Metabolism and acid secretory effect of sulfated and nonsulfated gastrin-6 in humans

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Received 21 January 2000; accepted in final form 13 May 2000

Palnæs Hansen, C., F. Stadil, and J. F. Rehfeld. Metabolism and acid secretory effect of sulfated and nonsulfated gastrin-6 in humans. Am J Physiol Gastrointest Liver Physiol 279: G903–G909, 2000.—The antral hormone gastrin is synthesized by processing progastrin into different peptides that stimulate gastric secretion. The effect on acid secretion depends mainly on the metabolic clearance rate of the peptides, but some of them may differ in potency and maximum acid output at similar concentrations in plasma. Sulfated and nonsulfated gastrin-6 are the smallest circulating bioactive gastrins in humans. Their effect and metabolism have now been investigated in nine normal subjects and compared with nonsulfated gastrin-17, a main product of progastrin. Maximum acid output after stimulation with gastrin-17, sulfated gastrin-6, and nonsulfated gastrin-6 were 28.3 ± 2.0, 24.5 ± 2.0 (P < 0.02), and 19.3 ± 2.3 (P < 0.05) mmol H⁺/50 min, respectively, and the corresponding EC₅₀ values were 43 ± 6, 24 ± 2 (P < 0.01), and 25 ± 2 (not significant) pmol/l. The half-life of gastrin-17 was 5.3 ± 0.3 min, the metabolic clearance rate (MCR) was 16.5 ± 3.7 ml·kg⁻¹·min⁻¹, and the apparent volume of distribution (Vₐ) was 124.3 ± 9.6 ml/kg. The half-lives of sulfated and nonsulfated gastrin-6 were 2.1 ± 0.3 and 1.9 ± 0.3 min, the MCRs were 42.8 ± 3.7 and 139.4 ± 9.6 ml·kg⁻¹·min⁻¹ (P < 0.01), and the Vₐ were 139.0 ± 30.5 and 392.0 ± 81.6 (P < 0.01) ml·kg⁻¹. All pharmacokinetic parameters differed significantly from gastrin-17 (P < 0.05). We conclude that gastrin 6 has a higher potency but a lower efficacy than gastrin-17. The efficacy of gastrin-6 is increased by tyrosine O-sulfation, which also enhances the protection against elimination.

gastric acid; pharmacodynamics; pharmacokinetics

Gastrin was the first gastrointestinal hormone to have its structure determined (9). Gastrin is a major regulator of gastric acid secretion and growth of gastric mucosa cells (for review, see Ref. 30). The active site of gastrin is the COOH-terminal tetrapeptide amide Trp-Met-Asp-Phe-NH₂ (17). Progastrin is synthesized in antral G cells and processed into a number of bioactive peptides, of which the heptadecapeptide gastrin-17 is the main product (9, 11, 23) (Fig. 1). All bioactive gastrin peptides are carboxyamidated and exist in nonsulfated and sulfated forms, due to O-sulfation of the tyrosyl residue (Tyr⁶), as counted from the COOH terminus (1, 9, 11). A minor fraction of gastrin-17 is cleaved in G cells and released as short COOH-terminal peptides (24). These peptides have been identified in porcine and human antral tissue as a mixture of gastrin-7, -6, and -5, of which sulfated gastrin-6 is the predominant form released to antral venous blood (10, 22).

The kinetics and pharmacodynamics of gastrin-52, -34, -17, and -14 have been well described (6, 8, 18, 31). Gastrin-17 is equipotent with gastrin-34 at similar plasma concentrations, and sulfation influences neither gastric acid secretion nor metabolic clearance rate (MCR) (4, 5, 8). In cats, however, short gastrin peptides have a lower potency than gastrin-17, and sulfation reduces their MCR (3, 12).

So far, human studies of gastrin-6 have not been reported. Therefore, we have now investigated the pharmacodynamics and pharmacokinetics of sulfated and nonsulfated gastrin-6 in humans. The peptides were compared with nonsulfated gastrin-17, which has been used in most studies of gastrin physiology.

MATERIALS AND METHODS

Peptides

Sulfated and nonsulfated human gastrin-6 were custom synthesized by Cambridge Research Biochemicals (Zeneca; Alderley Park, UK). The content and purity of the peptides were controlled by amino acid analysis (LKB amino acid analyzer 4000 with fluorescence detection; LKB Biochrom, Cambridge, UK) and reverse-phase HPLC (Hewlett-Packard 1084 B; Hewlett-Packard, Palo Alto, CA). Synthetic human nonsulfated gastrin-17 was purchased from Sigma Chemical (St. Louis, MO).

