incorporation of their cell nuclei into differentiated muscle fibers may play a definite role in their genesis. This process may participate in the mechanisms of the change in protein synthesis in the myocytes and the acquisition of more primitive functional qualities by the sarcoplasmic membranes of mature muscle cells after denervation.

LITERATURE CITED

1. V. V. Mikhailov and V. Vas Mikhailov, Byull. Éksp. Biol. Med., No. 12, 651 (1979).
2. R. J. Blunt, R. Jones, and G. Vrbova, Pflüg. Arch. Ges. Physiol., 355, 189 (1975).
3. L. W. Duchen and S. J. Stritch, Quart. J. Exp. Physiol., 53, 84 (1968).
4. G. F. Gauthier and S. F. Schaeffer, J. Cell. Sci., 14, 113 (1974).
5. W. Grampp, J. B. Harris, and S. Thesleff, J. Physiol. (London), 221, 743 (1972).
6. A. J. Harris and R. Miledi, J. Physiol. (London), 217, 497 (1971).
7. I. Jirmanova, M. Sobotkova, S. Thesleff, et al., Physiol. Bohemoslov., 13, 467 (1964).
8. H. F. MacConnachie, M. Enesco, and C. P. Leblond, Am. J. Anat., 114, 245 (1964).
9. F. P. Moss and C. P. Leblond, J. Cell Biol., 44, 459 (1970).
10. G. A. Nasledov and S. Thesleff, Acta Physiol. Scand., 90, 370 (1974).
11. S. Thesleff, J. Physiol. (London), 151, 598 (1960).
12. S. Thesleff, Ann. N. Y. Acad. Sci., 228, 89 (1974).
13. V. Verma, Experientia, 35, 40 (1979).
14. W. E. Watson, J. Physiol. (London), 202, 611 (1969).
15. R. Zak, D. Grova, and M. Ravinowitz, Am. J. Physiol., 216, 647 (1969).

EFFECT OF PENTAGASTRIN ON PERIODIC ACTIVITY OF THE STOMACH AND DUODENUM IN DOGS WITH INTACT AND DISTURBED GASTRIC INNERVATION

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KEY WORDS: Pentagastrin; gastroduodenal zone; duodenal mixture.

Pentagastrin (PG) and other synthetic analogs of gastrin stimulate gastric, pancreatic, and intestinal secretion and also the secretion of bile [2, 3, 5, 10]. Information in the literature on the effect of PG on the motor-evacuatory function of the gastrointestinal tract, obtained by using various preparations of PG and over a wide range of doses on different objects, is contradictory. There are no clear data on the effect of PG on periodic contractions of the gastrointestinal tract to serve as the essential physiological background for chronic experiments to study its effects and mechanisms of action.

With the introduction of a Soviet preparation of PG into clinical laboratory practice and with the possible standardization of its activity, including in chronic experiments on dogs, a wider study of the effect of PG on motor and secretory components of the periodic activity of the gastrointestinal tract has become a necessity [3, 4, 7]. The results of such investigations are given below.

EXPERIMENTAL METHOD

Chronic experiments were carried out on 11 mongrel dogs with fistulas of the fundal part of the stomach and duodenum below the point of entry of the greater pancreatic duct into it (in seven of the 11 animals). The experiments began 18-20 h after feeding, when the reaction of the gastric mucosa was alkaline. Periodic motor activity of the stomach and duodenum was recorded graphically by a balloon method with the fistulas open, so that the whole dynamics of the secretory process in the stomach and intestine could be analyzed every 15 min. PG in a dose of 6 μg/kg, which is the dose most commonly used in clinical laboratory investigations, was injected subcutaneously in some experiments during periods of contractions, and in others when the stomach was at rest 18-25 min after the end of periods of contractions. The principal

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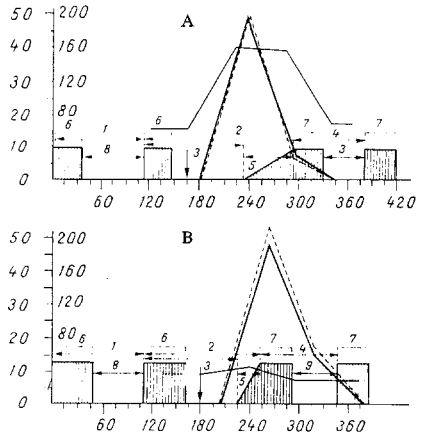

