Bovine Liver Glutamate Dehydrogenase

SEQUENCE OF A HEXADECAPETIDE CONTAINING A LYSYL RESIDUE REACTIVE WITH PYRIDOXAL 5'-PHOSPHATE*

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SUMMARY

Glutamate dehydrogenase is reversibly inhibited by the reaction of 1 mole of pyridoxal 5'-phosphate per mole of subunit polypeptide chain of the enzyme. Reduction of the pyridoxal 5'-phosphate-inactivated enzyme with NaBH₄, followed by alkylation of the thiol groups and subsequent tryptic digestion, yielded a single fluorescent peptide which after acid hydrolysis, gave approximately 1 eq of e-pyridoxyllysine. This peptide was recognized by its amino acid composition as an overlap of two tryptic peptides which had been isolated and sequenced independently. The hexadecapeptide has the sequence: Cys-Ala-Val-Val-Asp-Pro-Val-Phe-Gly-Gly-Ala-Lys*-Ala-Gly-Val-Lys.

For several years our laboratory has been engaged in a study of the amino acid sequence of bovine liver glutamate dehydrogenase (L-glutamate:DPN (TPN) oxidoreductase (deaminating), EC 1.4.1.3). We have found that the six subunit polypeptide chains are identical and contain a minimum of 507 residues. A tentative sequence has been almost completely deduced from peptides derived from tryptic, cyanogen bromide, and peptic digests of the X-carboxymethylated protein and from the maleylated X-carboxymethylated and oxidized protein. Having elucidated most of the sequence of the enzyme, we have now begun to investigate the functional groups which may be involved in its catalytic and regulatory behavior.

Anderson, Anderson, and Churchich (1) have reported that the enzyme is inactivated by incubation with pyridoxal-5'-P. This inactivation was reversed by dialysis and stabilized by NaBH₄ reduction. e-Pyridoxyllysine was identified in acid hydrolysates of the reduced phosphorylpyridoxyl-enzyme. By assuming a molecular weight of 56,000 per polypeptide chain of the enzyme is inactivated by incubation with pyridoxal-P. This inactivation was reversed by dialysis and stabilized by NaBH₄. e-Pyridoxyllysine was identified in acid hydrolysates of the reduced phosphorylpyridoxyl-enzyme. By assuming a molecular weight of 56,000 per polypeptide chain of the enzyme, based on our present sequence information, the quantitative data of Anderson et al. (1) have been recalculated to indicate that 0.7 to 0.9 mole of pyridoxal-5'-P reacted per peptide chain to give 90% inactivation. Thus, a stoichiometry of one pyridoxal-5'-P reacting to inactivate one subunit chain is indicated. We wish to report the isolation and sequence of a hexadecapeptide containing the e-amino group of the lysyl residue which is reactive with pyridoxal-5'-P.

EXPERIMENTAL PROCEDURES

Glutamate dehydrogenase was purchased from Boehringer (Mannheim, Germany). Trypsin treated with l-((1-tosylamido-2-phenyl)-ethyl chloromethyl ketone, carboxypeptidase A, and carboxypeptidase B were obtained from Worthington. Pyridoxal-5'-P and DPN were purchased from Calbiochem, NaBH₄ from Metal Hydrides, Inc., and aminopeptidase M from Henley and Company, Inc., of New York.

Glutamate dehydrogenase activity was determined by the method of Anderson et al. (1).

Preparation of Labeled Enzyme—Approximately 600 mg of protein were dissolved in 500 ml of 0.05 M phosphate buffer at pH 7.3. Pyridoxal-5'-P (45 mg) was added and inactivation was allowed to take place at 40° for 30 min. The reaction mixture was then adjusted to pH 4.5 and brought to 25°. The inactivated enzyme was reduced by the method of Dempsey and Christensen (2) by the slow addition of 250 mg of NaBH₄ in 10 ml of water. After 1 hour at room temperature the reaction mixture was reduced in volume by rotary evaporation under vacuum and then dialyzed. The cysteinyl residues of the protein were carboxymethylated by treatment with iodoacetic acid by the procedure of Appella and Tomkins (3).

