5 mg/kg) and phenazepam* (0.1 mg/kg), the cen-

TABLE 1. Pharmacologic Corection of Toxic Cerebral Edema during GABA-ergic Blockade (M ± m)

Experimental conditions	Sessional doses, mg/kg	Water content, %	Density of brain, g/cm³
Control	—	77,75±0,14 (13)	1,0412±0,0002 (13)
Nicotine, 40 μg/kg	—	79,44±0,26* (10)	1,0385±0,0002* (10)
Nicotine accompanied by:			
picrotoxin	1	79,43±0,35 (8)	1,0381±0,0002 (8)
diazepam + picrotoxin	0,5±1	78,88±0,26 (7)	1,0389±0,0002 (7)
diazepam + picrotoxin	0,5+0,5	78,37±0,37† (7)	1,0400±0,0004† (7)
phenazepam + picrotoxin	0,1+1	79,15±0,42 (8)	1,0390±0,0003 (8)
phenazepam + picrotoxin	0,1+0,5	78,50±0,17† (4)	1,0399±0,0003† (4)
fenibut + picrotoxin	50+1	78,64±0,26 (7)	1,0393±0,0004 (7)
fenibut + picrotoxin	50±0,5	78,41±0,28† (7)	1,0400±0,0004† (7)

Legend. *P < 0.05 compared with control, †P < 0.05 compared with nicotine. Here and in Table 2, number of animals given in parentheses.

*7-Bromo-1,3-dihydro-3-(2'-chlorophenyl)-2H-1,4-benzodiazepin-2-one.

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TABLE 2. Pharmacologic Correction of Traumatic Cerebral Edema during GABA-ergic Blockade (M ± m)

Experimental conditions	Sessional doses, mg/kg	Water content, %	Density of brain, g/cm³
Control	—	77,75±0,14 (13)	1.0412±0,0002 (13)
Trauma	—	78,92±0,23* (10)	1.0389±0,0002* (10)
Trauma accompanied by: picrotoxin	1	78,87±0,29 (6)	1.0389±0,0002 (6)
diazepam + picrotoxin	0,5+1	78,21±0,26 (6)	1,0393±0,0002 (6)
diazepam + picrotoxin	0,5+0,5	77,79±0,23† (5)	1,0402±0,0001† (5)
fenibut + picrotoxin	50+1	78,85±0,16 (6)	1,0390±0,0002 (6)
fenibut + picrotoxin	50±0,5	77,70±0,31† (6)	1,0403±0,0003† (6)

Legend. *P < 0.05 compared with control, †P < 0.05 compared with trauma.

tral muscarinic cholinolytic benactyzine (5 mg/kg), and the α-adrenoblocker phentolamine (5 mg/kg) were used. All substances were injected intraperitoneally: picrotoxin 15 min, fenibut, diazepam, and phenazepam 30 min, and benactyzine and phentolamine 1 h before injection of nicotine, but in the experiments with traumatic edema they were injected before the operation and then twice a day throughout the rest of the experiment. The animals were decapitated 1 h after injection of nicotine or 7 days after trauma. The results were subjected to statistical analysis [3].

EXPERIMENTAL RESULTS

Under the influence of nicotine and trauma the water content in the brain increased but the density of the tissue decreased, i.e., cerebral edema developed (Tables 1 and 2).

Picrotoxin in a dose of 1 mg/kg caused no significant change in the water content and density of the brain in toxic and traumatic edema. However, if injected into animals receiving diazepam, phenazepam, or fenibut, the antiedema effect of the latter was not exhibited. If the dose of picrotoxin was reduced to 0.5 mg/kg the drugs mentioned inhibited the development of edema. These results are evidence that the protective effect of diazepam, phenazepam, and fenibut against the development of toxic and traumatic cerebral edema is probable realized through the GABA-ergic system. Antagonism exists between the antiedema action of these drugs, on the one hand, and of picrotoxin, on the other hand.

