

Action of secretin on pancreatic enzyme secretion in man. Studies on pure pancreatic juice

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SUMMARY The action of pure, natural secretin on the pancreatic secretion of enzymes was investigated in six patients with external transduodenal drainage of the main pancreatic duct performed after biliary tract surgery. Secretin infused for five successive 50 minute periods at increasing doses of 0.03, 0.1, 0.3, 0.9 and 2.7 clinical units (CU)/kg/h, produced a dose dependent increase in protein and lipase output. A weak but significant ($p < 0.02$) increase of enzyme output above the fasting level was already observed with the lowest dose. The maximal output of protein and lipase, observed with the highest dose of secretin infused, corresponded to about 50% of that induced by maximal doses of cerulein (100 ng/kg/h) plus secretin (1 CU/kg/h). As far as bicarbonate is concerned, the lowest dose of secretin (0.03 CU/kg/h) significantly ($p < 0.001$) stimulated bicarbonate output. The dose of 0.9 CU/kg/h of secretin evoked a bicarbonate output of $526 \pm 49 \mu\text{mol}/\text{min}$; trebling the dose of secretin did not significantly increase the output of bicarbonate above this value. Increasing doses of secretin induced a dose related increase in calcium output. There was a close parallel between calcium and protein outputs, suggesting that the increase in calcium output reflected primarily an increase in the enzyme-associated fraction of pancreatic juice calcium. It is concluded that secretin stimulates pancreatic enzyme secretion in man probably by a direct action on the acinar cells.

The stimulation of water and bicarbonate secretion has been long considered the only action of secretin on pancreatic secretion. In recent years, however, several *in vivo* and *in vitro* studies have reported that secretin can also stimulate pancreatic enzyme secretion in some animal species.¹⁻⁵ The influence of secretin on pancreatic enzyme secretion in man is not well defined. Most of the old studies dealing with this problem led to negative conclusions.⁶⁻⁸ The rise in enzyme output observed by some investigators after secretin administration,^{9, 10} was generally considered a consequence of a 'washout' of previously secreted enzymes by secretin stimulated flow of fluid through the duct system.^{6, 10} The possibility that secretin might stimulate human pancreatic enzyme secretion was raised by Wormsley in 1968.¹¹ In a study carried out by means of duodenal intubation, this investigator found that the pancreatic output of trypsin increased with increasing doses of secretin at low levels of

stimulation, whereas supramaximal doses of secretin inhibited trypsin secretion. In this study, however, the majority of subjects received Boots secretin, which was contaminated with cholecystokinin,¹² and only four subjects received the pure secretin preparation of Jorpes and Mutt. Moreover, these findings were not confirmed in a more recent study by Domschke *et al*¹³ who evaluated the effects of increasing doses of secretin on pure pancreatic juice collected by endoscopic cannulation of the papilla of Vater and failed to detect any significant effect of the hormone on pancreatic enzyme secretion. The present study was designed in an attempt to obtain more precise information on the action of secretin on pancreatic enzyme secretion in man. In order to avoid possible interferences of bile or other gastrointestinal secretions, the study was carried out directly on pure pancreatic juice.

Methods

PATIENTS

Six patients with no clinical history or biochemical signs of pancreatic disease gave informed consent to

