EFFECT OF PYRAZIDOL (PIRLINDOL) ON RESISTANCE OF ANIMALS TO HYPOBARIC HYPOXIA

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Our previous investigations yielded evidence in support of the important role of mitochondrial monoamine oxidase (MAO) in the response of the body to extremal factors [3], including during exposure to hypoxia [4, 5]. Disturbance of the substrate specificity of type A MAO, leading to disturbance of coordination of mediator functions, intensification of lipid peroxidation, and membrane destabilization, must evidently be regarded as one of the most important stress-realizing systems during exposure to extremal environmental factors. An essential prerequisite for a possible change in substrate specificity of MAO is the presence of functionally normal catalytic centers. Type A MAO inhibitors block the catalytic centers of this form of the enzyme and thereby prevent its transformation under pathological conditions, suggesting that they may exert a protective action against hypoxia.

In this investigation we studied the effect of the selective reversible type A MAO inhibitor pyrazidol (pirlindol) to hypoxia. Pyrazidol, unlike irreversible MAO inhibitors, is well tolerated by the body and is used in medical practice as a drug with a regulatory action on the CNS [10]. We showed previously that pyrazidol can be used as an antihyperoxic protector during treatment by hyperbaric oxygen therapy [6].

EXPERIMENTAL METHOD

Experiments were carried out on adult male noninbred albino rats weighing 180-240 g. Two groups of animals were exposed to the action of hypoxia corresponding to altitudes of 9000 m and 12,000 m above sea level: control and receiving pyrazidol. Pyrazidol was injected intraperitoneally in a dose of 25 mg/kg three times: twice on the eve of the experiment with an interval of 6 h between injections and 0.5 h before the animals were placed in the hypoxic chamber. The sensitivity of the animals to hypoxia was judged by the survival time of the animals at an altitude of 12,000 m, assessed in accordance with the value of a coefficient K, the ratio of the survival time (the time from reaching the assigned altitude to the appearance of the second agonal inspiration) to the restitution time (the time from the beginning of "descent," which began after the second agonal inspiration, until restoration of the tone of the antigravity muscles and of the animal's physiological posture) [1]. After the animals had stayed for 3 h at an altitude of 9000 m the extraerythrocytic hemoglobin concentration (EHC) [7], the total free iron level [8], and the total peroxidase activity (PPA) [11] were determined in the blood plasma. The state of the animals also was assessed, being judged by the degree of hyperemia and the severity of petechial hemorrhages, and by the coefficient of edema of the lungs (CEL), determined as the ratio of the mass of the lungs (in mg) to the rat's body weight (in g).

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TABLE 1. Effect of Pyrazidol on Resistance of Rats to Hypoxia Corresponding to Altitude of 12,000 m Above Sea Level

Experimental conditions	Survival time (ST), min	Restitution time (RT), min	K (ST/RT)
Hypoxia	3,28±0,42 (11)	6,30±0,67 (11)	0,485±0,036
Pyrazidol + hypoxia	3,71±0,56 (14)	1,28±0,27 (14)	3,947±0,657
	$p>0,05$	$p<0,001$	$p<0,001$

Legend. Here and in Table 2 number of experiments shown between parentheses.

TABLE 2. Total Peroxidase Activity (TPA), Extraerythrocytic Hemoglobin Concentration (EHC), Total Plasma Free Iron Level, Coefficient of Edema of the Lungs (CEL), and Basal Edema of Lungs of Rats during Hypoxia Corresponding to Altitude of 9000 m Above Sea Level and Injection of Pyrazidol

