THE JOURNAL OF BIOLOGICAL CHEMISTRY
Vol. 245, No. 9, Issue of May 10, pp. 2189–2193, 1970
Printed in U.S.A.

Carboxyl-terminal Sequence of Human Gastricsin and Pepsin*

(Received for publication, January 12, 1970)

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SUMMARY

The tryptic peptides from human pepsin and gastricsin were purified and their sequences were determined. The sequence of 27 residues at the COOH-terminal end of human pepsin was found to be: -Ile-Leu-Gly-Asp-Val-Phe-Ile-Arg-Gln-Phe-Tyr-Thr-Val-Phe-Asp-Arg-Ala-Asn-Asn-Gln-Val-Gly-Leu-Ala-Pro-Val-Ala. The sequence of 19 residues at the COOH-terminal end of human gastricsin was found to be: -Gln-Phe-Tyr-Thr-Val-Phe-Asp-Arg-Ala-Asn-Asn-Lys-Glu-Gly-Leu-Ala-Pro-Val-Ala. These sequences are extensively homologous to each other and to the known COOH-terminal sequence of bovine rennin.

Experiments on isolation, characterization, and specificity of human gastricsin and pepsin, reported previously from our laboratory (2–6), indicate that the two enzymes are similar in their molecular weights, amino acid compositions, and enzymic properties. The data suggested that these enzymes may be related in primary structure. Since the amino acid sequence at the COOH terminus of porcine pepsin was recently reported by Dopheide, Moore, and Stein (7), it seemed advantageous to make a comparison of the sequence at this region in human pepsin and gastricsin.

The results of this study indicated that the COOH-terminal sequence from human gastricsin and human pepsin are structurally homologous.

EXPERIMENTAL PROCEDURE

Materials

Bovine α-chymotrypsin and diisopropylfluorophosphate-treated carboxypeptidase A were obtained from Worthington. Trypsin and thermolysin were obtained from Calbiochem. 1-*N*,*N*-Dimethylaminonaphthalene-5-sulfonyl chloride (dansyl chloride) was obtained from K and K Laboratories. Amberlite CG-50 was obtained from Mallinckrodt. All solvents were purified by distillation.

* This work was supported by Research Grant AM-01107 and AM-06487 from the National Institutes of Health. Preliminary results of this study have previously been communicated (1).

‡ Recipient of Career Development Award 5 KO4-AM-38638.

Human gastricsin and pepsin were prepared and stored as described previously (2) and were rechromatographed on a column of Amberlite CG-50 just befofe use. The enzymes thus obtained satisfied the criteria of homogeneity previously reported (3). In addition, these enzyme preparations gave a single band in polyacrylamide disc gel electrophoresis (8).

Methods

Tryptic Hydrolysis—The inactivated pepsin or gastricsin was digested with 1% of its weight of trypsin in 0.2 M *N*-ethylmorpholine acetate buffer, pH 8.0, at 37°. The protein concentration was 1.5 to 2%. Hydrolysis was carried out in either 1 hour or 3 hours.

Chymotryptic Hydrolysis of Peptides—Peptides were digested with chymotrypsin with an enzyme-substrate molar ratio of about 1:50. The digestion was carried out in a 0.2 M *N*-ethylmorpholine acetate buffer, pH 8.0, at 37° for 2 hours.

Thermolysin Hydrolysis of Peptides—The thermolysin digestion was carried out according to the procedure of Matsubara *et al.* (9), with slight modification in the buffer system. About 0.2 μmole of peptides was dissolved in 0.2 ml of 0.2 M *N*-ethylmorpholine acetate buffer, pH 8.0. An aliquot of 0.05 ml containing 0.002 mg of thermolysin in 0.002 M calcium chloride was added. The reaction was carried out at 37° for 4 hours. At the end of the reaction, 1 drop of glacial acetic acid was added and the solution was lyophilized. The dried products were separated by high voltage paper electrophoresis.

