ROLE OF CHOLINERGIC SYSTEMS IN THE RECOVERY PERIOD AFTER ACUTE HYPOBARIC ANOXIA

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Acceleration of recovery processes after exposure to acute anoxia, which accompanies the majority of pathological processes, is of great importance in the management of anoxic states. Various neurotransmitter systems, including cholinergic, are known to interact in the mechanism of adaptation to anoxia [3, 8]. However, the role of these systems, especially in the recovery period after exposure to acute hypobaric anoxia, has not been studied.

The aim of this investigation was to study the effect of cholinergic agents on the resistance of animals to repeated exposure to acute hypobaric anoxia (AHA) in different phases of the recovery period after exposure to acute anoxia.

EXPERIMENTAL METHOD

Experiments were carried out on male tetrahybrid (CBWA) mice weighing 16-22 g. The test drugs included the acetylcholinesterase inhibitor physostigmine (0.4 mg/kg), the total muscarinic cholinolytic atropine (10 mg/kg), the central muscarinic cholinolytic metamizil (5 mg/kg), and the central nicotinic cholinolytic eterofen (50 mg/kg). The drugs were injected intraperitoneally 60 min before repeated exposure to AHA. The effect of the drugs on the animals' resistance to repeated AHA was studied on a model of the recovery period [1, 5] in a continuous-flow pressure chamber with CO_2 absorber (30% NaOH solution). The animals were divided beforehand into groups of mice with high (HRM) and low (LRM) resistance to acute anoxia. For this purpose the mice were placed individually in the pressure chamber and withdrawn separately at the time of onset of convulsions at an "altitude" of 11 km, with a rate of ascent of 50 m/sec. Animals beginning to have convulsions before 5 min had elapsed were classed as LRM, those not developing convulsions for 30 min as HRM. At the 4th and 24th hours of the recovery period after exposure to acute anoxia for the first time, anoxic resistance was reassessed under identical experimental conditions. The antianoxic activity of the drugs also was assessed on the basis of the proportion of HRM (PHRM) in the control and experimental groups, using the equation

$$\text{PHRM} = \frac{\text{number of animals surviving for 30 min}}{\text{total number of animals}} \cdot$$

$$\text{Effect } (\Delta\text{PHRM}) = \text{PHRM}_e - \text{PHRM}_c,$$

where PHRM_e and PHRM_c denote the experimental and control values of PHRM, respectively.

The results were subjected to statistical analysis with calculation of arithmetic mean values and their confidence intervals by Student's test, and the significance of differences also was estimated by Fisher's test.

EXPERIMENTAL RESULTS

In the experiments of series I the effect of the drugs specified, when given prophylactically, on the resistance of the animals to acute anoxia was studied (Table 1; Fig. 1). It will be clear from Fig. 1 that physostigmine increased the resistance of the animals to acute anoxia by 87% compared with the control. Atropine and metamizil reduced the resistance to

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TABLE 1. Effect of Cholinergic Drugs, Given Prophylactically, on Resistance of Animals to Acute Anoxia (M ± m, n = 9)

Drug	Dose, mg/kg	Length of survival of animals during exposure to AHA, min	ΔPHRM
Control		11,2±4,01	
Physostigmine	0,4	20,9±4,52	+0,34
Atropine	10	4,97±3,14	—0,22
Control		10,5±4,45	
Metamizil	5	5,82±3,28	—0,11
Eterofen	50	12,5±4,39	+0,11

TABLE 2. Effect of Cholinergic Drugs on Resistance of HRM and LRM to Repeated Acute Anoxia in the Recovery Period

Drug	Dose, mg/kg	Length of survival at "altitude" of 11 km, min			
		HRM (4 h)	HRM (24 h)	LRM (4 h)	LRM (24 h)
Control		7,53±4,53 (n = 6)	17,9±5,71 (n = 7)	9,14±3,7 (n = 7)	16,8±5,04 (n = 8)
Physostigmine	0,4	30,0±0*** (n = 6)	26,9±3,13 (n = 6)	30,0±0*** (n = 6)	22,5±5,13 (n = 7)
ΔPHRM		+0,83	+0,26	+0,86	+0,21
Control		15,3±5,24 (n = 7)	23,5±4,27 (n = 8)	11,3±4,95 (n = 7)	11,5±4,91 (n = 7)
Atropine	10	13,9±5,69 (n = 7)	12,4±4,73 (n = 7)	1,82±0,37 (n = 6)	11,0±4,94 (n = 7)
ΔPHRM		0	—0,46	—0,29	0
Control		10,2±5,14 (n = 7)	15,9±5,34 (n = 6)	11,2±5,02 (n = 7)	13,2±6,89 (n = 5)
Metamizil	5	19,2±4,85 (n = 6)	20,2±6,20 (n = 6)	2,74±0,55 (n = 7)	3,02±0,41 (n = 7)
ΔPHRM		+0,21	+0,17	—0,29	—0,4
Control		12,4±5,63 (n = 6)	11,3±5,92 (n = 6)	11,2±5,02 (n = 7)	9,79±4,54 (n = 8)
Eterofen	50	26,4±3,64* (n = 7)	30,0±0** (n = 6)	16,8±5,95 (n = 6)	9,43±3,82 (n = 7)
ΔPHRM		+0,52	+0,67	+0,21	+0,11

