EFFECT OF SEROTONIN AND STRESS ON GASTRIC MUCOSA IN INTACT AND VAGOTOMIZED RATS

T. G. Karevina, V. P. Khokholya, and I. M. Shevchuk

UDC 617.33.018.73-02:616.833.191.089.85+616.33-018.73-02:613.863]-02:615.357:577.175.823

KEY WORDS: vagotomy; serotonin; stess; gastric mucosa; peritol

The writers previously suggested that the protective action of vagotomy against ulcer formation in rats is due mainly to its ability to correct hemodynamic disturbances in the stomach wall, which are accompanied by ischemia of areas of mucosa, making them readily accessible for peptic ulceration [8]. The role of serotoninergic structures in the development of neurogenic dystrophies of the stomach and, in particular, of their hemorrhagic component, has been established [1-3, 10, 15]. Investigations have shown that vagotomy depresses the serotonin level in tissues of the gastrointestinal tract [9, 14, 17]. Preliminary vagotomy on animals with immobilization stress prevents ulceration of the mucosa in rats and disturbance of its blood supply and also prevents elevation of the serotonin concentration in the gastric tissues [15]. Meanwhile there is evidence that vagotomy does not affect serotonin release from the tissue depots of the gastrointestinal tract [4], although electrical stimulation of the vagus nerve is known to be accompanied by a marked increase in the discharge of serotonin from enterochromaffin cells and to elevation of its level in the gastric juice [5, 13].

These contradictory data led us to undertake a comparative study of the ulcerogenic effect of serotonin and stress in vagotomized rats.

EXPERIMENTAL METHOD

Experiments were carried out on 60 noninbred male and female albino rats weighing 150-200 g, 15 of which were subjected to bilateral trunk vagotomy, together with the use of two models of ulcerogenesis: serotonin (intraperitoneal injection of serotonin adipinate, 10 mg/kg), and a "social stress" model, developed in the writers' laboratory [7]. The animals were deprived of food for 24 h before the experiment but were allowed free access to water. After the end of stress and 3 h after injection of serotonin (in the case of serotonin ulcerogenesis) the rats were killed, their stomach removed and divided along the lesser curvature, and after thorough washing, the state of the mucosa was investigated macroscopically with the aid of a magnifying glass and a transillumination gastroscope, designed in the writers' laboratory. The lesions were differentiated in accordance with the principle elaborated previously [7] into erosions and massive and punctate hemorrhages. The lesions were counted and measured in each animal and the number of animals with each type of lesion determined. The numerical data were subjected to statistical analysis on a BZ-21 microcalculator, using specially developed programs [12].

EXPERIMENTAL RESULTS

The experiments showed that bilateral trunk vagotomy reduced the intensity of the hemorrhagic lesions of the gastric mucosa following both intraperitoneal injection of serotonin and stress (Table 1). The protective effect of vagotomy was more marked in the case of stress-induced hemorrhages (the area of the hemorrhages was reduced by 16.5 times in the case of stress and by 9.2 times in the case of serotonin injection). Incidentally, under the influence of exogenous serotonin massive hemorrhages were observed in all the experimental animals,

---

Department of Physiology and Pharmacology of Digestion, Research Institute of Physiology, Kiev University. (Presented by Academician of the Academy of Medical Sciences of the USSR I. P. Ashmarin.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 108, No. 11, pp. 545-547, November, 1989. Original article submitted January 4, 1987.

TABLE 1. State of Gastric Mucosa after Exposure to "Social Stress" and Injection of Serotonin in Intact and Vagotomized Rats (M ± m)

Types of lesions	Serotonin model		Stress model	
	control	vagotomy	control	vagotomy
	$n=30$	$n=6$	$n=6$	$n=9$
Erosions:				
number of lesions in one animal	0,2±0,2	1,8±0,7	3,6±0,6	1,6±0,6
size of lesions in one animal, mm	1,7±0,2	3,9±1,6	7,9±1,5	5,9±2,8
percentage of animals with lesions	53,3	66,7	87,5	55,0
Massive hemorrhages:				
number of lesions in one animal	2,7±0,3	2,2±0,4	2,1±0,4	0,1±0,1
size of lesion in one animal, mm^2	74,4±31,7	8,1±2,3	3,3±1,7	0,2±0,2
percentage of animals with lesions	90,0	100	37,5	11,0
Punctate hemorrhages:				
percentage of animals with lesions	100	83,3	100	77,7

Legend. n) Number of animals.

whereas in the case of stress-induced ulceration, the frequency of massive hemorrhages was reduced by 3.4 times compared with the control.

The protective effect of vagotomy on the stomach was more marked in the case of punctate hemorrhages in the stress model: the number of animals with petechiae was reduced by 22.3% in the "social stress" model and by 16.7% under the influence of exogenous serotonin.

Under the influence of vagotomy, the severity of erosion of the gastric mucosa was reduced only in the case of stress: the length of the erosions, calculated per animal, was 25.3% less and the frequency of their occurrence was 36.5% less in the vagotomized rats than in the control animals with intact vagus nerves. Preservation of a certain level of erosion of the mucosa in the vagotomized rats, exposed to stress, can be taken as evidence of alternative ways of action of stress on the stomach wall, namely the sympathetic nervous system and the hypothalamic-hypophyseal-adrenocortical system.

