PROTECTIVE EFFECT OF THYMOPENTIN ON STRESS-INDUCED GASTRIC DAMAGE

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An essential role in the limitation of the damaging action of stress may be played by peptide bioregulators. The short protein fragment thymopentin (Arg–Lys–Asp–Val–Tyr–OH) has a marked neuroregulatory action under conditions of acute stress [7]. It is reasonable to suppose that besides correcting neurochemical processes, thymopentin may also have a protective effect against somatic injuries caused by exposure to stress.

The aim of this investigation was to study the effect of thymopentin on ulcers arising in the gastric mucosa and on the state of lipid peroxidation (LPO) processes in that tissue, due to acute and chronic stress and also to a combination of both.

EXPERIMENTAL METHOD

Experiments were carried out on 98 male Wistar rats weighing 170-210 g. The animals were subjected to acute or chronic stress and also to a combination of both. Acute stress was created by immobilizing the rats and immersing them in water at 22°C for 3 h, chronic stress by the same experimental procedure for 15 days according to the following schedule: 5 min on the 1st day, 15 min on the 2nd, 20 min on the 3rd, 30 min on the 4th, and 60 min on the 5th-15th days. The schedule of combined exposure to acute and chronic stress differed from the latter only in that the duration of exposure on the 16th day was 3 h.

Acute stress was corrected by a single intraperitoneal injection of thymopentin in a dose of 100 μg/kg 20 min before the beginning of stress. In the case of chronic or a combination of chronic and acute stress, the same dose was injected before the first and last sessions.

The rats were killed by exsanguination under hexobarbital anesthesia. The severity of stress was determined by the degree of ulceration of the stomach and the relative weight of the thymus and adrenals. The severity of the gastric ulcers was assessed on the basis of the number of ulcers: 1-5 ulcers) 1-5 points, 6-10) 6 points, 10-15) 7 points, 16-20) 8 points, 21-30) 9 points, 31-40) 10 points, 41-50) 11 points, 51-60) 12 points, and 61-65) 13 points. The multiplicity of the lesions was determined as the ratio between the total number of ulcers in all the rats and the number of animals in the group [3].

The intensity of LPO in the gastric tissues was judged by superoxide dismutase (SOD) activity [2]. The numerical results were subjected to statistical analysis by Student's test and by the nonparametric differences test [4].

EXPERIMENTAL RESULTS

Acute stress was accompanied by somatic disturbances, characterized by gastric ulcer formation in 11 of the 13 rats and by reduction of the relative weight of the thymus and adrenals by 18.5 and 14.5%, respectively (Table 1). It is assumed that an important role in the mechanism of stress-induced gastric ulceration is played by activation of LPO processes [1, 8, 9]. We found on a model of acute stress that gastric ulcer formation was accompanied by lowering of activity of SOD – the principal enzyme of the antioxidant system (Table 2).

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TABLE 1. Effect of Thymopentin on Somatic Lesions in Rats Exposed to Acute Stress (M ± m)

Group of animals	Experimental conditions	Gastric ulcer		Relative weight, mg/g body weight	
		multiplicity of lesion, number per rat	severity of damage, points	Thymus	Adrenals
1	Intact	0	0	0,920 (0,600—1,700) ($n = 8$)	0,178 (0,140—0,216) ($n = 8$)
2	Thymopentin	0	0	0,890 (0,470—1,800) ($n = 10$)	0,182 (0,140—0,244) ($n = 10$)
3	Acute stress	6,56±1,51 ($n = 13$)	4,8±0,76 ($n = 13$)	0,750 (0,540—0,930) ($n = 11$)	0,152 (0,120—0,176) ($n = 11$)
4	Acute stress + thymopentin	4,7±1,57* ($n = 13$)	3,1±0,81 ($n = 13$)	0,970* (0,660—1,360) ($n = 13$)	0,180* (0,136—0,240) ($n = 13$)

Legend. Here and in Table 2: (n) denotes number of animals; *$p \leq 0.05$ (for non-parametric differences test between groups 3 and 4).

