PROTECTIVE ACTION OF TRH AND ITS SYNTHETIC ANALOG (PR-546) IN CRANIOCEREBRAL TRAUMA

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Exogenous thyrotrophin releasing hormone (TRH) has an excitatory effect on several autonomic functions, including on the respiratory and circulatory systems [7, 8]. The strongest stimulating effect of the peptide has been found when the functions of these systems are disturbed and, in particular, in hemorrhagic shock [2, 6]. Recent investigations demonstrated the effectiveness of TRH in its action on parameters of the pulmonary hemodynamics and bronchial circulation [1, 3]. Taken as a whole, these data suggested that TRH possesses protective properties against other forms of respiratory failure also. Pulmonary edema is one of the chief causes of death, and the factor determining the length of survival, in brain damage following craniocerebral trauma (CCT) [5].

The aim of this investigation was to study the action of TRH on parameters of pulmonary hydration and gas exchange, on a model of neurogenic pulmonary edema. This model was chosen because of the absence of effective agents for preventing and treating pulmonary complications of CCT and cerebrovascular disturbances. The action of PR-546, a TRH analog which, as our previous investigations showed, also has a stimulating action under experimental conditions on the respiratory and circulatory systems, was studied on the same model [4]. The fact that the analog has no hormonal activity makes it more promising for clinical use.

EXPERIMENTAL METHOD

Experiments were carried out on 90 mature male rats weighing 180-220 g under intraperitoneal pentobarbital anesthesia (30 mg/kg). The model of CCT was created by the standard method, by inflicting a measured blow by a freely falling weight, and varying the quantitative parameters but keeping a constant force (about 1.3 N). Systemic blood pressure (BP) was measured by the direct method in the carotid artery, using an EMT strain-gauge transducer. To prevent blood clotting the animals were given heparin in a dose of 200 U/kg body weight. The ECG was recorded in standard lead II. BP, pulmonary ventilation, and the ECG were recorded on tape by a "Mingograf" automatic writer (Sweden). Respiratory movements were recorded by means of a carbon transducer fixed to the chest. The gas composition, p_aCO_2, p_aO_2, and pH of the blood were determined by means of a micro-Astrup gas analyzer (Radiometer, Denmark, 1981), and the hemoglobin and oxyhemoglobin levels were recorded on a 05M-26 hemoxymeter (Sweden). The degree of hydration of the lungs was estimated from the ratio of the weight of wet (P_w) and dry (P_d) tissue. The physiological parameters were recorded and arterial blood samples taken in the control and two experimental groups (each group consisted of 30 animals), 5-10 min before infliction of CCT. In the experimental groups TRH (in doses of 0.5-1 mg/kg) and PR-546 (in doses of 4-8 mg/kg) were injected intraperitoneally in a volume of 0.5 ml 20 min before trauma

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TABLE 1. Parameters of Hydration of the Lung P_w/P_d and Gas Exchange during CCT without (control) and with the Use of TRH and Its Analog PR-546 ($M \pm m$)

Parameter	Control		CCT (TRH)			CCT (PR-546)		
	initial	3-5 min after CCT	initial	3–5 min	30–60 min	initial	3–5 min	30–60 min
P_w/P_d	4,43±0,02	6,08±0,23*	4,43±0,02	—	4,56±0,05*	4,43±0,02	—	4,47±0,10**
pH	7,35±0,02	7,31±0,01	7,43±0,01	7,39±0,01*,**	7,34±0,03*	7,43±0,05	7,30±0,02*	7,33±0,02*
PCO_2, mm Hg	49,9±2,7	62,1±2,2*	42,5±1,0	48,5±2,4*,**	44,1±2,7*	33,3±2,4	38,7±3,1*,**	35,8±1,7*
PO_2, mm Hg	102,3±3,1	53,0±3,2*	104,1±2,2	70,0±5,8*,**	100,7±3,9*	125,1±6,5	75,4±11,0*,**	103,0±9,9*
Hb, g/liter	136,3±6,1	150,0±4,6*	138,0±3,2	146,4±2,7*	145,1±2,6*	136,8±5,9	145,3±4,1*	143,0±6,2*
HbO_2, %	82,9±0,9	37,8±2,0*	81,1±0,6	70,1±3,4*,**	78,5±0,8*	78,9±3,1	51,4±9,7*	62,3±5,4*

Legend. $*p \leq 0.05$ compared with initial values, $**p \leq 0.05$ relative to control values.