Experimental conditions	TPA, relative units/ml	EHC, μg/ml	Free iron, μg/ml	CEL	Assessment, points
Control	2,51±0,26 (11)	197,1±9,5 (11)	1,015±0,047 (11)	4,64±0,26 (12)	3,25±1,32 (12)
Hypoxia	6,61±0,64 (10)	319,1±23,0 (12)	1,599±0,112 (10)	6,25±0,29 (12)	40,83±6,94 (12)
	$p<0,001$	$p<0,001$	$p<0,001$	$p<0,001$	$p<0,001$
Pyrazidol	2,94±0,14 (11)	204,7±10,5 (12)	0,982±0,071 (11)	4,69±0,39 (12)	14,00±3,10 (12)
	$p>0,05$	$p>0,05$	$p>0,05$	$p>0,05$	$p<0,01$
Pyrazidol + hypoxia	2,61±0,21 (16)	203,2±9,3 (16)	1,140±0,067 (13)	5,06±0,36 (15)	18,53±3,99 (15)
	$p>0,05$	$p>0,05$	$p>0,05$	$p>0,05$	$p<0,01$
	$p_1<0,001$	$p_1<0,001$	$p_1<0,01$	$p_1<0,02$	$p_1<0,01$

Legend. p) Significance compared with control, p_1) significance compared with hypoxia.

EXPERIMENTAL RESULTS

After the third intraperitoneal injection of pyrazidol into the rats in a dose of 25 mg/kg the survival time of the animals at an "altitude" of 12,000 m above sea level was increased eightfold compared with animals not receiving pyrazidol. Under these circumstances injection of pyrazidol reduced the restitution time fivefold but did not affect the survival time (Table 1). Consequently, pyrazidol increases the ability of the recipient to abolish the immediate consequences of acute hypoxia.

As Table 2 shows, during hypoxia (9000 m, 3 h) TPA was increased by 163%, the EHC by 62%, and the total free serum iron level by 58%. The increase in all these parameters points to increased permeability of the blood cell membranes, especially of the erythrocytic membranes, and as was shown previously in the writers' laboratory, it reflects the state of the subject and can be used as a test of the depth of stress-induced injury [2, 9]. Preliminary injection of pyrazidol prevents the increase in TPA, EHC, and the free iron concentration under the influence of hypoxia, and also has a normalizing action on the state of the lungs, reducing CEL and the value of the rating in points, characterizing the severity of hyperemia and of petechial hemorrhages. Injection of pyrazidol into intact animals had no effect on TPA, EHC, the free plasma iron concentration, and CEL, and only a very small increase (not significant) was observed in the number of petechial hemorrhages in the lungs.

Thus pyrazidol has a marked protective effect against hypobaric hypoxia, it increases the ability of animals to tolerate an altitude of 12,000 m above sea level, has a stabilizing action on erythrocytic membranes, and restores the normal state of the lungs. It can be tentatively suggested that the positive action of pyrazidol is due mainly to its

effect on monoamine oxidase. By preventing changes in substrate specificity of type A MAO pyrazidol prevents the appearance of products with pro-oxidant properties and deamination of amino sugars, which are important structural components of membranes.

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REFERENCES

1. V. A. Berezovskii, Hypoxia and Individual Features of Reactivity [in Russian], Kiev (1978).
2. V. V. Vnukov, A. A. Ananyan, and Fan An, Mechanisms of Hibernation [in Russian], Makhachkala (1990), p. 34.
3. I. A. Goroshinskaya, Z. G. Bronovitskaya, A. A. Krichevskaya, et al., Neirokhimiya, **1**, No. 3, 282 (1982).
4. I. A. Goroshinskaya, Vopr. Med. Khim., **35**, No. 2, 3 (1989).
5. I. A. Goroshinskaya, T. Stoyanovich, D. V. Michich, et al., Vopr. Med. Khim., No. 5, 112 (1989).
6. I. A. Goroshinskaya, E. Z. Tsvetnenko, A. A. Khodakova, et al., Anest. Reanimatol., No. 1, 53 (1991).
7. A. V. Karakashov and E. P. Vichev, Micromethods in the Clinical Laboratory [in Russian], Sofia, Bulgaria (1973).
8. V. G. Kolb and V. S. Kamyshnikov, Handbook of Clinical Chemistry [in Russian], Minsk (1982).
9. A. I. Lukash, A. A. Ananyan, V. V. Vnukov, et al., Anest. Reanimatol., No. 3, 31 (1989).
10. M. D. Mashkovskii, Therapeutic Substances [in Russian], Vol. 1, Moscow (1985).
11. A. A. Pokrovskii, Biochemical Methods of Investigation in Clinical Medicine [in Russian], Moscow (1969).