High Voltage Paper Electrophoresis—The commercial apparatus produced by Savant was used with the following buffer systems: pH 6.5, pyridine-acetic acid-water (25:1:225, by volume); pH 3.5, pyridine-acetic acid-water (1:10:90, by volume); and pH 2.0, formic acid-acetic acid-water (1:4:45, by volume). For the separation of dansyl-amino acids, a Locarte, flat plate high voltage electrophoresis apparatus was used with pyridine-acetate buffer, pH 4.4, as described by Gray and Hartley (10).

Identification of Peptides by Paper Electrophoresis—The location of peptides on paper electrophoresis was determined by the use of ninhydrin-cadmium acetate reagent (11). Tyrosine- and histidine-containing peptides were detected by the Pauly reagent (12).

Amino Acid Analysis—Amino acids were determined with a Spinco model 120B automatic amino acid analyzer with a modified "range card" in the recorder to permit quantitative analysis in the range of 0.001 to 0.10 μmole of amino acid. Analysis was carried out according to the accelerated procedure of Spackman

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(13). The samples of purified peptide were hydrolyzed in 0.1 ml of 6 N HCl in a sealed evacuated tube for 24 hours at 110 ± 2°.

Amino-terminal Residue Determination—The NH_2-terminal residues of the purified peptides were determined after reaction with dansyl chloride according to the method of Gray and Hartley (10). The dansyl amino acids were identified by high voltage paper electrophoresis in pyridine-acetate buffer at pH 4.4 and by two-dimensional polyamide thin layer chromatography (14).

Carboxyl-terminal Residue Determination—A diisopropylfluorophosphate-treated carboxypeptidase A suspension was washed and dissolved as described by Ambler (15). Digestion of peptides was carried out for 5 hours at 37° in 0.2 M *N*-ethylmorpholine acetate solution, pH 8.0. The incubation mixture contained 0.02 to 0.1 μmole of peptide. Aliquots were taken for quantitative amino acid analysis.

Hydrazinolysis was also used for determination of the COOH-terminal amino acid peptides. The experimental conditions were essentially those of Fraenkel-Conrat and Tsung (16). Quantitative analysis of the COOH-terminal residue was performed with the amino acid analyzer.

Edman Degradation—The modified Edman sequential degradation procedure was followed, as described by Gray (17). In this method, after removal of a residue from the NH_2 terminus, the newly revealed NH_2 terminus was determined by the "dansyl procedure."

RESULTS

Separation of Tryptic Digests of Human Gastricsin and Pepsin

The tryptic digest obtained with pepsin (160 mg) or gastricsin was fractionated on a column (2 × 150 cm) of Sephadex G-75 in 0.1 M ammonium acetate at pH 10.4. The larger fragments were eluted first in a breakthrough peak, which was followed by a mixture of small peptides. The fractions containing smaller peptides were pooled and lyophilized. The peptides were submitted to high voltage paper electrophoresis at pH 2.0. The high voltage paper electrophoretic patterns of peptides obtained by hydrolysis of human gastricsin or pepsin with trypsin are shown in Fig. 1. The samples, incubated for 1 hour, produced only two major peptides from either pepsin or gastricsin. However, after 3 hours of incubation, several peptides were found in both cases. The peptides Tp1, Tp2, Tp3, Tp4, Tg1, Tg2, and Tg5 were obtained in better yield and purity. Further purification of peptide from preparative runs was carried out with high voltage paper electrophoresis at pH 3.5, to obtain pure peptides used for sequence studies.