TABLE 2. Effect of Thymopentin on Somatic Lesions and SOD Activity in Gastric Tissues of Rats Exposed to Chronic Stress and to a Combination of Acute and Chronic Stress (M ± m)

Group of animals	Experimental conditions	Gastric ulcer		Relative weight, mg/g body weight		SOD activity, conventional units
		multiplicity of lesion, number per rat	severity of damage, points	Thymus	Adrenals	
1	Intact	0 ($n = 10$)	0 ($n = 10$)	0,478 (0,338±0,700) ($n = 9$)	0,122 (0,100±0,150) ($n = 9$)	0,448±0,078 ($n = 7$)
2	Acute stress	11,1±2,60 ($n = 10$)	6,1±0,72 ($n = 10$)	0,412 (0,156±0,700) ($n = 10$)	0,133 (0,100±0,200) ($n = 10$)	0,175±0,044* ($n = 8$)
3	Chronic stress	0,1±0,08** ($n = 10$)	0,5±0,40** ($n = 10$)	0,263** (0,176±0,339) ($n = 9$)	0,170** (0,100±0,272) ($n = 10$)	0,195±0,049** ($n = 8$)
4	Chronic stress + thymopentin	0 ($n = 10$)	0 ($n = 10$)	0,276 (0,190±0,400) ($n = 9$)	0,159 (0,138±0,200) ($n = 10$)	0,409±0,094*** ($n = 7$)
5	Chronic + acute stress	18,1±4,82[4]* ($n = 10$)	7,4±4,82[4]* ($n = 10$)	0,288 (0,179±0,508) ($n = 10$)	0,174 (0,111±0,338) ($n = 10$)	0,099±0,020[4]* ($n = 9$)
6	Chronic + acute stress + thymopentin	4,3±1,56[5]* ($n = 9$)	3,2±0,99[5]* ($n = 9$)	0,287 (0,157±0,346) ($n = 9$)	0,157 (0,119±0,191) ($n = 9$)	0,332±0,91[5]* ($n = 9$)

Legend. Asterisk $p < 0.05$: *) between 1st and 2nd, **) between 1st and 3rd, ***) between 3rd and 4th, [4]*) between 1st and 5th, [5]*) between 5th and 6th groups.

Chronic stress, unlike acute, caused only slight damage to the gastric mucosa: the multiplicity of the ulcers was 11 times smaller. However, under these conditions involution of the thymus and hypertrophy of the adrenals increased. The maximal degree of ulceration produced by the combined effect of acute and chronic stress corresponded to the most marked fall (by 4.5 times) of SOD activity in the gastric tissues (Table 2). The parallel trend of the degree of ulceration and SOD activity thus revealed suggests that the antioxidant system is one of the most important mechanisms protecting the gastric tissues against the damaging action of LPO products (Schiff bases, hydroperoxides, malonic dialdehyde), concentrations of which rise under the influence of stress [1, 8]. The close correlation between ulceration and SOD activity in the gastric tissues confirms the pathogenetic role of SOD in gastric ulceration.

Injection of thymopentin into the rats 20 min before the beginning of creation of acute stress led to a decrease of 27% in the multiplicity and of 24% in the severity of gastric

ulceration. Normalization of the relative weight of the thymus and adrenals was observed at the same time (Table 1).

Selectivity of the protective action of thymopentin was exhibited in chronic stress. The peptide had a protective effect on the stomach, but it did not prevent the poststressor response of the thymus and adrenals. Inhibition of gastric ulceration by thymopentin was accompanied by prevention of inhibition of SOD activity in its tissues (Table 2).

The marked stress-protective effect of thymopentin also was observed against combined exposure to acute and chronic stress, for the multiplicity of gastric ulcers was reduced by 4 times and their severity by 2.3 times. SOD activity in the gastric tissues was increased under these circumstances by 3.3 times compared with that in the control group of rats.

The regulatory effect of thymopentin on activity of SOD, an enzyme involved in protection of the gastric tissues against the damaging action of free oxygen radicals, will be noted. These data are in agreement with the results of research by Zvershkhanovskii et al. [6], who found that exogenous SOD exerts a protective effect against damage to the gastric mucosa of rats exposed to acute emotional-painful stress.

The facts described above are evidence that thymopentin has a marked antiulcerogenic action in the types of stress studied, and that it is determined by its regulating influence on the mechanism of antioxidant protection of the gastric tissues.

Some workers have ascribed an important role in the pathogenesis of stress-induced gastric damage to excess release of catecholamines [5]. Thymopentin has a modulating influence on catecholaminergic, serotoninergic [7], and GABA-ergic systems of the brain and adrenals. Consequently, the antiulcerogenic mechanism of thymopentin can be explained by the regulating influence of thymopentin on the absolute or relative levels of the mediators controlling the circulation of blood in the stomach. However, this mechanism of action of thymopentin is evidently not the only one. Taking into account the correlation which we found between the degree of severity of the gastric ulcers and SOD activity, and also the normalizing effect of thymopentin on SOD activity, one possible mechanism of the antiulcerogenic action of the peptide may be its protective influence on the antioxidant system of the cells.

It was thus shown that thymopentin has an antiulcerogenic effect on the stomach during stress, thus broadening the spectrum of its pharmacologic action and also substantiates the role of peptides in regulation of the function of the antioxidant system.

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