Legend. *p < 0.05, **p < 0.01, ***p < 0.001 compared with control.

anoxia to 44.4 and 55.4%, respectively, whereas eterofen had no significant effect on the survival rate of the animals.

The experiments on intact HRM and LRM showed that at the 4th hour of recovery resistance to repeated acute anoxia changed. The resistance of HRM to repeated acute anoxia was reduced, and some LRM appeared among the HRM, whereas in the LRM, on the other hand, resistance to acute anoxia increased in the recovery period, so that HRM appeared among them. At the 24th hour of the recovery period a tendency was observed in both groups of animals for resistance to acute anoxia to increase [5].

The effect of these same drugs on the resistance of the animals to repeated acute anoxia in the recovery period is shown in Table 2 and Fig. 2. As will be clear from Fig. 2, physostigmine increased the resistance of both HRM and LRM to acute anoxia considerably at the 4th hour of the recovery period ($p < 0.001$). At the 24th hour of the recovery period physostigmine increased resistance of both HRM and LRM to anoxia, although not significantly, evidently due to the fact that observations ceased after 30 min. Atropine, on the other hand, reduced resistance of both groups of animals to acute anoxia at the times of the recovery period tested; the decrease was more marked in HRM after 24 h and in LRM after 4 h.

Administration of the central cholinolytics metamizil and eterofen showed that in animals of both groups cholinergic mechanisms play a different role in the formation of resistance to acute hypoxia in the recovery period. After administration of methyldiazine an increase of the resistance of HRM to repeated acute anoxia by 88.2 and 27.2%, respectively, was observed at the 4th and 24th hours of the recovery period, compared with the control. Conversely, in LRM resistance to anoxia fell sharply at the times of testing. Eterofen sharply increased the survival rate of HRM during exposure to acute anoxia at the 4th ($p < 0.05$) and 24th ($p < 0.01$) hours, whereas resistance of LRM to acute anoxia did not change significantly.

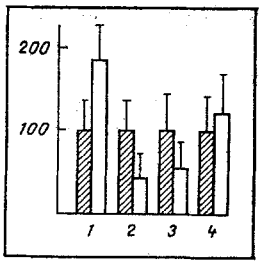

Fig. 1. Effect of cholinergic drugs when given prophylactically on resistance to acute anoxia. Ordinate, antianoxic resistance (in %). 1) Physostigmine, 2) atropine, 3) metamizil, 4) eterofen; shaded columns indicate control.