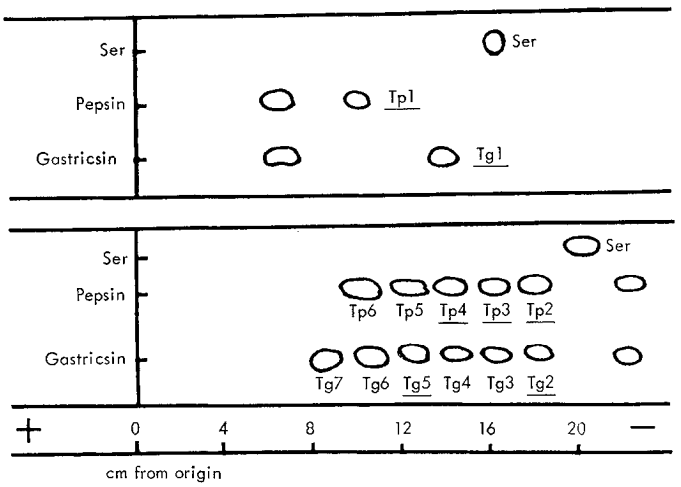

FIG. 1. High voltage paper electrophoresis of tryptic peptides from human pepsin and gastricsin. The *upper pattern* is the separation of a 1-hour digest. The electrophoresis was carried out in pH 2.0 at 70 volts per cm for 40 min. The *lower pattern* shows the separation of a 3-hour digest. The electrophoresis was carried out in pH 2.0 at 53 volts per cm for 60 min. Free serine was used as a mobility marker. The number of peptides are labeled *below* the spots. The prefix Tp designates the peptides from pepsin and Tg designates the peptides from gastricsin.

TABLE I

Amino acid compositions of tryptic peptides

Amino acid	Tp1	Tp2	Tp3	Tp4	Tg1	Tg2	Tg5
Lysine					1.00 (1)	1.00 (1)	1.00 (1)
Histidine							
Arginine		1.04 (1)	2.06 (2)	1.00 (1)			1.26 (1)
Aspartic acid	1.83 (2)	1.02 (1)	3.15 (3)	1.30 (1)	1.83 (2)	1.83 (2)	2.61 (3)
Threonine			0.90 (1)	1.20 (1)			0.92 (1)
Serine							
Glutamic acid	1.27 (1)		2.00 (2)	1.04 (1)	1.21 (1)	0.93 (1)	1.78 (2)
Proline	1.40 (1)				0.90 (1)		0.90 (1)
Glycine	1.05 (1)	1.40 (1)	1.40 (1)		1.36 (1)	1.10 (1)	1.02 (1)
Alanine	2.57 (3)		1.41 (1)		2.81 (3)	2.43 (2)	2.91 (3)
Half-cystine							
Valine	1.63 (2)	0.82 (1)	2.15 (2)	0.91 (1)	0.74 (1)		2.24 (2)
Isoleucine		2.06 (2)	0.90 (1)				
Leucine	1.00 (1)	1.33 (1)	0.58 (1)		0.88 (1)	0.67 (1)	1.38 (1)
Tyrosine			1.28 (1)	0.88 (1)			0.80 (1)
Phenylalanine		0.99 (1)	1.95 (2)	1.60 (2)			1.97 (2)
Total residues	11	8	17	8	11	8	19

