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Effect of Somatostatin Analogs on Gastric and Pancreatic Secretion (39842)[1]

STANISLAW J. KONTUREK,* JANINA TASLER,* RYSZARD KROL,* ARTUR DEMBINSKI,* DAVID H. COY,† AND ANDREW V. SCHALLY†,[2]

* *Institute of Physiology, Medical Academy, Krakow, Poland, and* † *Veterans Administration Hospital and Tulane University School of Medicine, New Orleans, Louisiana 70146*

Somatostatin, the growth hormone release-inhibiting hormone (GH-RIH) has been shown to suppress exocrine and endocrine gastric (1, 2) and pancreatic secretions (3) induced by various stimuli. Since somatostatin-like immunoreactivity was detected in gastric mucosa and pancreatic tissue (4) and was localized in special paracrine–endocrine cells in close vicinity of gastric and pancreatic glandular cells (5), a possible role for GH-RIH as a local inhibitor of gastric and pancreatic secretions has been suggested.

Recently, several analogs of the cyclic GH-RIH tetradecapeptide were prepared in which certain amino acids residues were replaced by their D isomers in an attempt to increase biological activity (6, 7). The preliminary reports indicate that some of these analogs show dissociated actions on the release of growth hormone, insulin, and glucagon (8). No study, however, has been undertaken to determine whether these analogs possess selective effects in relation to gastric and pancreatic exocrine secretion.

The present study was designed to compare the relative effectiveness of GH-RIH and its synthetic analogs on gastric and pancreatic responses to exogenous stimuli in chronic gastric and pancreatic fistula dogs.

Materials and methods. Four mongrel dogs, weighing 20–22 kg, were prepared with gastric fistula (GF), Heidenhain pouches (HP), and pancreatic fistula (PF) constructed according to the modified method of Herrera *et al.* (9). The studies reported here started about 6 months after surgery. Food was withheld from the cages for at least 18 hr before each test.

Secretions from GF, HP, and PF were collected continuously and were divided into 15-min samples. Acid and pepsin output in gastric juice and bicarbonate and protein output in pancreatic juice were determined in each sample by the methods described previously (2, 3). Throughout each test an infusion of 0.15 *M* NaCl was given by a peristaltic pump through a polyethylene tube (PE 50) inserted into a leg vein.

Basal secretion was collected for two 15-min periods, and then the secretory stimulant for gastric secretion (pentagastrin) or pancreatic secretion (secretin) was infused intravenously for 225 min in increasing doses, either alone (control tests) or in combination with a constant dose of GH-RIH or one of its analogs. Stimulants and doses used were 0.25, 0.5, 1.0, 2.0, and 4.0 μg/kg-hr of pentagastrin (I.C.I., England) and 0.25, 0.5, 1.0, 2.0, and 4.0 U/kg-hr of pure synthetic secretin (Squibb Institute, New Brunswick, N.J.). In control experiments, all doses of pentagastrin or secretin were infused alone in one day's test, and the dose level was changed every 45 min (45 min × 5 doses = 225 min). In tests measuring the interaction of GH-RIH or one of its analogs with secretory stimulants, pentagastrin or secretin was infused using also an incremental 45-min step-dose method (as in control tests), but GH-RIH or its analog was added to the intravenous infusion in a constant dose given throughout the entire period of stimulant administration.

GH-RIH was infused intravenously in a constant dose (2.5 μg/kg-hr) which has been shown previously (2, 3) to produce about 50% inhibition (ID_{50}) of near maximal gastric acid response to pentagastrin or near maximal pancreatic bicarbonate response to secretin in these animals. Two

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[2] To whom all correspondence should be addressed at: Endocrine and Polypeptide Laboratory, Veterans Administration Hospital, 1601 Perdido Street, New Orleans, Louisiana 70146.

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GH-RIH analogs, D-Trp^{8}-somatostatin and D-Cys^{14}-somatostatin, were used in doses identical to that of GH-RIH (2.5 μg/kg-hr). GH-RIH as well as somatostatin analogs were synthesized by solid-phase methods in the cyclic form, as previously described by Coy *et al.* (7, 8) and were used in the pure form.

The infused doses and the combined outputs of the last 30 min of each 45-min dose step were used for the calculation of the kinetic constants of the dose response: V_{max} (calculated maximal output) and K_m (the dose of stimulant giving 50% of the V_{max} response) (10, 11).

The responses to gastric and pancreatic stimulants with and without GH-RIH or its analogs were compared using the *t* test for paired values. Differences were regarded as significant if $P < 0.05$.

Results. Pentagastrin alone, given in graded doses up to 4.0 μg/kg-hr, produced a dose-dependent increase in acid output from both the GF and the HP. Mean V_{max} (±SE) for the GF was 6.85 ± 0.92 mequiv of acid/30 min, and mean K_m (±SE) was 0.85 ± 0.13 μg of pentagastrin/kg-hr (Fig. 1 and Table I).

