EFFECT OF DOPA AND TYROSINE ON HEALING OF ULCERS AND NORADRENALIN CONTENT IN THE STOMACH WALL

O. N. Zabrodin

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The nonradrenalin content in the stomach wall was studied in male albino rats during healing of ulcers in the mucous membrane produced by immobilization and electrical stimulation for 3 h. The stimulation produced a marked decrease in the noradrenalin content in the stomach wall, which persisted for 3 days. The normal noradrenalin content was restored 6 days after stimulation, at the time of healing of the gastric ulcers. Administration of L-tyrosine (300 mg/kg body weight) or L-dopa (150 mg/kg) after stimulation led to earlier restoration of the normal noradrenalin content in the stomach wall and earlier healing of the ulcers.

The role of the sympathetic nervous system in the development of neurogenic disturbances in organs following exposure of animals to intensive and unusual stimuli has been investigated by Anichkov and his co-workers [1-3, 7-9]. In particular, a marked decrease was found in the content of the sympathetic mediator noradrenalin in the stomach tissue during the development of neurogenic dystrophy [2], accompanied by the appearance of ulcers in the gastric mucous membrane. Having regard to the possible role of exhaustion of the catecholamine reserves in the stomach wall in the development of the neurogenic changes, it was decided to study the dynamics of restoration of the normal noradrenalin content in the stomach tissues during the healing of gastric ulcers.

For this purpose, the noradrenalin content in the stomach wall of rats was determined at various times after the onset of morphological manifestations of dystrophy in the organ.

EXPERIMENTAL RESULTS

Experiments were carried out on 262 male albino rats weighing 160-200 g. After preliminary fasting for 24 h the rats were immobilized on a frame, and stimulated with square pulses (5-7 V, 50/sec, 10 msec) through needle electrodes inserted into the muscles of the forelimbs [6]. The rats were sacrificed by decapitation at different times after the end of stimulation: immediately after stimulation, and thereafter daily for 6 days. The stomach of the rats was opened along the lesser curvature, examined visually for lesions of the mucous membrane, and immersed in liquid oxygen. Proteins of the tissue homogenate were precipitated by 5% TCA. The catecholamines were adsorbed on Al_2O_3 by the noncolumn method of Anton and Sayre [18] and eluted with 0.25 N acetic acid. Noradrenalin and adrenalin were determined by the fluorometric method of Euler and Floding [21] in Govyrin's modification [5]. The fluorescence activation spectrum had a maximum at 365 nm, and the fluorescence spectrum a maximum at 535 nm. Adrenalin was differentiated from noradrenalin by taking advantage of differences in their oxidizability, using $K_3Fe(CN)_6$ at pH 6.5 and 3.0. Other details of the method are described previously [10]. To promote biosynthesis of the catecholamines in the stomach tissues, their precursors dopa (150 mg/kg) and tyrosine (300 mg/kg) were injected intravenously, twice a day for 2.5 days after stimulation.

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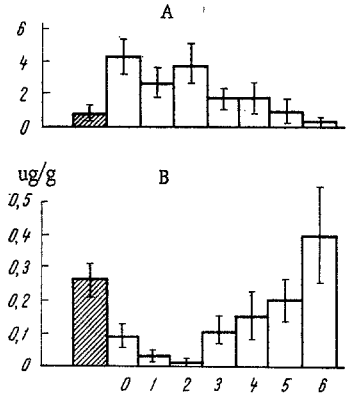

Fig. 1. Number of ulcers of the gastric mucous membrane (A) and noradrenalinc content in the stomach wall (B; in μg/g moist tissue) after electrical stimulation of rats for 3 h. Shaded columns represent intact rats; unshaded columns stimulated rats. Abscissa, time (in days) after end of stimulation and before sacrifice.

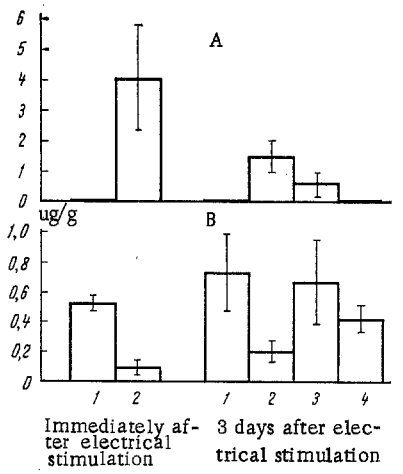

Fig. 2. Effect of dopa on number of ulcers in stomach wall (A) and noradrenalin content (in μg/g) in the stomach wall (B): 1) control; 2) electrical stimulation; 3) electrical stimulation + administration of dopa; 4) administration of dopa.

