The question accordingly arises: What is the effect of gentle adaptation on an integral parameter of myocardial contractility such as IFS. It will be clear from Table 1 that stress for 6 h induces a characteristic fall of IFS by 2.5 times. By itself gentle adaptation does not depress this parameter, but prevents its depression arising under the influence of long-term stress.

Hence, by the use of a rational strategy of adaptation to stress, i.e., by reducing the number of exposures and lengthening the time intervals between them, the negative effect of adaptation itself on myocardial contractility can be completely prevented and, at the same time, depression of the contractile function of heart muscle arising during long-term stress can be completely prevented. In other words, the "price" of adaptation to repeated stress, measured in depression of the contractile function of the heart, is not inevitable, complete protection of cardiac contractility against the effects of long-term stress can be achieved through the use of a correct strategy of adaptation without this undesirable effect.

LITERATURE CITED

1. F. Z. Meerson, Adaptation, Stress, and Prophylaxis [in Russian], Moscow (1981).
2. F. Z. Meerson, L. S. Katkova, Yu. P. Kozlov, et al., Byull. Éksp. Biol. Med., No. 12, 25 (1983).
3. F. Z. Meerson, G. T. Sukhikh, L. S. Katkova, et al., Dokl. Akad. Nauk SSSR, 274, No. 1, 241 (1984).
4. J. A. Deutsch, Science, 174, 788 (1971).

ADENYLATE CYCLASE ACTIVITY OF THE GASTRIC MUCOSA AND MORPHOLOGICAL CHANGES IN THE GASTROINTESTINAL TRACT IN EXPERIMENTAL DUODENAL ULCERATION FOLLOWED BY TRUNCAL VAGOTOMY

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UDC 616.342-002.44-092.9-089:616.833.191-089.85-07:616.33-018.73-008.931:577.152.633

KEY WORDS: duodenal ulcer, truncal vagotomy, cysteamine.

Duodenal ulcer is a polyetiologic disease whose pathogenesis is based on an imbalance between protective and injurious factors in the stomach and duodenum. Because it is impossible to analyze the role of each factor and their dynamic interaction in the development of the disease completely under clinical conditions, experimental approaches have been used. By now many different methods of inducing duodenal ulcers in animals of different species have been developed [3-5, 7, 10].

In the present investigation a cysteamine model of experimental duodenal ulcer [11] was used with some modifications. A study of the mechanism of action of cysteamine revealed a considerable and significant increase in secretion of hydrochloric acid and pepsin and also an increase in blood levels of gastrin and corticosterone [9]. Disturbances of the microcirculation and edema of the mucosa also develop under these circumstances in different parts of the gastrointestinal tract [6]. Administration of cysteamine thus increases the aggressiveness of the acid-peptic factor and also weakens the protective properties of the duodenal mucosa, phenomena which correspond to a considerable degree to the pathogenesis of this disease.

EXPERIMENTAL METHOD

Experiments were carried out on 40 noninbred male albino rats weighing 160-180 g. The rats were deprived of food for 24 h before receiving cysteamine and kept in special cages preventing coprophagy. Instead

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Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 100, No. 8, pp. 144-147, August, 1985. Original article submitted November 16, 1984.

0007-4888/85/0008-1010 $09.50

TABLE 1. AC Activity in GM of Animals of Different Experimental Groups

Group of animals	Experimental conditions	Basal AC activity, picomoles cAMP/mg protein/min		AC activator (in vitro)		
		Fundus of stomach	Antrum of stomach	Histamine 10^{-3} M	Secretin 10^{-6} M	PGE_2 (10^{-4} M)
				% of basal activity		
1-	Intacts rats	7,48±0,68	5,29±0,36	182±15 / 121±17	350±38 / 216±34	205±28 / 177±42
2-	Laparotomy	9,0±0,88	5,65±0,74	115±26 / 97±26	154±28 / 159±13	146±25 / 213±64
3-	Duodenal ulcer	16,64±1,71	10,9±1,1	103±14 / 92±18	162±11 / 162±35	127±4 / 169±16
4-	Experimental Ulcer + Truncal vagotomy	7,69±0,19	6,68±0,79	138±15 / 106±3	154±22 / 187±43	111±15 / 174±19

