Duodenal mucosal bicarbonate secretion in man. Stimulation by acid and inhibition by the α_2 -adrenoceptor agonist clonidine

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SUMMARY A multi-channel small diameter tube was used to study the secretion of bicarbonate by 3 cm long segments of the proximal duodenum isolated between balloons. The tube had an outer diameter of 5.3 mm and two central and four smaller, peripheral channels. Measurements of infused phenol red, ^{14}C -PEG and vitamin B_{12} and of trypsin activity were performed to rule out contamination of the perfusate by gastric and pancreatic secretions. Basal secretion of bicarbonate by the duodenal mucosa in healthy subjects varied between 135 and 220 $\mu\text{mol}/\text{cm}$ of intestine per hour. Perfusion of the lumen with acid (100 mM HCl for five minutes) increased the secretion to $>400 \mu\text{mol}/\text{cm}/\text{h}$ and the α_2 -adrenoceptor agonist clonidine (150 μg iv) decreased the HCO_3^- secretion by 70 $\mu\text{mol}/\text{cm}/\text{h}$. Clonidine simultaneously reduced the mean arterial blood pressure and plasma noradrenaline concentration, but did not affect the plasma glucose or adrenaline concentration. Duodenal bicarbonate secretion is important in the protection of this mucosa against acid discharged from the stomach. Increased sympathetic activity may, by inhibiting the bicarbonate secretion, decrease the protection in proximal duodenum in man and facilitate ulceration.

Gastric and duodenal mucosa secretes bicarbonate to the lumen by processes that depend on tissue metabolism.¹ The secretion increases the pH in the mucus gel adherent to the epithelial surface and is important in the protection against luminal acid. Acid in the lumen is a potent stimulus of the bicarbonate secretion, but a decrease in the exposure to acid by longterm treatment with potent acid inhibitory drugs does not affect the duodenal secretion in rats.² Electrical stimulation of the vagal nerves in cats and rats increases the secretion in both the stomach and duodenum, while administration of α_2 -adrenoceptor agonists or electrical stimulation of the splenic

nerves has an inhibitory effect^{3,4}. Elicitation of sympathetic reflexes results in similar inhibition of the duodenal secretion.⁵ Evidence for autonomic nervous influence on gastric and duodenal secretion has also been obtained in man: sham feeding has been found to be a stimulant of both gastric^{6,7} and duodenal⁸ mucosal bicarbonate secretion in healthy volunteers.

A method for determination of bicarbonate secretion in the proximal duodenum in man, was recently described by Isenberg and his collaborators using a multilumen tube with two or three balloons to occlude the duodenal lumen.^{9,10} We have modified this technique by using a small diameter tube and report rates of basal and acid stimulated bicarbonate secretion in healthy volunteers. The inhibition of secretion in humans by the α_2 -adrenoceptor agonist clonidine is also described.

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Fig. 1 The first part of the study was performed with a two balloon tube. Later a pear-shaped balloon proximal to and a button shaped balloon just distal to the pylorus anchored the segment. The third balloon was also button-shaped so as not to interfere with the pancreatic biliary outlet.

Methods

TUBE DESIGN AND PLACEMENT

An intestinal tube of polyvinylchloride with an outer diameter of 16 French (5.3 mm), containing six channels and provided with two to three balloons, was constructed. The small diameter made it possible

to introduce the tube through either one nostril or the mouth. There were two wide channels in the centre of the tube for infusion and removal of fluid. Four smaller peripheral channels were used for injection of air into the balloons and for administration of marker substances.

In the first seven experiments a tube with one

larger gastric balloon occluding the pylorus, and a smaller balloon occluding the duodenum, was used. The length of the intervening duodenal segment was 4 cm. Later and in most experiments a tube with a pear shaped balloon in the stomach and two button shaped balloons in the duodenum was used. This ensured isolation of a 3 cm long segment in the proximal part of the duodenum (Fig. 1). The 1 cm shorter length of the test segment in this version of the tube ensured that the pancreatic outlet was not included in the segment. Furthermore, the location of the balloons excluded the possibility of obstruction of the pancreaticobiliary outlet at the papilla of Vater.