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participate in this study. They were five men and one woman, aged 41–68 years, mean 50 years. Their weights ranged from 50 to 75 kg, with a mean of 63 kg. The method for collecting pure pancreatic juice has been described previously.^{14 15} The patients had transduodenal drainage of the main pancreatic duct performed after papillotomy and sphincteroplasty for common bile duct stones. The appearance of the pancreas at operation was normal in all patients. The drainage was not carried out specifically for the purpose of this study, but as a part of the therapeutic programme to prevent the formation of duodenal fistulae and postoperative acute pancreatitis.¹⁶ Polyethylene tubes provided with several additional holes in the intraductal portion were inserted into Wirsung's canal to a depth of about 3–4 cm and were tied to the duodenal wall by a stitch of catgut. Their diameter was accurately selected in each patient according to the calibre of the main pancreatic duct. After insertion of the tube, an intravenous injection of secretin, 0.5 CU/kg/h, was given to confirm the efficacy of the drainage and to exclude leakage of pancreatic juice around the cannula. Studies were performed in the morning after an overnight fast, and were started at least six days after the operation. It has been shown that pancreatic secretion is depressed during the first two to three days after the operation and returns to normal thereafter.^{14 16} In order to avoid the entry of acid into the duodenum, gastric juice was continuously aspirated by a nasogastric tube positioned before the study. Pancreatic juice was collected in ice chilled graduated tubes at 10 minute intervals. Initially, pancreatic juice was collected for five 10 minute periods to estimate the fasting secretion. Then, pure natural secretin (GIH Research Unit, Karolinska Institutet, Stockholm, Sweden) was infused into an arm vein for five successive 50 minute periods at the following increasing rates: 0.03, 0.1, 0.3, 0.9, and 2.7 clinical units (CU)/kg/h (equivalent to 2.8, 9.3, 28, 84, and 252 pmol/kg/h, respectively). Each dose of secretin was dissolved in 100 ml isotonic saline containing 0.3% human serum albumin. To assess pancreatic enzyme response to maximal stimulation, a second study was carried out on a separate day in five of the six subjects. In this study, an intravenous infusion of cerulein, at a maximal dose¹⁷ of 100 ng/kg/h, plus secretin, 1 CU/kg/h, was given for 60 minutes.

Each 10 minute sample of pancreatic juice was analysed for volume, bicarbonate, total protein, lipase, and calcium. Bicarbonate was determined by the method of Van Slyke and Neil,¹⁸ total protein by the absorbance at 280 nm,¹⁹ lipase by the method described by Sarles *et al.*,²⁰ and calcium by atomic absorption spectrophotometry. There was no

evidence of bile contamination in any of the samples.

The first three 10 minute periods of each 50 minute period of secretin infusion served for equilibration of the pancreatic secretion to increasing doses of secretin. The pancreatic responses were thus calculated from data obtained during the last two 10 minute periods of each dose rate of secretin, when secretory outputs were stable.

The results are presented as mean values \pm SEM. Statistical analysis was performed using Student's *t* test for paired values.

Results

Pancreatic secretory data recorded during the five successive 50 minute periods of secretin infusions are summarised in the Table. Generally, there was a steady increase in pancreatic outputs during secretin infusions. A plateau was usually reached within 20–30 minutes from the start of the infusion of each dose of hormone.

Figure 1 shows pancreatic juice volume, bicarbonate concentration, and bicarbonate output during the last two 10 minute periods of each dose rate of secretin. The hormone produced a dose dependent increase in volume and bicarbonate output. A significant rise in pancreatic juice flow and bicarbonate output above the fasting level was already elicited with the lowest dose used (0.03 CU/kg/h). The maximal volume flow (4.32 ± 0.46 ml/min) and bicarbonate output (569 ± 59 μ mol/min) was observed during infusion of the highest dose of secretin used (2.7 CU/kg/h). The bicarbonate output observed with this dose of secretin, however, was not significantly higher than that attained with 0.9 CU/kg/h (526 ± 49 μ mol/min).

The concentration of bicarbonate rose with increasing dose rates of secretin up to 0.3 CU/kg/h. At higher hormone doses the concentration declined while the volume continued to increase.

Figure 2 shows the concentrations of protein, lipase, and calcium during the last two 10 minute periods of each dose rate of secretin. These parameters showed a parallel behaviour. In all subjects, the concentrations of protein, lipase, and calcium were greater in the fasting than in post-secretin collections. They were high in the first 10–20 minutes after starting secretin stimulation, likely reflecting a 'washout' phenomenon, and then fell rapidly to a plateau level when secretin stimulation was continued (Table). In each subject, concentration levels declined slightly during infusions of secretin from the dose of 0.03 to the dose of 0.3 CU/kg/h, and then remained almost constant from the dose of 0.3 to that of 2.7 CU/kg/h.