Legend. Gastric fundus above the line, antrum below the line.

of water, the rats drank a 0.5% solution of hydrochloric acid. Cysteamine was given in a dose of 40 mg/100 g body weight. Between 12 and 16 h after administration of cysteamine, autopsy revealed ulcers which had developed in the esophagus, stomach and, in particular, the duodenum. The animals were decapitated, the stomach and duodenum removed and opened, and the presence of ulcers established. With a scalpel the gastric mucosa (GM) was separated from the other layers of the stomach and used to determine adenylate cyclase (AC) activity by the method in [12], with certain modifications [3]. Some material was used for histologic and histochemical investigation.

To study the effect of truncal vagotomy on AC activity in GM four groups of experiments were carried out on 10 rats in each group: 1) intact animals; 2) animals undergoing laparotomy followed by suture of the wound in the abdominal wall: These rats were killed 10-14 days after the operation to determine the effect of the operation itself on AC activity in GM; 3) animals with experimental ulcers receiving cysteamine by subcutaneous injection as described above, and decapitated 12-24 h later; 4) animals with experimental ulcers treated by truncal vagotomy, during which both trunks of the vagus nerve running along the anterior and posterior walls of the esophagus were divided [8].

Basal AC activity in GM in the fundal and antral portions of the stomach and activation of AC in vitro by histamine (10^{-3} M), secretin (10^{-6} M), prostaglandin PGE_2 (10^{-4} M), and sodium fluoride (10^{-2} M) were investigated. Some of the material taken for histological investigation was fixed in Carnoy's fluid or in 10% buffered neutral formalin, after Lillie, and embedded in paraffin wax. Sections were stained with hematoxylin and eosin, with picrofuchsine by Van Gieson's method, and with methyl green and pyronine to detect ribonucleoproteins (RNP). Some material was cut on a cryostat and frozen sections were used to reveal activity of succinate dehydrogenase (SDH) and NAD- and NADP-disphorases by Pearse's method. SDH also was determined by Nachlas' method. The results of the biochemical tests are given in Table 1.

EXPERIMENTAL RESULTS

In the animals of group 1 basal AC activity in the fundus was significantly higher than in the antrum. Activation of AC by histamine (in vitro) in the fundus was twice as high as in the antrum. Activation of AC by secretion also was more marked in the fundus than in the antrum. PGE_2 activated AC in the mucosa of both the fundus and the antrum of the stomach, more so in the antrum.

In the animals of group 2 basal levels of AC activity did not differ from those in the rats of group 1. Activation of AC by histamine in the fundus was not significant and was less than in the rats of groups 1, whereas in the antrum no activation was present. Secretin activated AC equally in the mucosa of both parts of the stomach. Activation by PGE_2 was identical in character to that in the animals of group 1.

In the first two groups of animals no changes in the histological structure and results of the histochemical tests revealed no abnormality in the wall of the stomach and duodenum.

In the animals of group 3 with experimental ulcers basal levels of AC activity in the fundus and antrum of the stomach were significantly raised to twice their value observed in the rats of group 1. AC activity in the fundus was significantly higher than in the antrum. Histamine in vitro did not stimulate AC activity in the mucosa of either part of the stomach. On histological investigation of the animals swelling, edema, and

