Protective Effects of Trimetazidine in Acute Hypoxia

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Trimetazidine improves resistance to acute hypobaric hypoxia. Intraperitoneal injection of this preparation in an optimal protective dose (25 mg/kg) to rats prevents serious disturbances of energy metabolism and activation of lipid peroxidation in the brain, heart, and liver.

Key Words: *acute hypoxia; trimetazidine; energy metabolism; lipid peroxidation*

Trimetazidine (TM, Preductal, Vastarel, 2,3,4-trimetoxybenzyl)-piperazine dichloride), a new antianginal preparation, is now successfully used for the treatment of ischemic heart disease and in the postinfarction period [3,10]. Apart from its antianginal action, the preparation has a positive effect in ischemia of neurosensory tissue accompanied by serious cochleovestibular and retinal disorders [12].

The protective effect of TM in ischemia prompted us to study its protective effects in acute hypoxia.

MATERIALS AND METHODS

Experiments were carried out on 64 male albino rats weighing 160-180 g (8 animals per group). Experimental animals were intraperitoneally injected with TM (Vastarel, Biopharma) in doses of 12.5, 25, 50, and 100 mg/kg 30 min prior to lifting in a pressure chamber. Control animals received an equivalent volume of 0.9% NaCl. The "altitudes" for the study of survival rate and metabolic experiments were 10,000 and 8000 m, respectively, the rate of lifting was 50 m/sec, and exposure 30 min. When studying metabolic effects of TM, the preparation was injected in the dose that ensures maximum survival rate in critical hypoxia. Metabolic activities of the brain, heart, and liver were assessed by the content of glycogen [14], lactate [15], phosphocreatine [1], ATP [5], and inorganic phosphate [11]. Intensity of lipid peroxidation (LPO) was evaluated by the content of lipoperoxides and malonic dialdehyde [8] in tissues, and functional activity of antioxidant systems was assessed by activity of catalase [9] and superoxide dismutase (SOD) [4]. The data were processed statistically using the Student *t* test.

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RESULTS

Injection of TM (12.5-100 mg/kg) improved resistance of experimental animals to acute hypoxia. All control animals died, while 75% rats injected with 25 and 50 mg/kg TM survived (Fig. 1).

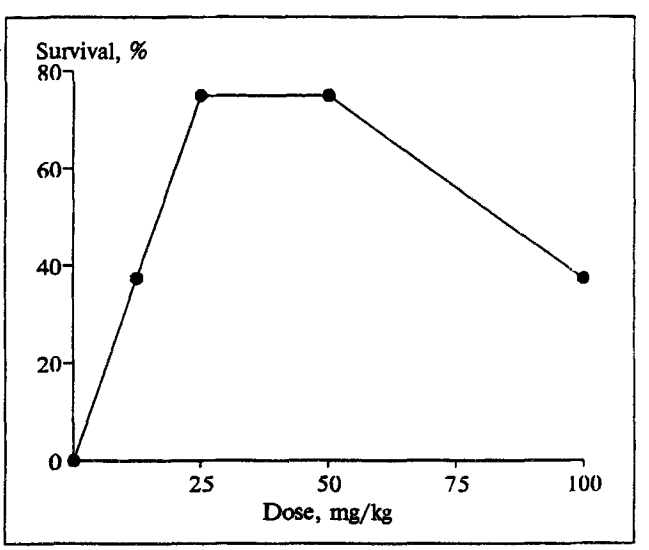

Fig. 1. Effect of trimetazidine on survival rate in acute hypoxia.

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In the brain, heart, and liver organs, 30-min stay at 8000 m above the see level induced similar shifts of studied parameters except catalase activity (Table 1): the contents of glycogen, phosphocreatine, and ATP decreased, while those of glucose, lactate, and inorganic phosphate increased. Activation of glycolysis and energy deficit in hypoxia were accompanied by activation of LPO against the background of reduced SOD activity (Table 2). Catalase activity decreased only in the heart and increased in the brain and liver. This may represent an adaptive shift, which did not yet attained its suppressive stage.

