Lower oesophageal sphincter response to gastrin—pharmacological or physiological?

J. M. HENDERSON, G. LIDGARD, D. H. OSBORNE, D. C. CARTER, AND R. C. HEADING

From the Departments of Clinical Surgery and Therapeutics, University of Edinburgh Medical School and the Regional Hormone Laboratory, Edinburgh

SUMMARY The response of the lower oesophageal sphincter (LOS) to intragastric instillation of protein was assessed in 10 healthy volunteers. Sphincter pressures were measured by a rapid pull-through technique and serum gastrin concentrations during each test were determined by radio-immunoassay. Despite stimulation of gastrin release by protein instillation, no significant change in LOS pressure was observed. However, intravenous pentagastrin (0.25 and 0.5 $\mu\text{g/kg}$) produced an immediate increase in sphincter pressure, which then returned to the basal level within four minutes. Thus, although pentagastrin is an effective pharmacological stimulant of the sphincter, endogenous gastrin appears not to be a physiological determinant of LOS pressure in man.

The role of endogenous gastrin in control of the lower oesophageal sphincter (LOS) is still a subject of controversy. There is no doubt that exogenous gastrin increases sphincter pressure (Giles *et al.*, 1969; Cohen and Lipshutz, 1971; Trindade *et al.*, 1975; Kaye *et al.*, 1976) but the evidence that endogenous gastrin is a physiological determinant of sphincter pressure is less convincing (Grossman, 1973; Roszkowski *et al.*, 1973; Farrell *et al.*, 1974; McCall *et al.*, 1975; Dodds *et al.*, 1975a, b; Dent and Hansky, 1976). Central to the controversy is the methodology of LOS pressure measurement. Most studies have used static pressure recording catheters or a station pull-through technique in which the recording catheter is withdrawn across the sphincter in 1 cm steps, pausing after each step to record LOS pressure during three or four respiratory cycles. Rapid pull-through techniques are now available which minimise error in pressure recording (Dodds *et al.*, 1975a, b 1976) and a rapid pull-through method was used in the present study to measure the LOS pressure response to endogenous gastrin release provoked by intragastric instillation of protein.

Methods

TECHNIQUE OF LOS PRESSURE MEASUREMENT

LOS pressure was measured by a rapid pull-through technique based on that described by Waldeck

(1972) and modified by Osborne and his colleagues (1977). Recordings were made with a single lumen polyvinyl tube which was perfused at 6 ml/min as it was withdrawn across the LOS at 0.9 cm/s. This system was capable of recording a pressure rise rate of 70 mmHg/s when tested on the bench. By convention, LOS pressure is measured as the peak height of the profile relative to intragastric pressure.

RESPONSE OF LOS TO PENTAGASTRIN

Four healthy male volunteers (aged 26-32 years), without a previous history of dyspepsia, were given graded doses of pentagastrin (Peptavlon, ICI) to determine the LOS pressure response. Doses of 0.0625, 0.125, 0.25, and 0.5 $\mu\text{g/kg}$ were used, the pentagastrin being diluted in 10 ml/150 mm sodium chloride solution and injected intravenously over 60 seconds. The four doses were given in a random order which was not known to the subject. LOS pressure was measured every two minutes for 10 minutes before pentagastrin injection, and every minute for 10 minutes afterwards. LOS pressure had invariably returned to basal values at the end of this 10 minute period, and the whole sequence was then repeated using the next dose of pentagastrin. The LOS pressure recordings were made with the subject holding his breath after normal expiration.

RESPONSE OF LOS TO INTRAGASTRIC PROTEIN INSTILLATION

Seven male and three female healthy volunteers aged

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21 to 35 years were studied. None had a previous history of dyspepsia. LOS pressure was measured at 10 minute intervals with two recordings in inspiration and two in expiration, throughout a 30 minute basal period. A protein solution was then instilled *via* the tube over a 10 minute period, and LOS pressures measured both in inspiration and expiration at 10 minute intervals for the following 60 minutes.

The protein solution consisted of three beef Oxo cubes (18 g protein) dissolved in 200 ml water at 37°C and adjusted to pH 7.0 with 8.4% sodium bicarbonate solution.

Blood samples for serum gastrin estimation were taken 10 minutes before the end of the basal period, immediately before protein instillation, and at 10 minute intervals for 60 minutes thereafter. All were stored for assay in a single batch. Gastrin was measured by radioimmunoassay using Amberlite resin CG-4B to separate bound from free gastrin. The antiserum had an association constant of $4.7 \times 10^{11} \text{ l mol}^{-1}$ for human gastrin I. Cross-reaction with cholecystokinin and pentagastrin was 1×10^4 on a molar basis, and 60% for big gastrin. Porcine gastrin I-I₁₂₅ was used as the tracer, and calibration of human gastrin I was in terms of MRC Standard 68/539, relative potency 1:1. The within-assay coefficient of variation was 7.0% and the between-assay coefficient of variation 8.0%. The assay sensitivity was 10 ng/l.

STATISTICAL ANALYSIS

Statistical analyses were performed using Student's *t* test for paired data and coefficient of correlation.

