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Effect of exogenous tetragastrin on gastric myoelectrical activity in humans

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It is known that cutaneous electrogastrography (EGG) undergoes a change after food ingestion, showing increases in frequency and amplitude compared with preprandial values, but the factors regulating such changes remain to be elucidated. Paying special attention to gastrin, one of gastrointestinal peptides released after food ingestion, we administered tetragastrin in an exogenous manner and evaluated its effects on EGG in the present study. In healthy subjects, the intramuscular injection of tetragastrin significantly increased EGG frequency dose-dependently, but caused no significant change in amplitude. These results suggest that the increase in endogenous gastrin release is one of the mechanisms which underlies the increase in EGG frequency after food ingestion.

Key words : Electrogastrography (EGG), Gastric motility, Gastrin

INTRODUCTION

Gastric contraction is regulated by myoelectrical activity generated at the pacesetting area which is considered to exist in the greater curvature of the upper gastric body. This pacesetter potential is generated at a frequency of about 3 cycles per min (cpm), and the recording of myoelectrical activity by percutaneous measurement on the abdominal surface is called cutaneous electrogastrography (EGG), which has been proved to closely correlate with myoelectrical activity directly from the gastric mucosa or serosa [1] and changes in gastric contraction measured by the intraluminal balloon method or force transducer method [2]. EGG is thus expected to be clinically useful as an easy and non-invasive technique to examine gastric motility. It is known that food ingestion causes an increase in EGG frequency or amplitude [3, 4], but the mechanism involved in this reaction remains to be determined. With special emphasis on gastrin, one of gut peptides released after food ingestion, we administered tetragastrin, a gastrin derivative, in an exogenous manner and evaluated its effects on EGG in the present study. The terms concerning gastric myoelectrical activity such as basal electrical rhythm, slow wave, pacesetter potential and electrical control activity (ECA) are used almost synonymously [5]; in the present paper, ECA is used.

SUBJECTS AND METHODS

1. Subjects

The study population consisted of 8 healthy male volunteers, 23 to 30 years of age (mean age 27.4) without symptoms or a history of gastrointestinal and other diseases who consented to participate in this study.

2. Methods

Cutaneous electrogastrography was applied to record gastric myoelectrical activity. Before placement of the electrodes, abdominal skin of the recording sites was cleaned with sandy skin paste (OA-426, Fukuda Denshi) to reduce the impedance. With Ag-AgCl electrodes (NE-155, Nippon Koden) placed at 3 sites on the surface of the upper abdomen along the longitudinal axis of the stomach [6, 7], EGG was conducted with bipolar leads (Fig. 1). Myoelectrical activity was amplified with a bioamplifier (AB-621G, Nippon Koden), passed through a band pass filter (BPF) and

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subjected to A/D transformation to measure frequency and amplitude at intervals of 10 min by fast Fourier transformation. The frequency with the highest power in 10-min EGG recording periods was defined as the ECA dominant frequency. The power at the ECA dominant frequency was defined as the ECA amplitude. The BPF was used the Butterworth type with a low-cut off frequency of 0.025 Hz, a time constant of 6.37 sec, a high cut-off frequency of 0.2 Hz and a frequency response of 24 decibel/octave. This method permitted precise measurements of electrical signals in a range of 1.5 to 12 cpm. (Fig. 2).

After overnight fasting for at least 12 hours, fasting EGG was recorded for 20 min in the supine position early in the morning. Tetragastrin was then admiministered intramuscularly (i.m.) in the upper arm at doses of 1, 2 and 4 μg/kg, and EGG was continuously recorded for 60 min after administration. The single blind randomized multi-dose cross-over method was applied with each