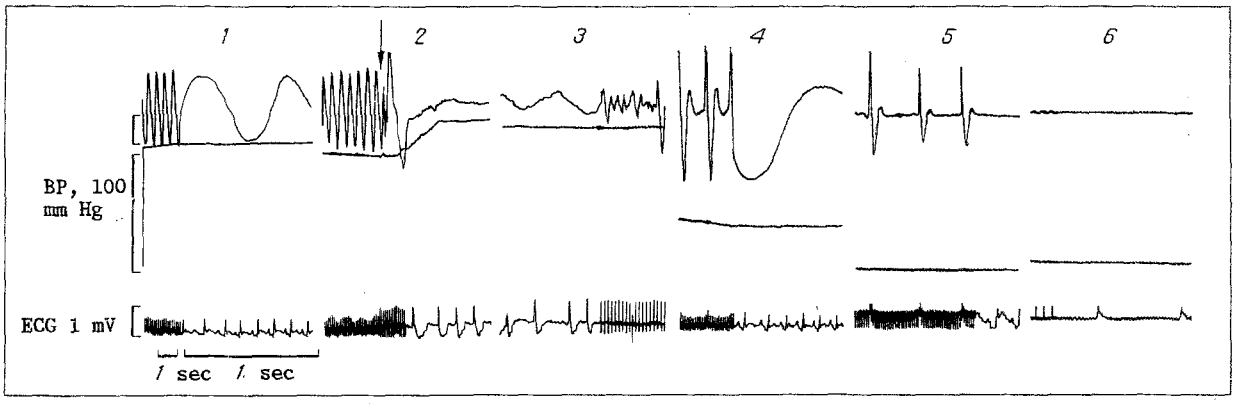

Fig. 1. Character of change in respiration, BP, and ECG in rats after CCT. Initial state (1), infliction of CCT (2), 3rd (3), 5th (4), 7th (5), and 10th (6) minutes after CCT. Arrow indicates time of trauma. Disturbance of frequency and depth of respiration followed by arrest, and elevation of BP during first 3 min and its subsequent fall can be seen.

(this interval was determined by preliminary experiments). With a shorter time interval after intraperitoneal injection, the substance had no action. In the control group the animals were given isotonic physiological saline in the same volume and by the same route as the test preparations. The physiological parameters were recorded and blood samples taken successively 3-5 min and 30-60 min after trauma.

EXPERIMENTAL RESULTS

The experimental results are given in Table 1. In the control group the animals died in 80% of cases during the first 3-5 min after CCT against the background of severe pulmonary edema, as shown by the high degree of hydration of the lungs (P_w/P_d), disturbance of the acid–base balance (pH), and the development of hypoxemia and hypercapnia (p_aO_2, p_aCO_2). The significant increase in the blood hemoglobin concentration is evidence of hemoconcentration, which is characteristic of edema. In some experiments convulsions and respiratory arrest for up to 1 min were observed and BP rose from 110 ± 8 to 124 ± 11 mm Hg (Fig. 1).

Stimulation of respiratory activity was observed 10-15 min after injection of the test preparations, as shown by an increase in the frequency and depth of respiration (Fig. 2) and oxygenation of arterial blood (Table 1). After infliction of CCT and administration of TRH and PR-546 the number of deaths fell significantly to 10-20%. Respiratory arrest and convulsions were not observed. In the course of 3-5 min respiratory activity was completely restored and BP stabilized. The hypoxemia, which developed during the first few minutes after trauma, was transient in character and disappeared in the course of 1 h. The degree of hypoxemia was significantly weaker than in the control. The oxygen saturation of the hemoglobin showed similar changes. Pulmonary edema did not develop in animals receiving TRH or PR-546.