Results

RESPONSE OF THE LOS TO PENTAGASTRIN

The effect of intravenous pentagastrin on LOS pressure is shown in Fig. 1. The response to each pentagastrin dose has been assessed relative to the three mean basal pressures before its injection. The two lowest doses of 0.0625 and 0.125 $\mu\text{g/kg}$ did not produce a significant rise in sphincter pressure over their basal levels. Following 0.25 $\mu\text{g/kg}$ the mean LOS pressure rose 16 mmHg above basal values ($P < 0.05$). After 0.5 $\mu\text{g/kg}$ pentagastrin, the mean response was 44 mmHg above the preceding basal pressure ($P < 0.01$). The response to the pentagastrin dose was very rapid, occurring within two minutes, and also short-lived, sphincter pressure returning to basal levels within four minutes of the injection.

RESPONSE OF LOS TO INTRAGASTRIC PROTEIN INSTILLATION

Serum gastrin concentrations for the group of 10 subjects were $32 \pm 5 \text{ ng/l}$ (mean $\pm$ SEM) at the end of the basal period, rising to a peak of $78 \pm 18 \text{ ng/l}$ 10 minutes after completion of protein instillation

Fig. 1 Effect of intravenous bolus doses of pentagastrin on LOS pressure in four subjects. Significant rises occur only with 0.5 and 0.25 $\mu\text{g/kg}$.

($P < 0.01$). The concentration then fell steadily to 46 ± 10 ng/l 60 minutes after instillation.

Basal LOS pressure measurements measured during inspiration ranged from 27.1 ± 3.8 mmHg (mean $\pm$ SEM) to 31.4 ± 3.7 mmHg. In the 60 minutes following protein instillation, the mean pressures measured at 10 minute intervals varied between 23.7 ± 3.5 and 30.6 ± 4.0 mmHg. The corresponding mean expiratory pressures ranged from 26.1 ± 2.7 to 27.8 ± 2.2 mmHg in the basal period and from 22.4 ± 3.6 to 25.6 ± 2.6 mmHg after protein instillation. At no time after protein instillation did either mean inspiratory or mean expiratory pressure show any statistically significant change from the basal values.

The relationship between individual changes in LOS pressure and serum gastrin concentration produced by the protein instillation is shown in Fig. 2. For each individual, the difference between basal LOS pressure and the pressure recorded at the time of the peak serum gastrin concentration is plotted against the gastrin response. In all subjects, peak gastrin levels were attained within 30 minutes of protein instillation, and from the results obtained with pentagastrin, any LOS pressure change attributable to a rise in serum gastrin should occur within minutes. However, Fig. 2 shows that in all subjects except one, the sphincter pressure was lower at the time of the peak serum gastrin concentration than during the basal period. The coefficient of correlation between the increase in serum gastrin and the sphincter pressure change is -0.75 but is not statistically significant. When rises in serum gastrin concentration and the LOS pressure changes are calculated as percentage changes from the appropriate basal values, a similar relationship is obtained.

Fig. 2 Relationship between the change in LOS pressure and the rise in serum gastrin following intragastric instillation of protein in 10 subjects. There is no significant correlation.

The coefficient of correlation is again not statistically significant.

Discussion

Castell and Harris (1970) were among the first to suggest that endogenous gastrin controls LOS pressure, but their observations were based on the sphincter response to manipulation of intragastric pH, rather than on concurrent changes in serum gastrin concentrations. Similarly, many of the studies reporting a rise in LOS pressure after protein feeding (Nebel and Castell, 1972; Lipshutz *et al.*, 1973; Roszkowski *et al.*, 1973) have assumed rather than demonstrated an effect on circulating gastrin levels. In studies which have included serum gastrin determinations there has been a varied temporal relationship between administration of the stimulus to gastrin release, the peak gastrin response, and the change in LOS pressure (Higgs *et al.*, 1974; McCall *et al.*, 1975; Dent and Hansky, 1976). Furthermore, while Dent and Hansky (1976) report a rise in LOS pressure 30 minutes after the peak gastrin response to protein instillation, a similar rise was observed after intragastric instillation of a control solution of saline, this time without accompanying variation in the serum gastrin concentrations. They concluded that the response of the LOS to feeding may be unrelated to protein and is not related to serum gastrin levels.

Our results differ from those of Dent and Hansky in that no rise in LOS pressure was observed following protein administration. In nine of our 10 subjects, the pressures actually fell, implying that under our conditions of study, the aggregate effect of neural and hormonal responses to the meal was a reduction in LOS pressure. While this finding does not discount the possibility that endogenous gastrin had a minor influence on the LOS, it does indicate that after the most important physiological stimulus of gastrin release, ingestion of a meal, influences other than gastrin predominated in the regulation of LOS pressure. In this respect, our results are in accord with those of Dent and Hansky (1976).

Three criteria should be fulfilled before the action of any gastrointestinal hormone is considered to be physiological. Firstly, the action should be achieved with concentrations of the hormone which are submaximal for its primary action; secondly, the exogenous hormone given in physiological doses should produce the effect in question; and thirdly, the action should be observed following physiological release of the hormone. While the present results and those reported by others fulfil the first of these criteria (Giles *et al.*, 1969; Cohen and Lipshutz, 1971; Freeland *et al.*, 1975; Trindade *et al.*, 1975;

Kaye *et al.*, 1976), the second is disputed (Freeland *et al.*, 1975; Jensen *et al.*, 1977), and the third, which is the most important, is not fulfilled. In consequence, we believe that presently available evidence supports the opinion of Grossman (1973) that the action of gastrin on the LOS is pharmacological rather than physiological.

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