Antihypoxants, Thiasolo[5,4-b]Indole Derivatives, Increase Exercise Performance in Rats and Mice

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The actoptrotective activity of 12 new antihypoxants of the thiasolo[5,4-b]indole series was studied on the model of treadmill running until exhaustion 1 and 24 h after intraperitoneal injection. Highly active compounds more effective than the reference drugs bemithyl and phenamine were found. They increased exercise performance 1 or 24 h after injection or maintained high performance throughout 24 h.

Key Words: *antihypoxants; physical performance; thiasolo[5,4-b]indole; phenamine; bemithyl*

Physical endurance is an important parameter of health status and adaptation to changing environmental conditions. Humans are exposed to numerous adverse factors promoting the development of fatigue. Physical exhaustion of soldiers and rescue rangers prevents their effective work and creates risk for life. Retention of high performance capacity and its rapid recovery can be attained by administration of some drugs (actoprotectors) [4]. The best known of them are phenamine, a psychomotor stimulant characterized by exhausting action, and bemithyl, an antihypoxant and actoprotector [4,8]. However, the available drugs are little effective and/or have side effects.

Thiasolo[5,4-b]indole derivatives seem to be interesting perspective agents for improving exercise performance. Actoprotective activity was demonstrated for some of them. These compounds were synthesized at Department of Pharmacology of S. M. Kirov Military Medical Academy. The antihypoxic effects of these compounds were demonstrated on the models of hypobaric, hypercapnic, and hemic hypoxia, their activities being comparable or even superior to those of amtisole (reference drug) [1]. Thiasolo[5,4-b]indole derivatives exhibited membranotropic activity [9], antiedematous [3] and hepatoprotective effects [2], indicating their high biological activity directed to many targets. It is also known that other antihypoxants of similar condensed indole structures containing fragments of isothiourea also exhibited actoprotective activity [4,7].

We studied the actoprotective effects of new chemical compounds, thiasolo[5,4-b]indole derivatives, on various models of physical endurance in rats and mice.

MATERIALS AND METHODS

Twelve thiasolo[5,4-b]indole derivatives were studied (Fig. 1).

Experiments were carried out in autumn-winter on 140 male Wistar rats (200-250 g) and 480 outbred male mice (16-22 g) from Rappolovo Breeding Center (Leningrad region).

Exercise performance (swimming until drowning) was studied on male mice (10 per group) intraperitoneally injected with a single dose (10, 25, or 50 mg/kg) of the studied compound (fine suspension in Twin-20; 0.2 ml). After 30 min, the animals with charge (5% body weight) swam in a basin (24-26°C water) until drowning; the duration of swimming was recorded. A special control group

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corresponded to each experimental series; controls were injected with saline. Physical performance of animals was expressed in percent of control. This method was used for selecting the optimal dose of the studied substances.

Physical performance was studied by treadmill running to exhoustion (groups of no less than 10 animals). A 4-track treadmill was used with the band moving at a velocity of 38-42 m/min. The absence of reaction to electric shock of 40 V indicated complete fatigue. The time of running cessation was recorded and the rat was removed from the track. This measurement served as the control. The rats were then allowed to rest for 3 days, after which they received a single injection of the test substance (fine suspension in Twin-20) in the optimal dose. A well-known actoprotectors bemithyl (50 mg/kg) and phenamine (psychostimulant; 1.5 mg/kg) served as the reference drugs. The animals repeated the running to exhoustion test 1 and 24 h after the drug injection. Endurance was calculated as the proportion of repeated running duration to the initial running duration and expressed in percent.

The results were processed using Student's *t* test.

RESULTS

Optimal doses of compounds were selected by the results of mouse swimming to the limit. All the studied compounds improved mouse endurance to this or that degree (Table 1). For example, compound 2b (10 mg/kg) prolonged the duration of swimming by 84%, while compound 2c (25 mg/kg) prolonged it by just 5%.

The next stage was the study of physical performance. Compound 4a improved the endurance by 23% 1 h after injection, while compounds 1a and 1c by 204 and 16%, respectively, 24 h after injection (Table 2). Compounds 2a-c increased the endurance 1 and 24 h after injection; the most active compound was 2b increasing the endurance 2-fold after 1 h and 5.9 times after 24 h.

Succiniminic acid (4b) was the most active of the compounds with substituted terminal amino group. It increased physical performance 2-fold 1 h postinjection and 1.8 times 24 h postinjection. Hence, compound 4b (like compounds 2a and 2b) maintained the endurance during a long period. Succinimides 3a, 3b, and acetyl derivative 4a reduced the performance after 24 h. Structures 1 and 2 were most active in the form of hydrobromides, hydrobromide 2b, containing bromine in the benzene ring, exhibited the highest activity (Table 2).

Bemithyl (reference drug) reduced the performance by 32% 1 h after injection and increased it by

TABLE 1. Effects of Thiasolo[5,4-b]Indole Derivatives on the Duration of Swimming in Mice (*M*±*m*)