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TABLE II

Summary on amino acid composition and sequence determination of peptides

Peptide no.	R_{Ser}[a]	Charges at pH 6.5[b]	Amino acid compositions[c]	Sequence determination[d]
Tp1	0.61		Asp_2 Glu_1 Pro_1 Gly_1 Ala_3 Val_2 Leu_1	Ala–Asn–Asn–Gln–Val–Gly–Leu–Ala–Pro–Val–Ala
Tp1-C_1[e]	0.96		$Pro_{1.0}$ $Ala_{1.3}$ $Val_{0.9}$	Pro–Val–Ala
Tp1-C_2	0.70		$Asp_{0.8}$ $Glu_{0.8}$ $Gly_{1.1}$ $Ala_{1.0}$ $Val_{1.4}$ $Leu_{1.4}$	Asn(Gln,Val,Gly,Leu)Ala
Tp1-Th_1	0.91		$Pro_{1.1}$ $Ala_{1.2}$ $Leu_{1.0}$	Leu–Ala–Pro
Tp1-Th_2	0.76	N	$Asp_{2.0}$ $Glu_{1.0}$ $Ala_{1.4}$	Ala–Asn–Asn–Gln
Tp1-Th_3	1.20		$Val_{0.9}$ $Gly_{1.1}$	Val–Gly
Tp1-Th_4	1.10		$Val_{0.9}$ $Ala_{1.0}$	Val–Ala
Tp2	0.89	N	Arg_1 Asp_1 Gly_1 Val_1 Ile_2 Leu_1 Phe_1	Ile–Leu–Gly–Asp–Val–Phe–Ile–Arg
Tp2-C_1	1.60		$Ile_{1.1}$ $Arg_{1.0}$	Ile–Arg
Tp2-C_2	0.65		$Asp_{1.1}$ $Gly_{1.2}$ $Val_{1.0}$ $Ile_{1.1}$ $Leu_{1.0}$ $Phe_{0.9}$	Ile–Leu–Gly–Asp–Val–Phe
Tp3	0.79		Arg_2 Asp_3 Thr_1 Glu_2 Gly_1 Ala_1 Val_2 Ile_1 Leu_1 Tyr_1 Phe_2	Ile–Arg–Gln–Phe–Tyr–Thr–Val–Phe–Asp–Arg(Ala,Asn,Asn,Gln,Val,Gly)Leu
Tp3-T_1	1.60		$Ile_{1.1}$ $Arg_{1.0}$	Ile–Arg
Tp3-T_2	1.62	N	$Asp_{1.2}$ $Arg_{1.0}$	Asp–Arg
Tp3-T_3	0.50			Tyr–Thr–Val–Phe–Asp–Arg–Ala–Asn–Asn–Gln–Val–Gly–Leu
Tp4	0.70	N	Arg_1 Asp_1 Glu_1 Thr_1 Val_1 Tyr_1 Phe_2	Gln–Phe–Tyr–Thr–Val–Phe–Asp–Arg
Tp4-Th_1	0.85		$Asp_{1.4}$ $Val_{1.0}$ $Phe_{0.9}$	Val–Phe–Asp
Tg1	0.85	N	Lys_1 Asp_2 Glu_1 Pro_1 Gly_1 Ala_3 Val_1 Leu_1	Ala–Asn–Asn–Lys–Glu–Gly–Leu–Ala–Pro–Val–Ala
Tg1-C_1[f]	1.37	N	Glu_1 Gly_1 Ala_1 Leu_1 Lys_1	Lys–Glu–Gly–Leu–Ala
Tg1-C_2[f]	1.30	N	Asp_1 Glu_1 Gly_1 Ala_1 Leu_1 Lys_1	Asn–Lys–Glu–Gly–Leu–Ala
Tg1-C_3[f]	1.20		Asp_1 Glu_1 Gly_1 Ala_2 Pro_1 Val_1 Leu_1 Lys_1	Asn–Lys–Glu–Gly–Leu–Ala–Pro–Val–Ala
Tg1-Th_1	1.10		$Val_{1.0}$ $Ala_{1.0}$	Val–Ala
Tg1-Th_2	0.91		$Pro_{1.0}$ $Ala_{1.2}$ $Leu_{1.0}$	Leu–Ala–Pro
Tg1-Th_3	0.70		$Asp_{2.2}$ $Glu_{1.1}$ $Gly_{1.3}$ $Ala_{1.3}$ $Lys_{1.0}$	Ala–Asn–Asn–Lys–Glu–Gly
Tg2	0.89		Lys_1 Asp_2 Glu_1 Gly_1 Ala_2 Leu_1	Ala(Asn,Asn,Lys,Glu,Gly,Leu)Ala
Tg5	0.61		Lys_1 Arg_1 Asp_3 Thr_1 Glu_2 Pro_1 Gly_1 Ala_3 Val_2 Leu_1 Tyr_1 Phe_2	Gln–Phe–Tyr–Thr–Val–Phe–Asp–Arg(Ala,Asn,Asn,Lys,Glu,Gly)Leu–Ala–Pro–Val–Ala
Tg5-T_1	1.62	N	$Asp_{1.2}$ $Arg_{1.0}$	Asp–Arg
Tg5-T_2	0.48		$Lys_{0.8}$ $Arg_{0.9}$ $Asp_{2.8}$ $Thr_{1.4}$ $Glu_{1.0}$ $Pro_{0.9}$ $Gly_{1.2}$ $Ala_{2.7}$ $Val_{1.8}$ $Leu_{1.2}$ $Tyr_{0.8}$ $Phe_{1.0}$	Tyr(Thr,Val,Phe,Asp,Arg,Ala,Asn,Asn,Lys,Glu,Gly,Leu,Ala,Pro)Val–Ala
Tg5-Th_1	0.52	N	$Lys_{0.9}$ $Arg_{1.2}$ $Asp_{3.0}$ $Thr_{1.4}$ $Glu_{0.7}$ $Gly_{1.5}$ $Ala_{0.9}$ $Val_{1.1}$ $Leu_{1.2}$ $Tyr_{0.9}$ $Phe_{2.1}$	Phe–Tyr–Thr–Val–Phe(Asp,Arg,Ala,Asn,Asn,Lys,Glu,Gly)Leu

[a] R_{ser} designates the relative mobility of the peptides to that of serine in high voltage electrophoresis at pH 2.0.

