New Symbols for the Amino Acid Residues of Peptides and Proteins

Abstract. *A system of symbols for the amino acid residues of proteins and peptides is proposed. The symbols convey immediate meaning in chemical terms and therefore allow rapid recognition of the distribution and frequency of occurrence of the various functional groups. The system is readily adaptable to description of new amino acids and amino acid modifications.*

Information concerning the amino acid sequences of proteins and peptides is accumulating rapidly, and there is a real need for concise representation of these data. The most widely used symbols are three-letter abbreviations for the trivial names of the amino acids. Simpler systems, such as those with single-letter abbreviations, have been suggested; long ago Kossel (*1*) stated: "We can obtain some idea of the possible variety in the combination of the protein Bausteine by recalling the fact that they are as numerous as the letters in the alphabet, which are capable of expressing an infinite number of thoughts." The advantage of single-letter abbreviations is conciseness, but there are some disadvantages. The trivial names of several amino acids begin with the same letter, and therefore some fairly arbitrary designations have to be made and memorized. Furthermore, representation of the primary structure of a protein in terms of a series of single letters conveys no immediate understanding in chemical terms. Several single-letter systems have already been proposed, but there has been no general agreement on any one system.

The system suggested here is essentially a chemical shorthand; the symbols are readily understood by anyone familiar with the chemical structures. In the symbols for the residues of amino acids commonly found in proteins (Fig. 1) the amino acids are linked in a peptide chain by their respective α-amino and α-carboxyl groups. Circles represent oxygen atoms, and squares, nitrogen. Each of the dots in the amino acid side chains represents a carbon atom. The square symbol at the left-hand side of the peptide chain indicates that this is the amino-terminal end; the two circles at the right-hand side of the chain indicate that this is the carboxyl terminus. When a protein such as ribonuclease (Fig. 2) is represented in this manner, one can immediately see the pertinent functional groups; it is not necessary to translate a word or letter abbreviation for a trivial name into its chemical meaning. The proposed system is universal and not influenced by a particular language. It is a simple matter to recognize the distribution in a protein of the various functional groups (aromatic, aliphatic, basic, and others).

The symbols occupy little linear space, even less than needed for the three-letter abbreviations. Printers could prepare a series of such symbols, and these might also be attached to typewriters or made into rubber stamps. The symbols can also be written freehand without difficulty.

A further advantage of the proposed system lies in its ready adaptability to amino acid modifications, amino acid analogs, and amino acids that do not commonly occur in proteins. For example, as shown in Fig. 3, symbols can readily be designed for *N*-acetyl and amide end groups and such amino acids as alloisoleucine, allothreonine, cysteic acid, phosphoserine, carboxymethylcysteine, and D-amino acids. In the symbols for the isoleucine and threonine residues of proteins, the methyl groups extend toward the right; these designations are consistent with the known configuration of the β-carbon atoms of these amino acids. Thus, a β-carbon atom of the L-configuration is indicated when the significant functional group is on the right. The β-carbon atom of isoleucine has the L-configuration (if one considers the methyl group to be analogous to the amino group). The β-carbon atom of threonine has the D-configuration; the methyl group is on the right and the hydroxyl group is at the top of the molecule to be analogous to the symbol for serine.

In conclusion, by making the sym-

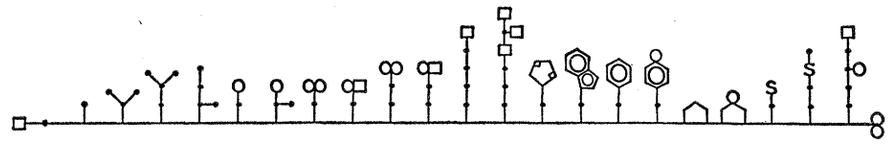

Fig. 1. Symbols for the common protein amino acids: glycine (amino terminal), alanine, valine, leucine, isoleucine, serine, threonine, aspartic acid, asparagine, glutamic acid, glutamine, lysine, arginine, histidine, tryptophan, phenylalanine, tyrosine, proline, 4-hydroxyproline, cysteine, methionine, 5-hydroxylysine (carboxyl terminal).