Subjects

The studies were carried out in nine healthy volunteers (6 men and 3 women, ages 22–36 yr; Table 1) without a history of medical or surgical illness. Peak acid output was determined in all subjects before the studies by intramuscular injection of 6 μg pentagastrin (Peptavlon; Zeneca). Informed consent was obtained, and the study was approved by the Ethics Committee for Medical Research in Copenhagen in accordance with the Helsinki II declaration.

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Experimental Procedures

Gastric acid secretion during infusion of nonsulfated gastrin-17, sulfated gastrin-6, and nonsulfated gastrin-6. Three experiments were carried out randomly in each subject on separate days. After an overnight fast, a nasogastric tube was inserted with the tip in the antrum under fluoroscopic control. After residual gastric content was evacuated, gastric juice was aspirated continuously by intermittent pump suction (Egnell) in periods of 10 min with the subject in the supine position. The recovery of gastric juice was determined by continuous infusion of a marker in the lateral lumen of the tube (230 kBq 57Co-labeled cobalamin, 1.25 mg cobalamin, and 1 g human albumin diluted in 1,000 ml isotonic saline; 60 ml/h). The lateral lumen ended 10 cm proximal to the openings of the central canal. The volume of gastric juice was measured for each 10-min period, and the concentration of H⁺ was determined by titration to pH 7.0 with an autotitrator (PHM 26; Radiometer, Copenhagen, Denmark). Sterile filtrated gastrin peptides were diluted in isotonic saline containing 1 g/l of human albumin. The syringes were weighed before and after the infusions, and remaining peptide was stored at −20°C until radioimmunoassay.

Each infusion experiment began with a 50-min control period during which isotonic saline was infused intravenously at 30 ml/h with a pump (Perfusor VII; Braun, Melsungen, Germany). After the control period, one of three peptides was infused in four consecutive doses (nonsulfated gastrin-17 and sulfated gastrin-6: 40, 80, 120, and 160 pmol kg⁻¹ h⁻¹; nonsulfated gastrin-6: 120, 240, 360, and 480 pmol kg⁻¹ h⁻¹). The dose rate at which maximum acid output was achieved was determined in pilot studies. Each dose interval lasted 50 min, and venous blood samples were taken from the opposite arm every 10 min from the start of the infusion.

Metabolism of nonsulfated gastrin-17, sulfated gastrin-6, and nonsulfated gastrin-6. After termination of the infusion, the intravenous catheter was rapidly removed and blood samples were taken at 1, 2, 3, 4, 5, 10, 15, 20, 30, 45, and 60 min to determine the half-life of the peptides in plasma. In vitro degradation of nonsulfated gastrin-17, sulfated gastrin-6, and nonsulfated gastrin-6. Venous blood from normal subjects who had fasted overnight was collected in dry heparinized tubes. Known amounts of the peptides were added to plasma and incubated at 37°C for 0, 1, 2, 4, 8, and 24 h. Then the incubation samples were immediately frozen in liquid nitrogen and stored at −20°C until radioimmunoassay.

Table 1. Age, body surface, and peak acid output after intramuscular injection of 6 μg pentagastrin in 9 subjects

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
<th>All</th>
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</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>29.3(22–35)</td>
<td>29.7(24–36)</td>
<td>29.4(22–36)</td>
</tr>
<tr>
<td>Body surface, m²</td>
<td>1.89 ± 0.03</td>
<td>1.72 ± 0.13</td>
<td>1.83 ± 0.05</td>
</tr>
<tr>
<td>Peak acid output, mmol H⁺/h</td>
<td>39.0 ± 4.4</td>
<td>27.6 ± 3.2</td>
<td>35.2 ± 3.6</td>
</tr>
</tbody>
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Values are means ± SE for body surface and peak acid output; age is given as mean, and range is in parentheses.
were performed by previously described assays developed in our laboratory. The concentration of gastrin-17 was measured using antisera 2604 (25, 28). This antisera was raised against the 2–17 sequence of human nonsulfated gastrin-17 and is specific for the bioactive COOH-terminal heptapeptide. It binds both sulfated and nonsulfated gastrin-71, -52, -34, and -17 with equimolar potency, whereas the reactivity with the homologous hormone cholecystokinin is <0.5% (25). Synthetic human gastrin-17 was used as standard, and moniodinated \(^{125}\)I-gastrin-17 was used as tracer (27).