In the next series of experiments the effect of benactyzine and phentolamine on the development of toxic cerebral edema was studied after blockade of GABA-ergic strucutres. The antiedema effect of these drugs was demonstrated in the writers' laboratory by Kozlov [2]. Combined administration of benactyzine and picrotoxin (1 mg/kg) did not prevent the development of edema. The water content was high (79.58 ± 0.25%) and the brain density low (1.0393 ± 0.0002 g/cm³). Under analogous conditions phentolamine inhibited the development of toxic edema, but this effect of the drug was weak (water content 78.51 ± 0.20%, brain density 1.0398 ± 0.0002 g/cm³; P < 0.05). Consequently, GABA-ergic blockage abolishes or considerably weakens the correction of cerebral edema even by those substances whose action is effected through cholinergic and adrenergic systems.

The effect of picrotoxin on the water content and density of brain tissue was studied in control animals. In an acute experiment 30-90 min after injection of picrotoxin in doses of 1 and 2 mg/kg there were no significant changes in the parameters studied, although the animals' condition was grave. In a dose of 2 mg/kg picrotoxin caused the development of clonicotonic convulsions, which ended in death of the animals.

During prolonged administration (twice a day for 1 week) to animals with a burr-hole drilled beforehand in the skull, picrotoxin in a dose of 1 mg/kg increased the water content in the brain to 78.88 ± 0.36% and reduced its density to 1.0393 ± 0.0005 g/cm³ (P < 0.01). Prolonged daily blockage of GABA-ergic structures by picrotoxin after trephining of the skull thus leads to the development of cerebral edema.

The results of this investigation can be summed up in the statement that complex mechanisms of interdependent disturbances of function of transmitter structures are involved in

the formation of cerebral edema. The GABA-ergic system plays an important role in this process. Its functional activity in edema is probably depressed, and this is also confirmed by data in the literature [1]. For the combined treatment of cerebral edema it is therefore important to use preparations with a GABA-positive action.

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EFFECT OF β-NEOENDORPHIN, A κ-OPIATE RECEPTOR AGONIST, ON CEREBRAL CORTICAL UNIT ACTIVITY

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KEY WORDS: β-neoendorphin; various types of opiate receptors; microiontophoresis of opioid peptides.

β-neoendorphin (Tyr-Gly-Gly-Phe-Leu-Arg-Lys-Tyr-Pro) is a peptide with opioid activity which was isolated from pig hypothalamus in 1981 [4]. In experiments *in vitro*, using various isolated organs (guinea pig and rabbit ileum, vasa deferentia of mice, rats, and rabbits), containing peripheral opiate receptors of various types, it was shown that β-neoendorphin is an agoinst of κ-opiate receptors [5]. However, the action of the peptide on electrical activity of CNS neurons, on whose membranes opiate receptors also are located, had not been studied.

The aim of this investigation was to study the effect of microiontophoretic applications of the preparation on unit activity in the cerebral cortex. The effects of β-neoendorphin were compared with the action of morphine (an agonist of μ-opiate receptors), Leu-enkephalin (an agonist of δ-opiate receptors), and β-endorphin (an agonist of μ-, δ-, ε-opiate receptors) in experiments on the same cortical neurons.

EXPERIMENTAL METHOD

Experiments were carried out on six curarized cats of both sexes weighing 2.6-4.1 kg, with artificial ventilation of the lungs. The animals' body temperature was maintained at 37-38°C by means of an electric heater. The preliminary surgical manipulations (tracheotomy, scalping, etc.) were performed under general anesthesia (pentobarbital sodium, 50 kg/mg, intraperitoneally). Single unit activity was recorded extracellularly (14-16 h after injection of pentobarbital sodium) and the physiologically active substances were applied microiontophoretically by means of multichannel glass microelectrodes [2]. An Élektronika DZ-28 microcomputer, coupled with the apparatus for recording unit activity, analyzed information on spontaneous and evoked unit activity in the course of the experiment and plotted it graphi-

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