Preparation of Pyridoxal-5'-P-labeled Peptide—Inactivated, carboxymethylated enzyme (560 mg) was hydrolyzed with trypsin (25 mg) in a volume of 50 ml at 25°. The pH was maintained at 8.1 by the addition of 0.1 N NaOH by a Radiometer TTTl titrator. The reaction was terminated after 3 hours when the rate of NaOH uptake reached a minimum.

The pyridoxal-5'-P-labeled tryptic peptide was isolated by column chromatography on Dowex 1-X2 with the buffers described by Schroeder et al. (4), followed by column chromatography on Sephadex G-50 with 30% acetic acid as solvent, and then by descending paper chromatography with 1-butanol-pyridine-acetic acid-water (15:10:3:12) as solvent. This solvent system was also used in descending paper chromatography of column eluate fractions. Peptides were detected in column eluates with ninhydrin after alkaline hydrolysis (5). The
The course of the reaction of pyridoxal-5'-P (3.2 x 10^{-4} M) with the dehydrogenase (4 x 10^{-5} M) at 40° in 0.05 M phosphate buffer at pH 7.30 is shown in Fig. 1. Aliquots of the reaction mixture were added to assay mixtures, and the initial velocities of DPN reduction were determined at 25° (1). When pyridoxal-5'-P was added to the enzyme in a molar ratio of 80:1, activity dropped rapidly to a minimum after about 15 min. Thus, the observation of glutamate dehydrogenase inactivation by pyridoxal-5'-P (1) was confirmed.

Isolation and Characterization of Pyridoxal-5'-P-labeled Peptide—The dehydrogenase (10 μmoles), which was inactivated with pyridoxal-5'-P, was reduced with NaBH₄. It was then carboxymethylated and hydrolyzed with trypsin, as described above. The tryptic digest was applied to a column of Dowex 1-X2. The elution profile of the tryptic peptides is shown in Fig. 2. Aliquots of all pooled fractions were run on descending paper chromatography. Only Fraction 1 showed the fluorescence characteristic of a pyridoxal-5'-P-derivative.

Fraction 1 from the Dowex 1-X2 column was then applied to a column of Sephadex G-50; its elution profile is shown in Fig. 3. Fractions A and B, which contained fluorescent material, were concentrated by rotary evaporation. Each fraction was then applied to paper for descending chromatography. Although six or seven ninhydrin-positive bands could be detected, only one band (RF, 0.22) was fluorescent under ultraviolet light. This peptide was eluted from paper with 30% aqueous acetic acid.

The acidic hydrolysate of the pyridoxal-5'-P-labeled peptide was detected by its fluorescence under ultraviolet light when spotted on paper.

Amino Acid Analysis—Samples were hydrolyzed in evacuated glass tubes at 110° for 22 or 72 hours with 6 N HCl containing 1 drop of 1% phenol in water. Analyses were performed with the Spinco automatic amino acid analyzer, model 120B (6). e-Pyridoxyllysine was identified by its elution time in this system (7) with the color value for leucine (6). Reported yields of peptides are uncorrected for losses in handling during the isolation procedures, removal of aliquots, etc.

Sequence Studies—Techniques used in sequence studies, that are not specifically described, have been previously given by Kasper and Smith (8).

RESULTS

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Fraction 1 from the Dowex 1-X2 column was then applied to a column of Sephadex G-50; its elution profile is shown in Fig. 3. Fractions A and B, which contained fluorescent material, were concentrated by rotary evaporation. Each fraction was then applied to paper for descending chromatography. Although six or seven ninhydrin-positive bands could be detected, only one band (RF, 0.22) was fluorescent under ultraviolet light. This peptide was eluted from paper with 30% aqueous acetic acid.

The acidic hydrolysate of the pyridoxal-5'-P-labeled peptide...
revealed a fluorescent spot with a mobility similar to that of arginine on paper electrophoresis at pH 1.9. Amino acid analysis gave the following results (values from the sequence are given parenthetically): Cm-Cys, 0.43(1); Ala, 2.83(3); Val, 3.52(4); Asp, 1.23(1); Pro, 0.92(1); Phe, 0.80(1); Gly, 3.25(3); \( \epsilon \)-pyridoxyllysine, 0.50(1); Lys, 0.18(1). Although the yield of the pyridoxal-5'-P-labeled peptide was only 5.8% of theoretical, it should be noted that the yields of the authentic tryptic peptides of which it is composed, T1 and T2 (see below), were approximately 16% of each. The lower yield of the pyridoxal-5'-P-peptide may also reflect incomplete reduction by borohydride at the acidic pH value at which this was performed.

