Effect of vagotomy on secretin release in man

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SUMMARY The release of secretin by intraduodenal acid has been measured by means of a highly sensitive radioimmunoassay in 12 normal subjects, 23 duodenal ulcer patients, and 14 vagotomized patients (6 TV + P; 4 SV + P; 4 HSV). A highly significant response occurred in all three groups. There was no significant difference between the groups either in the magnitude or timing of this response, though the absolute values for pre-stimulation and peak secretin were significantly smaller in preoperative duodenal ulcer patients than in either the normal subjects or the vagotomized patients. The secretin response was similar after truncal, selective, and highly selective vagotomy. These results suggest that secretin release is not dependent on intact vagal innervation of the small intestine in man.

Vagal influences are known to be important in the release of gastrin (Grossman, 1967), but whether the vagus is involved in secretin release has not been established. The secretin response to duodenal acid has recently been measured in man using a radioimmunoassay (Ward and Bloom, 1974) and in the present study this work has been extended to include an assessment of the post vagotomy response.

Methods

SUBJECTS

Twelve normal subjects (10 males; two females), 23 duodenal ulcer patients (21 males; two females), and 14 vagotomized patients (12 males; two females) were investigated. The mean ages in the three groups were 38 years (21-63 years), 42 years (27-67 years), and 45 years (30-66 years). The mean weights were 71 kg (55-83 kg), 68 kg (52-82 kg), and 68 kg (48-79 kg) respectively. In the vagotomized group, tests were undertaken six months or more after truncal vagotomy and pyloroplasty (six), selective vagotomy and pyloroplasty (four), and highly selective vagotomy (four). All the patients were insulin negative at the time of testing according to Hollander's original criteria (Hollander, 1948), as well as the criteria of subsequent authors (Waddell, 1957; Bachrach, 1962; Ross and Kay, 1964; Bank *et al.*, 1967).

Intraduodenal acid may inhibit gastric secretion in addition to provoking secretin release (Johnston and Duthie, 1964) and the present results were

obtained during tests in which both phenomena were studied. Details regarding the changes in acid output are described more fully elsewhere (Ward, 1974).

Gastric secretion was stimulated by a continuous intravenous infusion of pentagastrin (6 $\mu\text{g/kg/hour}$ in normal subjects and preoperative ulcer patients, 9 $\mu\text{g/kg/hour}$ in vagotomized patients) and 10 minute gastric collections were made throughout each test. Once a secretory plateau had been reached, which was usually by an hour, 40 ml 0.1 N hydrochloric acid, at 37°C, were infused into the distal duodenum over a five minute period. Gastric collection was then continued for a further hour. Secretin levels were monitored at intervals throughout each test. Blood was withdrawn from an antecubital vein into heparin-trasylol, then rapidly centrifuged and deep frozen. Samples were taken at 10 minute intervals before acidification then at minute intervals for 10 minutes after the start of the duodenal infusion. Further blood samples were taken at 12, 15, 20, 30, and 40 minutes. Plasma secretin levels were measured by radioimmunoassay using the same technique as in previous reports. (Ward and Bloom, 1974). Changes in individual samples of 2.5 pmol/l were detected with 95% confidence.

METHOD OF ASSESSING RESPONSE

The plasma secretin level before duodenal infusion was represented by the mean of the three values taken at 10 minute intervals during the pentagastrin plateau. This level was termed the pre-stimulation-plasma secretin and was compared with the peak level recorded after acidification in each patient. A paired *t* test was used to assess the significance

of the difference between these two values in each group of subjects, while the response in dissimilar groups was compared by means of an unpaired *t* test. In view of the relatively small population size in each group, a non-parametric test (Wilcoxon's signed rank test) was also performed to confirm the significance of the difference between pre- and post-infusion values independently of the normality of the distribution. Changes in gastric acid output were assessed using methods previously described (Ward, 1974).