Sulfated and nonsulfated gastrin-6 were measured using antisera 2609 after extraction of the peptides from plasma. Antiserum 2609 was also raised against the 2–17 fragment of human nonsulfated gastrin-17 (20, 25). But contrary to antisera 2604, which requires an epitope of seven residues or more for binding, antisera 2609 requires only the COOH-terminal tetrapeptide amide sequence, although increasing chain length increases antibody binding. The reactivity with gastrin-34 is 63% and with cholecystokinin-8 is 20%. The cross-reactivity with cholecystokinin was without significance. The reactivity with gastrin-34 is 63% and with cholecystokinin-8 is 20%. The chain length increases antibody binding. The reactivity with gastrin-34 is 63% and with cholecystokinin-8 is 20%. The cross-reactivity with cholecystokinin was without significance.

Antiserum 2609 was also raised against the 2–17 fragment of human nonsulfated gastrin-17 (20, 25). But contrary to antisera 2604 (25, 28). This antiserum was assayed with antisera 2604 and 2609. The elution positions, min and 22NaCl, and fractions of 1 ml were collected and monoiodinated \(^{125}\)I-labeled gastrin-17 was used as tracer.

Blood samples drawn at the termination of the last dose interval during infusion of nonsulfated gastrin-17, sulfated gastrin-6, and nonsulfated gastrin-6 were studied by gel chromatography. Plasma from all subjects was pooled, and 1-ml samples were applied to Sephadex G-50 superfine columns (10 × 1,000 mm; Pharmacia, Uppsala, Sweden) and eluted with 0.125 mol/l NH\(_4\)HCO\(_3\), pH 8.2, at room temperature with a flow rate of 3 ml/h. Void volume and total volume were determined by elution of \(^{125}\)I-labeled albumin and \(^{22}\)NaCl, and fractions of 1 ml were collected and assayed with antisera 2604 and 2609. The elution positions, \(K_d\), were calculated as

\[ K_d = (V_e - V_v)/(V_t - V_v) \]

where \(V_e\) is the elution volume of the peptides, and \(V_v\) and \(V_t\) are the elution volumes of \(^{125}\)I-labeled albumin and \(^{22}\)NaCl, respectively.

Calculations and Statistical Analysis

Correction for nonrecovered gastric juice was made for every sampling period as

\[ V_e = V_a(Q_v/Q_a) \]

where \(V_e\) is the corrected volume (in ml), \(V_a\) is the aspirated volume, \(Q_v\) is the amount of radioactivity infused (in counts/s), and \(Q_a\) is the amount of aspirated radioactivity. Maximum acid output was defined as the maximum acid secretion during one dose interval (mmol H\(^+\)/50 min). Peak acid output, expressed as mmol H\(^+\)/h, was defined as the two highest consecutive samples multiplied by 2 (pentagastrin test) or 3 to yield a 1-h value (2).

The pharmacodynamics of the peptides were evaluated by three parameters: EC\(_{50}\), efficacy (maximum response), and potency. EC\(_{50}\) was estimated from a Hill plot (14), which is the logit of the secretory response vs. log plasma concentration.

The theoretical maximum acid output (\(E_{\text{max}}\)) was estimated by linear transformation of the Michaelis-Menten kinetics according to Hofstee (7). This transformation has the equation

\[ E_x = E_{\text{max}}/(E_{\text{max}} + C) \]

where \(E_x\) is the response and \(C_x\) the plasma concentration of the peptide. The slope of the line \((k_e)\) corresponds to EC\(_{50}\) and the intercept of the ordinate corresponds to \(E_{\text{max}}\). Potency was defined as effect at a given plasma concentration evaluated from the course of the log concentration-response (LCR) curve. The curve was computed from the equation

\[ E_x = E_{\text{max}} C_x/E_{\text{max}} + C_x \]

where \(E_{\text{max}}\) is the maximum response and the coefficient \(s\) is the slope of the Hill plot.