Hydrolysis of the peptide with carboxypeptidase B for 5 hours released only lysine, whereas hydrolysis with carboxypeptidases A plus B for the same time liberated alanine, glycine, valine, and lysine in apparently equivalent amounts (paper electrophoresis at pH 1.9). Thus, the COOH-terminal terminal sequence is (Ala,Gly,Val)-Lys.

Further, the COOH-terminal data obtained for unlabeled glutamate dehydrogenase revealed a fluorescent spot with a mobility similar to that of arginine on paper electrophoresis at pH 1.9. Amino acid analysis gave the following results (values from the sequence are given parenthetically): Cm-Cys, 0.43(1); Ala, 2.83(3); Val, 3.52(4); Asp, 1.23(1); Pro, 0.92(1); Phe, 0.80(1); Gly, 3.25(3); \( \epsilon \)-pyridoxyllysine, 0.50(1); Lys, 0.18(1). Although the yield of the pyridoxal-5'-P-labeled peptide was only 5.8% of theoretical, it should be noted that the yields of the authentic tryptic peptides of which it is composed, T1 and T2 (see below), were approximately 16% of each. The lower yield of the pyridoxal-5'-P-peptide may also reflect incomplete reduction by borohydride at the acidic pH value at which this was performed.

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The above results indicate that the labeled component has the composition of a hexadecapeptide containing 1 residue of unlabeled lysine at the COOH terminus and 1 residue of pyridoxal-5'-P-lysine substituted at the \( \epsilon \)-amino group. Thus the isolated material should represent the sum of the compositions of two overlapping tryptic peptides. Comparison of the composition of the pyridoxal-5'-P-peptide with the sequence data obtained for unlabeled glutamate dehydrogenase revealed that the sum of two tryptic peptides uniquely fitted the composition of the hexadecapeptide. Further, the COOH-terminal data obtained with the labeled peptide were consistent with the composition of a unique tetrapeptide derived from the protein (see below, Peptide T2). The isolation of these two tryptic peptides will be presented together with others isolated from the same digest, but the sequence information is given here in order to render complete the description of the pyridoxal-5'-P-hexadecapeptide. For convenience the complete sequence is shown in Fig. 4 with the two tryptic peptides and an overlapping peptide derived from a peptic digest.

The abbreviations used are: Cm, carboxymethyl; PTH, \( \epsilon \)-pyridoxyllysine.

The values for Cm-cysteine and \( \epsilon \)-pyridoxyllysine are uncorrected for destruction during acid hydrolysis.

Hydrolysis for 72 hours.

Peptide T1—The composition of Peptide T1 was ascertained by acidic hydrolysis for 24 and 72 hours and by hydrolysis with aminopeptidase M (9). The results indicate the presence of 1 residue each of Cm-cysteine and aspartic acid; asparagine was absent from the enzymic digest. All of the data for this peptide are summarized in Table I.

Five steps of the Edman degradation allowed identification of the NH2-terminal sequence as Cm-Cys-Ala-Val-Ala-Asp. Hydrolysis by carboxypeptidases A plus B released lysine and almost as much alanine, indicating the COOH-terminal sequence as Ala-Lys. Significant quantities of glycine and phenylalanine were also liberated, but the presence of 2 glycine residues in the peptide allowed several possible interpretations of these data.

Hydrolysis with chymotrypsin yielded two peptides which were separated by preparative paper electrophoresis at pH 1.9. Peptide T1-C1 had a lower electrophoretic mobility than Peptide T1-C2. The composition of Peptide T1-C1 indicated that it was derived from the NH2 terminus of the parent peptide. Since the NH2-terminal pentapeptide sequence of Peptide T1 had been determined, the COOH terminus of Peptide T1-C1 was obviously (Pro,Val)-Phe, in accord with chymotryptic hydrolysis at the aromatic residue. Carboxypeptidase A, which does not remove residues adjacent to prolyl residues, liberated only phenylalanine from Peptide T1-C1, indicating the COOH-terminal sequence to be Pro-Val-Phe. Peptide T1-C2 contained alanine and lysine, which were COOH-terminal in the parent peptide, plus 2 residues of glycine which must be NH2-terminal. Two steps of the Edman degradation confirmed the sequence Gly-Gly for the NH2 terminus, and indicated the sequence of Peptide T1-C2 to be Gly-Gly-Ala-Lys.

