Effects of Regulatory Peptides on Changes in the Content of Brain Stem Catecholamine in Rats during Hypoxia and Hemorrhage

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Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 128, No. 11, pp. 518-520, November, 1999
Original article submitted September 8, 1997

Effects of regulatory peptides FMRFa, thyroliberin, and Semax ($ACTH_{4-10}$ analogue) on changes in the content of biogenic amines in rat brain stem observed 1 and 20 min after termination of hypoxia and 5 min after bloodletting (hemorrhage) were studied. The content of norepinephrine decreased to 82% of the control level 20 min after hypobaric hypoxia, while preliminary administration of the peptide complex abolished this effect.

Key Words: *hypobaric hypoxia; hemorrhage; biogenic amines; brain stem*

Disturbances of the systemic hemodynamics, in particular centralization of blood flow due to activation of the sympathoadrenal system, play a key role in the pathogenesis of hemorrhage and hypoxia. These processes reduce oxygen supply of peripheral tissues, i.e. cause hypoxia [5]. Correction of sympathoadrenal system hyperactivity can normalize hemodynamics and prevents hemorrhage and hypoxia [2].

This correction can be to a certain extent performed by modulation of the endogenous opioid system, a functional antagonist of the sympathoadrenal system [4].

Our previous experiments demonstrated protective effects of FMRFa, thyroliberin, and Semax (the $ACTH_{4-10}$ analogue) modulating activity of the opioid system during acute hemorrhage and hypobaric hypoxia [3].

Administration of these peptides in subthreshold doses elevated blood pressure and heart rate in rats after hemorrhage and improved animal resistance to hypoxia.

Hemorrhage and hypoxia induce marked changes in the content of biogenic amines in peripheral tissues (epinephrine and serotonin in the adrenal glands and spleen, respectively), while preliminary administration of the above mentioned peptide mixture abolished these effects [1]. Therefore, the effects of this peptide mixture on the content of biogenic amine in rat CNS during hypoxia and hemorrhage are of considerable interest.

MATERIALS AND METHODS

Experiments were performed on 96 outbred albino male rats weighing 210-300 g. The rats were exposed to acute hypobaric hypoxia at a simulated altitude of 11,000 m for 5 min. The time of posture loss (period from the start of hypoxia to complete relaxation of skeletal muscles) was estimated.

Fifteen minutes before the "ascent", control animals were intraperitoneally injected with 1 ml/kg physiological saline, while experimental rats received test complex of regulatory peptides.

Hemorrhage was modeled in conscious rats by taking blood through a catheter introduced into the common carotid artery 1 day before the experiment. Physiological saline and peptide mixture were administered into the carotid artery through the catheter at a rate of 1.2 ml/h for 40 min (total volume 0.8 ml). Immediately after infusion, blood (30 ml/kg+0.8 ml cor-

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0007-4888/99/0011-1106$22.00

responding to the volume of administered solutions) was taken from the carotid artery at a rate of 1 ml/min.

Our previous experiments established subthreshold doses of these regulatory peptides (in relation to their effects on functional parameters during hypoxic shock and hemorrhage). In hypoxia, FMRFa, thyroliberin, and Semax were injected intraperitoneally in doses of 0.5, 0.5, and 0.05 mg/kg, respectively, while during hemorrhage, these agents were injected intraarterially in doses of 0.4, 0.4, and 0.08 mg/kg, respectively. The peptide complex contained these doses of peptides.

The contents of biogenic amines in the brain stem were measured 1 and 20 min after hypoxia and 5 min after bloodletting by routine biochemical methods [6,7].

RESULTS

The administration of the peptide mixture 15 min before hypoxia prolonged the latency of posture loss from 45.5±3.31 to 125.7±10.0 sec ($p<0.001$). The infusion of this peptide complex prior to hemorrhage increased animal survival rate from 21 to 80% ($p<0.025$).

Hypoxia considerably decreased the contents of serotonin in the spleen and epinephrine in the adrenal glands to 67 and 71% of the control levels, respectively (Table 1). These changes disappeared 20 min after the end of hypoxia. During hemorrhage, the concentration of serotonin in the spleen increased to 131% of the control (Table 1).

The content of norepinephrine in the brain stem immediately after hypoxia did not change, but 20 min later decreased to 82% of the control. Dopamine content tended to increase to 133% of the control immediately after hypoxia and did not differ from the control level 20 min later (Table 2). There were no significant changes in the level of biogenic amines in the brain stem after hemorrhage, but the content of dopamine tended to decrease to 85% of the control in hemorrhagic rats.

The peptide mixture had no effect on the content of biogenic amines in control animals.

However, the administration of this peptide mixture to rats prior to hypoxia or hemorrhage prevented changes in the content of biogenic amines.

The peptide mixture administered before hypoxia normalized the content of dopamine in the brain stem (92% *vs.* 133% of the control in rats receiving physiological saline).

The peptide mixture also normalized the content of norepinephrine in rat brain stem 20 min after the end of hypoxia from 82% to 95% of the control, i.e. practically to the control level.

The content of dopamine in the brain stem of rats receiving the peptide mixture prior to hemorrhage practically did not differ from the control (96% *vs.* 85%).

TABLE 1. Contents of Serotonin in the Spleen and Epinephrine in the Adrenal Glands of Rats during Hypoxia, Hemorrhage, Injection of the Peptide Complex, and Combined Action of These Factors (*M±m*)

Factor	Epinephrine	Serotonin
	μg/kg	
Hypoxia		
Control	368±33	3.6±0.4
Peptide complex	348±47	4.1±0.4
Hypoxia	260±24*	2.4±0.2*
Hypoxia+peptide complex	295±38	3.9±0.4
Hemorrhage		
Control	364±31	3.5±0.3
Peptide complex	356±27	3.4±0.3
Hemorrhage	362±11	4.5±0.2**
Hemorrhage+peptide complex	350±16	4.7±0.3**

Note. Here and in Table 2: *$p<0.02$ and **$p<0.05$ compared with the control (Student's *t* test and Fisher test).

TABLE 2. Content of Catecholamines in the Brain Stem of Rats during Hypoxia, Hemorrhage, Injection of the Peptide Complex, and Combined Action of These Factors (*M±m*)

Factor		Norepinephrine	Dopamine
		ng/g	
Control		197±12	410±40
Peptide complex		187±8	390±25
Hypoxia	1 min	203±14	545±148
	20 min	161±4*	430±53
Hypoxia+peptide complex	1 min	199±20	377±33
	20 min	187±8	406±49
Hemorrhage		181±10	348±20
Hemorrhage+peptide complex		189±8	394±37

The peptide mixture induced similar effects on the level of biogenic amines in peripheral tissues (except for the content of epinephrine in the adrenal glands after hypoxia).

Thus, hypoxia and hemorrhage induced different changes in the content of biogenic amines. This was probably due to the fact that the content of biogenic amines in the brain stem of rats subjected to hemorrhage was measured at the early stage of sympathoadrenal response, when cerebral blood flow was maintained at a relatively normal level and prevented the development of hemorrhage-related hypoxia.

In both cases, the peptide mixture prevented changes in the content of biogenic amines in the CNS and peripheral tissues induced by hypoxia and hemorrhage.

Our findings suggest that protective effects of this peptide mixture with antiopioid activity are partially due to its action on the content of biogenic amines reflecting the stress reaction of the body.

This study was supported by the Russian Foundation for Basic Research (grant No. 99-04-48019).

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