[b] N designates the peptides having no net charge (neutral) in high voltage electrophoresis at pH 6.5.

[c] The data on amino acid composition of major tryptic peptides, Tp1, Tp2, Tp3, Tp4, Tg1, Tg2, and Tg5, are shown in Table I.

[d] The arrows pointing to the right show the residues determined by Edman-dansyl procedure. The arrows pointing to the left show the residues determined by either carboxypeptidase A or hydrazinolysis.

[e] The peptides obtained from enzymic digestions of major tryptic peptides are given a number after a hyphen. The prefix letters indicate the enzyme used. C, α-chymotrypsin; T, trypsin; Th, thermolysin.

[f] The amino acid compositions of these peptides were determined semiquantitatively on high voltage paper electrophoresis in pH 2.0. The amino acid spots were revealed with a ninhydrin-collidine reagent (12).

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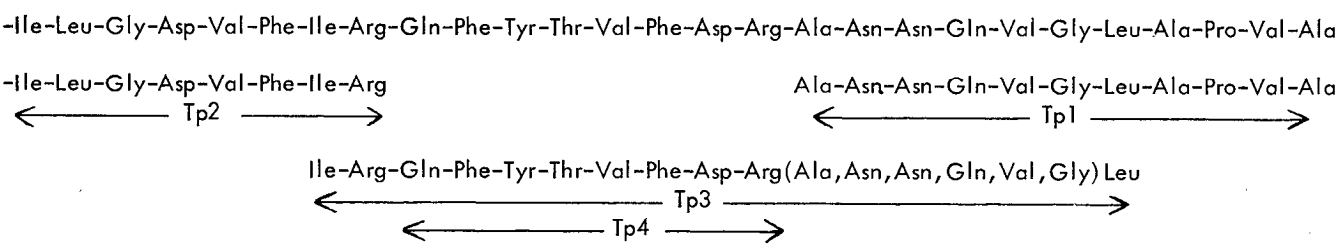

FIG. 2. Carboxyl-terminal sequence of human pepsin as constructed from tryptic peptides

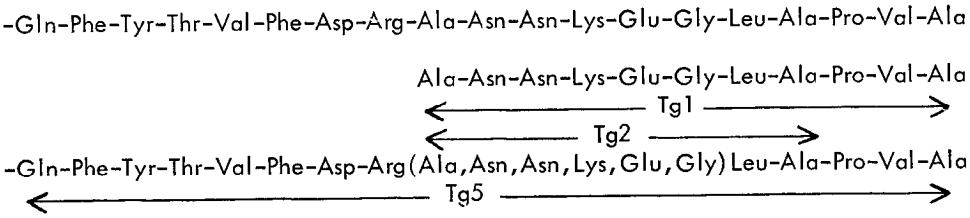

FIG. 3. Carboxyl-terminal sequence of human gastricsin as constructed from tryptic peptides

The amino acid compositions of purified tryptic peptides are shown in Table I. The summaries of sequence determination are shown in Table II.

Peptide Tp1—The NH_2 and COOH termini of Tp1 were Ala residues. Chymotryptic digestion of Tp1 yielded two peptides, Tp1-C1 and Tp1-C2. Thermolysin digest (4 hours) yielded four peptides, Tp1-Th_1 to Tp1-Th_4. As shown in Table II, the information on the sequences of these peptides was sufficient to construct the sequence of Tp1 as: Ala–Asn–Asn–Gln–Val–Gly–Leu–Ala–Pro–Val–Ala. The fact that Peptide Tp1-Th_2 was neutral in high voltage electrophoresis at pH 6.5 indicated that two Asx and one Glx were amides.