The pharmacokinetic analysis was made according to a one-compartment, open model

\[ C_t = C_0 e^{-kt} \]

where the subscripts refer to plasma concentrations (C) at zero time and \(t\). Postinfusional plasma concentrations were plotted on semilogarithmic graph paper after subtraction of basal values. Linear regression of the logarithm of concentrations vs. time was computed to yield the slope \((k_e)\) from which the half-life was determined by division with 0.693. The MCR was calculated by dividing dose rate with the plateau increment in plasma gastrin, and the apparent volume of distribution \((V_d)\) was calculated by dividing clearance with \(k_e\). The plateau concentration of gastrin was taken as the mean of the two values obtained during the final 20-min infusion of the last dose.

Results are expressed as means ± SE. Curve fitting was made from linear and nonlinear regression using GraphPad Prism (GraphPad Software, San Diego, CA). Data were analyzed using Wilcoxon’s test for paired samples and Friedman’s test for analysis of variance. \(P\) values <0.05 were considered significant.

RESULTS

Effective Dose Rates and Gastrin Concentration in Plasma

The effective dose rates were calculated from the concentration of peptide in the infusion lines as shown in Fig. 2. During infusion, a concentration plateau was reached for all peptides within each of the four dose intervals.

Acid Output

The acid output before infusion of nonsulfated gastrin-17 was 5.2 ± 0.7 mmol H\(^+\)/50 min and increased stepwise to 15.7 ± 2.2 (\(P < 0.01\)), 26.2 ± 3.1 (\(P < 0.01\)), and 32.7 ± 2.3 mmol H\(^+\)/50 min (\(P < 0.01\) respectively.)
0.001), 25.6 ± 2.8, and 26.4 ± 2.4 [not significant (NS)] mmol H⁺/50 min during the four consecutive dose intervals (Fig. 2). During infusion of sulfated gastrin-6, acid output increased from 5.7 ± 0.7 to 12.5 ± 1.2 (P < 0.05), 20.1 ± 2.5 (P < 0.005), 22.3 ± 2.2, and 23.6 ± 1.7 (NS) mmol H⁺/50 min, and the output of nonsulfated gastrin-6 increased from 4.5 ± 0.9 to 10.6 ± 1.6 (P < 0.005), 17.3 ± 1.7 (P < 0.001), 19.6 ± 2.0 (P < 0.001), and 18.9 ± 1.9 (NS) mmol H⁺/50 min. Maximum and peak acid output of nonsulfated gastrin-17, sulfated gastrin-6, and nonsulfated gastrin-6 differed significantly, as shown in Table 3. The theoretical Em of nonsulfated gastrin-17 and sulfated gastrin-6 were similar, both being significantly above the Em of nonsulfated gastrin-6 (Table 3). The EC₅₀ of nonsulfated gastrin-17 exceeded the EC₅₀ of sulfated and nonsulfated gastrin-6 (P < 0.01); the respective concentrations in plasma estimated from the regression lines were 43 ± 6 (r = 0.91), 24 ± 2 (r = 0.92), and 25 ± 2 (r = 0.90) pmol/l (Fig. 3). LCR curves computed from EC₅₀ and the respective Hill coefficients are shown in Fig. 4.

### Metabolism

The elimination of COOH-terminal immunoreactivity in plasma after infusion of the three peptides was monoexponential (Fig. 5). The half-life, MCR, and Vd of nonsulfated gastrin-17 were 5.3 ± 0.3 min, 16.5 ± 1.3 ml·kg⁻¹·min⁻¹, and 124.3 ± 9.6 ml/kg, respectively. For sulfated and nonsulfated gastrin-6, half-lives were

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### Table 3. Pharmacodynamic and pharmacokinetic parameters of 3 gastrin peptides in 9 subjects

<table>
<thead>
<tr>
<th></th>
<th>Nonsulfated gastrin-17</th>
<th>Sulfated gastrin-6</th>
<th>Nonsulfated gastrin-6</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAO, mmol H⁺/50 min</td>
<td>28.3 ± 32.7</td>
<td>24.5 ± 2.0*</td>
<td>19.3 ± 2.3*</td>
</tr>
<tr>
<td>PAO, mmol H⁺/50 min</td>
<td>35.0 ± 4.8</td>
<td>32.8 ± 2.6*f</td>
<td>27.6 ± 2.4*f</td>
</tr>
<tr>
<td>Em, mmol H⁺/50 min</td>
<td>33.3 ± 3.3</td>
<td>33.0 ± 3.1*d</td>
<td>29.7 ± 2.3*d</td>
</tr>
<tr>
<td>EC₅₀, pmol kg⁻¹·h⁻¹</td>
<td>43 ± 6</td>
<td>24 ± 2*a</td>
<td>25 ± 2*a</td>
</tr>
</tbody>
</table>

Values are means ± SE. MAO, maximum acid output; PAO, peak acid output; Em, maximum effect estimated from Hofstee plot. Significant difference vs. gastrin-17: *P < 0.01, *P < 0.02, and *P < 0.05. Significant difference between sulfated and nonsulfated gastrin-6: *P < 0.01, *P < 0.02, and *P < 0.05.