Table Volume of pancreatic juice, and concentrations and outputs of bicarbonate, protein, lipase, and calcium, in response to intravenous infusion of graded doses of secretin. * Means ± SE.

	Volume		Bicarbonate		Protein		Lipase		Calcium	
	ml/10 min	mmol/10 min	mg/ml	mg/10 min	U/ml	U/10 min	mmol/l	μmol/10 min		
Basal	2.0±0.1	95.0±6.9	8.47±0.9	16.7±1.3	1995±704	3712±1058	0.343±0.03	0.68±0.05		
	2.5±0.5	101.3±5.9	8.95±1.2	20.7±3.1	2282±853	4639±990	0.360±0.04	0.93±0.24		
0.03 CU/kg/h	6.9±1.2	109.7±6.5	7.86±1.3	52.0±11.1	2272±972	12 811±3146	0.336±0.04	2.36±0.56		
	8.8±1.2	123.9±5.9	5.11±0.9	41.0±3.6	1513±552	10 825±2353	0.263±0.02	2.27±0.25		
	8.7±0.9	128.6±6.3	3.32±0.6	26.9±3.3	1275±431	10 492±3600	0.212±0.02	1.89±0.31		
	9.9±0.8	129.4±5.7	3.36±0.6	32.6±4.7	979±259	9369±2109	0.211±0.02	2.11±0.27		
	10.8±1.1	128.2±4.6	3.08±0.3	33.4±4.8	888±200	9409±1882	0.198±0.02	2.22±0.37		
0.1 CU/kg/h	11.7±0.6	132.6±4.9	2.54±0.3	39.6±3.4	816±147	9621±1866	0.195±0.02	2.32±0.29		
	16.8±1.6	131.9±6.1	2.48±0.6	38.0±4.9	849±223	12 782±2091	0.172±0.01	2.89±0.37		
	16.2±2.2	137.7±4.9	2.30±0.5	38.5±4.5	828±206	13 577±2201	0.175±0.02	3.08±0.32		
	19.4±1.2	139.8±3.6	2.20±0.4	40.9±5.0	764±173	14 160±2504	0.178±0.02	3.43±0.42		
	19.3±1.5	140.0±4.4	2.25±0.5	40.2±3.8	782±203	13 667±2098	0.180±0.02	3.41±0.41		
0.3 CU/kg/h	19.8±1.9	138.1±4.2	2.01±0.4	38.5±5.2	753±180	14 216±2537	0.182±0.02	3.68±0.58		
	23.7±2.6	142.5±2.4	1.59±0.2	42.3±3.4	627±111	15 006±3147	0.148±0.02	3.64±0.82		
	26.0±2.9	145.7±2.3	1.60±0.2	38.8±2.0	593±90	15 377±3056	0.152±0.02	4.10±0.97		
	28.3±2.4	145.3±2.4	1.55±0.2	36.0±2.8	563±81	16 019±2637	0.149±0.02	4.33±0.92		
	30.9±2.0	145.4±2.3	1.58±0.2	48.2±4.9	580±80	18 344±3095	0.145±0.02	4.57±0.81		
0.9 CU/kg/h	31.5±3.0	142.2±3.4	1.54±0.1	46.8±3.1	563±70	18 203±3338	0.141±0.02	4.60±0.98		
	34.1±4.2	142.6±1.4	1.47±0.2	47.3±1.6	544±64	18 948±3823	0.135±0.02	4.85±1.27		
	34.7±4.6	142.6±1.8	1.46±0.2	47.6±1.8	549±70	19 305±3956	0.141±0.02	5.17±1.51		
	37.1±4.0	142.8±2.2	1.50±0.2	53.1±3.0	544±68	20 352±3473	0.148±0.02	5.72±1.35		
	37.0±3.5	142.2±2.2	1.47±0.2	52.2±2.3	541±63	20 198±3220	0.144±0.02	5.58±1.29		
2.7 CU/kg/h	38.3±3.9	139.3±2.4	1.64±0.2	59.8±6.0	583±85	22 542±4064	0.161±0.02	6.29±1.14		
	40.9±6.0	137.6±2.2	1.47±0.2	56.7±4.9	520±72	21 533±4249	0.147±0.02	6.35±1.58		
	41.8±4.7	136.0±2.8	1.43±0.2	57.4±4.1	522±65	22 084±3789	0.153±0.02	6.75±1.62		
	43.5±4.5	134.1±3.7	1.41±0.1	59.0±2.9	521±62	22 826±3733	0.153±0.02	7.00±1.67		
	42.2±4.6	131.9±3.1	1.38±0.1	55.6±1.7	520±61	21 977±3564	0.143±0.01	6.10±0.97		