In a dose 25 mg/kg TM corrected hypoxia-induced metabolic alterations in organs. In protected animals, the content of ATP in the brain and glycogen in the heart and liver was higher, while the content of lactate and inorganic phosphate was lower than in the control group (Table 1). The content of phosphocreatine in the brain and heart also surpassed the control value. An equal rise of glucose con-

TABLE 1. Effect of TM on Energy Metabolism in Rat Organs in Acute Hypoxia (*M±m*)

Parameter	Group	Brain	Heart	Liver
Glycogen, mg/kg	Intact	1.24±0.10	9.73±1.04	56.00±10.76
	Hypoxia	0.85±0.15*	4.04±0.69*	37.6±4.12*
	TM+hypoxia	1.88±0.42**	6.41±0.70**	60.0±7.03**
Glucose, μmol/g	Intact	0.470±0.051	4.03±0.45	6.74±0.20
	Hypoxia	1.454±0.073*	4.15±0.30	8.76±0.38*
	TM+hypoxia	1.695±0.117**	4.24±0.27	9.51±0.58
Lactate, μmol/g	Intact	2.16±0.26	4.66±0.20	1.57±0.24
	Hypoxia	4.20±0.74*	7.58±0.73*	4.93±0.44*
	TM+hypoxia	3.00±0.22**	4.38±0.49**	1.57±0.24**
Phosphocreatine, μmol/g	Intact	2.70±0.23	5.65±0.62	—
	Hypoxia	1.18±0.09*	2.87±0.51*	—
	TM+hypoxia	1.66±0.21**	5.04±0.15**	—
ATP, μmol/g	Intact	2.88±0.20	6.25±0.56	3.08±0.10
	Hypoxia	2.23±0.25	4.43±0.48*	1.53±0.16*
	TM+hypoxia	2.38±0.26	5.99±0.41**	2.92±0.21**
Inorganic phosphate, μmol/g	Intact	9.13±1.14	6.02±1.21	5.90±0.20
	Hypoxia	16.95±1.94*	12.39±2.95*	15.62±1.33*
	TM+hypoxia	7.34±0.67**	4.92±0.31**	6.21±0.37**

Note. Here and in Table 2: $p<0.05$: *compared with intact rats, **compared with the control.

TABLE 2. Effect of TM on LPO and Activity of Antioxidant Enzymes in Acute Hypoxia (*M±m*)

Parameter	Group	Brain	Heart	Liver
Lipoperoxides, OD_{480}	Intact	0.097±0.003	0.186±0.013	0.176±0.004
	Hypoia	0.124±0.002*	0.205±0.011	0.188±0.002*
	TM+hypoxia	0.112±0.003**	0.257±0.011**	0.195±0.005**
Malonic dialdehyde, μmol/g	Intact	31.67±2.48	19.38±5.43	12.17±1.27
	Hypoia	41.71±2.96*	26.46±5.48	19.50±0.60*
	TM+hypoxia	31.22±3.11**	21.47±3.84	17.55±1.36
SOD, units of activity/mg protein	Intact	0.952±0.102	1.93±0.17	1.03±0.11
	Hypoxia	0.636±0.090*	1.05±0.13*	0.58±0.13*
	TM+hypoxia	0.880±0.070**	1.51±0.09**	1.05±0.06**
Catalase, units of activity/mg protein	Intact	0.245±0.024	0.343±0.027	0.122±0.004
	Hypoxia	0.353±0.040*	0.258±0.010*	0.151±0.007*
	TM+hypoxia	0.289±0.039**	0.614±0.084**	0.110±0.007**

centration in organs of experimental and control rats together with a lower decrease in glycogen content and a lower rise of lactate in TM-treated animals implies that the preparation can activate glyconeogenesis. TM inhibited LPO activation in hypoxia (Table 2). This resulted in a lower rise of the content of malonic dialdehyde and lipoperoxides in experimental rats compared with the control. TM prevented the decrease in SOD activity and normalized catalase activity: decreased it in the brain and liver, and increased in the heart.

Thus, preliminary injection of TM to rats improved their resistance to hypoxia, prevented serious disturbances of energy metabolism, development of acidosis, activation of LPO, and suppression of antioxidant systems in the brain, heart, and liver.

^{31}P-NMR spectroscopy showed that TM reduces accumulation of inorganic phosphate and stimulates ATP synthesis and creatine rephosphorylation in isolated rat heart during ischemia and reperfusion [13]. Moreover, TM inhibits generation of free radicals and activates antioxidant systems, thus protecting cell membranes from ischemia-induced damage and preserving cell integrity and functions [12]. These findings suggest that TM produces similar effects in ischemia and "true" hypoxia. Analogous metabolic shifts are characteristic of antihypoxic drugs which normalize mitochondrial oxidative phosphorylation [2,7]. The potent protective antihypoxic activity of TM suggest that the study of its effect on mitochondrial functions can be useful for elucidation of biochemical mechanisms of its pharmacological activity.

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