PREVENTION OF CEREBROVASCULAR DISORDERS BY ADRENERGIC DRUGS

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An experimental model of cerebrovascular disorders of neurogenic (adrenergic) nature, arising after injection of KCl into the lateral ventricles of cats and dogs, is suggested. Surgical desympathization greatly weakened spasms of the cerebral vessels produced by the central effect of KCl. Dihydroergotoxin, phenoxybenzamine, tropaphen, octadine*, and nialamide had both a therapeutic and a prophylactic effect on these experimental disturbances of the cerebral circulation.

KEY WORDS: pharmacology of the cerebral circulation; experimental cerebrovascular disorders.

The functional role of the sympathico-adrenal system in regulating the tone of the intracranial vessels and in the pathogenesis of cerebrovascular disorders has not yet been finally established [3, 4, 9, 12, 14]. In particular, it has been suggested that changes in the pH of the cerebrospinal fluid play the leading role in the development of the vascular pathology of the brain [10, 13]. According to Bendikov's observations [1, 2], if KCl is injected into the lateral ventricles of cats it leads to increased electrical activity in the inferior cardiac nerve, hypertension, increased tone of the coronary vessels, and ischemic changes in the ECG.

The object of this paper is to discuss an experimental model of neurogenic disturbances of the cerebral circulation caused by the action of KCl on the central nervous system.

EXPERIMENTAL METHOD

Experiments were carried out on 22 dogs weighing 18-25 kg under general anesthesia with morphine (10 mg/kg) and urethane (1.0 g/kg) and 124 cats weighing 3-4 kg under general anesthesia with urethane (0.5 g/kg) and chloralose (50 mg/kg), with artifical ventilation of the lungs. The cerebral blood flow was determined with the aid of radioactive Xe^{133} [8] and an electromagnetic measuring device with simultaneous recording of the ECG, EEG, and arterial blood pressure [6]. The vascular component of the action of the drugs on the cerebral hemodynamics was differentiated by separate bilateral perfusion of the carotid and vertebral arteries [7]. Disturbances of the cerebral circulation were induced by a 0.25 M solution of KCl injected into the lateral ventricles of cats (0.5 ml) and dogs (1 ml) [1, 11].

EXPERIMENTAL RESULTS AND DISCUSSION

During the first 10-15 sec after intraventricular injection of KCl a decrease was observed in the volume velocity of the cerebral blood flow by 15-20% on average. Next, besides a marked rise in the arterial blood pressure and tachycardia, the intracranial blood flow began to increase and reached its maximum

*Guanethidine – Translator.

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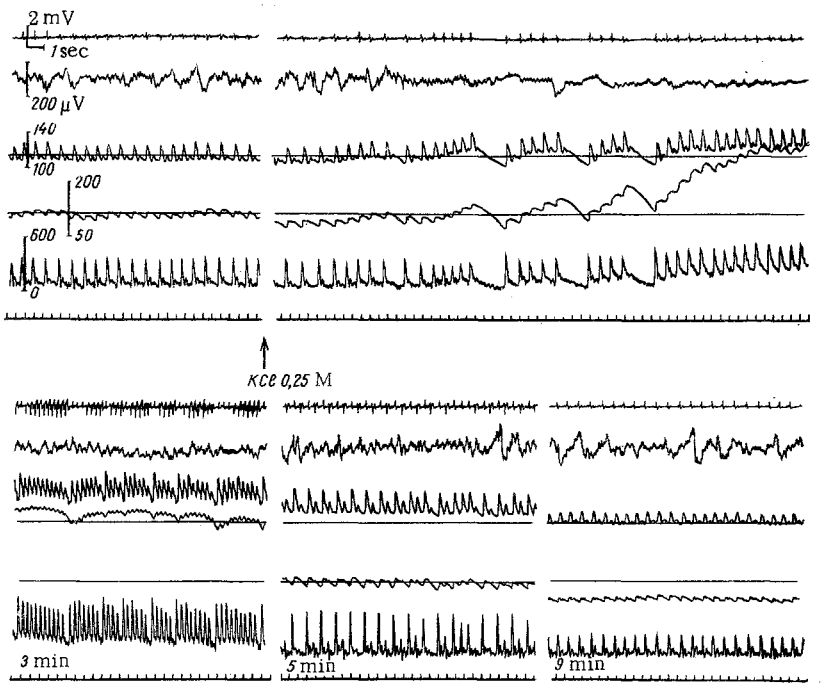

Fig. 1. Changes in cerebral blood flow, EEG, ECG, and arterial pressure in a dog following intraventricular injection of KCl (0.25 M solution). From top to bottom: ECG in lead II; EEG of parietal region; arterial pulse pressure (in mm Hg); averaged and phasic blood flow in right internal maxillary artery (in ml/min). Times after injection of KCl are shown below.