* Each dose of secretin was administered for 50 minutes. Pancreatic juice was collected at 10 minute intervals. The basal values indicate the values of the last two periods of the five 10 minute periods before secretin administration.

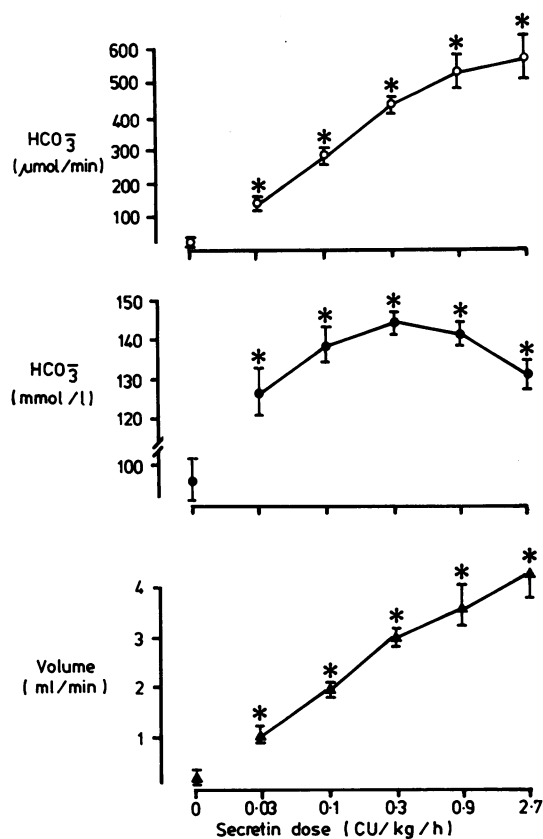


Fig. 1 Pancreatic volume flow, bicarbonate concentration, and bicarbonate output in response to intravenous infusion of graded doses of secretin. Values quoted for volume and bicarbonate output indicate response during last 20 minutes of 50 minute infusion of each dose rate of secretin. Bicarbonate concentrations indicate mean concentrations during this period. Mean \pm SE. * $p < 0.001$ when compared with fasting level.