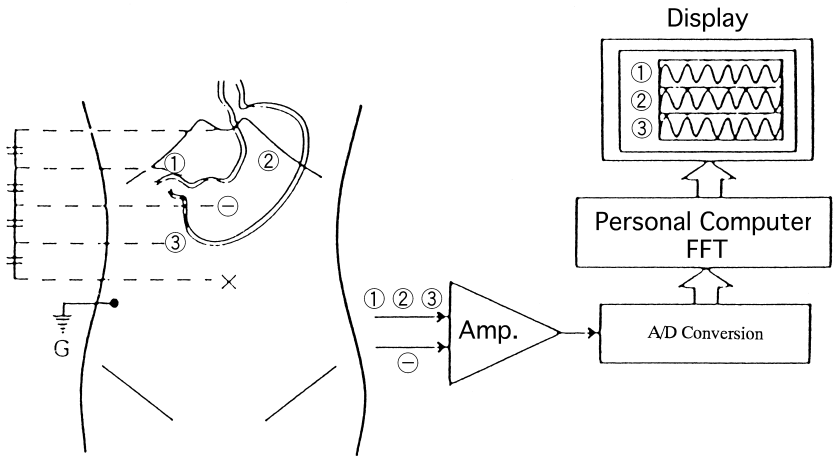
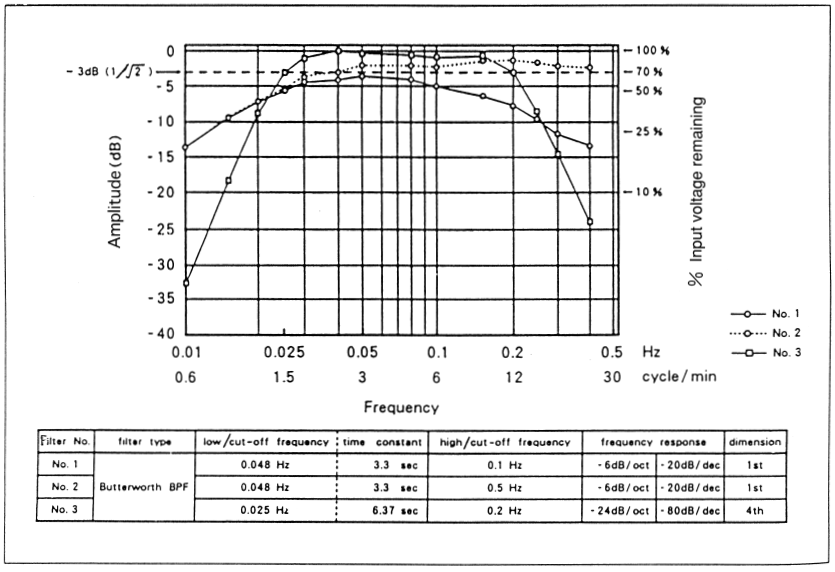


Fig. 1 Placement of the cutaneous electrodes and representation of the recording system for electrogastrography. Electrode ⊖ is the reference electrode.



Filter No.	filter type	low/cut-off frequency	time constant	high/cut-off frequency	frequency response		dimension
No. 1	Butterworth BPF	0.048 Hz	3.3 sec	0.1 Hz	- 6dB/oct	- 20dB/dec	1st
No. 2		0.048 Hz	3.3 sec	0.5 Hz	- 6dB/oct	- 20dB/dec	1st
No. 3		0.025 Hz	6.37 sec	0.2 Hz	- 24dB/oct	- 80dB/dec	4th

Fig. 2 Frequency response curve of each Butterworth type BPF

subject receiving the 3 different doses on different days.

All data were presented as means ± SEM. The Wilcoxon signed-rank test was used for statistical analysis, and $p<0.05$ was considered as significant.

RESULTS

In Subject 1 (Figs. 3 and 4), the ECA dominant frequency was 2.8 cpm before treatment, gradually increased after i.m. administration of tetragastrin at 1 μg/kg, peaked at 20 to 30 min (3.5 cpm), and then returned to the pre-treatment value at 60 min. However, the amplitude underwent no marked change. In Subject 2 (Fig. 5), the ECA dominant frequency was 3.5 cpm before treatment, increased to a peak value of 3.9 cpm at 20 to 30 min after i.m. administration of tetragastrin at 2 μg/kg, and then decreased gradually.

1. Time course of ECA dominant frequency on EGG (Fig. 6)

ECA frequency started to increase significantly over the pre-treatment value at 10 to 20 min after i.m. injection of tetragastrin at each dose, reached a peak at 20 to 30 min, and then gradually decreased; dose-dependency was noted. The pre-treatment frequency and post-treatment peak values were 2.93 ± 0.10 and 3.23 ± 0.11 cpm at 1 μg/kg, 2.98 ± 0.10 and 3.35 ± 0.13 cpm at 2 μg/kg, and 2.94 ± 0.06 and 3.50 ± 0.09 cpm at 4

