EFFECT OF BLOCKING THE CENTRAL CHOLINERGIC SYNAPTIC SYSTEMS ON RESISTANCE OF THE CEREBRAL CORTEX TO ASPHYXIA AND ISCHEMIA

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Having regard to the important role of the cholinergic synaptic systems in brain activity, we investigated the effect of substances modifying the transmission of impulses in these structures on the development and course of terminal states resulting from asphyxia or ischemia.

EXPERIMENTAL METHOD

Altogether 66 experiments were performed on the same number of cats, 56 of them under automatic endotracheal ether anesthesia (by Yu. N. Shanin's method) in the stage of analgesia with controlled respiration. The muscle relaxant Paramyon was injected in frequent, small doses. To produce a state of asphyxia (44 animals), at the height of active expiration, when the pressure in the anesthetic apparatus was −7 mm Hg, the trachea was clamped for 6 min. In 10 animals (of these 44) the same experimental technique was used, but without anesthesia.

Cerebral ischemia was produced (in 22 animals) by clamping the ascending part of the aorta for 4 or 5 min.

The animals were revived by means of automatic artificial respiration and direct or indirect cardiac massage.

The preparations to be studied were the muscarine-like cholinolytic Metamysil (1-3 mg/kg), the nicotine-like cholinolytics Difacil (3-5 mg/kg) and Gangleron (1-3 mg/kg), and the acticholinesterase drug Nivalin (2 mg/kg). These were injected intravenously 15 min before the production of asphyxia or cerebral ischemia. The animal's condition and its brain function were judged by the character of the electrocorticogram (1 bipolar and 2 unipolar leads from the somatosensory zone of the cortex and 2 unipolar leads from both parieto-occipital regions of the cerebral cortex), the electrocardiogram (ECG) (lead 2), and the level of the arterial pressure (measured directly in the femoral artery).

EXPERIMENTAL RESULTS

Experiments with Asphyxia and without Anesthesia. In the control experiments the period of extinction of the cortical electrical activity varied from 1 min to 1 min 15 sec (mean 1 min 5 sec). During resuscitation after asphyxia loasting 6 min, none of the five animals showed signs of recovery of the cortical electrical activity for 1 h, although an adequate circulation was recorded in four of these animals within 40-50 sec of starting resuscitation measures (Fig. 1, B).

In five experiments in which a preliminary injection of the central muscarine-like cholinolytic Metamysin (1 mg/kg) was given, the period of extinction of cortical electrical activity after clamping the trachea was between 2 min and 2 min 20 sec (mean 2 min 10 sec), i.e., 1 min 5 sec longer than in the controls. In all five experiments resuscitation of the animals after asphyxia lasting 6 min resulted in restoration of the potentials of the electrocorticogram to their initial level (Fig. 1, A). If a satisfactory circulation was restored during the first 30 sec of resuscitation, the waves appeared during the 3rd-4th min after the beginning of resuscitation, and the initial level was restored at