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Fig. 2. Plasma concentrations (●) and gastric acid output per 10 min (○) (means ± SE) during infusion of nonsulfated gastrin-17 (A), sulfated gastrin-6 (B), and nonsulfated gastrin-6 (C) in normal subjects.

Fig. 3. Hill plot. Logit to gastric acid output E (mmol H⁺/10 min) vs. concentration of nonsulfated gastrin-17, sulfated gastrin-6, and nonsulfated gastrin-6 in plasma. The Hill coefficient (s) is the slope of the curve, and r is the coefficient of correlation. Nonsulfated gastrin-17: s = 4.9, r = 0.91; sulfated gastrin-6: s = 4.9, r = 0.92; nonsulfated gastrin-6: s = 7.4, r = 0.90.
2.1 ± 0.3 and 1.9 ± 0.3 min (NS), MCRs were 42.8 ± 3.7 and 139.4 ± 9.6 ml·kg⁻¹·min⁻¹ (P < 0.01), and $V_d$ were 139.0 ± 30.5 and 392.0 ± 81.6 ml/kg (P < 0.01). All parameters of the hexapeptides differed significantly from those of nonsulfated gastrin-17 (P < 0.01).

Chromatography

Gel chromatography of plasma sampled during infusion of sulfated and nonsulfated gastrin-6 revealed peaks that eluted at the positions of the standard calibration peptides (Fig. 6).

In Vitro Degradation of Peptides

There was a time-dependent loss of nonsulfated gastrin-17 as well as of sulfated and nonsulfated gastrin-6 after incubation in plasma. The concentrations of nonsulfated gastrin-17 declined to 85, 73, 56, 30, and 18% after 1, 2, 4, 8, and 24 h of incubation, respectively. The concentrations of sulfated gastrin-6 declined to 47, 28, 20, 12, and 4%, and the concentrations of nonsulfated gastrin-6 declined to 55, 15, 4, 2, and 1% at the same intervals (Fig. 7).

DISCUSSION

This study showed that gastrin-6 has a higher potency but a lower efficacy than nonsulfated gastrin-17. The efficacy of gastrin-6, however, increased by tyrosine sulfation, which also decreased the MCR. When the theoretical $E_m$ was calculated from Michaelis-Menten kinetics of the concentration-response data, the efficacy of sulfated gastrin-6 and nonsulfated gastrin-17 was not significantly different but exceeded the $E_m$ of nonsulfated gastrin-6. Comparison between potencies were more complex because of the different slope of the LCR curve. Thus different values would emerge depending on the intensity of effect at which comparisons were made. However, the $EC_{50}$ of the hexapeptides was lower than the $EC_{50}$ of nonsulfated gastrin-17.

Due to the different rates of metabolism, dose rates of the peptides had to be different. Although plasma concentrations of the hexapeptides did not reach the same level as nonsulfated gastrin-17, no further increase in acid output was recorded after the third dose interval of either sulfated nor nonsulfated gastrin-6. Fading, i.e., decreased response with time, may distort dose-response studies when increasing doses are administered consecutively without intervening rest periods. Our secretory data did not suggest fading, and peak acid output during infusion of nonsulfated gastrin-17 reached the same level as observed during the preceding pentagastrin test. Calculation of the theoretical value $E_m$ remains controversial. The method requires that concentration and response follow Michae-
lis-Menten kinetics, a precondition that was met in our study. But the reliability of the calculations also depends on the mathematical transformation of the Michaelis-Menten equation and the error of the data. However, it has been shown experimentally that the Hofstee transformation is acceptable even when response is subject to a considerable error (7).