A Teflon coated guide wire was used for insertion of the tubes (Amplatz Extra Stiff Wire Guide Ø0.035 inch, William Cook Europe A/S, Bjaereskov, Denmark). This facilitated the passage through the pylorus and rapid advancement of the tube in the distal direction.^{11,12} To further increase the ease of insertion the distal end of the tube was supplied with an 8 cm long weight consisting of short tungsten plates. When the tube had been positioned in the desired segment the guide wire was withdrawn, making the tube less stiff and thus more comfortable for the subject. The tube was inserted under fluoroscopic guidance (Philips BV 21-S) and its position was recorded on video tape or an image store with automatic 200 msec shut-off (Fig. 2). The total fluoroscopic time required for positioning of the tube, when the image store was used, ranged between three and 10 seconds. The stomach was drained by means of a separate Salem-sump tube (12 French).

The subjects were free to choose a comfortable position, sitting or lying in a bed. On completion of the study fluoroscopy was used to confirm that the balloons had remained in position during the experiment.

Twenty three healthy volunteers, students, medical staff and firemen, participated in the study (17 men, six women, mean age 28.5 years, range 21–47). The study was approved by the Ethics Committee of the Medical Faculty, Uppsala University.

PERFUSIONS AND ANALYSES

The gastric balloon was inflated with 30 ml air and the duodenal balloons with 5–15 ml. The temperature of the solutions was 37°C and they were infused into the stomach or duodenum by syringe pumps (Model 355, Sage Instruments, Orion Research Inc, Cambridge, Mass, USA). The effluent was collected from the stomach by suction and from the duodenal segment by gravity drainage. Non-absorbable markers were used to check for any leakage of perfusate from the duodenal segment and to exclude entrance into this

Fig. 2 The three-balloon tube in place with the balloons inflated (arrows).

segment of gastric contents and pancreatic secretion. Phenol red (50 mg/l in 154 mM NaCl) was infused into the stomach by the sump line of the Salem-sump tube at a rate of 1 ml/min and measured in the effluent from the duodenal segment. Polyethylene glycol (¹⁴C PEG 4000, 2.5 µCi/l) was added to the perfusate entering the duodenum (154 mM NaCl) at a rate of 2 ml/min and measured in the fluid drained from the stomach. This enabled measurement of leakage from the test segment into the stomach. Vitamin B₁₂ (40 mg/l in 154 mM NaCl) was infused at a rate of 1 ml/min beyond the distal duodenal balloon in the seven experiments in which a two-balloon tube was used. Its concentration in the effluent from the duodenum was determined, making it possible to quantitate flux from the intestine into the test segment. Vitamin B₁₂ was not infused when the three balloon tube was used, that channel being used for filling the third balloon with air. To further rule out the possibility of contamination of the segment by pancreatic secretion, the trypsin content of the duodenal effluent was always measured. The presence of ¹⁴C-PEG in the test segment and measurement of its concentration in the effluent also permitted calculation of the volume of the secretion by the

test segment by means of standard equations for dilution.¹³

The concentration of bicarbonate in 100 μ l samples from the duodenal effluent was determined in triplicate (Corning 965 Carbon Dioxide Analyzer, Corning Ltd, Halstead, England). Before analysis, samples were gassed with N₂ for five minutes to remove dissolved CO₂. The analyser was calibrated daily against known concentrations of bicarbonate. The use of the Corning Analyzer in the HCO₃⁻ analyses provided very good accuracy (Fig. 3).¹⁴ ¹⁴C-PEG in duplicate samples was determined by liquid scintillation for 15 minutes (LKB Rackbeta II, Wallac Oy, Turku, Finland). Phenol red was measured spectrophotometrically at 520 nm (Hitachi model 101, Hitachi Ltd, Tokyo, Japan) after alkalisation to pH 11 with Na₃PO₄ buffer.¹⁵ Vitamin B₁₂ was measured spectrophotometrically at 361 nm (pH 6.7) after removal of the bile salts by washing in chloroform.¹⁶ Trypsin was measured by a pH-stat method with TAME (n-p-tosyl-L-arginine methyl ester) as substrate.^{17,18}