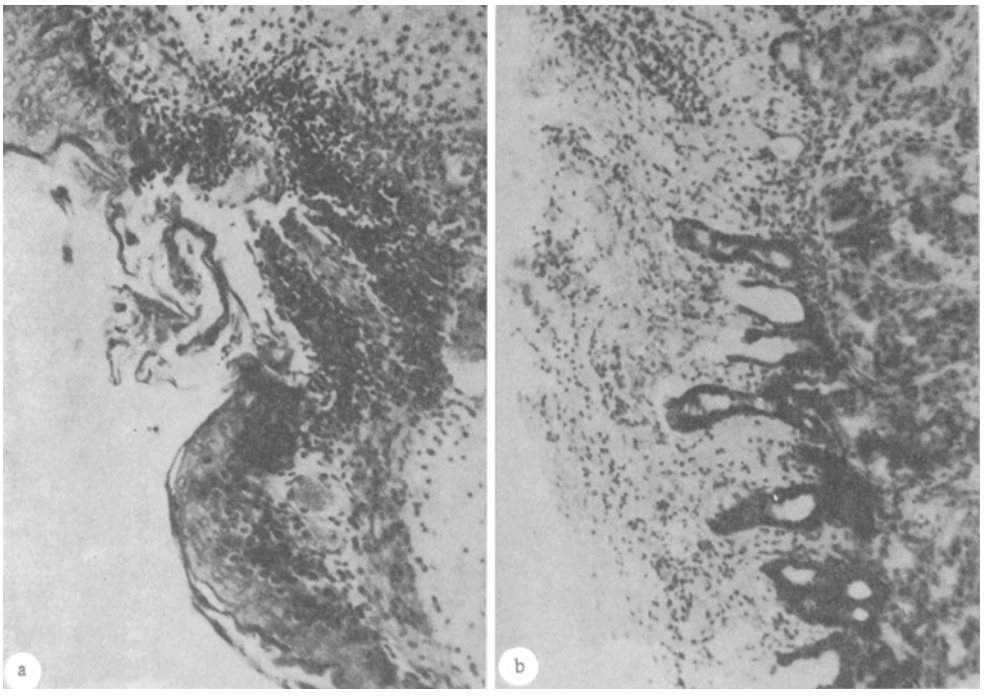

Fig. 1. Morphologic changes in acute ulcer: a) acute esophageal ulcer appearing 36 h after injection of cysteamine into rats: base of would unfiltrated by PNL and lymphoid cells, surrounding mucosa is edematous, congested vessels can be in thickness of tunica propria of mucosa; b) acute duodenal ulcer 48 h after injection of cysteamine: destruction of epithelium of glands, cystic transformation of glands in some places and necrosis in their edges, marked edema and congestion of vessels in floor of ulcer. Hematoxylin and eosin. 160 ×.

congestion of the mucosa and submucosa were found in the esophagus, stomach, and duodenum. Against the background of these changes the formation of deep, small (not exceeding 0.2 cm) ulcers, filled with debris and infiltrated by clusters of polymorphonuclear leukocytes (PNL), was observed. In the base and edges of the ulcer small vessels with fresh thrombi in their lumen could be seen (Fig. 1a). In the pepsin-forming cells of the gastric fundus a high RNP content and high activity of SDH and of NAD- and NADP-diaphorases were noted (Fig. 2a).

After complete truncal vagotomy AC activity in the mucosa of the gastric fundus was indistinguishable from that in animals of the first two groups, but was significantly lower than in the rats of group 3. AC activity in the mucosa of the gastric antrum also was significantly lower than in the rats of group 1 but did not differ significantly from its level in the animals of group 2.

Truncal vagotomy, by creating favorable conditions for healing of the ulcer, thus reduced AC activity in GM and hydrochloric acid secretion. Histamine activated AC in the mucosa of the gastric fundus, but not of the antrum. The response to injection of the hormone (secretin) was the same as in the other groups, i.e., activation by 50% was observed. Histological investigation (10-14 days after truncal vagotomy) revealed a decrease in intensity of the microcirculatory disturbances in the gastric mucosa and submucosa in different parts of the gastrointestinal tract. Epithelization of the ulcer was observed. The RNP content and activity of SDH and of NAD- and NADP-diaphorases were reduced in the pepsin-forming cells of GM (Fig. 2).

