New Property of the Heparin-Serotonin Complex

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The antihypoxic activity of the heparin-serotonin complex was studied under conditions of acute hypobaric hypoxia. Rats were given an intraperitoneal injection of the complex in a dose of 300 μg/kg and "lifted" on a height of 12,000 m. In these rats, the intervals before the posture loss and the second agonal inhalation were 9.6- and 8.8-fold as long as those in control rats. The survival of the complex-treated rats was 90%, 70% in rats injected with heparin or serotonin, and 50% in the control group.

Key Words: *antihypoxic agents; heparin; serotonin; complex*

The search and investigation of new effective antihypoxic preparations with minimal untoward effects remain an important task. A broad spectrum of cellular metabolism disorders caused by hypoxia that occurs almost in all pathologies points to the prospectiveness of pharmacological preparations exerting a combined effect.

The serotoninergic system plays an important role in the mechanisms responsible for the resistance of an organism to acute hypoxia. The therapeutic effect of serotonin has been demonstrated in diabetic angiopathy [5]. The mobility of neutrophils was shown to increase after the addition of serotonin or serotonin adipinate to the culture medium [6]. However, the use of serotonin as an antihypoxic agent is associated with hemodynamic and blood rheology disorders [4].

We have suggested that the heparin-serotonin complex (HSC), which exhibits anticoagulant activity [1], is effective in acute hypoxia. Our goal was to assess the HSC ability to prevent the disorders induced by acute hypoxic hypoxia.

MATERIALS AND METHODS

Experiment were performed on outberd male albino rats weighing 200-250 g. High-molecular-weight heparin (Serva) and serotonin creatine sulfate (Reanal) were used to prepare HSC (3:1 w/w) [3].

Acute hypoxic hypoxia was attained by "descending" the rats in a pressure chamber to a "height" of 12,000 m above the sea level for 1 min. The time intervals before the loss of physiological posture and before the second agonal inhalation (TSAI) were recorded at this "height". The rats were then quickly "descended", and the time of the posture restoration (TPR) was recorded. A ratio between these parameters was calculated. During the experiment and one hour after it some rats died. The number of survived rats (survival) was employed as another indicator of antihypoxic activity of the studied compounds.

The rats were divided into 4 groups (20 rats each). Group I rats were injected with 0.3 ml normal saline 10 min before the "lift" (control). Group 2 rats received 0.3 ml 0.1% HSC solution, and groups 3 and 4 were given 0.3 ml serotonin or heparin in doses equal to their contents in the HSC.

The data were analyzed by Fischer-Student test and Fischer exact test.

RESULTS

The time of physiological posture restoration was practically the same in control and HSC-, heparin-, or serotonin-treated rats (Table 1). When administered alone in a dose equal to its content in the HSC, serotonin had no protective effect against

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TABLE 1. Parameters of Adaptation to Acute Hypoxia (*M±m*)

Experimental conditions	Time before posture loss, min	TSAI, min	TPR, min	TSAI/TPR	Survival, %
Control (0.85% normal saline)	1.23±0.09	3.2±0.4	2.1±0.17	1.5±0.06	50
HSC	11.8±0.74*+	28.0±0.39*×+	2.2±0.31	12.7±1.4*×+	90*
Serotonin	1.03±0.12	3.8±0.51	2.97±0.26	1.3±0.07	70
Heparin	11.3±0.64*	14.6±0.43*	2.1±0.27	6.9±0.61*	70

Note. $p<0.01$: *compared with the control, ×compared with heparin-treated rats; +compared with serotonin-treated rats.

acute hypoxia, as evidenced by the absence of statistically significant differences in the time before the posture loss, TSAI, and TPR in serotonin-treated and control rats. It should be noted that serotonin slightly increased the survival of rats after acute hypoxia: 14 out of 20 rats survived *vs.* 10 out of 20 in the control group.

Heparin and HSC prolonged the period before the posture loss 9.2- and 9.6-fold, respectively, in comparison with the control. The HSC prolonged TSAI 8.8-fold, the difference being statistically significant ($p<0.01$) in comparison with heparin-treated rats. Heparin prolonged TSAI 4.6-fold in comparison with the control. The TSAI/TPR ratio, which reflects the resistance of the rats to hypoxia, increased considerably after HSC injection (8.5-fold compared with the control and 1.8-fold compared with heparin-treated rats). A 4.6-fold increase in the TSAI/TPR ratio indicates that heparin also increases rats' resistance to hypoxia.

The HSC provided the highest survival of rats after acute hypoxia: 18 out of 20 animals. After injection of heparin, 14 out of 20 rats survived, and 10 out of 20 rats survived in the control group.

Antihypoxic activity of HSC and heparin is comparable to that of the antihypoxic agents mexidol, carnosine, Semaks, and arginine. Mexidol is effective in a dose of 40 mg/kg. It prolongs TSAI 2.5-fold in comparison with the control. At 20 mg/kg carnosine prolongs the time before posture loss and TSAI 2-fold. Semaks (0.1 mg/kg) prolongs TSAI 3-fold. Arginine exerts antihypoxic effect in a dose of 500-1200 mg/kg, as evidences by a 1.7- to 3-fold increase in TSAI. Heparin and HSC were effective after administration in a much lower dose (0.36 mg/kg) and exhibited higher antihypoxic activity than these preparations: HSC prolonged the time before posture loss 9.6-fold and TSAI 8.8-fold, while for heparin these parameters were 9.2- and 4.6-fold, respectively.

From our findings it can be concluded that the heparin-sulfate complex protects rats from hypoxia in a pressure chamber and does not accelerate normalization of physiological functions during the posthypoxic period. It should be noted that heparin, but not serotonin, exert antihypoxic effect after being administered alone. Bearing in mind that heparin elicits both anticoagulant [2] and antihypoxic effects, it can be suggested that the mechanisms providing these activities possess common biochemical pathways. The anticoagulant heparin can be used for the treatment of various disorders leading to tissue hypoxia since it prevents hypoxia-related disturbances by increasing tissue saturation with oxygen.

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