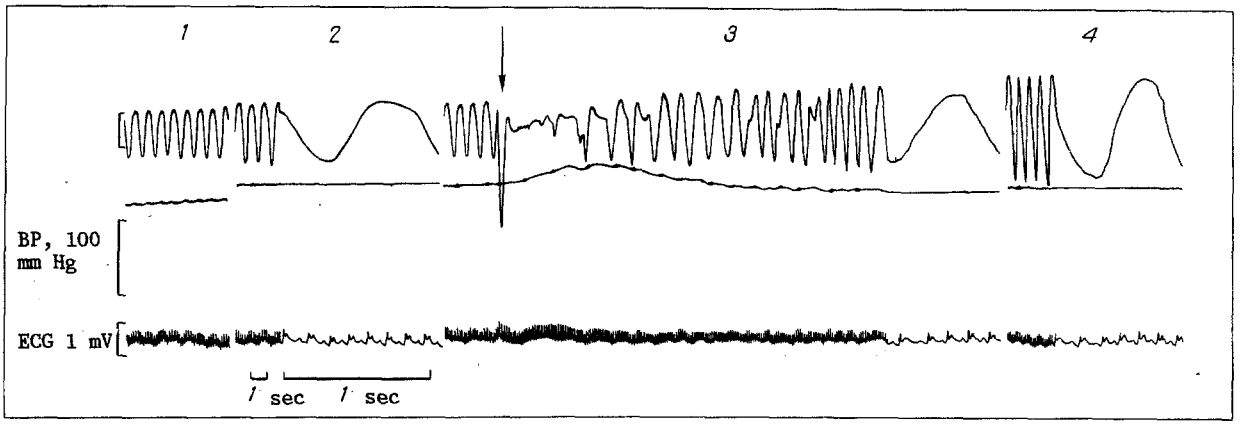

Fig. 2. Changes in physiological parameters in model of CCT in animals receiving TRH. Initial state (1), 15th minute after injection of TRH (2), infliction of CCT (3), 30th minute of observation (4). Increased respiratory activity of BP can be seen after injection of TRH. After CCT the phase of apnea was virtually absent and respiration was restored during the first few minutes.

TRH and its analog thus prevented the development of lung damage following CCT. The results of this investigation confirmed our previous hypothesis that the test peptides may have a protective action, preventing respiratory arrest and the development of acute pulmonary edema after brain damage. This action is realized only when a period of 20 min has elapsed after injection of the test compounds, which is necessary for maximal activity of the respiratory center to be attained [4]. Comparison of the results indicates that the protective action of the test peptides takes place against a background of increased activity of the respiratory and vasomotor centers. The reason why the preparations were given before trauma was inflicted is that in this model pulmonary edema occurred immediately after CCT. Since neurogenic edema of the lungs develops at later stages in clinical practice (after a few hours), the desirability of using the preparations for therapeutic purposes after CCT will be evident. The fact that the analog PR-546, which does not possess hormonal properties, has the same action as TRH is evidence that the effect can be produced without involvement of the hormonal system. The results described above, together with those of previous investigations on other models of respiratory failure, indicate that clinical application of these preparations in order to prevent respiratory disturbances and pulmonary edema is a definite possibility.

LITERATURE CITED

1. I. P. Ashmarin, I. E. Gurskaya, and S. A. Kuz'michev, Role of the Bronchial and Pulmonary Circulation in Fluid and Protein Exchange in the Lung [in Russian], Leningrad (1989), p. 5.
2. V. A. Voinov, N. I. Losev, and V. M. Bulaev, Byull. Éksp. Biol. Med., No. 10, 408 (1984).
3. I. E. Gurskaya, S. A. Kuz'michev, N. A. Belyakov, and Ts. V. Serbenyuk, Proceedings of a Scientific Conference to Commemorate the 160th Anniversary of I.M. Sechenov's Birth [in Russian], Odessa (1989), pp. 11-13.
4. I. E. Gurskaya, Ts. V. Serbenyuk, A. D. Slyuta, and P. Ya. Romanovskii, Byull. Éksp. Biol. Med., No. 7, 32 (1989).
5. L. Z. Tel', "Central nervous mechanisms of pulmonary edema," Author's Abstract of Dissertation for the Degree of Doctor of Medical Sciences, Moscow (1983).
6. J. W. Holaday and R. J. Amato, Science, **213**, 216 (1981).
7. J. R. Holtman, A. L. Buller, P. Hamosh, and R. A. Gillis, Peptides, **7**, No. 2, 207 (1986).
8. C. Oliver, R. L. Eskay, N. Ben-Jonathan, and J. C. Porter, Endocrinology, **96**, 540 (1984).