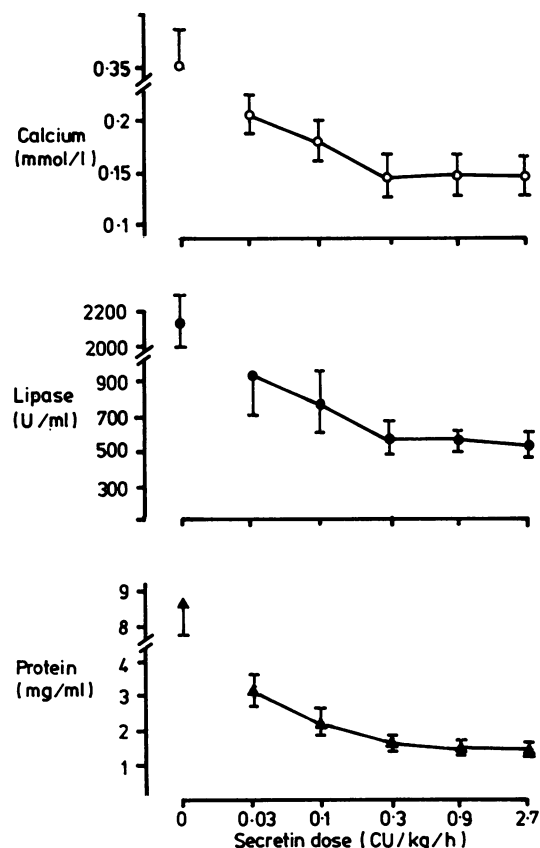


Fig. 2 Protein, lipase, and calcium concentrations during infusion of graded doses of secretin. Values denote mean concentration during last two 10 minute periods of each 50 minute infusion of secretin. Mean \pm SE.

In analogy to concentrations, outputs of protein, lipase, and calcium (Fig. 3) also behaved in a parallel fashion. The infusion of the lowest dose of secretin (0.03 CU/kg/h) produced a weak but significant increase in enzyme ($p < 0.02$) and calcium ($p < 0.005$) output above the fasting level. Increasing doses of secretin induced a dose related increase of these outputs. The mean maximal output of protein, lipase, and calcium, observed during the highest dose of secretin used (2.7 CU/kg/h), were 49%, 46%, and 54% of the protein, lipase, and calcium output, respectively, in response to a maximal dose of cerulein (100 ng/kg/h) combined with secretin (1 CU/kg/h).

Discussion

The present study shows that secretin is able to stimulate pancreatic enzyme secretion in man. Graded doses of secretin induced graded increase in protein and lipase output, a significant effect being already evident at 0.03 CU/kg/h. The increase was rather pronounced, the protein and lipase output in response to the highest dose of secretin was about 50% of that attained with a maximal dose of cerulein, and well sustained as it persisted for the whole period of the study (four hours and 10 minutes). Because of the concomitant increase in the pancreatic juice volume during secretin infusion,

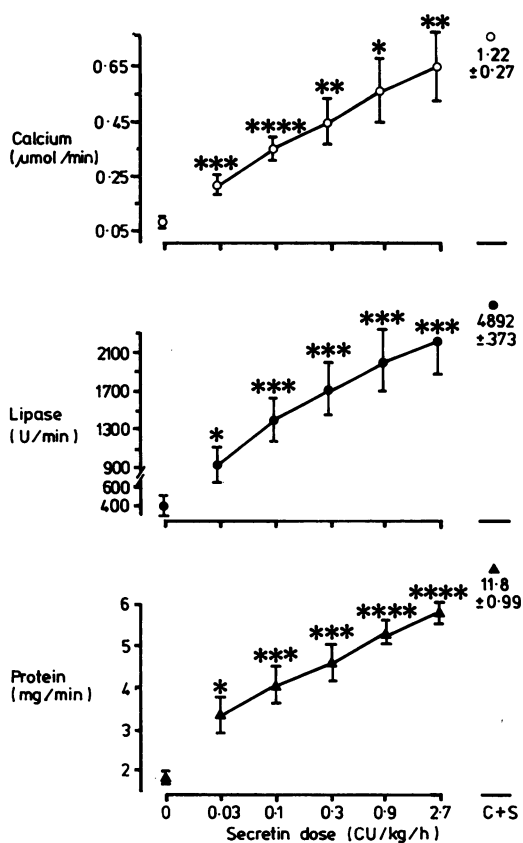


Fig. 3 Protein, lipase, and calcium outputs in response to intravenous infusion of graded doses of secretin. Values indicate response during last 20 minutes of 50 minute infusion of each dose rate of secretin. Mean \pm SE. * $p < 0.02$, ** $p < 0.01$, *** $p < 0.005$, **** $p < 0.001$. C+S = pancreatic outputs in response to cerulein, 100 ng/kg/h, plus secretin, 1 CU/kg/h.

