EFFECT OF ANTIDEPRESSANTS ON TOLERANCE TO HYPOXIA AND PHYSICAL EXERCISE

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By acting essentially on central neurotransmitter systems, antidepressants have not only an antidepressive action proper, with the stimulating or sedative effects accompanying it, but they also have several other effects, whose realization also is linked with neuromediator transmission (anticonvulsant, antiamnesic, etc.) [1, 2, 4]. The effect of antidepressants, it can be suggested, ought to extend also to processes of general adaptation. This paper describes the study of the action of certain antidepressants on some forms of hypoxia and on physical tolerance in experiments on animals.

EXPERIMENTAL METHOD

The antihypoxic action was studied under conditions of hypoxic, hemic, and circulatory hypoxia. A model of hypoxic hypoxia with hypercapnia was created [3]. Experiments were carried out on male and female albino mice weighing 20-22 g. Each mouse was placed separately on a hermetically sealed vessel (an airtight chamber with a capacity of 250 ml) 60 min after receiving antidepressants.

Hemic hypoxia was induced in male and female mice of the same weight by subcutaneous injection of sodium nitrite in a dose of 300 mg/kg. The antidepressants were injected 60 min before the sodium nitrite. In both tests the length of survival of the mice was estimated in minutes. All antidepressants (pyrazidol, inkazan, azaphen, imipramine, moclobemide) were injected in doses of 10, 25, 50, and 100 mg/kg, and for comparison, the nootropic piracetam was injected in doses of 100 and 250 mg/kg.

On a model of circulatory hypoxia [5] experiments were carried out on male rats weighing 180-220 g. Under pentobarbital anesthesia (40 mg/kg, intraperitoneally) both carotid arteries of the rats were ligated. Before the operation and immediately after recovery of the animals from the anesthetic, they were given antidepressants (25 mg/kg internally) or piracetam (250 mg/kg internally). Administration of the drugs continued for the next 5 days of observation. The number of animals which died was noted.

The effect of the antidepressants on the length of time the animals swam carrying a load until complete physical exhaustion and drowning also was studied [6]. The load amounted to 5% of body weight. The water was boiled (to remove all air bubbles) and its temperature was 22°C.

In addition, the effect of the antidepressants in a dose of 25 mg/kg and of piracetam in a dose of 250 mg/kg internally on motor activity also was studied (as an indicator of the stimulating action of the drugs). The motor activity was assessed on an "Animex" apparatus for 10 min, 60 min after injection of the drugs, i.e., at the times when their effect on physical endurance was being studied.

In all tests (except circulatory hypoxia) the results were subjected to statistical analysis (Tables 1 and 2) by Student's t test, and the error of the arithmetic mean was determined at the $p = 0.05$ level. In the test of circulatory hypoxia, statistical analysis was carried out by the chi-square test.

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TABLE 1. Effect of Antidepressants on Duration of Survival of Animals in Hypoxic, Hemic, and Circulatory Hypoxias

Preparation	Dose, mg/kg (internally)	Length of survival of mice, min				Circulatory hypoxia		Number of surviving rats	
		hypoxia				day after operation			
		hypoxic		hemic		1 h	5 h	%	P_{χ^2}
		$M \pm m$	n	$M \pm m$	n				
Distilled water		31±1,2	50	19±0,6	50	14/20	9/20	45	
Pyrazidol	25	33±1,6	50	22±0,5*	30	18/20	18/20	90	<0,05
	50	35±1,2*	50	21±0,4*	20				
	100	40±2,4*	30						
Inkazan	25	33±1,8	30	18±0,6	30	14/20	9/20	45	
	50	35±1,7	50	18±0,4	20				
	100	32±2,4	20						
Azaphen	25	34±1,6	30	22±0,5*	30	10/10	10/10	100	<0,05
	50	37±0,7*	20	21±0,4*	20				
	100	44±0,4*	20						
Imipramine	25	35±1,8	30	25±0,6*	30	10/10	10/10	100	<0,05
	50	28±1,6	50	23±0,4*	20				
	100	29±1,2	20						
Moclobemide	25	43±1,4*	30	32±1,1*	30	9/10	9/10	90	<0,05
	50	46±1,2*	20	28±0,7*	20				
Piracetam	100	31±0,6	30	23±1,2*	30				
	250	41±1,1*	20	25±0,8*	50	9/10	9/10	90	

Legend. Here and in Table 2, asterisk indicates significant difference from control at $p < 0.05$; numerator gives number of surviving rats after bilateral ligation of carotid artery; denominator shows total number of rats used with that dose.

TABLE 2. Effect of Antidepressants on Duration of Swimming with a Load and on Motor Activity of Mice (M ± m)

Preparation	Dose, mg/kg (internally)	n	Duration of swimming with load, min	Number of groups of mice	Number of runs per group of three mice during 10 min, 1 h after administration of drug
Distilled water		60	6,9±0,3	4	600±70
Pyrazidol	5	10	7,7±0,6		
Inkazan	10	20	8,7±0,2*		
	25	40	9,3±0,2*	4	565±33
Inkazan	5	10	6,8±0,6		
	10	20	8,9±0,3*		
	25	20	8,7±0,2*	4	734±42
Azaphen	5	10	8,0±0,3*		
	10	40	11,8±0,2*		
	25	40	12,1±0,2*	4	508±45
Imipramine	5	10	8,4±0,6*		
	10	20	11,2±0,2*		
Moclobemide	25	20	12,2±0,2*	4	704±56
	5	10	8,8±0,2*		
	10	40	11,4±0,2*		
	25	40	11,7±0,2*	4	489±18
Peracetam	100	10	9,0±0,5*		
	250	30	10,1±0,6*	4	509±15

EXPERIMENTAL RESULTS

In the experiments with hypoxic hypoxia, pyrazidol and azaphen in doses of 50 and 100 mg/kg, and moclobemide in doses of 25 and 50 mg/kg increased the length of survival of the mice by a short time (Table 1). Piracetam had a similar action in a dose of 250 mg/kg. Inkazan and imipramine were inactive in these experiments.

In the experiments with hemic hypoxia all the antidepressants studied except inkazan, in doses of 25 and 50 mg/kg (and also of moclobemide in a dose of 10 mg/kg) increased the length of survival of the mice. In the case of piracetam, an antihypoxic effect similar to that of the antidepressants was observed in doses of 100-250 mg/kg. With an increase in the dose, of both antidepressants and piracetam, no increase was observed in the antihypoxic action of the drugs (Table 1).

The results of the experiments with circulatory hypoxia are given in Table 1. In these experiments all the antidepressants except inkazan had a marked protective effect on hypoxia and prevented death of the animals.

Circulatory hypoxia accompanies severe physical exercise, and determines the level of endurance to it; for that reason, it was interesting to study the effect of antidepressants on physical endurance. The experiments showed that antidepressants increased the duration of swimming by the mice with a load, although this effect did not increase significantly with an increase in the dose (Table 1). Piracetam had a similar effect, but in much larger doses.

In a dose of 25 mg/kg, in which they delay the onset of fatigue, the antidepressants had no stimulating effect by the motor activity test (Table 2). On the basis of this state of affairs, the increase in tolerance of physical exercise can be linked more probably with the antihypoxic properties of the antidepressants than with the stimulating component in their action.

Our results showing the antihypoxic properties of antidepressants, like data obtained previously relative to their antiamnesic anticonvulsant properties [1, 4], show that the spectrum of action of antidepressants includes not only an effect on mood, motivation, and general activity, but also on effects characteristic of nootropics and, in particular, piracetam. These effects are manifested when antidepressants are used in much smaller doses than when piracetam is used.

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