Fig. 1. Effect of PG on secretion, periodic motor activity of the stomach, and periodic secretion of "duodenal mixture of secretions" (DMS) in dogs with intact (A) and disturbed (B) gastric innervation. Abscissa: time of observation from beginning of experiment (each vertical line separates intervals of 15 min). Ordinate: on left, volume of gastric juice (in ml/h, bold line on graph), volume of DMS (in ml/h, thin line); on right, output (in mg/h, broken line). Shaded rectangles correspond to periods of contractions or "intermediate" contractions; each line corresponds to one contraction. Horizontal arrows with numbers indicate parameters of gastric periodic activity: 1) duration of cycles before injection of PG, 2) the same, with injection of PG during rest period (arrows); 3) time before appearance of first weak contractions (beginning of "intermediate" contractions); 4) cycle after injection of PG; 5) duration of "intermediate" contractions; 6, 7) duration of periods of contractions before and after injections of PG; 8, 9) the same, periods of rest, respectively.

parameters of gastric secretion (as a factor influencing periodic processes) were the quantity of secretion and the output of HCl and pepsin (in mg/kg body weight) throughout the period of stimulated secretion. The duodenal periodic secretion was estimated in milliliters for each period of activity and in total, on average per experiment, in ml/h. The rhythm of periodic motor activity was assessed as the duration of the cycles [6] before and after injection of PG, the duration of phases of activity and rest, and "intermediate contractions" (Fig. 1). The results were subjected to statistical analysis [1, 8].

To assess the role of nervous mechanisms in the effects of PG, corresponding parameters were compared in two groups of dogs: in five animals with intact gastric innervation (group 1) and in six dogs on which circular gastrotomy was performed 2-5 months before the beginning of the experiments in the upper third of the fundal region (region 2). During the operation branches of the right and left vagosympathetic trunks, nerves traveling along the vessels in the stomach wall and lesser omentum, and intramural connections were divided, so that the lower portions of the stomach, the proximal part of the duodenum, and the pancreas were denervated.

EXPERIMENTAL RESULTS

Secretory responses of the stomach to PG were higher in dogs whose gastric innervation had been disturbed. For instance, whereas in group 1, in experiments with duodenal fistulas, the output of secretion averaged 3.5 $\pm$ 0.4 ml/kg and acid production was 13.8 $\pm$ 2.9 mg HCl/kg body weight, in the dogs of group 2 the corresponding values were 4.2 $\pm$ 0.4 ml/kg and 18.0 $\pm$ 2.6 mg/kg. In experiments with closed duodenal fistulas the secretory responses to the same doses of PG were higher: 4.9 $\pm$ 0.2 ml/kg and 24.8 $\pm$ 2.3 mg/kg in the dogs of group 1 and 6.4 $\pm$ 1.2 ml/kg and 31.5 $\pm$ 5.0 mg/kg in the dogs of group 2. The differences in the secretory responses were due to differences in the structure of the hourly dynamics of secretion: In the dogs of group 1 the contribution of each hourly portion to the total secretory response (100%) was 83 and 13%, respectively, for the 1st and 2nd hours. Secretory response to the same doses of PG lasted 3 h in the dogs of group 2 and the mean contributions of the corresponding hourly portions were 71, 25, and 4% (Fig. 1).

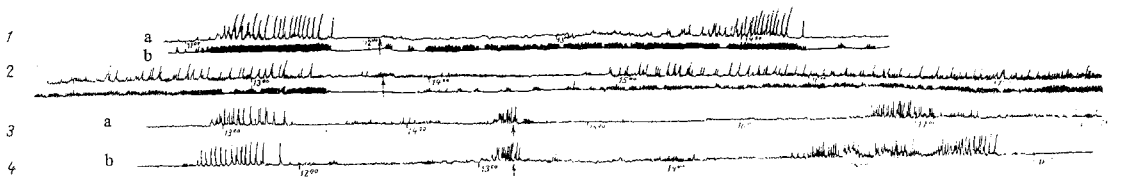

Fig. 2. Kymograms of experiments: effect of PG on periodic contractions of stomach (a) and duodenum (b) in dogs with intact (1) and disturbed (2) gastric innervation; inhibition of periodic contractions by PG when injected during periods of work (3, 4) (injections of PG indicated by arrows).