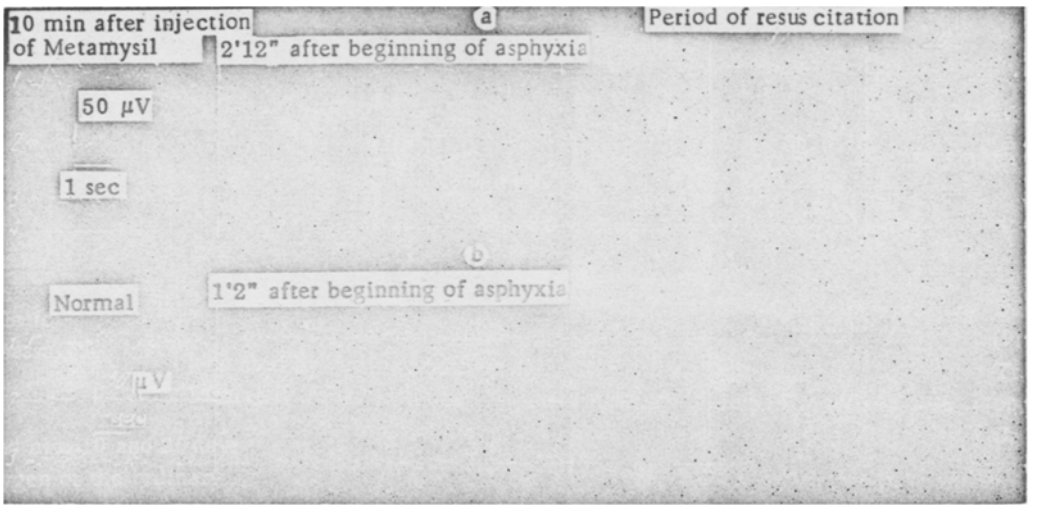

Fig. 1. Effect of asphyxia lasting 6 min on the cortical electrical activity of unanesthetized cats. A) Experiment with Metamysil (1 mg/kg); B) control; 1) bipolar leads from somatosensory zone of cerebral cortex; 2) unipolar lead from right parieto-occipital zone of the cerebral cortex; 3) unipolar lead from left parieto-occipital zone of the cerebral cortex; 4) marker of photic stimulation (5 cps).

the 20th min. In the experiment in which the blood flow was restored 1 min after the beginning of resuscitation, the first waves appeared after 22 min, and a level close to that observed initially was reached at the end of the first hour.

In the series of experiments without anesthesia, observations on the subsequent restoration of the vital functions were maintained for 6 h. In all the animals spontaneous respiration was restored when the pulsator was discontinued 1 h after the beginning of resuscitation, and the reaction of the pupils to light and the corneal reflex were restored slightly earlier. All five animals of the control group at this time were in a state of decerebrate rigidity, which gave way during the subsequent 5 h to a state of plastic tonus in only two animals. No general reaction to a bright photic stimulus could be observed. The cats did not drink milk brought up to their mouth. In the experiments with Metamysil, when the pulsator was discontinued the animals were in a state of plastic tonus. After 4 h, 3 of the 5 animals raised their heads, sat up, reacted to a bright light with turning the head, and drank milk brought up to their mouth. When left without supervision, all 10 animals (control and experimental) died from multiple atelectases and obstruction of the tracheotomy tube with viscid sputum.

Experiments with Asphyxia and with Ether Anesthesia. In the 10 control experiments (without administration of the test drugs) the period of extinction of the cortical electrical activity was between 55 sec and 1 min 20 sec (mean 1 min 3 sec). During resuscitation the cortical electrical activity was restored in 4 of the 10 animals. In the experiment in which a satisfactory circulation was observed during the first seconds of resuscitation, waves appeared on the electrocorticogram after 4 min, and the initial level of cortical electrical activity was restored 40 min after the beginning of resuscitation. When the circulation was restored 1 min 30 sec after the beginning of resuscitation, the first cortical potentials were recorded at the 32nd min, and they approximated to their initial level after 90 min. In 4 experiments resuscitation proved impossible because of the development of fibrillation of the heart muscle; in two cats, despite satisfactory indices of the circulation 1 min 30 sec - 2 min after the beginning of resuscitation, signs of restoration of the cortical electrical activity had not appeared after 2 h.

In 13 experiments in which the central, muscarine-like cholinolytic Metamysil (1-3 mg/kg) was given, the period of extinction of the cortical electrical activity varied from 1 min 55 sec to 2 min 20 sec (mean 2 min 9 sec), i.e., 1 min 6 sec longer than in the controls. The cortical potentials were restored in 11 of the 13 experimental animals. In 2 experiments with Metamysil, obstacles to resuscitation were fibrillation of the heart muscle, developing during massage (in one experiment), and hemorrhage (in another). Where a satisfactory circulation was restored during the first seconds of resuscitation, the appearance of waves on the electrocorticogram was recorded 2 min after the beginning of resuscitation. The cortical electrical activity was restored to its initial level after 10-14 min.