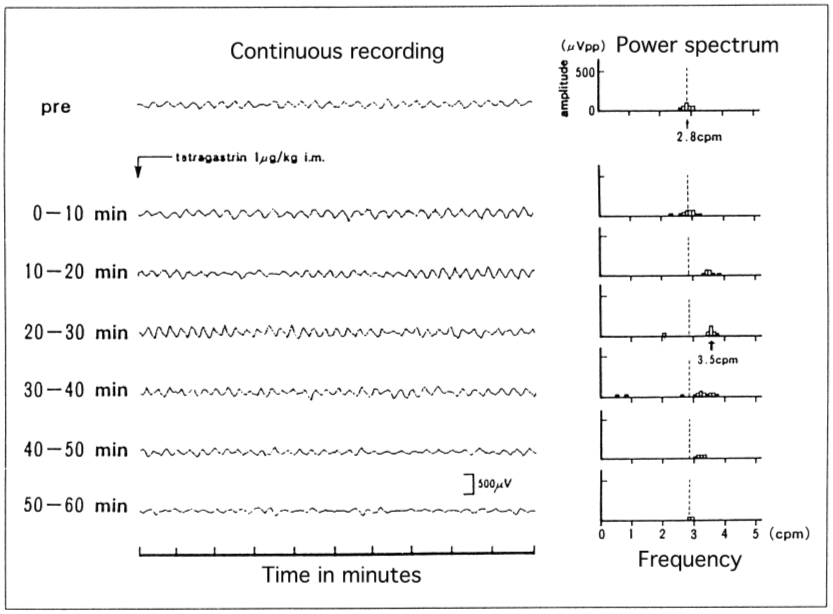


Fig. 3 Effect of i.m. administration of tetragastrin at 1 μg/kg on continuous recording and power spectrum in EGG (subject 1)

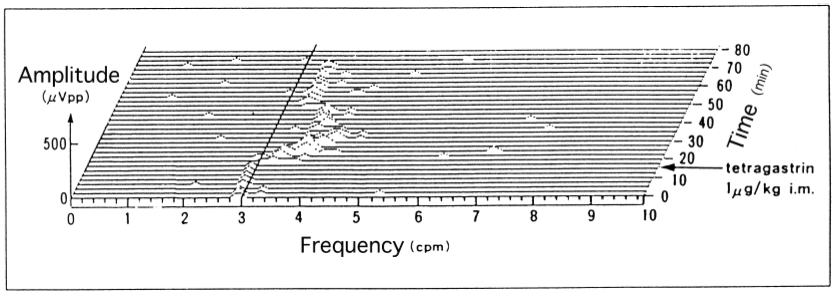


Fig. 4 Pseudo-three-dimensional display in EGG (subject 1)

μg/kg, respectively. At 4 μg/kg, a significant increase over the pre-treatment value persisted even at 60 min after administration.

2. Time course of ECA amplitude on EGG (Fig. 7)

The ECA amplitude underwent little change after administration of tetragastrin at 1 and 2 μg/kg. A slight decrease was noted after administration at 4 μg/kg, but the difference was not significant. ECA amplitudes before and 20 to 30 min after treatment were 129.5 ± 37.4 and 143.3 ± 17.6 μ Vpp at 1 μg/kg, 138.5 ± 47.0 and 135.5 ± 16.5 μ Vpp at 2 μg/kg, and 111.0 ± 21.9 and 92.6 ± 19.2 μ Vpp at 4 μg/kg, respectively.