During GH-RIH infusion, the dose-response curve for acid secretion from the GF was shifted to the right. There was an almost threefold increase in K_m, while V_{max} was only slightly decreased (Table I). Both D-Trp^{8}-somatostatin and D-Cys^{14}-somatostatin also shifted the acid dose-response curve to the right with a small reduction in V_{max} and with a doubling of K_m. The difference in K_m was significant, while the difference in V_{max} was not.

The acid responses of the HP to pentagastrin were also dose-dependent. GH-RIH and D-Trp^{8}-somatostatin did not change these responses significantly at any dose level of pentagastrin, whereas D-Cys^{14}-somatostatin caused a significant inhibition at all dose levels of pentagastrin, except the lowest two (0.25 and 0.5 μg/kg-hr).

Pepsin output in tests with pentagastrin showed a dose-dependent increase from the GF while that from the HP was elevated above basal throughout pentagastrin infusion, but was not related to its dose. GH-RIH and its analogs resulted in a marked reduction of pepsin outputs from both GF and the HP (Fig. 2).

Secretin alone infused intravenously in graded doses produced a dose-dependent increase in pancreatic bicarbonate secretion with a mean V_{max} of 8.52 ± 1.32 mequiv of bicarbonate/30 min and a mean K_m of 1.75 ± 0.34 U of secretin/kg-hr. With GH-RIH infusion there was an increase in K_m from 1.75 to 3.05 μg of secretin/kg-hr, whereas V_{max} remained virtually unchanged (Fig. 3 and Table I). Both GH-RIH analogs shifted the bicarbonate dose-response curve to the right. This was accompanied by an increase in K_m and only a small decrease in V_{max}.

Pancreatic protein secretion was increased above basal throughout secretin infusion, but not related to the dose of secretin. GH-RIH and its analogs strongly suppressed the protein outputs at all doses of secretin (Fig. 4).

Discussion. This study provides evidence that GH-RIH causes a potent and competitive inhibition of gastric acid and pancreatic bicarbonate secretion and that the GH-RIH analogs, D-Trp^{8}-somatostatin and D-Cys^{14}-somatostatin, produce effects similar to

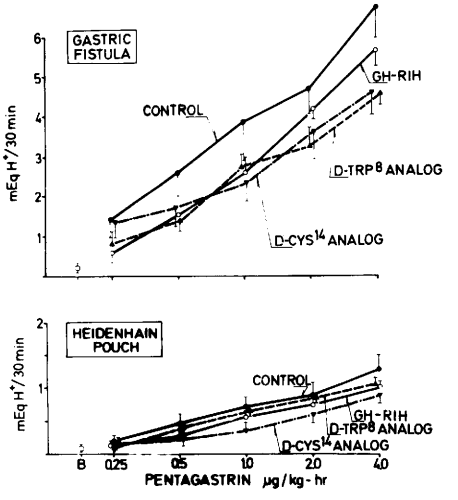

FIG. 1. Effect of GH-RIH and its two analogs, D-Trp^{8}-somatostatin and D-Cys^{14}-somatostatin given in a constant dose (2.5 μg/kg-hr) on acid secretion from the GF and HP in response to graded doses of pentagastrin. In this and subsequent figures, each point represents mean of the combined outputs of the last 30 min of each 45-min dose step and the standard error of the mean (SEM) in two experiments on each of four animals.

TABLE I. CALCULATED CONSTANTS FOR ACID OUTPUTS (FROM THE GF) IN RESPONSE TO GRADED DOSES OF PENTAGASTRIN ALONE AND IN COMBINATION WITH GH-RIH OR ITS ANALOGS AND FOR BICARBONATE OUTPUTS (FROM THE PF) IN RESPONSE TO GRADED DOSES OF SECRETIN ALONE AND IN COMBINATION WITH GH-RIH OR ITS ANALOGS

Type of stimulant	V_{max}, (mequiv/30 min)	K_m (μg/kg-hr)
Pentagastrin alone	6.85 ± 0.92	0.85 ± 0.13
Pentagastrin + GH-RIH	6.43 ± 0.73	2.41 ± 0.51*
Pentagastrin + D-Trp^8-somatostatin	5.79 ± 0.83	1.97 ± 0.61*
Pentagastrin + D-Cys^{14}-somatostatin	5.47 ± 1.05	2.01 ± 0.40*
Secretin alone	8.52 ± 1.32	1.75 ± 0.34
Secretin + GH-RIH	8.75 ± 0.64	3.05 ± 0.52*
Secretin + D-Trp^8-somatostatin	7.42 ± 0.85	3.14 ± 0.42*
Secretin + D-Cys^{14}-somatostatin	8.10 ± 1.25	3.25 ± 0.63*

* $P < 0.05$.

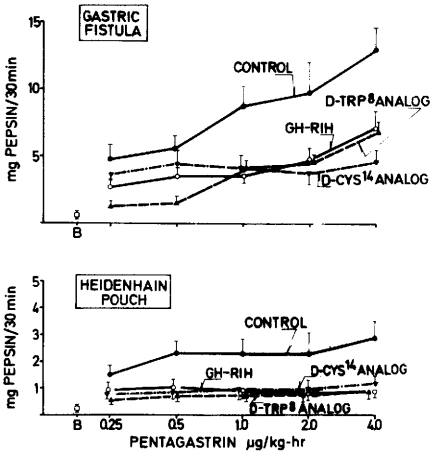

FIG. 2. Pepsin outputs in tests as in Fig. 1.