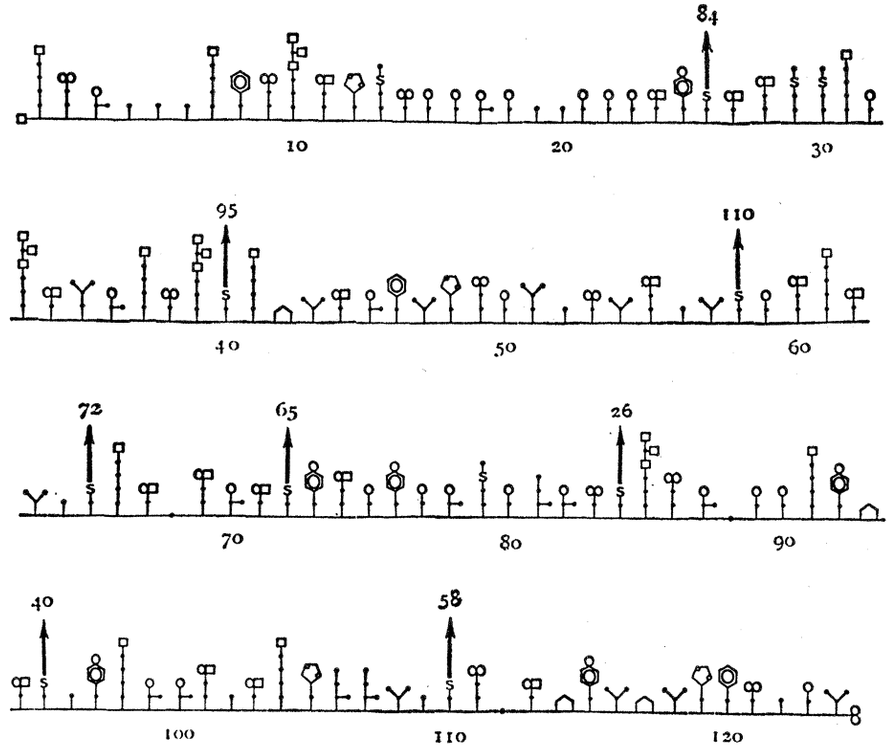

Fig. 2. Amino acid sequence of bovine pancreatic ribonuclease (*2*). The disulfide bonds are indicated by arrows pointing to the number of the corresponding half-cystine residue.

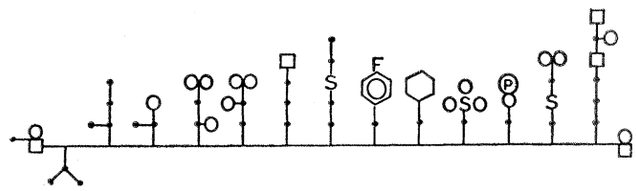

Fig. 3. Symbols for several amino acids not commonly found in proteins: *N*-acetyl-D-valine, and the L-isomers of alloisoleucine, allothreonine, erythro-β-hydroxyglutamic acid, threo-γ-hydroxyglutamic acid, ornithine, ethionine, *p*-fluorophenylalanine, cyclohexylalanine, cysteic acid, phosphoserine, *S*-carboxymethyl-cysteine, citrulline amide.

bols for amino acid residues meaningful in chemical terms, they are immediately and universally understandable, and it becomes easier to think of proteins represented in this manner in terms of the interactions between the side chains of the molecule. The proposed system can be readily adapted to the description of new amino acids as they are discovered, and to new amino acid modifications as further progress is made in the field of protein chemistry.

Note added in proof: The potential usefulness of this system has become apparent in discussions with various investigators who have already used shorthand symbols for amino acid residues in informal research conferences and as an aid in teaching [see, for example, G. H. Haggis, Ed., *Introduction to Molecular Biology* (Wiley, New York, 1964), p. 38].