Consequently, highest AC activity in GM was discovered in animals with experimental ulcer. Truncal vagotomy reduced AC activity in GM and this effect was most marked in the fundus (the acid-producing zone of the stomach). On activation of AC in vitro the opposite picture was observed, i.e., the lowest level of AC activation was observed in animals with experimental ulcer (group 3). After complete truncal vagotomy, sensitivity of AC in GM to histamine was restored (the receptor "desensitization" phenomenon).

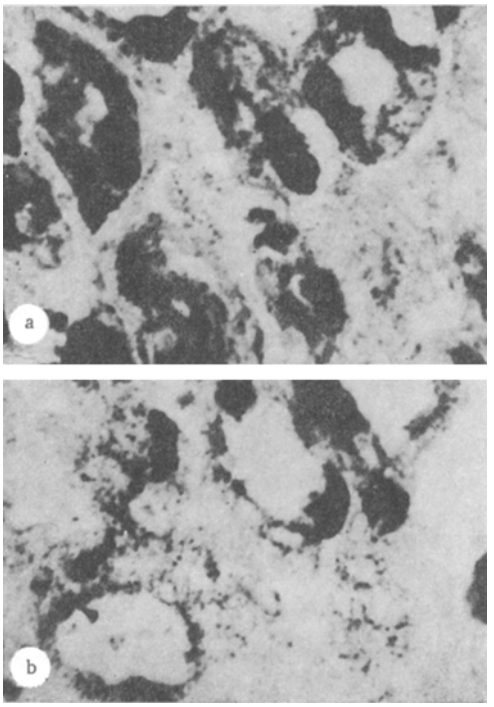

Fig. 2. Indicators of SDH activity: a) high SDH activity in pepsin-forming cells of chief glands of gastric fundus; b) marked decreases in SDH activity in pepsin-forming cells of chief glands of gastric fundus. Nachlas' reaction. 650 ×.

The results of the biochemical and morphological tests show that an important role in the pathogenesis of peptic ulcer is played by changes in the adenylate cyclase – cyclic nucleotides system, confirming yet again data in the literature [1, 2]. Truncal vagotomy in experimental duodenal ulcer was shown to depress activity of AC (an important intracellular factor controlling hydrochloric acid secretion in the stomach) in GM, inhibited hydrochloric acid secretion and, consequently, reduced the metabolic activity of the parietal and chief cells of the stomach and created favorable conditions for healing of the ulcer.

LITERATURE CITED

1. G. I. Dorofeev, L. A. Kozhemyakin, and V. T. Ivashkin, Klin. Med., No. 1, 45 (1975).
2. G. I. Dorofeev and V. M. Uspenskii, Gastroduodenal Diseases in the Young [in Russian], Moscow (1984).
3. V. A. Tkachuk and V. M. Uspenskii, Biokhimiya, No. 2, 333 (1981).
4. I. I. Triiger, in: Proceedings of the 5th Volga Conference of Physiologists, Biochemists, and Pharmacologists, with Participation of Morphologists [in Russian], Yaroslavl' (1969), pp. 290-291.
5. J. Alumets, M. Ekelund, R. Hakanson, et al., J. Physiol. (London), 323, 145 (1982).
6. Y. Ikeda and M. Kitajima, Microvasc. Res., 24, 220 (1982).
7. A. Gairard and Q. Marnay, C. R. Soc. Biol., 166, 35 (1972).
8. O. Kairaluoma, Acta Chir. Scand., Suppl. 418 (1971).
9. Y. Nazaraki, Sapporo Med. J., 48, 195 (1979).
10. A. Robert and J. E. Neramis, Experientia, 30, 781 (1974).
11. H. Selye and S. Szabo, Nature, 244, 458 (1973).
12. A. A. White, Methods Enzymol., 38-C, 41 (1974).