DISCUSSION

Endogenous gastrin released from the

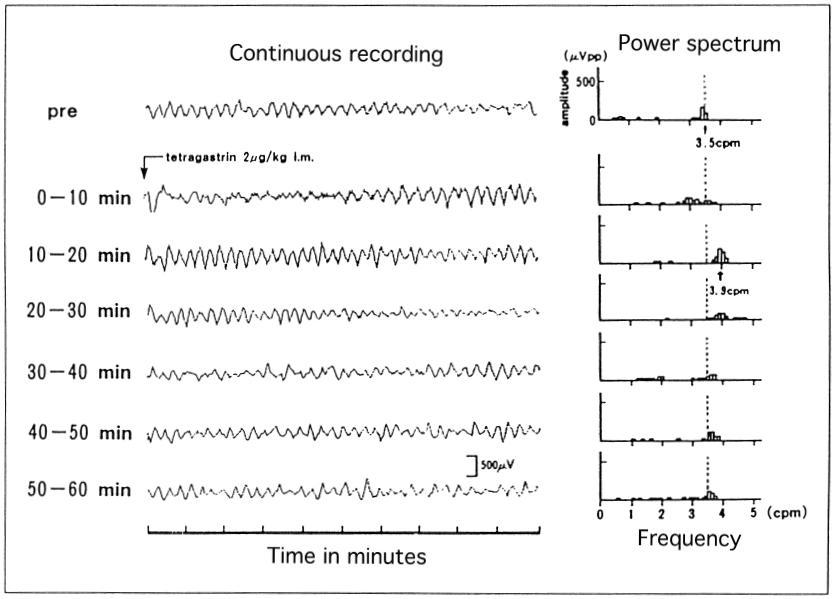


Fig. 5 Effect of i.m. administration of tetragastrin at 2 μg/kg on continuous recording and power spectrum in EGG (subject 2)

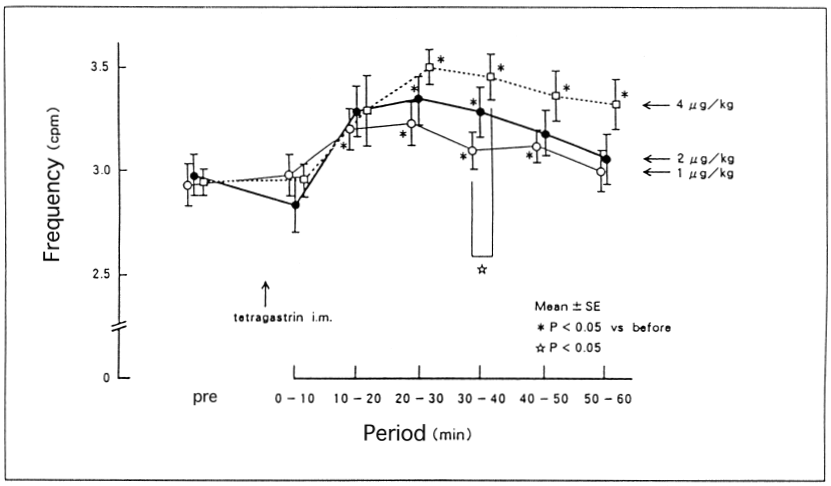


Fig. 6 Time courses of ECA dominant frequency on EGG after i.m. administration at each dose of tetragastrin

gastric antrum not only has a stimulatory effect on gastric acid secretion, but also regulates smooth muscle activity through muscarinic (mainly M_3) receptors by acting hematogenously on the cholinergic nerve endings in the gastric nervous plexus to stimulate acethylcholine release. In addition, among the mechanisms by which gastrin regulates the smooth muscle, gastrin has been reported to act directly on gastrin receptors in the smooth muscle or to be mediated by smooth muscle histamine (H_1) receptors by acting on gastric histamine-secreting cells to stimulate histamine release [8]. Fasting gastric motility is shifted to postprandial motility when stimulated by food ingestion, and endogenous gastrin released under chemical (or partially mechanical) stimulation by gastric content is considered to play a major role in the occurrence of postprandial gastric motility [8, 9]. The administration of exogenous gastrin inhibits characteristic fasting motility, which is shifted to a pattern similar to postprandial motility [10].

EGG is a technique for recording, from the abdominal surface, the spontaneous myoelectrical activity (slow wave) inherent in the stomach which is generated at the pacesetting area existing in the greater curvature of the upper gastric body with a frequency of about 3 cpm and transmitted to the aborad antral side. It has proved to correlate well with gastric contraction.

According to reports on the effects of exogenous gastrin on gastric myoelectrical activity and mechanical force, drip infusion (1, 5 and 10 μg/kg/hr [10], 4 μg/kg/hr [11]) or i.m. injection (4 μg/kg) [10] of tetragastrin and the drip infusion (1 and 4 μg/kg/hr) [12] or subcutaneous injection (2.5 μg/kg/hr) [13] of pentagastrin in dogs produced a dose-dependent increase in ECA frequency, an increase in the frequency of action potential, and increases in the frequency and contractility of pyloric contraction determined by the strain gauge method both in the fasting condition and after feeding. When examined by the balloon method using a pyloric pouch, the drip infusion (3 μg/kg/hr) or intravenous injection (1 μg/kg) of pentagastrin increased contraction frequency but decreased contraction pressure [14]; by the infusion method, the drip infusion of pentagastrin (0.8 μg/kg/hr) was reported to similarly increase contrac-

