Stress-Protective Effect of Glutapyrone Belonging to a New Type of Amino Acid-Containing 1,4-Dihydropyridines on Periodontal Tissues and Stomach in Rats with Different Resistance to Stress

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Glutapyrone belonging to a new type of amino acid-containing 1,4-dihydropyridines produced a protective effect on periodontal tissues and gastric mucosa in rats with different resistance to stress during acute emotional and pain stress.

Key Words: *stress resistance; periodontium; stomach; glutapyrone; 1,4-dihydropyridine*

Functional state of the connective tissue determines the outcome of acute stress and organism's resistance to pathogenic factors [3]. Since the connective tissue is the main component of the periodontium and gastric mucosa (GM), it can be hypothesized that the resistance of these tissues to stress depends on metabolic properties of connective tissue biopolymers. Glutapyrone (disodium salt of 2-2,6-dimethyl-3,5-diethoxycarbonyl-1,4-dihydropyridyl-4-carboxamido)glutaric acid) is a new stress-protective substance synthesized at the Latvian Institute of Organic Synthesis. This compound contains 1,4-dihydropyridine and sodium glutamate bound to the dihydropyridine ring in position 4. Glutapyrone possesses antiarrhythmic [12], anticonvulsive [4], stress-protective [10], and antioxidant properties [2].

Here we studied the effects of glutapyrone on stress resistance of periodontal tissues and stomach in rats with different emotional reactivity.

MATERIALS AND METHODS

Experiments were performed on 125 male Wistar rats weighing 150-200 g. Emotional and pain stress (EPS) was modeled as described elsewhere [9]. The severity of stress was assessed by the number and size of gastric ulcers [1]. The resistance to stress was evaluated in the open-field test. Intact animals with the corresponding emotional reactivity served as the control.

Soft tissues of the periodontium and GM were examined. The total collagenolytic activity was measured as described previously [10]. The content of fucose [8] and the concentration of hexuronic acids [7] were determined. Glutapyrone was injected intraperitoneally in a dose of 1 mg/kg 3 h before EPS.

The results were analyzed by Student's *t* test.

RESULTS

Acute EPS induced the development of gastric ulcers in 100% stress-predisposed rats and in 45.5% stress-resistant animals (Table 1). The number of ulcers in stress-predisposed rats 3-fold surpassed that in stress-resistant animals (Table 1).

Collagenase activity in periodontal tissues and GM increased during EPS only in stress-predisposed rats (Table 1). These results indicate that stress modulates activity of enzymes catalyzing collagenolysis in periodontal tissues and GM, which is consistent with our previous observations [6].

The contents of fucose (monomer of oligosaccharide chains in glycoproteins) and hexuronic acids (com-

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ponents of connective tissue proteoglycans) reflect disorganization of the connective tissue in the periodontium and GM.

Acute EPS was followed by an increase in fucose content in soft tissues of the periodontium and GM in stress-predisposed rats (compared to intact animals). In stress-resistant rats this parameter did not differ from the control (Table 2). After EPS the content of hexuronic acid in periodontal tissues and GM increased only in stress-predisposed animals (Table 2).

These results indicate that disorganization of the connective tissue due to activation of collagenolysis and depolymerization of non-collagen proteins, i. e. glycoproteins and proteoglycans (as confirmed by high content of fucose and hexuronic acids), contribute to stress-induced damages to the periodontium and GM.

The protective layer of the stomach determining the resistance of GM consists of proteins and carbohydrates. In our experiments EPS-induced ulceration in stress-predisposed rats coincided with maximum degradation of fucoproteins and proteoglycans in GM, which decreased its protective activity.

Stress-predisposed rats are characterized by more intensive catabolism of matrix biopolymers of connective tissues in the periodontium and stomach (compared to stress-resistant animals). Pretreatment with the 1,4-dihydropyridine derivative glutapyrone markedly decreased the count and incidence of gastric ulcers in rats during acute EPS (Table 1). Under these conditions glutapyrone protected periodontal tissues and GM, normalized total collagenolytic activity in stress-predisposed rats, and prevented intensive

TABLE 1. Effects of Glutapyrone on Ulceration in the Stomach and Total Collagenolytic Activity (CA) in Soft Tissues of the Periodontium and GM in Rats with Different Resistance to Stress ($M \pm m$, n=7-9)

Parameter	Intact	Glutapyrone	Acute EPS	
			without correction	+glutapyrone
Animals with gastric ulcers, %	19.5 11.2	18.6 11.3	100 45.2	42.9 25.6
Number of ulcers per rat	0.57±0.61 0.87±0.54	0.19±0.63 0.10±0.68	16.85±0.51* 4.95±0.62	2.71±0.64+ 1.16±0.56+
CA, mmol/g/min				
periodontium	4.06±0.26 4.08±0.56	4.05±0.15 4.18±0.36	4.95±0.25* 4.28±0.32	4.19±0.16+ 4.22±0.36
GM	2.55±0.16 2.49±0.36	2.69±0.31 2.58±0.21	3.98±0.22* 2.87±0.29	2.62±0.18+ 2.64±0.19

Note. Here and in Table 2: numerator, stress-predisposed rats; denominator, stress-resistant rats. p<0.05: *compared to intact rats, +compared to EPS without correction.

TABLE 1. Content of Fucose and Hexuronic Acids in Soft Tissues of the Periodontium and GM of Rats with Different Resistance to Stress during Acute Stress ($M \pm m$, n=7-9)

Parameter	Intact	Glutapyrone	Acute EPS	
			without correction	+glutapyrone
Fucose, mmol/g				
periodontium	1.01±0.10 0.85±0.11	1.11±0.15 1.09±0.14	1.52±0.11* 1.02±0.12	1.15±0.13+ 1.14±0.15
GM	0.95±0.10 0.99±0.12	0.96±0.11 0.85±0.10	1.64±0.12* 1.12±0.15	0.85±0.10+ 0.96±0.12
Hexuronic acids, mmol/g				
periodontium	9.4±0.9 8.9±0.9	11.9±0.7 10.8±0.9	12.9±0.8* 9.8±0.6	9.6±0.8+ 9.7±0.8
GM	7.4±0.8 6.9±0.7	10.8±0.8 10.4±0.5	12.5±0.9* 9.5±0.8	8.6±0.7+ 9.8±0.6

degradation of glycoproteins and proteoglycans in the connective tissue of GM and periodontium, which was confirmed by a significant decrease in the contents of fucose and hexuronic acids. Glutapyrone prevents the stress-induced decrease in γ-aminobutyric acid content in the brain [4] and inhibits lipid peroxidation [2], which probably underlies its stress-protective activity.

Our results indicate that the stress-protective effect of glutapyrone on periodontal tissues and GM is related to inhibition of depolymerization of collagen and non-collagen proteins in the connective tissue.

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