TABLE 1. Intensity of Liberation of Periodic DMS (in ml/h) before and after Injection of PG in a Dose of 6 μg/kg in Dogs with Intact and Disturbed Gastric Innervation (M ± m)

Group of animals	Normal, ml/kg	After injection of PG			
		1 h	2 h	3 h	4 h
1	15,6±0,7	43,6±5,2	41,1±3,4	17,2±1,7	13,3±2,5
2	9,2±0,5	10,8±1,3	7,0±0,5	7,0±1,2	7,3±1,8

In all dogs regular periodic activity of the stomach and duodenum was observed. The regular periods of duodenal motor activity were combined with periodic liberation of the duodenal mixture of decretions (DMS), including secretion of the pancreas and of Brunner's glands, bile and, possibly, secretion of the pyloric glands of the stomach. The cycles did not differ significantly in duration, but in the dogs of group 2 protracted periods of gastric contractions with reduced amplitude were observed. Injection of PG in a dose of 6 μg/kg during periods of contractions inhibited them for between 1.5 and 2 h in the dogs of group 1 (Fig. 2). The duration of the cycles in the resting phase of which PG was injected increased significantly only in dogs with intact gastric innervation. The appearance of typical periods of work in the dogs of groups 1 and 2 was preceded by "intermediate" contractions of gradually increasing amplitude (of the "acid" movements type). Their appearance on the kymogram, in the form of weak contractions, coincided in time with the beginning of the next "expected" period of gastric contractions. It is important to note that the duration of the "intermediate" contractions was on average only half as long in dogs with disturbed gastric innervation (Fig. 1).

The intensity of the secretory responses to PG in the dogs of group 1 as a rule decreased with an increase in amplitude of the "intermediate" contractions, and with the appearance of a typical period of gastric contractions secretion ceased. In dogs with disturbed innervation of the stomach a high level of secretion also was observed against the background of a typical period of contractions (Fig. 1A, B). Accordingly inertia and an increase in secretion in these dogs in response to PG may have been due not only due hypergastrinemia [9], to changes in cholinergic mediation in the gastric mucosa, but also, perhaps, to the abolition of a certain hibitory mechanism linked reciprocally with periodic gastric motor activity.

Unlike the stomach, contractions of the duodenum appeared immediately after injections of PG until the onset of an acid reaction and they were recorded without interruption until the end of the regular period of gastric contractions (Fig. 2). Duodenal contractions in dogs of group 2 were not stimulated by PG, and they appeared at a time which corresponded to the period of contraction. Circular gastrotomy also led to a decrease in the reactivity of organs taking part in the formation of periodic DMS, both to endogenous physiological stimuli and to exogenous stimulation by PG. The total volume of DMS liberated during each period of secretion and per hour was significantly higher in the dogs of group 1 (Fig. 1 and Table 1). Injection of PG caused the appearance of an unusual production of DMS, much greater than in a usual period, only in dogs with an intact gastric innervation (Fig. 1, Table 1). In dogs with intact gastric innervation PG thus inhibits periodic contractions of the stomach but stimulates duodenal motor activity and liberation of DMS. If the gastric innervation is disturbed these effects are much weaker or they disappear completely, and in this respect they are similar to the action of physiological food excitation on periodic activity of the organs of the gastroduodenal zone. Since the zone of the acid of the gastric juice in the mechanism of the effects of PG in this particular experimental situation was practically completely ruled out, the results are evidence of the important role of the central parasympathetic innervation in the mechanism of action of PG on periodic activity of organs of the gastroduodenal zone. Whether the thresholds of sensitivity of the peripheral organs to PG are altered when gastric innervation is disturbed or whether PG has a central action of its own on the mechanisms of regulation of periodic activity, only further investigations can show.

LITERATURE CITED

1. I. P. Ashmarin, N. N. Vasil'ev, and V. A. Ambrosov, Rapid Methods of Statistical Analysis and Planning of Experiments [in Russian], Leningrad (1975).
2. G. M. Barashkova, Fiziol. Zh. SSSR, 61, No. 5, 763 (1975).
3. L. I. Geller, Z. P. Kozlova, and G. A. Bessonova, Lab. Delo, No. 5, 281 (1978).