EXPERIMENTAL PROTOCOL

Studies were carried out on healthy volunteer subjects after an overnight fast. Ranitidine (150 mg, Zantac[®], Glaxo, Greenford, England) was given orally one hour before the experiment to suppress gastric acid secretion. As shown previously this histamine H₂ blocker does not affect either basal or acid stimulated duodenal bicarbonate secretion.² After rinsing of the segment by perfusion with isotonic NaCl for 30 minutes, the effluent was collected at 15 minute intervals for analyses. Basal bicarbonate secretion alone was studied in some experiments. Before examining the effects on the secretion of luminal acid, steady state basal secretion was recorded for four sampling periods. Twenty millilitres of 100 mM HCl was then instilled into the segment and removed after five minutes by gentle flushing with isotonic NaCl. The latter flushing was continued during the following 10 minutes or until the pH was neutral again. Acid in the segment was thus removed and the HCO₃⁻ measurements were not restarted until neutrality had been restored.

The effects of the α_2 -adrenoceptor agonist clonidine were studied after recording of steady state rates of basal secretion for three 15 minute periods. Ten millilitres of isotonic NaCl was then given intravenously as a placebo. After another two 15 minute periods, 150 μ g clonidine (Catapresan[®], Boehringer-Ingelheim, Ingelheim, FRG) was slowly injected intravenously in 10 subjects. The blood pressure was monitored every 15 minutes throughout these experiments. Plasma adrenaline, noradrenaline and glucose concentrations were measured before

Fig. 3 Validation of Corning 965 Carbon Dioxide Analyzer in vitro. Observed results are compared with actual HCO₃⁻ values (n=50). Vertical bars represent range.

and 30 and 60 minutes after the injection of clonidine.

The results are expressed as means (SEM). The two tailed Student's *t* test for paired values was used for testing the statistical significance of differences. A *p* value <0.05 was regarded as significant.

Results

A good correlation between the volume infused and the effluent collected was a mandatory test of the isolation of the segment. The volume infused into the duodenal test segment was 30 ml/15 minute period. The mean volumes recovered in each group of experiments are listed in the Table and the mean recovery of infused ¹⁴C-PEG was 98.1 (2.5)%. A small amount of gastric secretion entered the duodenal segment, as detected by the presence of phenol red (mean amount 1.7 (0.1)% of that in the stomach). Special care was taken to avoid contamination of the

Table Validation of methods

	Effluent volume (ml)	¹⁴ C-PEG %	Phenol red %
Basal HCO ₃ ⁻ secretion (n=7)	28.3 (1.7)	95.5 (5.6)	1.4 (0.2)
Acid stimulation (n=6)	31.2 (1.1)	95.7 (4.2)	1.4 (0.3)
Clonidine (n=10)	28.0 (1.3)	99.8 (3.6)	2.0 (0.2)

The effluent volume is the amount collected from the segment in each 15 minute period after infusion of 30 ml isotonic NaCl solution ¹⁴C-PEG and phenol red are the amounts of these non-absorbable markers collected in the effluent from the segment. ¹⁴C-PEG was infused into the segment and phenol red was infused into the stomach.

Fig. 4 Basal bicarbonate secretion was determined and found to be stable in healthy subjects during a period of 150 min (unfilled circles, $n=7$). Intraluminal acid (100 mM HCl for 5 min, $n=6$) increased the HCO_3^- secretion to >400 $\mu\text{mol}/\text{cm}/\text{h}$ ($p<0.02$). Mean values (SEM) are presented.

segment with pancreatic or biliary secretion, since these contain bicarbonate. Only very small amounts of vitamin B_{12} , which was infused distal to the duodenal segment, were detected in the segment in the first seven experiments in which the two balloon tube was used. B_{12} was not infused in the experiments with the three balloon tube. Similarly, the concentration in the segment of trypsin secreted by the pancreas was very low (0.44 (0.17) U/ml = 37.6 (15.3) nkat/l,¹⁸ confirming the efficiency of the distal balloon in preventing contamination of the segment. Now and then the duodenum showed a tendency to 'telescoping'; that is, the intestine and tested segment shortened causing inclusion of the biliary-pancreatic outlet in the segment. In such cases it was not possible to readjust the segment and the experiment was terminated. With the three balloon tube this was only a minor problem.