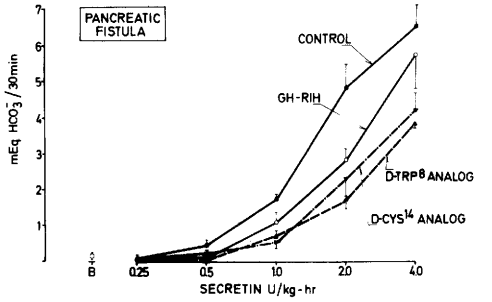

FIG. 3. Effect of GH-RIH and its two analogs, D-Trp^8-somatostatin and D-Cys^{14}-somatostatin given in a constant dose (2.5 μg/kg-hr) on pancreatic bicarbonate secretion from the PF in response to graded doses of secretin.

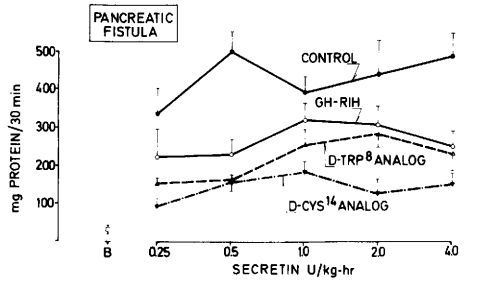

FIG. 4. Protein outputs in tests as in Fig. 1.

those obtained with GH-RIH.

The finding that GH-RIH is capable of inhibiting gastric acid response to pentagastrin, urecholine, protein meal, and, to a lesser degree, histamine has been reported previously (2). It was suggested that the major action of GH-RIH on gastric secretion, by direct inhibition of oxyntic glands through the suppression of gastrin release, could also contribute to this action (2, 3). This study confirms previous observations regarding the direct inhibitory action of GH-RIH on gastric acid secretion and shows that two GH-RIH analogs are also potent inhibitors of acid and pepsin secretion.

Our recent studies in cats (12) showed that GH-RIH effectively prevents the formation of duodenal ulcers produced by prolonged administration of pentagastrin or histamine. Ideally, GH-RIH or its analogs designed for the treatment of peptic ulcers should inhibit gastric acid and pepsin secretion and not inhibit the secretion of pancreatic bicarbonate. Unfortunately, GH-RIH is a very potent competitive inhibitor of pancreatic bicarbonate secretion (3), and the GH-RIH analogs are equally effective in this regard. It appears that D-Trp^8-somato-

statin, which displays about five times the activity of GH-RIH on the inhibition of release of growth hormone (6), is only as equally effective as GH-RIH in blocking gastric and pancreatic secretions. D-Cys^{14}-somatostatin has been reported by Meyers *et al.* (8) to inhibit pancreatic glucagon release to a far greater extent than insulin release. However, it did not exhibit any clear dissociation in the inhibition of exocrine gastric and pancreatic secretions. This suggests that the inhibitory action of GH-RIH and its analogs on the oxyntic and pancreatic excretory cells could involve blockage of the cellular mechanisms common to these different cells, such as the adenyl cyclase-cyclic AMP system.

The finding of the present study that the GH-RIH and its analogs do not affect significantly the V_{max} of gastric acid and pancreatic bicarbonate dose-response, but do increase two- to threefold the K_m, indicates that their action on the gastric acid- and pancreatic bicarbonate-producing cells is competitive. Although simple competition between GH-RIH or its analogs and gastric or pancreatic stimulants for a common receptor site might be involved in the interaction of these compounds, their action at a single site may also be determined by factors other than competitive kinetics. The inhibitory effect of GH-RIH or its analogs on gastric acid and pancreatic bicarbonate secretion could be attributed to some other as yet unknown actions of these compounds, including the effect on the catabolism of secretory stimulants or their delivery to the target secretory cells.

The present study indicates that GH-RIH or its analogs can strongly suppress secretin-stimulated pancreatic enzyme secretion at the dose tested. Moreover, their additional ability to inhibit the effects of circulating plasma gastrin on acid secretion as well as to reduce the requirement for exogenous insulin (13) makes them potentially useful therapeutic adjuncts in the treatment of acute pancreatitis (14).

Summary. GH-RIH and its two analogs, D-Trp^{8}-somatostatin and D-Cys^{14}-somatostatin have been tested for their effects on gastric and pancreatic secretion in chronic gastric and pancreatic fistula dogs. All three peptides caused similar competitive inhibition of pentagastrin-induced gastric acid and secretin-induced pancreatic bicarbonate secretions. This study indicates that GH-RIH analogs, which were shown to have a dissociated action on pituitary and endocrine pancreatic secretion, are essentially as equipotent as GH-RIH itself on gastric and pancreatic secretions.

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