4. A. A. Kimenis and Z. A. Atare, Farmakol. Toksikol., No. 3, 333 (1970).
5. P. K. Klimov, Functional Interrelations in the Digestive System [in Russian], Leningrad (1976).
6. N. N. Lebedev, Physiology and Pathology of Periodic Activity of the Digestive Tract [in Russian], Leningrad (1967).
7. Z. S. Rakhimov, Abstract No. 1228-80 Deposited on March 31, 1980, with the All-Union Institute of Scientific and Technical Information.
8. I. V. Polyakov and N. S. Sokolova, Practical Handbook on Medical Statistics [in Russian], Leningrad (1975).
9. H. D. Becker, Clin. Gastroenterol., 9, 755 (1980).
10. H. Schapiro, F. E. Rosato, N. J. Jackson, et al., Am. J. Gastroenterol., 71, 53 (1979).

EFFECT OF "MEDIUM-SIZED MOLECULES" OF UREMIC SERUM IN HEMATOPOIESIS IN INTACT MICE

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An important role in the regulation of erythropoiesis is played by erythropoietin, which is produced mainly in the kidneys. It has been suggested that besides erythropoietin, there is also a humoral regulator with the opposite action – an inhibitor of erythropoiesis. Their interaction probably maintains the erythron system at the physiological level. A disturbance of the excretory functions of the kidneys in chronic renal failure (CRF) is accompanied as a rule by anemia, of uncertain pathogenesis. It has been shown that the main stage in the development of this anemia is a disturbance of erythropoietin production [3, 4]. Meanwhile it has been observed that substances with medium molecular weight (MMW) accumulate in the blood of these patients. It has been suggested that these substances may inhibit erythropoiesis. However, the mechanism of inhibition of erythropoiesis by these substances is not clear, and it may be due both to toxic metabolites and also to a specific inhibitor of erythropoiesis. The writers showed previously that uremic serum inhibits erythropoieses in intact and polycythemic mice, and likewise that it has no inhibitory or cytotoxic action on the pluripotent stem cell [1, 2].

The aim of this investigation was to study the effect of the MMW fraction from patients with CRF on hematopoiesis in intact animals.

EXPERIMENTAL METHOD

Twenty patients (children and adolescents aged from 3 to 17 years) with CRF in the terminal stage of kidney disease (creatinine 11.4 ± 3.2 mg %, urea 91.4 ± 25.7 mg %) were investigated. All the children had anemia: hemoglobin concentration 6.2 ± 2.0 g %, hematocrit index 18.6 ± 2.0 %, both kept at a constant level by transfusions of red cells (on average 0.9 transfusion of 300 ml per month). The patients were being treated by hemodialysis 3 times a week, for 3-4 h each time, on the NGAK-4 capillary dialyzer (1.3 m^2).

The MMW fraction was separated from the serum of the patients with CRF by ultrafiltration on XM-50 disks (from Amicon), and the ultrafiltrate was then fractionated on Sephadex G-25 (from Pharmacia, Sweden). Fractionation was carried out on a 2.6 × 100 cm column (from LKB) in the presence of 0.02 M NaCl solution, pH 7.4, and extinction was measured at 210 nm. The resulting MMW fraction (3000-800) was lyophilized. The MMW fraction was injected into intact mice weighing 25 g over a period of 2 days in a total dose (as protein) of 2.5 mg per mouse (concentration 130 mg %), in accordance with the following scheme: 0.5 ml subcutaneously, interval of 5 h, 0.5 ml intraperitoneally. The absolute number of myelokaryocytes per femur and the morphological composition of the bone marrow were determined in the animals before injection and 1, 2, and 4 days after the last injection of the MMW fraction. Marrow from the femur was suspended in 2 ml of 3% acetic acid solution; the homogeneous bone marrow suspension was introduced into a white cell mixing chamber. The absolute number of myelokaryocytes was counted in a Goryaev's chamber. Bone marrow was obtained from the other mouse femur and films were prepared from it to study its morphological composition; the total myelogram was derived from

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