BASAL SECRETION AND STIMULATION BY ACID

The segment was continuously perfused with isotonic NaCl solution for 150 minutes in seven subjects (Fig. 4). The basal rate of duodenal bicarbonate secretion was 180.5 (8.2) $\mu\text{mol}/\text{cm}/\text{h}$.

Instillation into the segment of 20 ml 100 mM HCl decreased the pH, which was 2 after five minutes. The acid was then removed. This exposure strongly stimulated the bicarbonate secretion, which

Fig. 5 *Iv* placebo (10 ml 154 mM NaCl) did not alter the duodenal HCO_3^- secretion but clonidine (150 μg) decreased this secretion ($p<0.05$) and also the mean arterial blood pressure ($p<0.001$) and plasma noradrenaline concentration ($p<0.05$). Mean (SEM) are presented ($n=10$).

increased to >400 $\mu\text{mol}/\text{cm}/\text{h}$ ($p<0.02$, Fig. 4). It should be noted that the bicarbonate secretion was not measured until the pH had returned to normal – that is, 10 minutes after termination of the stimulation. The secretion declined to the pre-exposure value during the following 45 minutes.

INHIBITION BY INTRAVENOUS CLONIDINE

Intravenous injection of placebo (NaCl alone) did not affect the basal secretion of bicarbonate. Clonidine (150 μg), on the other hand, decreased the secretion by 55 $\mu\text{mol}/\text{cm}/\text{h}$ in the first 15 minute period after injection and by a further 15 $\mu\text{mol}/\text{cm}/\text{h}$ ($p<0.05$) in the second 15 minute period (Fig. 5). The bicarbonate secretion then remained at a low level throughout the rest of the experiment. The blood pressure had decreased from 120 (8) 92 (6) mmHg after 30 minutes ($p<0.001$). The basal plasma noradrenaline concentration was 3.2 (0.5) nM and this had declined to 1.2 (0.3) nM ($n=3$) 30 minutes after the clonidine injection ($p<0.05$). The plasma adrenaline concentration (basal and after 30 minutes <0.03 nM, $n=3$) was not affected and nor was the blood glucose concentration (basal 4.8 (0.4) mM, after 30 minutes 4.7 (0.5) mM, $n=7$). Clonidine had a mild sedative effect and many subjects fell asleep after the injection.

Discussion

Results from studies in experimental animals indicate that the alkaline secretion by the duodenal mucosa is important in the protection of this epithelium against

acid discharged from the stomach.¹ The secretion of bicarbonate is stimulated by the presence of acid in the lumen¹⁹ and deficits in basal secretion as well as in the response to acid have been observed in patients with chronic ulcer disease.⁹ In line with the latter deficit, it has been reported that when exposed to acid the duodenum in such patients has a significantly lower ability to maintain neutrality in the mucus gel at the mucosal surface.²⁰ One aim of the present study was to modify and evaluate the technique for isolation and perfusion of duodenal segments described by Isenberg and collaborators.⁸ An easily introducible small diameter tube system was developed. The rates of basal secretion by the proximal duodenum found in our experiments (mean 180.5 and range 135–220 μmol base per cm of intestine and hour, $n=70$) are almost identical to those reported by Isenberg.

