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EFFECT OF DALARGIN ON CELL MULTIPLICATION IN THE GASTRIC EPITHELIUM DURING STRESS

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Dalargin, a synthetic Leu-enkephalin analog, is regarded as an effective and promising drug for the treatment of peptic ulcer [8]. The ability of dalargin to normalize the microcirculation [2, 13] and its antistressor [3] and cytoprotective [7, 9] action constitute the grounds for widening the indications for its use.

Dalargin stimulates proliferative processes in epithelial tissues [10, 11]. It has also been found to prevent the formation of a structural trace of disadaptation during stress; administration of dalargin reduced the level of pathological mitoses induced by stress, normalized DNA synthesis, and delayed vertical migration of cells in the corneal epithelium [12].

It was decided to study the effect of dalargin on proliferative processes in the gastric epithelium during stress, for disturbances of structural homeostasis in the gastric mucosa and ulcer formation are an indication of the severity of stress. An essential role in the pathogenesis of structural disorders under the influence of extremal factors is played by activation of peroxidation [1, 6], and it was therefore decided to study the effect of dalargin on malonic dialdehyde (MDH) accumulation in gastric tissue.

In the modern view, injury to the gastric mucosa takes place against the background of exhaustion of endogenous catecholamine reserves. Hence the need to investigate the effect of dalargin on the noradrenalin concentration in gastric tissue.

EXPERIMENTAL METHOD

Experiments were carried out on male rats weighing 150-180 g. The animals were divided into three groups: 1) intact control, 2) rats subjected to immobilization for 4 h, and 3) a group which received dalargin intramuscularly in a dose of 10 μg/kg 40 min before fixation. The animals were fixed in a special frames from 6 a.m. until 10 a.m., by the method described previously [12]. Proliferative processes and biochemical parameters were studied during the first hour after the end of immobilization, and again after 12 and 24 h. The animals were sacrificed 40 min after receiving an injection of ^{3}H-thymidine in a dose of 0.6 μCi/g body weight, with specific radioactivity of 87 Ci/mmole. Autoradiographs were prepared by the method described previously [4]. Proliferative changes in the pyloric division of the stomach were judged from the size of the ^{3}H-thymidine-labeled nuclei (ILN, %) and the

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TABLE 1. Effect of Dalargin on DNA Synthesis (ILN, LI), and Noradrenalin (NA) and MDA Concentrations in Pyloric Part of Albino Rat Stomach After Immobilization Stress for 4 h

Group of animals	Time after end of immobilization, h											
	1				12				24			
	ILN	LI	NA	MDA	ILN	LI	NA	MDA	ILN	LI	NA	MDA
1	5,9	22,3	0,08	159,6	8,4	30,1	0,02	162,2	7,05	31,3	0,4	1432
2	1,33*	13,5*	0,02*	227,7*	1,65*	28,4	0,01	175,3	5,86	25,78	0,001*	155,4
3	2,7	22,4	0,34	195,0	3,32	25,63	0,04	145,7	8,54	27,03	0,24	143

Legend. Asterisk indicates significant differences between control and groups, **) between groups 2 and 3.

labeling intensity (LI – the number of tracks above the cell nucleus), characterizing the rate of DNA synthesis. The malonic dialdehyde (MDA) concentration in the gastric tissue was expressed in fluorescence units per gram, and the noradrenalin concentration in the gastric tissues in μg/g tissue.

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Experiments were carried out on male rats weighing 150-180 g. The animals were divided into three groups: 1) intact control, 2) rats subjected to immobilization for 4 h, and 3) a group which received dalargin intramuscularly in a dose of 10 μg/kg 40 min before fixation. The animals were fixed in special frames from 6 a.m. until 10 a.m., by the method described previously [12]. Proliferative processes and biochemical parameters were studied during the first hour after the end of immobilization, and again after 12 and 24 h. The animals were sacrificed 40 min after receiving an injection of ^{3}H-thymidine in a dose of 0.6 μCi/g body weight, with specific radioactivity of 87 Ci/mmole. Autoradiographs were prepared by the method described previously [4]. Proliferative changes in the pyloric division of the stomach were judged from the size of the ^{3}H-thymidine-labeled nuclei (ILN, %) and the labeling intensity (LI – the number of tracks above the cell nucleus), characterizing the rate of DNA synthesis. The malonic dialdehyde (MDA) concentration in the gastric tissue was expressed in fluorescence units per gram, and the noradrenalin concentration in the gastric tissues in μg/g tissue.

EXPERIMENTAL RESULTS

Dalargin weakens stress-induced depression of proliferative processes in the mucosa of the pyloric part of the stomach (Table 1). Exposure to stress led to a fourfold reduction of ILN in the epilethelium of the pyrloric part of the stomach 1 h after the end of immobilization. Preliminary administration of dalargin prevented the fall of LI, but ILN under these conditions was reduced only by half. The results are evidence that dalargin prevents stress-induced disturbances of DNA synthesis and also weakens reduction of the proliferative pool.

ILN in the pyrloric part of the stomach of the stressed rats 12 h after the end of immobilization was 5 times less than in the intact group. Although after injection of dalargin a significant decrease in ILN was preserved, the value of this parameter was twice as high as in animals not receiving dalargin. LI at this period of the investigation showed no significant changes in any of the three groups.

ILN in the gastric mucosa of the stressed and intact rats 24 h after the end of immobilization did not differ significantly, but in animals receiving dalargin before stress ILN was significantly higher than in animals exposed to stress. LI in all three groups likewise showed no significant changes at this stage of the investigations.

The results confirm data on the ability of dalargin to prevent stress-induced disturbances of cell division [12]. Administration of dalargin prevented the decrease in the rate of DNA synthesis during the first few hours after stress and also weakened the decrease in size of the proliferative pool. Dalargin accelerated the onset of compensatory stimulation of DNA synthesis in the late stages (24 h).

The results of the study of MDA in the gastric mucosa helped to explain the mechanism of the cytoprotective action of dalargin in stress. Immediately after immobilization the MDA level in the gastric mucosa was 1.5 times higher than in the intact group. Preliminary

injection of dalargin prevented the increase in the MDA concentration in the gastric tissues. This observation is in agreement with data [5] on the involvement of ligands of opiate receptors in the realization of antioxidative effects. No significant changes in the MDA concentrations were observed after 12 and 24 h.

According to the generally accepted views, activation of peroxidation leads to inhibition of cell division. Dalargin, by preventing an increase in the MDA concentration in the gasttric mucosa, thereby prevents inhibition of cell division.

Another mechanism mediating the ability of dalargin to maintain structural homeostasis during stress is its ability to prevent the fall of the noradrenalin concentration in the tissues. Exposure to stress led to a marked fall of the noradrenaline concentration in the stomach at all times of investigation. Preliminary injection of dalargin not only prevented a decrease in noradrenalin concentration during stress after 12 and 24 h, but actually led to a significant increase in the concentration of this mediator during the first hour after immobilization compared with the intact control. It will be recalled that the formation of erosions and ulcers during stress takes place against a background of exhaustion of endogenous catecholamiens in the tissues [2]. In the modern view, an important mechanism of the antistressor action of opioid peptides and, in particular, of dàlargin, is their ability to prevent reduction of the tissue catecholamine reserves [13, 15].

Inhibition of cell division in the stomach is the crucial pathogenetic mechansim of formation of poststress ulcers. The results are grounds for the use of dalargin not only as a means of treatment of exacerbations of gastric and duodenal ulcer in man, but also for the prevention and treatment of acute ulcers and erosions.

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