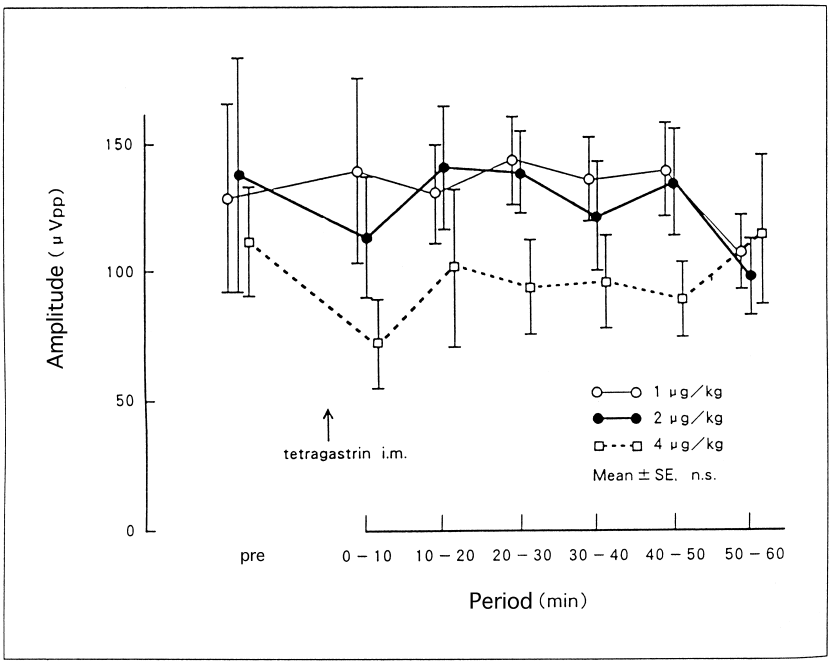


Fig. 7 Time course of ECA amplitude on EGG after i.m. administration at each dose of tetragastrin

tion frequency but cause no change in contraction pressure [15].

On the other hand, the drip infusion of pentagastrin (0.01 to 0.1 μg/kg/hr) in human subjects by the catheter infusion method elevated the motility index at the pylorus, but caused no change in the gastric body [16]. A study of synthetic human gastrin administered by drip infusion at different doses showed that an unchanged frequency and a decreased amplitude were observed in pyloric contraction after administration of the gastrin at the dose producing a similar blood concentration to the postprandial increased blood gastrin level, and both contraction frequency and amplitude tended to increase after administration at higher doses. Since gastric motility varied with the dose, the study suggested that physiological variations in gastrin after food ingestion have little effect in elevating gastric motility [17]. However, in these studies, problems may have been encountered with the open tip catheter infusion method such as the difference in measurement site, the difficulty in recording weak contraction, etc. A study using strips of isolated human smooth muscle revealed that gastrin increased contractility but caused no change in contraction frequency [18]. As described above, many reports have provided results supporting the influence of gastrin on gastric myoelectrical activity and its regulation of gastric contraction, but complete agreement has not been obtained yet.

In the present study, we found that the ECA dominant frequency in EGG increased dose-dependently and significantly after healthy subjects received tetragastrin by i.m. injection, which appears to represent increased contraction frequency. However, the ECA amplitude underwent no significant change. It is known that food ingestion causes an increase in both ECA frequency and amplitude [3, 4]. An increase in the ECA amplitude has been observed in association with both gastric contractions and physical distention of the stomach [19]. The latter reflects the shortening of the distance between the gastric wall and abdominal surface electrode. One of the reasons the ECA amplitude underwent little change in the present study may be that exogenous gastrin does not induce gastric distention even though it causes an increase in gastric contractions. In addition, the absolute values of ECA amplitude are susceptible to several factors unrelated to gastric motility, such as skin conductance, thickness of the abdominal wall and placement of the electrodes, and the relationship of ECA amplitude and gastric tonic contractions remains to be determined. Further studies on this problem are necessary.

We concluded that these results suggest that an increase in endogenous gastrin release is one of the mechanisms which underlies the increase in ECA frequency after food ingestion.

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