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Bradykinin: Effect on Ureteral Peristalsis

Abstract. *Bradykinin, a known smooth-muscle stimulant, affects ureteral peristalsis in the dog; the changes were judged by cinefluorography, peristaltic pressures, and ureteral perfusions. No effect on urine flow was detected. Experiments with rats also demonstrated the effect of the drug on the ureter.*

There are few drugs that have ureteral action. Histamine, the antihistamines, serotonin, and now, bradykinin are effective (*1, 2*). Reserpine is not effective even though significant amounts of catecholamine are found in dog and human ureters (*3*).

Bradykinin, a polypeptide, is formed from the α-globulin of plasma by the enzyme kallikrein and can be formed by proteolytic enzymes of snake venom (*4, 5*). Bradykinin has several effects: stimulation of smooth muscle, vasodilation, increasing capillary permeability, stimulation of leucocyte migration, and production of pain (*6, 7*). It has been suggested to be an active agent in inflammation, allergy, pruritus, dermatitis, the pain of migraine and intermittent claudication, and other disorders (*4*). The substance has been synthesized successfully (*8*); we used synthetic bradykinin.

Experiments were performed in dogs to determine the effect of bradykinin on ureteral pressures, each consisting of a control experiment followed by the administration of several doses of bradykinin at suitable intervals. In two of the experiments, seven different graded doses were given, while in one a continuous infusion was given for 10 minutes. Peristalsis was allowed to return to the frequency, amplitude, and wave form of the control before a subsequent dose was administered. Five experiments were performed under simultaneous cinefluorographic observation. The intravenous dosage ranged between 0.25 μg and 10.5 μg per kilogram of body weight. The threshold intravenous dose was 0.25 to 0.50 μg/kg. In one experiment, a continuous intravenous infusion of 2.8 μg/kg per minute for 10 minutes produced a continuous effect.

In general, there was an increased frequency of peristalsis within 15 seconds after administration. When the doses were higher, the onset was noted within 10 to 12 seconds (see Fig. 1).

The base line of intraluminal resting pressure tended to rise with the larger doses. Frequencies of 11 to 16 peristaltic contractions per minute were recorded; the frequencies in controls had ranged between 3 and 8 per minute. The duration of effect varied from 30 seconds to 2 minutes. Subsequently, there was a period of inactivity lasting 1 to 3 minutes during which occasional, slightly irregular peristalsis was noted. Complete recovery occurred between the 10th and 20th minutes.

Whatever doubt may have arisen about the real nature of an effect of bradykinin on the ureter during the studies of peristaltic pressure was removed by the changes in peristalsis observed cinefluorographically. Four intact unoperated animals were observed in five experiments, and four animals with bladder explants were observed in five experiments under cinefluorography in the course of our study of their peristaltic pressures. Two dogs with bladder explants were observed in the absence of catheters, and two dogs with ureteral stenoses and three with transureteroureterostomy were also observed.

The dosage varied between 2.6 and 30 μg/kg. Peristaltic frequency generally increased for a period of 30 to 60 seconds during which time the bolus diminished in size and the ureter emptied itself more or less completely. The intensity and duration of this effect were dose dependent. There was then a gradual lessening of peristaltic hyperactivity with dilatation of the system and with the ureter filled so as to outline the calyces and the renal pelvis. The effect sometimes lasted into the 5th minute, though often it was over in the 2nd minute. Occasionally a peristaltic block, retrograde waves, ineffective peristalsis, or complete inactivity were noted in the ureters that were abnormal or operated upon. In the recovery period, occasional dyskinetic peristalsis was noted as late as 10 to 35 minutes. During some experiments, filling seemed to be temporarily greater than it had been during the control period. In one experiment in which bradykinin and histamine were administered one after the other, the effect was greater than that seen after each drug was used singly.

Bradykinin did not change the urine flow of the animals with bladder explants. In one experiment, the urine flow in a dehydrated dog was measured