By contrast with this, vagotomy more than doubled the intensity of the effect of exogenous serotonin on erosion development; the number of animals with erosions in the vagotomized group was 25.1% greater than in animals with intact vagus nerves. Intensification of erosion of the gastric mucosa observed in this case was evidently connected with the fact that vagotomy, by sharply reducing the serotonin level in the stomach tissue [9], increases its sensitivity to this amine. As an activator of proteolytic enzyme formation by the chief cells [6, 11], exogenous serotonin intensifies the proteolytic activity of the gastric mucosa, and as a result the adhesiveness of its epithelium is reduced, which leads to disturbances of the barrier function of the epithelium, and this is the main factor in erosion development.

Evidence in support of the role of serotonin in ulcerogenesis is given by the effect of the serotonin blocker peritol on stress-induced ulcerogenesis in rats with intact and divided vagus nerves, which is consistent in direction but differs in its strength. In both cases peritol completely abolished the formation of hemorrhages, did not affect the

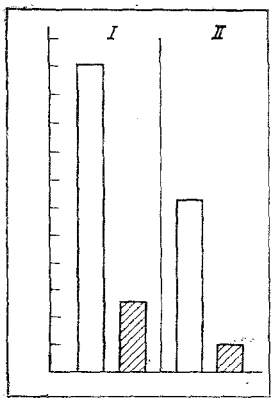

Fig. 1. Effect of peritol on intensity of erosion of gastric mucosa of rats exposed to stress. I) Intact animals; II) vagotomized animals. Unshaded columns – size of erosions (in mm, calculated for one animal) in control experiments, shaded columns – the same after injection of peritol.

appearance of petechiae, and reduced the degree of erosion of the gastric mucosa, the last effect being most marked in the vagotomized animals: intraperitoneal injection of peritol in a dose of 5.0 mg/kg reduced the size of the erosions by 4.3 times in rats with intact vagus nerves and by 6.3 times in vagotomized rats (Fig. 1). This difference in strength of the protective effect of peritol against erosions in intact and vagotomized animals is evidently linked with the fact that in the first case the vagus nerves also are involved in the development of erosions, and peritol, which possesses weak anticholinergic activity, has a weaker action on their response than on serotonin receptors of the gastric mucosa [16], whereas the effect of the vagus nerves on the dystrophic process in vagotomized rats is abolished by division of the nerves, and the observed decrease in the severity of the erosions is the result of blocking of the serotonin component of this response.

The antiulcerogenic action of vagotomy in stress is thus largely determined by its ability to reduce the tissue serotonin level in the gastric mucosa of rats. Potentiation of the ulcerogenic effect of exogenous serotonin in vagotomized animals compared with the intact is evidently due to increased sensitivity of the mucosa to this amine, developing as a result of vagotomy.

LITERATURE CITED

1. I. L. Bilich and N. V. Fedorova, Biogenic Amines in Clinical Medicine [in Russian], Moscow (1970), pp. 57-61.
2. V. K. Bolondinskii and V. A. Pastukhov, Abstracts of Proceedings of the 12th All-Union Conference on the Physiology and Pathology of Corticovisceral Relations [in Russian], Leningrad (1986), p. 43.
3. V. V. Bul'on, Abstracts of Proceedings of the 12th All-Union Conference on the Physiology and Pathology of Corticovisceral Relations [in Russian], Leningrad (1986), p. 244.
4. V. A. Vasil'ev, Manuscript deposited with the All-Union Institute of Scientific and Technical Information, Moscow (1985), No. 1962-85.
5. V. A. Vasil'ev, Manuscript deposited with the All-Union Institute of Scientific and Techical Information, Moscow (1985), No. 1991-85.
6. L. L. Grechishkin, Farmakol. Toksikol., 35, No. 5, 625 (1972).
7. S. D. Groisman and T. G. Karevina, Bibliographic Index, All-Union Institute of Scientific and Technical Information, Depository of Manuscripts [in Russian], No. 12, Section (b/o) 131 (1979).
8. S. D. Groisman and T. G. Karevina, Bibliographic Index, All-Union Institute of Scientific and Technical Information, Depository of Manuscripts [in Russian], No. 2, Section (b/o) 509 (1985).
9. Yu. O. Krivokhats'ka and N. V. Stepanova, Abstracts of Proceedings of the 12th Congress of the Ukrainian Physiological Society [in Russian], L'vov (1986), p. 207.
10. I. N. Pidevich, Pharmacology of Serotoninergic Structures [in Russian], Moscow (1977).
11. I. E. Trubitsyna, "Role of biologically active substances and gastric proteases in ulcer formation," Author's abstract of dissertation for the degree of Candidate of Biological Sciences (1984), p. 26.
12. L. I. Frantsevich, Analysis of the Results of Biological Experiments on the "Élektronika BZ-21" Microcomputer [in Russian], Kiev (1979), pp. 3-89.
13. C. H. Cho, K. M. Kung, and C. W. Ogle, Eur. J. Pharmacol., 110, No. 2, 211 (1985).
14. T. Drapanas, W. C. Woolverton, J. W. Reeder, et al., Ann. Surg., 173, 628 (1971).
15. N. Ito, M. Kodama, Y. Ogawa, et al., Hiroshima J. Med. Sci., 32, No. 3, 329 (1983).

16. E. Mathov, N. Salmun, S. Grinstein, et al., Pren. Med. Argent., 62, 233 (1985).
17. G. G. M. Portala, A. Dahlstrom, L. Grimelius, et al., J. Surg. Res., 38, No. 1, 13 (1985).