Peptide Tp2—The NH_2-terminal amino acid of Tp2 was Ile. Two chymotryptic peptides, Tp2-C1 and Tp2-C_2, showed the sequence of Tp2 to be: Ile–Leu–Gly–Asp–Val–Phe–Ile–Arg. Tp2 was neutral in high voltage electrophoresis at pH 6.5. Since it contained one Arg, the Asx must be the free acid.

Peptide Tp3 and Tp4—The NH_2- and COOH-terminal amino acids of Tp3 were Ile and Leu, respectively. A 3-hour tryptic digest of Tp3 yielded three peptides. Tp3-T_1 is a dipeptide, Ile–Arg, derived from the NH_2 terminus of Tp3. Tp3-T_2 was a dipeptide having the sequence Asp–Arg. Tp3-T_3 contained 13 residues derived from the COOH terminus of Tp3. Tp4 apparently contained part of the sequence of Tp3 and Tp3-T_3. From these peptides, the NH_2-terminal portion of Tp3 was constructed as: Ile–Arg–Gln–Phe–Tyr–Thr–Val–Phe–Asp–Arg (Table II). Peptides Tp3-T_2 and Tp4 were neutral in high voltage electrophoresis at pH 6.5, indicating that one Gln and one Asp were present in this portion of sequence. The sequence of 7 residues at the COOH terminus of Tp3 apparently overlapped with the NH_2-terminal portion of Tp1. Therefore, the sequence of these 7 residues in Tp3 was not further determined.

Peptide Tg1—The Edman-dansyl procedure established the NH_2-terminal 6 residues of Tg1. The COOH-terminal amino acid was Ala. Thermolysin digest (4 hours) yielded three peptides and the sequences of these peptides were established by the Edman-dansyl procedure. From thermolysin peptides, the sequence of Tg1 was constructed as: Ala–Asn–Asn–Lys–Glu–Gly–Leu–Ala–Pro–Val–Ala (see Table II). The overlaps, as well as amides, were confirmed by chymotryptic peptides.

Peptide Tg2—The NH_2- and COOH-terminal groups of Tg2 were Ala residues. This peptide apparently consists of the

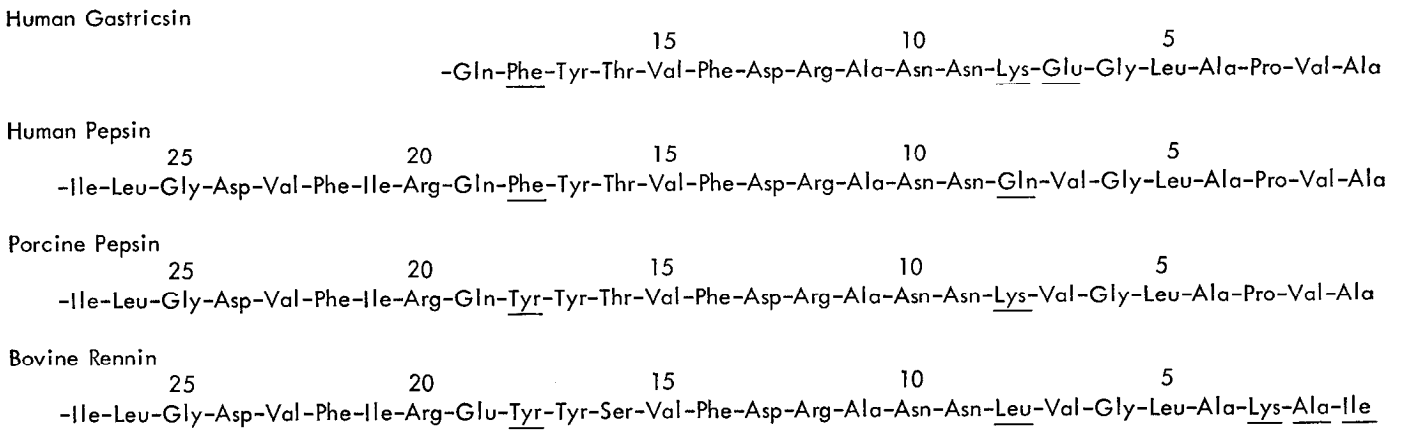

FIG. 4. Comparative carboxyl-terminal sequence of human gastricsin, pepsin, porcine pepsin (from Reference 7), and bovine rennin (from Reference 18). The *underlined* residues are those differing from that in other sequences. The numbers of the residues in the figure start from the COOH-terminal end.