CONTROL STUDIES

In four normal subjects, four duodenal ulcer patients, and four patients after truncal vagotomy and pyloroplasty, 40 ml 0.15 M sodium chloride were infused into the distal duodenum over a five minute period during pentagastrin stimulation. There was no effect on plasma secretin in any instance and the response observed after intraduodenal acid may be attributed to a specific effect unassociated with change in intraduodenal volume.

Results

Duodenal acidification produced an increase in plasma secretin in all the normal subjects, duodenal ulcer patients, and vagotomized patients. The mean results in each group are shown in the Table. The peak plasma level was reached at a mean time of six minutes after the start of the acid infusion and thereafter the secretin activity rapidly decayed (Figs. 1, 2). The response in patients after vagotomy

was not significantly different, either in magnitude or in timing, from that observed in the normal subjects and preoperative duodenal ulcer patients. In addition, there was no significant difference between truncal, selective, and highly selective vagotomy in the magnitude of the secretin response. The absolute values for pre-stimulation and peak secretin were significantly smaller in the duodenal ulcer group than in either the normal subjects or the vagotomized patients ($P < 0.001$). The mean incremental response was also smaller in the duodenal ulcer patients than in the other groups, though this difference was not of statistical significance.

Significant inhibition of gastric acid output occurred in the normal subjects ($P < 0.01$) and duodenal ulcer patients ($P < 0.001$) after duodenal acid infusion. However, there was no response in any of the patients after truncal, selective, or highly selective vagotomy despite continuing secretin release (Figs. 1, 2). This disparity between the gastric and secretin responses to duodenal acidification is shown in graphic form in Fig. 3.

Discussion

The present results confirm that distal duodenal acidification may release secretin in man. The mean incremental response was smaller in the duodenal ulcer patients than in the other groups, though this difference did not reach statistical significance. The absolute values for pre-stimulation and peak secretin, however, were significantly smaller in the preoperative ulcer patients than in either the normal

	<i>Pre-stimulation plasma secretin (pmol/l)</i>	<i>Peak plasma secretin (pmol/l)</i>	<i>Increment (pmol/l)</i>	<i>P</i>	<i>Acid output during plateau (mmol/10 min)</i>	<i>Acid output after intra- duodenal acid (mmol/10 min)</i>	<i>Inhibition (mmol/10 min)</i>	<i>P</i>
<i>Normal subjects (12)</i>								
Mean	6.1	18.5	12.4	<0.001	4.77	2.88	1.91	<0.01
SE	0.3	1.2	1.1		0.64	0.55	0.48	
<i>Duodenal ulcer patients (23)</i>								
Mean	4.2	13.7	9.5	<0.001	7.41	5.53	1.89	<0.001
SE	0.3	1.2	1.2		0.52	0.43	0.41	
<i>Truncal vagotomy + pyloroplasty (6)</i>								
Mean	5.1	18.2	13.1	<0.001	2.32	2.44	+0.12	NS
SE	0.3	2.6	2.6		0.42	0.48	0.09	
<i>Selective vagotomy + pyloroplasty (4)</i>								
Mean	7.3	21.7	14.4	<0.001	2.07	2.05	0.02	NS
SE	0.8	1.8	2.2		0.36	0.34	0.04	
<i>Highly selective vagotomy (4)</i>								
Mean	6.3	18.4	12.1	<0.001	4.19	4.03	0.16	NS
SE	0.6	2.0	2.5		0.55	0.52	0.03	

Table 1 *Effect of intraduodenal acid on secretin release and gastric acid output in man*

Fig. 1 Effect of intraduodenal O.IN hydrochloric acid on gastric acid output and secretin release in a patient after truncal vagotomy and pyloroplasty.

Fig. 2 Effect of intraduodenal O.IN hydrochloric acid on gastric acid output and secretin release in a patient after highly selective vagotomy.