Studies of small gastrin peptides have so far been restrained due to a lack of useful radioimmunoassays. Dose-response studies of tetra- and pentagastrin as well as the commercial analog of pentagastrin (Peptavlon) have previously been undertaken to examine their use in gastric function tests (21). Experiments in cats showed that the potencies of tetra- and pentagastrin were lower than the potency of nonsulfated gastrin-17. But since the results were evaluated from the respective dose rates of the peptides, the difference could be explained by the higher MCR of the small peptides (3). In another study, the efficacy of the modified hexapeptide amide fragment of gastrin-17, butyl-oxycarbonyl gastrin-6 (BOC-gastrin-6), was equal to that of nonsulfated gastrin-17, but potency was lower when circulating concentrations were taken into account (12). This observation was explained by a higher binding affinity of nonsulfated gastrin-17 to its receptor (30). Extrapolation of results between species needs caution, especially for peptide analogs. However, other studies suggest that not only the structure but also the size of the peptide may influence the secretory response. Hence, gastrin-17 has a similar efficacy and potency to gastrin-34 and -14 in humans and animals (6, 8), whereas gastrin-52 studied under conditions similar to the present study revealed a lower efficacy than nonsulfated gastrin-17 (18). Gastrin-52 is the largest progastrin product examined so far, and since the half-life is ~50 min, the concentration-response was not studied during steady state concentration in plasma. Therefore, it is possible that differences in equilibrium time between plasma and receptor may have influenced the results. In the present study, steady state was achieved for all three peptides during each dose interval. With reference to earlier results, it looks as if medium-sized gastrins like gastrin-34, -17, and -14 may have a higher efficacy than peptides with either a shorter or a longer chain length.

Sulfation of gastrin peptides is another modification that we found had an effect on gastric acid output. Tyrosine O-sulfation is a common posttranslational modification of peptides and proteins, and for some peptides it is necessary for biological activity (5, 15, 26). Gastrin retains its biological activity after desulfation, and studies in both animals and humans have shown that the efficacy and EC50 of sulfated and nonsulfated gastrin-17 are similar (4, 13). However, the higher efficacy of sulfated gastrin-6 compared with its nonsulfated counterpart, as found in the present study, suggests that the biological activity of short gastrin peptides is enhanced by sulfation of tyrosine. Gastrin-6 had a higher MCR than gastrin-17, which is in keeping with the general experience of an inverse relationship between MCR and peptide length. Whether or not sulfation of gastrin also changes the MCR has been a subject of discussion. In one study, sulfation of gastrin-17 was found to decrease MCR (19). Other investigations, however, showed that nonsulfated and sulfated gastrin-17 had the same potency evaluated from plasma concentrations of the peptides and, therefore, the same MCR (4, 5). Studies in cats supported the conclusion (13). We found that sulfation of gastrin-6 reduced the MCR, and similar observations were made from sulfation of BOC-gastrin-6 in cats (12). But these findings may apply only to small gastrin peptides. In vitro studies have shown that
sulfation of peptides protects against degradation (16, 19), as recorded in the present study with gastrin-6. But since ~50% of the immunoreactivity was still present after incubation for 1 h, enzymatic degradation in plasma does not contribute significantly to the MCR. Nonsulfated gastrin-17 had a lower MCR than gastrin-6 because of a different distribution and extraction in the vascular beds, as recently shown in pigs (unpublished observations). The difference between the MCR of sulfated and nonsulfated gastrin-6 was due to the different Vd. The half-life of the hexapeptides was not significantly different. This secondary pharmacokinetic parameter depends on the two primary parameters MCR and Vd through the expression t1/2 = (0.693 Vd/MCR). Since the MCR and Vd both differed to the same extent with a factor of ~3, a major difference between the half-lives was not to be expected.

We conclude that gastrin-6 has a higher potency but a lower efficacy than nonsulfated gastrin-17. The efficacy of gastrin-6 was increased by sulfation, which also reduced the MCR. Since preliminary studies have identified a specific G cell enzyme active in the processing of gastrin-6, the peptide should not be regarded merely as a waste product. In spite of its modest contribution to the pool of circulating gastrin, gastrin-6 may still contribute to subtle modifications of gastric acid secretion.

The expert technical assistance of Inge Mortensen and Winna Stavnstrup is gratefully acknowledged.

The study was supported by grants from the Danish Hospital Foundation, Region of Copenhagen, the Faroe Islands and Greenland, the Danish Foundation for the Advancement of Medical Science, the Danish Biotechnology Program for Signal Peptide Research, and Mogens Andreassen’s Foundation.

REFERENCES