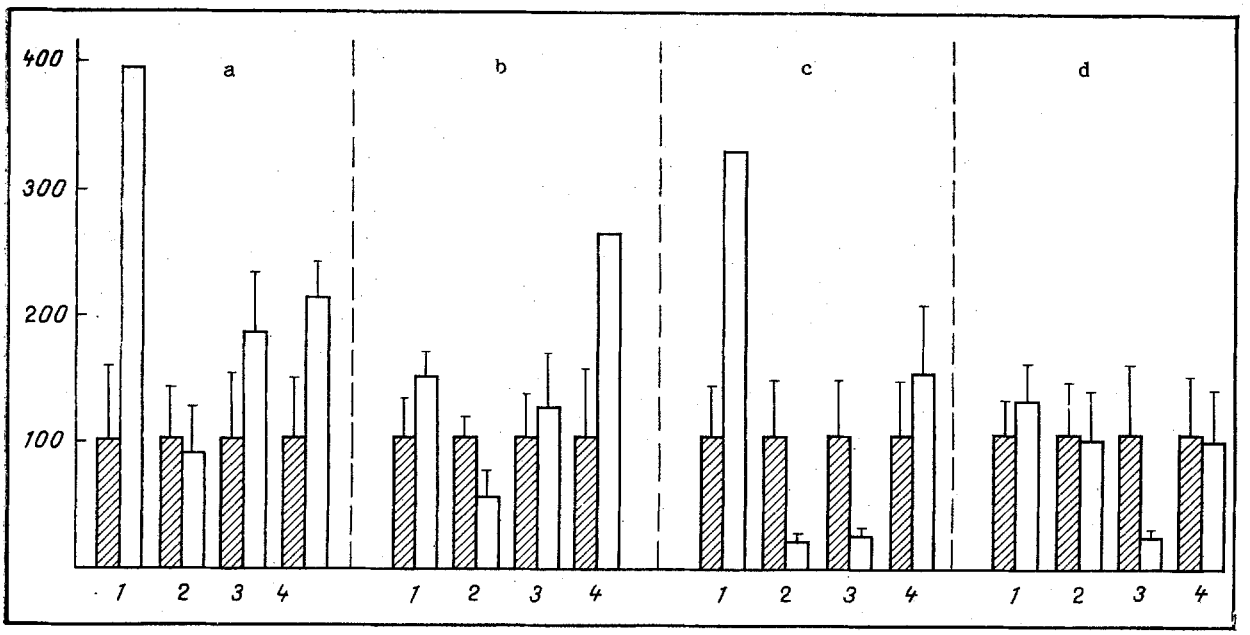

Fig. 2. Effect of cholinergic drugs on resistance to repeated acute anoxia in the recovery period: a) HRM (4th hour of recovery period), b) HRM (24th hour), c) LRM (4th hour), d) LRM (24th hour). Remainder of legend as to Fig. 1.

Analysis of the results relating to the prophylactic uses of cholinergic drugs revealed that the cholinomimetics increased the animals' resistance to acute anoxia whereas cholinolytics aggravated the course of anoxia. There is no information in the literature on the effect of cholinergic drugs on the course of the recovery period after exposure to acute anoxia. Data in the literature show the effects of these compounds when given prophylactically [4, 7, 8], and they are in agreement with our own experimental results.

The investigations in the recovery period draw attention to the fact that the same drug may have opposite actions on the resistance of animals to repeated acute anoxia in this period. The antianoxic effect of the drugs tested depends both on individual sensitivity of the animals to oxygen deficiency and the degree of anoxic damage, and on the times of observation after exposure to primary anoxia. On the basis of these data it can be postulated that the recovery period after exposure to acute anoxia is phasic in character: periods of increased resistance alternate with periods of reduced resistance. Probably the effects of drugs during these different phases of the recovery period give rise to different antihypoxic effects.

Furthermore, if one considers individual differences in the resistance of animals to anoxia [2] and also information in the literature on the existence of certain metabolic differences in animals differing in their sensitivity to anoxia when exposed to normoxic and acute hypoxic conditions [2, 6], it can be tentatively suggested that processes of tissue metabolism follow different courses in HRM and LRM during the recovery period, and it is this which is evidently reflected in the resistance of animals to re-exposure to anoxia.

The cholinergic system thus is involved in the resistance of animals to acute anoxia in the recovery period.

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EFFECT OF BENZAMIDE DERIVATIVES ON TOXIC OXYGEN SEIZURES IN RATS

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Traditional anticonvulsants are known not to prevent or delay the onset of "oxygen epilepsy" [8]. In recent years monoaminergic neurotransmitter systems have been shown to play an important role in the mechanism of onset and development of this form of oxygen poisoning [1]. It has been shown, for instance, that during oxygen seizures the brain concentration of monoamine transmitters falls sharply [6, 9]. If serotonin is injected into animals before they are placed in the pressure chamber, oxygen convulsions may be considerably delayed [7]. In the light of these data the protective effect of typical antidepressants, which are monoamine oxidase (MAO) inhibitors, such as iproniazid, nialamide, and tranylcypromine, is evidently by delaying oxidative deamination of monoamines, with their resulting accumulation in the CNS [8, 10]. The ability of chlorgiline, an irreversible selective type A MAO inhibitor, to exert a protective action on rats exposed to hyperbaric oxygen, was demonstrated in [5].

The aim of this investigation was to study the effect of the reversible selective type A MAO inhibitor moclobemide, which has antidepressant properties, and also of original benzamide derivatives closely resembling moclobemide in structure, on the appearance of oxygen seizures in rats.

EXPERIMENTAL METHOD

The convulsive form of oxygen poisoning was simulated by exposing male albino rats weighing 180-250 g in a pressure chamber containing oxygen under a pressure of 6 atm for 27 and 60 min (the periods of compression and decompression were each of 20 min). The drugs were injected intraperitoneally in a dose of 1 or 5 mg/kg in the form of aqueous solutions 15 min before the animals were placed in the pressure chamber. The time of onset of seizures was recorded as the time when the rats lay in the side position. At the end of decompression the

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