Fig. 3 Comparison of the gastric and secretin responses to intraduodenal acid in normal subjects (N), duodenal ulcer patients (DU), and patients after truncal vagotomy and pyloroplasty (TV + P), selective vagotomy and pyloroplasty (SV + P), and highly selective vagotomy (HSV).

subjects or the vagotomized patients. On the basis of this apparent trend, it is possible to speculate that impaired secretin release in duodenal ulcer patients may be secondary to the presence of an ulcer; vagotomy may reverse the pathological changes in the duodenum and restore the secretin response to 'normal'. The numbers in the vagotomy group are small and there is no information on the secretin response in the same patients both before and after surgery so that, for the moment, these claims must remain purely speculative. Other aspects of the relative failure of secretin release in duodenal ulcer patients are discussed more fully elsewhere (Bloom and Ward, 1975).

Secretin release appears to occur independently of extrinsic vagal innervation in man and preservation of the duodenal nerve supply at vagotomy does not confer any benefits in terms of secretin release. These findings do not, of course, exclude a neural mechanism from operating at a more local intestinal level. Indeed, application of local anaesthetics

to the intestinal mucosa may abolish the pancreatic response to acid (Thomas and Swena, 1963; Slayback *et al.*, 1967), while a similar effect may also be produced by intravenous anticholinergic drugs both in animals (Thomas, 1964; Schapiro *et al.*, 1968) and in man (Doubilet and Fishman, 1961). It seems possible, therefore, that a local cholinergic mechanism may be involved in the liberation of secretin in much the same way as gastrin release is thought to be influenced by local neural activity (Grossman, 1967).

In contrast to the present results in man, previous work in the dog has suggested that a vagal element may be involved in the mechanism for secretin release. Thus, Moreland and Johnson (1970) observed a reduction in the pancreatic exocrine response to duodenal acid after vagotomy. There was no associated diminution in pancreatic sensitivity to exogenous secretin and these authors concluded that endogenous secretin release was impaired by vagal section. Wormsley (1962), however, found that, in man, the pancreatic response to

Effect of vagotomy on secretin release in man

intestinal acid increased after vagotomy, whereas the sensitivity to exogenous secretin appeared to diminish after vagal section. He suggested that the former effect was due to a decrease in acid-induced inhibition of pancreatic secretion.

Previous work in this field has suffered from the disadvantage that an accurate method of measuring secretin release was not available, reliance being placed instead on the indirect evidence of a pancreatic bicarbonate response. However, agents such as vasoactive intestinal peptide (VIP), which may also be released by intestinal acid, may produce a pancreatic effect indistinguishable from that observed after exogenous secretin (Bodanszky *et al.*, 1973), while Wormsley (1973) has indicated that secretin release alone cannot account for either the pancreatic or the intestinal response to duodenal acid in animals or in man. In the present study, plasma secretin levels were directly measured before and after duodenal acidification. The results confirm that secretin is released by acid in the distal duodenum in man and that this event appears to take place irrespective of the presence or absence of extrinsic vagal innervation. Whether there is an associated pancreatic exocrine response at this level of stimulation, however, has not yet been established.

The present results are of interest in relation to the suggested mechanism of gastric secretory inhibition by intraduodenal acid. Exogenous secretin may inhibit gastric acid output both in animals (Greenlee *et al.*, 1957; Gillespie and Grossman, 1964) and in man (Brooks and Grossman, 1970; Chey *et al.*, 1970) and strong claims have been made that the gastric inhibitory response to duodenal acidification is mediated by secretin, at least in dogs (Johnson and Grossman, 1968). However, previous work in this laboratory has failed to establish any correlation between secretin release and gastric inhibition in subjects with intact vagi (Ward and Bloom, 1974). Moreover, the gastric inhibitory effects of duodenal acidification are abolished by all grades of vagal section (Ward, 1974), whereas secretin release clearly persists in this situation. The present evidence, taken in conjunction with this previous work, therefore supports the view that gastric secretory inhibition by intraduodenal acid is more closely dependent on a vagal reflex than on secretin release in man.

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