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NH_2-terminal 8 residues of Peptide Tg1. The sequence was not further examined.

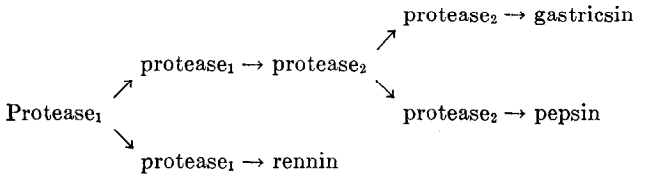
Peptide Tg5—This peptide contained 19 residues. The NH_2 terminus was Glu and the COOH terminus was Ala. Two peptides were purified from tryptic digest. Tg5-T_1 was a dipeptide with the sequence Asp–Arg. Tg5-T_2 contained the COOH-terminal 17 residues of Tg5. Thermolysin digest of Tg5 gave rise to a 14-residue peptide, Tg5-Th_1, which had a COOH-terminal Leu and an NH_2-terminal 5-residue sequence of Phe–Tyr–Thr–Val–Phe, as determined by the Edman-dansyl procedure. By placing the residues in these four peptides, it was apparent that the COOH-terminal 11 residues of Tg5 were identical in sequence with those in Tg1 (Table II). The sequence of this portion of Tg5 was not further investigated. The sequence of Tg5 was deduced to be: Glu–Phe–Tyr–Thr–Val–Phe–Asp–Arg(Ala,Asn,Asn,Lys,Glu,Gly)Leu–Ala–Pro–Val–Ala.

Carboxyl-terminal Sequence of Human Pepsin and Gastricsin—From the sequence of Peptides Tp1, Tp2, Tp3, and Tp4, the sequence of 27 residues of human pepsin shown in Fig. 2 was constructed. Since the COOH-terminal amino acid of human pepsin is Ala (4) and bears similarity to the sequence in porcine pepsin (7), it appears certain that this sequence represents the COOH-terminal 27 residues of human pepsin. The sequence of the COOH-terminal 19 residues in human gastricsin was constructed from the sequences of Peptides Tg1, Tg2, and Tg5 (Fig. 3).

DISCUSSION

Determination of the COOH-terminal sequences of human gastricsin and pepsin clearly indicates that the two enzymes are homologous in primary structure (Fig. 4). Among the 19 residues at the COOH-terminal ends of the two enzymes, only 2 residues differ. The 7th and 8th residues from the COOH terminus in gastricsin are –Lys–Glu–, but in pepsin they are –Gln–Val–. Human and porcine pepsin, as expected, are largely similar—showing only two substitutions of residues among 27 residues known (Fig. 4).

It is known that the COOH-terminal sequence of bovine rennin (18) and porcine pepsin (7) are homologous. This knowledge, combined with the data on the sequences of human gastricsin and pepsin from this laboratory, makes it almost inevitable that all three enzymes descended from a common ancestral gene during evolution through a "gene-doubling" process. This is not unexpected since it is well known that groups of pancreatic proteases (*i.e.* α-chymotrypsin, chymotrypsin B, trypsin, and elastase) are homologous in primary structure and are evolutionally connected (19–21). Functionally, rennin is more of a "milk-clotting" enzyme, while gastricsin and pepsine are "proteolytic" enzymes. It appears that rennin must have branched off earlier in the evolutional process as shown in the following scheme:



Since the COOH-terminal sequences of human gastricsin and pepsin are different but homologous, the enzymes must derive from different zymogens. The close similarity in the sequences of the two enzymes strongly suggests that the activation mechanism for the zymogen of gastricsin resembles that for the zymogen of pepsin; *i.e.* a portion of the polypeptide chain of the zymogen is cleaved off near the NH_2 terminus.

Acknowledgments—We wish to thank Dr. Robert Delaney for helpful criticisms, Mrs. Barbara Cox for valuable assistance in the preparation of this paper, and Mrs. Vivian Davis for her skillful assistance during the course of this work.

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