Code of compound	Dose, mg/kg	Duration of swimming	
		min	% of control
Control	—	7.4±2.7	100
1a	10	10.8±5.4	148
	25	9.3±3.3	127
	50	6.2±4.6	84
Control	—	8.2±4.7	100
1c	10	8.5±4.8	105
	25	4.6±2.7	56
	50	7.2±2.6	88
Control	—	11.8±7.9	100
1b	10	9.4±3.9	80
	25	13.5±6.3	116
	50	15.3±6.7	130
Control	—	17.2±8.3	100
1d	10	19.2±7.5	111
	25	12.6±2.7	73
	50	25.3±7.1	146
Control	—	8.9±2.8	100
2a	10	11.3±5.2	127
	25	10.2±5.0	115
	50	5.9±2.5	67
Control	--	15.5±6.9	100
2c	10	14.1±7.7	92
	25	16.1±10.3	105
	50	14.0±9.1	91
Control	—	11.2±4.0	100
2b	10	20.7±4.5	184
	25	10.6±2.5	94
	50	10.8±6.1	97
Control	—	18.4±5.4	100
2d	10	14.0±3.3	76
	25	19.0±5.3	103
	50	14.3±4.1	78
Control	—	22.4±9.1	100
3a	10	32.7±16.6	146
	25	15.0±7.9	68
	50	22.0±9.0	98
Control	—	18.8±7.8	100
3b	10	12.3±6.3	66
	25	21.2±17.0	112
	50	10.8±4.3	58
Control	--	18.0±5.0	100
4a	10	15.2±2.4	85
	25	22.8±3.8	127
	50	17.4±3.0	97
Control	—	16.5±7.2	100
4b	10	15.0±3.5	91
	25	21.1±7.4	127
	50	17.8±4.8	93

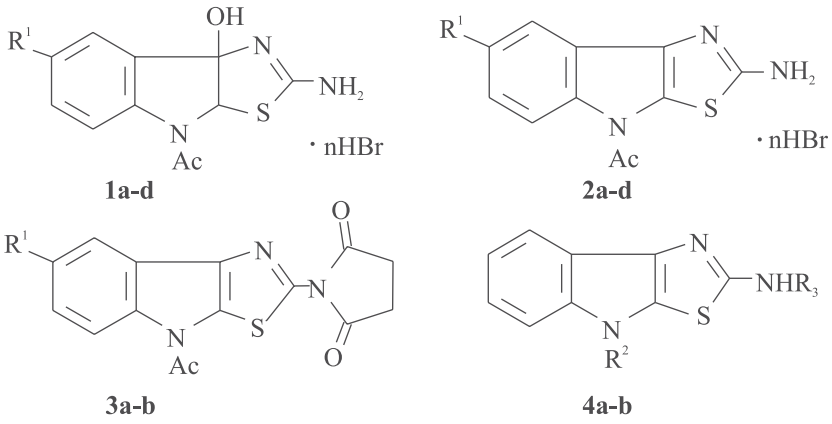

Fig. 1. Structural formulas of the studied compounds. 1 — R^1=H, *n*=1 (a); R^1=Br, *n*=1 (b); R^1=H, *n*=0 (c); R^1=Br, *n*=1 (d). 2 — R^1=H, *n*=1 (a); R^1=Br, *n*=1 (b); R^1=H, *n*=0 (c); R^1=Br, *n*=1 (d). 3 — R^1=H (a); R^1=Br (b). 4 — R^2=$COCH_3$, R^3=$COCH_3$ (a); R^2=$COCH_3$, R^3=COC_2H_4COOH (b).

TABLE 2. Effects of Thiasolo[5,4-b]Indole Derivatives on Physical Performance of Rats in the Running to Exhausion Test (*M*±*m*)

Code of compound	Dose, mg/kg	Duration of rats' running	1 h postinjection		24 h postinjection	
			min	%	min	%
Control		—	13.3±4.1	100	13.3±4.1	100
	1a	10	14.0±9.8	105	40.3±11.0*	304
Control		—	20.8±7.1	100	20.8±7.1	100
	1c	10	13.3±3.6	65	24.3±8.5	116
Control		—	18.6±1.0	100	18.6±1.0	100
	1d	50	10.1±1.4***	55	12.1±4.0	65
Control		—	8.1±2.7	100	8.1±2.7	100
	2a	10	19.0±3.3**	234	14.3±10.1	176
Control		—	15.0±3.6	100	15.0±3.6	100
	2c	25	16.1±5.6	107	28.2±10.0	188
Control		—	8.0±3.7	100	8.0±3.7	100
	2b	10	15.7±4.7	196	47.2±9.8**	590
Control		—	16.0±8.3	100	11.1±1.3	100
	2d	50	8.6±4.1	53	14.8±3.7	133
Control		—	9.8±2.8	100	9.8±2.8	100
	4a	25	12.1±2.9	123	6.5±2.0	66
Control		—	17.5±2.2	100	17.5±2.2	100
	3a	10	9.2±1.6*	52	12.5±5.5	71
Control		—	32.8±7.5	100	32.8±7.5	100
	3b	25	24.2±9.0	73	33.7±15.0	102
Control		—	13.0±4.5	100	13.0±4.5	100
	4b	25	26.1±5.2	200	23.1±8.3	177
Control		—	16.4±2.7	100	16.4±2.7	100
Bemithyl		25	11.2±4.7	68	19.6±5.5	117
Control		—	22.4±5.6	100	22.4±5.6	100
Phenamine		1.5	44.7±6.2*	200	20.5±8.8	91

Note. *p<0.05, **p<0.01, ***p<0.001 compared to the control.

17% after 24 h. Contrary to it, phenamine (psychostimulant) increased the performance 2-fold 1 h postinjection and moderately reduced it 24 h postinjection.

Hence, thiasolo[5,4-b]indole derivatives exhibited actoprotective activity, often superior to that of the reference drugs phenamine and bemithyl, particularly during delayed period (compounds 1a, 2a-d, 4b).

Compound 2b exhibited highest activity. It increased rat physical performance almost 6-fold 24 h after injection. Compounds 2a, 2b, and 4b maintained high performance during 24 h, surpassing 1.8-5.9 times the level in the controls.

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