the concentration of both protein and lipase declined slightly or remained constant. It is unlikely that the increase in protein and lipase output seen in the present study was because of contamination with pancreozymin, as the secretin preparation used did not contain any trace of pancreozymin.²¹ Moreover, several comparative studies of the effects of natural and synthetic secretins on pancreatic secretion failed to show significant differences between the two preparations.^{1 22-24} It is also highly unlikely that the increase in enzyme output was because of an indirect 'washout' phenomenon. In fact, each dose of secretin was infused at a constant rate for 50 minutes and the enzyme output measured during the last 20 minutes, when a steady state was attained after the early washout. Moreover, the stepwise

increase of the infused secretin concentration brought about corresponding increases in enzyme output (during infusion of the last three doses of secretin, from 0.03 to 2.7 CU/kg/h, protein and lipase concentrations remained practically unchanged while the volume of pancreatic juice continued to rise). We interpret these data as an indication that secretin can act directly on the acinar cells to stimulate enzyme secretion. This possibility is supported also by several experimental findings, including the demonstration of the existence of specific receptors for secretin in the acinar cells,²⁵ and the observation that secretin can potentiate cholecystokinin-stimulated enzyme secretion *in vitro* as well as *in vivo*.^{3 12 26 27}

The results of this study confirm the observations of Wormsley,¹¹ but are at variance with the results of Domschke *et al*,²³ who in their study on pure pancreatic juice failed to detect an increase in protein output in response to graded doses of secretin (ranging from 0.03 to 4 CU/kg/h). The latter investigators, however, infused each dose of secretin during a short period (20 minutes each dose), which may not have been enough to detect the increase in protein output induced by secretin. We have observed, like others,^{11 17 28} that the volume of pancreatic juice and the protein output show a gradual increase and reach the highest levels 20-30 minutes after the beginning of the infusion of each dose of secretin. Moreover, the possibility that premedication needed for endoscopic cannulation of the papilla may have influenced the pancreatic enzyme response to secretin cannot be excluded.

The mechanism through which secretin can increase pancreatic enzyme secretion has received considerable attention. Experimental evidence suggests that in pancreatic acinar cells enzyme secretion can be stimulated by two parallel mechanisms, the first activated by pancreozymin, bombesin, cholinergic agonists and their analogs, the second by secretin and VIP.²⁹ This second mechanism involves binding of secretin to the acinar cell receptor, activation of adenylate cyclase, increased cellular cyclic AMP, activation of cyclic AMP-dependent protein kinase, and, after a series of undefined steps, stimulation of enzyme secretion.³⁰ It is possible that a similar mechanism is involved in the secretin-induced stimulation of pancreatic enzyme secretion in man, but conclusive evidence for this mechanism in the human acinar cell is lacking.

The effects of secretin on the juice volume and bicarbonate concentration and output are in agreement with previous data in the literature.³¹⁻³⁶ In particular, they confirm that a secretin dose as low as 0.03 CU/kg/h significantly stimulates volume

and bicarbonate output,^{31 32} and that maximal bicarbonate response occurs at a secretin dose of about 1 CU/kg/h.^{33 34} Only in the study of Domschke *et al*¹³ a lower dose (which produced effects much smaller than the maximal observed in the present study) was reported to be maximal. Again, differences in the study protocol (in particular, the short periods of stimulation used by Domschke *et al*) may possibly account for this discrepancy.

The effect of secretin infusion on calcium secretion into pure human pancreatic juice had never been investigated up to now. With increasing doses of the hormone a close parallelism between calcium and protein was found, similar to that observed after cholecystokinin stimulation.³⁷ It is known that calcium is secreted into the pancreatic juice in two fractions, one associated with enzymes, and the other with the electrolyte component.^{38 39} Because of the parallel behaviour of calcium and protein secretion, it is likely that the increase in calcium output during infusions of secretin reflected primarily an increase of the enzyme associated fraction of pancreatic juice calcium.

In conclusion, the results of the present study indicate that, as in several animal species, secretin is able to increase pancreatic enzyme secretion in man. This effect is probably the result of a direct action exerted by the hormone on the acinar cells of the gland.

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