The previous observation⁸ that a low pH in the lumen stimulates alkaline secretion by the duodenal mucosa in humans was confirmed in the present study, though the magnitude of the stimulation seems somewhat smaller. It should be noted in this context that no analyses of acidified perfusates were performed in the present experiments and that only the concentrations of HCO_3^- *per se* (in contrast with HCO_3^- plus dissolved CO_2 ,²¹) were measured. CO_2 is formed from HCO_3^- during reaction with acid and the duodenal (but not the gastric) mucosa has a high permeability to CO_2 .^{21, 22} Rapid diffusion of CO_2 from the lumen into the tissue apparently decreases the rate of bicarbonate secretion as judged by measurements of perfusate PCO_2 , and the results might be influenced by variations in the permeability to CO_2 rather than in mucosal bicarbonate secretion.

Special care was taken in the present study to remove acid instilled into the segment and measurement of bicarbonate in the effluent after exposure to acid was not restarted until neutrality had been attained. Our choice of method avoids the possibility that diffusion of CO_2 from the tissue into the lumen will increase the secretion as measured at a neutral luminal pH. Its disadvantage is that the bicarbonate secretion during or immediately after acid exposure cannot be measured. The results provide clear evidence that, as in other species, luminal acid is a stimulant of the duodenal bicarbonate secretion in man. The magnitude of the response to acid might be greater than could be recorded here.

Leakage of pancreaticobiliary secretions containing bicarbonate into the studied duodenal segment is a possible source of error but this must have been negligibly small, as only small amounts of vitamin B_{12} , which was infused distal to the segment, or of trypsin, which is secreted by the pancreas, were detected in the effluent. Distension of the small

intestinal wall increases its secretion of fluids and electrolytes and also its motility. These effects are mediated by the enteric nervous system, which has been observed to influence bicarbonate secretion by the gastroduodenal mucosa in a similar way.^{23–25} The possibility that the distended balloons might have stimulated the duodenal secretion could not be avoided in the present study. This disadvantage was small, however, compared with the contamination of the effluent in an open system by gastric contents or pancreatic juice. It has been observed in dogs and man^{26, 27} that the basic duodenal bicarbonate secretion varies in phase with the motor (myoelectric) activity, with an increase in secretion during phase III of the migratory motor complex. Manometry was not performed in the present study, but no periods with increased basal secretion were observed (Fig. 3).

The sympathetic influence on duodenal mucosal bicarbonate secretion has previously been studied in anaesthetised animals. Intravenous administration of α_2 -adrenoceptor agonists, electrical stimulation of the splanchnic nerves or elicitation of sympathetic reflexes potentially inhibited the secretion in the cat and rat.^{1, 4, 5, 28, 29} Infusion of the α_2 -agonist clonidine (15 $\mu\text{g}/\text{kg}/\text{h}$) in the rat (unpublished data), or splanchnic nerve stimulation in this species³⁰ also decreased the ability of the duodenal mucosa to respond to luminal acid (pH 2 for 10 min) with a rise in bicarbonate secretion. The α_1 -agonist phenylephrine in contrast has been found to be a weak stimulant.³⁰ Inhibition of bicarbonate secretion has also been observed in some gastrointestinal tissues *in vitro*, including mucosae isolated from the frog gastric fundus³¹ and the rabbit ileum.³² This suggests that adrenoceptor agonists and antagonists affect the secretion by effects on the enterocytes or possibly on local nervous tissue. Anaesthetic agents or isolation procedures may, however, profoundly modulate the response to neurohumoral stimuli. Such effects of anaesthesia have recently been reported with respect to alkaline secretion by the rabbit duodenum.³³

It was thus of considerable interest to examine the influence of an adrenergic agent on the duodenal mucosal bicarbonate secretion in unanaesthetised human subjects. It was shown in the present study that clonidine, an α_2 -receptor agonist, inhibits the secretion in man. The drug (150 μg) decreased the plasma noradrenaline concentration but did not affect the blood glucose. This finding strongly suggests that as in animals, the duodenal mucosal alkaline secretion and protection in man are under α_2 -adrenergic inhibition. This is interesting in view of the observations that in duodenal ulcer patients the plasma concentrations of catecholamines and the urinary output of their metabolites are increased.^{34, 35} Furthermore, it has been reported that splanchnico-

tomy ameliorates stress induced ulceration in animals,³⁶ and studies of the longterm sympathetic influence on mucosal protection could provide valuable information.

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