Extinction and Restoration of Cortical Electrical Activity of Cats in Experiments with Ischemia

Experimental condition	No. of experiments	Period of extinction (in seconds)		Time of recovery (in minutes)			
				after ischemia for 4 min		after ischemia for 5 min	
		limits of variation	mean data	first waves	initial level	first waves	initial level
Control (Fig. 2, A)	7	13-16	14	3	7	6	70
				4	11	8	Not restored
Metamysil, 1 mg/kg (Fig. 2, C)	9	17-21	19	1-1/2	4		
				2	5	4	14
				2	6	5	22
Gangleron, 1 mg/kg	2	15 and 16		4	8		
				13	Not restored		
				3	8	26	Not restored
Nivalin, 2 mg/kg (Fig. 2, B)	4	8-11	9	4	9	31	Ditto

In four experiments with the other nicotine-like cholinolytic, Difacil (3-5 mg/kg), the period of extinction of the waves on the electrocorticogram was between 1 min and 1 min 53 sec (mean 1 min 26 sec), i.e., longer than in the controls but shorter than in the experiments with Metamysil. The cortical electrical activity reappeared and was restored in only one animal, in which a satisfactory circulation was obtained during the first few seconds of resuscitation, after intervals of 5 and 44 min, respectively.

Despite the fact that in the experiments with drugs possessing nicotine-like cholinolytic properties (Gangleron, Difacil) the animals were difficult to resuscitate, and in 5 of the 8 experiments resuscitation was impossible because of arterial hypotension caused by these drugs, the periods of maintenance and restoration of the cortical electrical activity showed an improvement on those in the control animals. We consider that the increased viability of the brain in these cases was due, on the one hand, to the blocking of the nicotine-like chlinergic systems of the brain, and on the other hand, to changes in the blood flow to the brain resulting from the action of the nicotine-like cholinolytics [6, 7]. This hypothesis is confirmed by the experiments with Difacil and Gangleron, in which recovery of the waves on the electrocorticogram was observed at a time when the arterial blood pressure did not exceed 15-25 mm Hg, which was not observed in the other series of experiments.

To elucidate the special features of the course of the terminal states during stimulation of the central cholinergic structures, five experiments were carried out using the anticholinesterase drug Nivalin (2 mg/kg). The period of disappearance of the waves from the electrocorticogram in the experiments with Nivalin was between 1 min and 1 min 25 sec (mean 1 min 9 sec). During the recovery period the stimulating effect of Nivalin was apparent to some degree only when the circulation was adequately restored during the first few seconds of resuscitation; any delay in the restoration of an effective blood flow at this time had a much more marked adverse effect on restoration of the cortical potentials than in the other series of experiments (especially those with Metamysil).

The results of the investigations involving cerebral ischemia are given in the table and in Fig. 2 (A, B, C). All 22 experiments were conducted under automatic ether anesthesia by Yu. N. Shanin's method. In 7 of the 22 experiments with ischemia resuscitation was impossible on account of the profuse bleeding which developed after removal of the clamp from the aorta.

It may be concluded from these investigations that blocking the central cholinergic systems, especially with muscarine-like cholinolytics, increases the resistance of the central nervous system to hypoxia and ischemia and facilitates recovery of the animal from a terminal state. Excitation of the central cholinergic structures of the brain by means of anticholinesterase drugs apparently leads to rapid exhaustion of the energy resources of the central nervous system and adversely affects the restoration of the cortical electrical activity during resuscitation after prolonged asphyxia or ischemia.

Having regard to the well-known tranquilizing action of the central muscarine-like cholinolytic Metamysil [1-5], and also the results of the present investigation demonstrating the increased resistance of the central nervous system to hypoxia under the influence of Metamysil, this central cholinolytic drug may be recommended for widespread use in anesthesiological practice.

SUMMARY

Sixty six experiments were staged on cats by a specially elaborated method under intratracheal automatic ether-air anesthesia with controlled breathing. Out of this number 44 experiments were done with asphyxia (in 10 experiments of this series the ether supply was switched off) and 22 with ischemia (occlusion of the ascending aorta). EEG, ECG and arterial blood pressure were recorded. Metamysil block of the central muscarine-like cholinergic synaptic systems increased the resistance of the cortex to asphyxia and ischemia. The effect of nicotine-like cholinolytics (difacil, gangleron) structures by nivalin, an anticholinesterase agent, inhibited the restoration of the bioelectric activity of the cerebral cortex following prolonged asphyxia or ischemia.

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