EXPERIMENTAL RESULTS AND DISCUSSION

Electrical stimulation and immobilization of the rats for 3 h led to the development of hemorrhagic erosions in the gastric mucous membrane. The dynamics of healing of the ulcers in the stomach wall, illustrated in Fig. 1, agrees with previous results obtained by the present writer [7] and by others [19, 20], who produced gastric ulcers by immobolizing rats for 24 h.

Determination of the noradrenalin level in the stomach tissue immediately after the end of stimulation of the rats revealed a sharp decrease compared with the control animals which were not stimulated. This decrease was still found in the rats sacrificed during the next 2 days. A statistically significant recovery of the noradrenalin level took place by the 4th–5th day, coinciding with the time of a statistical decrease in the number of ulcers in the gastric mucosa. Almost complete disappearance of the degenerative changes in the stomach was found by the 6th day, when the noradrenalin content in the stomach tissues had returned to the level observed in the control rats.

The decrease in the noradrenalin level in the stomach tissues can be explained by its increased liberation from the sympathetic nerve endings under the influence of the electrical stimulation, followed by enzymatic breakdown of the mediator. The fact that this decrease continued for a long time (3 days) and the initial level was restored by the 6th day suggests injury to the mechanism of storage or the inadequate synthesis of noradrenalin. The result of the experiments in which tyrosine and dopa were administered confirm the second of these hypotheses.

Tyrosine and dopa led to the earlier recovery of the noradrenalin level in the stomach wall and at the same time facilitated healing of the ulcers in the gastric mucosa of the rats by the 3rd day after stimulation (Figs. 2 and 3); dopa was more effective in this respect. The ability of dopa to restore the normal catecholamine level in the heart, brain, and adrenals, when reduced by stress, was observed by Matlina, et al. [12, 13] in their investigations. The ability of tyrosine to accelerate the healing of gastric ulcers in rats is in agreement with the findings of Takago and Okabe [23].

The therapeutic effect of tyrosine and dopa on the ulcers of the gastric mucosa can be explained on the assumption that these precursors of noradrenalin promoted its synthesis in the stomach wall, in which, according to Häkanson [22], it takes place most intensively in the mucous membrane. Stimulation of the sympathetic nerves is known to increase the rate of metabolism of ATP, required for DNA, RNA, and

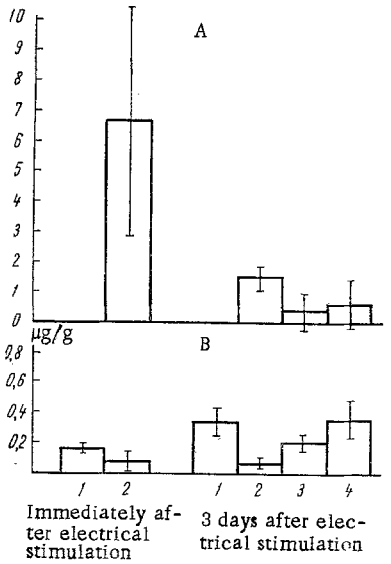

Fig. 3. Effect of tyrosine on number of ulcers in stomach wall (A) and noradrenalin content (in μg/g) in stomach wall (B): 1) control; 2) electrical stimulation; 3) electrical stimulation + administration of tyrosine; 4) administration of tyrosine.

protein synthesis [14], and also to provide for the intensive cell division taking place during regeneration of injured tissues, in the heart tissue [15, 16]. Probably when the reserves of noradrenalin in the stomach wall were exhausted, as observed in the present investigation, these processes take place more slowly. Restoration of the noradrenalin reserves could naturally promote healing of the gastric ulcers by stimulating protein synthesis and cell division.

Various workers [4, 17] have observed evidence of a lowered sympathetic tone in patients with peptic ulcer: hypotension, bradycardia, hypoglycemia, hypocholesteremia, leukopenia, and so on. Recently a decrease in the excretion of catecholamines and their precursors in the urine, and also a decrease in the excretion of adrenalin in the insulin test [11] have been found in patients with intractable and chronic peptic ulcers. This indicates a decrease in the reserve powers of the sympathico-adrenal system.

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