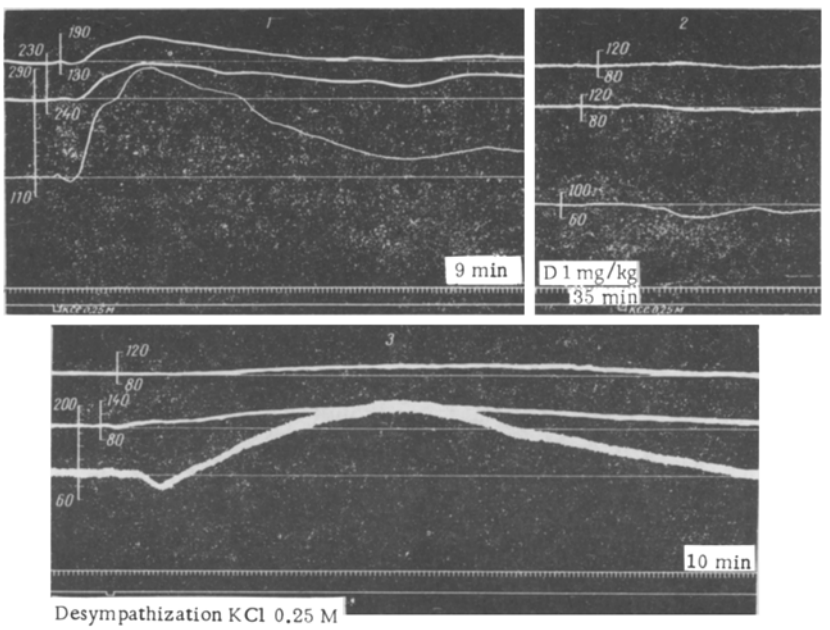

Fig. 2. Effect of KCl (0.5 ml of 0.25 M solution), injected into lateral ventricles of cats, on tone of intracranial vessels and arterial pressure: 1) control experiments, 2) 35 min after injection of dihydroergotoxin (D), 3) after surgical desympathization. From top to bottom: perfusion pressure in internal maxillary arteries; resistogram of vertebral arteries; arterial pressure; time marker (5 sec), marker of injection of KCl.

during the first 3 min after injection of KCl. The volume velocity of the cerebral blood flow, it will be noted, returned to its initial level while the arterial pressure was considerably higher, whereas restoration of the original blood pressure readings was accompanied by a marked decrease in the cerebral blood flow. Changes characteristic of acute coronary insufficiency and disturbance of the cardiac rhythm appeared in the ECG (Fig. 1).

Changes in the EEG under the influence of KCl depended on the initial level of cortical electrical activity. If the original EEG was dominated by slow waves (2-3/sec) with an amplitude of 200 μV, slowing of the initial activity to 1-2 waves/sec and an increase in the amplitude of the slow waves to 270-330 μV were observed. If the EEG was dominated by low-amplitude fast waves, during the first minute after intraventricular injection of KCl the amplitude decreased and the frequency increased. Later the low-amplitude activity disappeared and was replaced by slow activity with an amplitude of up to 200-220 μV, which began to predominate in the EEG and to become high-amplitude slow activity (Fig. 1).

Under the influence of KCl there was an increase not only in the systemic arterial pressure (on the average by $97 \pm 14\%$), but also in the resistance of the cerebral vessels in the region supplied by the carotid (by $17 \pm 2.4\%$) and vertebral arteries (by $48 \pm 5.6\%$) (Fig. 2, 1). After injection of the same concentrations of KCl into the arterial systems of the brain, no increase in tone of the intracranial vessels was found.

After injection of KCl into the lateral ventricles, the pH of the cerebrospinal fluid shifted toward the acid side. Consequently, the constrictor response of the cerebral vessels in this case cannot be explained by a change in the pH of the CSF, for acidification of the CSF leads to a decrease in tone of the intracranial vessels.

To determine the role of the sympathetic innervation in the production of experimental cerebrovascular disturbances KCl was injected after surgical desympathization of the intracranial vessels (by removal of the superior cervical and stellate ganglia). Under these conditions the increase in tone in the region supplied by the carotid arteries was only $5 \pm 1.25\%$, whereas in the system of the vertebral arteries it was $24 \pm 7.3\%$ compared with the initial level (Fig. 2, 3). The difference between the changes in tone of the cerebral vessels in the intact and desympathized animals was statistically significant ($P < 0.001$). These findings demonstrate the role of the sympathetic innervation in the production of spasm of the cerebral vessels after injection of KCl into the lateral ventricles. It was interesting to investigate the effect of drugs acting on different components of the adrenergic regulatory mechanism on the cerebral circulation under these conditions. For this purpose the α-adrenoblockers dihydroergotoxin (1 mg/kg), phenoxybenzamine (1 mg/kg), and tropaphen (1 mg/kg), the sympatholytic drug octadine (10 mg/kg), and the MAO inhibitor nialamide (20 mg/kg), with a marked inhibitory effect on the centers of vasomotor regulation [5], were used. All these drugs had a therapeutic and prophylactic effect on the experimental disturbance of the cerebral circulation produced by KCl (Fig. 2, 2).

These results demonstrate the role of the sympathetic nervous system in the origin of cerebrovascular disorders.

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