Peptide T2—This peptide had the composition: Ala, 0.08(1); Gly, 0.13(1); Val, 1.04(1); Lys, 1.02(1); yield, 16%. Two steps of the Edman degradation established the NH2-terminal sequence, Ala-Gly, and allowed valine to be placed by difference.

Step 1: PTH-Ala; residue: Ala, 0.98(1); Gly, 0.97(1); Val, 1.05(1); Lys(1) (not determined).

Step 2: PTH-Gly; residue: Ala, 0.97(0); Gly, 0.20(0); Val, 1.00(1); Lys(1) (not determined).

The sequence of this tetrapeptide is in accord with its position at the COOH-terminal end of the labeled hexadecapeptide inasmuch as these are the 4 residues released by the carboxypeptidases. It is noteworthy that the action of these enzymes is blocked by the presence of pyridoxal-5'-P attached to the lysyl residue.

A dodecapeptide isolated from a peptic digest of Cm-cysteine-glutamyl dehydrogenase had the following composition: Ala, 2.52(3); Val, 2.03(3); Asp, 1.00(1); Pro, 1.08(1); Phe, 0.92(1); Gly, 2.08(2); Lys, 1.08(1). Tryptic hydrolysis of this peptide yielded two components which were separated by preparative paper electrophoresis at pH 1.9. Peptide Pe-T1 (Fig. 4) had a lower electrophoretic mobility than Pe-T2. Peptide Pe-T1 had the composition: Ala, 2.05(2); Val, 2.46(3); Asp, 1.00(1); Pro, 0.98(1); Phe, 0.94(1); Gly, 2.01(2); Lys(1) (not analyzed). Pe-T2 proved to be free alanine, identified by electrophoresis at pH 1.9. This dodecapeptide clearly lacks the amino-terminal Cm-cysteine residue and the COOH-terminal 3 residues of the labeled hexadecapeptide. Thus, it could have been derived only from this portion of the sequence of the dehydrogenase.

This value is low after only 24-hour hydrolysis because of the presence of a Val-Val bond.
the e-amino group of a specific lysine in the protein. After inactivates glutamate dehydrogenase by covalently bonding to NaBH₄ reduction and tryptic digestion, a hexadecapeptide containing this pyridoxal-5'-P-labeled lysine residue was isolated. 

Thus, we conclude that pyridoxal phosphate and the substituted maleimide react with the same lysyl residue of the dehydrogenase. This reaction results in the addition of the e-amino group of lysine across the double bond of the maleimide portion of this compound. A partial sequence of the chain of the dehydrogenase indicates that this hexadecapeptide comprises residues 86 to 101 and places the labeled lysyl residue around this labeled lysine, as presented by these authors, in comparison with that of the pyridoxal-5'-P-labeled hexadecapeptide determined in this investigation and that given by Holbrook and Jeckel (11) for a peptide labeled with a maleimide derivative (ASPM). SCMC, S-carboxymethylcysteine; PLP, pyridoxal-5'-P.

### DISCUSSION

The results reported above show that pyridoxal 5'-phosphate inactivates glutamate dehydrogenase by covalently bonding to the e-amino group of a specific lysine in the protein. After NaBH₄ reduction and tryptic digestion, a hexadecapeptide containing this pyridoxal-5'-P-labeled lysine residue was isolated. Its composition uniquely places it as an overlap of two tryptic peptides which were isolated independently. Examination of the sequence information presently available for the polypeptide chain of the dehydrogenase indicates that this hexadecapeptide comprises residues 86 to 101 and places the labeled lysyl residue at position 97, according to the present tentative numbering of the residues.⁶

Holbrook and Jeckel (11) have recently reported the labeling of the e-amino group of a specific lysine residue of glutamate dehydrogenase by reaction with the inhibitor, N-(N'-acetyl-L-sulfamoylphenyl)maleimide. This reaction results in the addition of the e-amino group of lysine across the double bond of the maleimide portion of this compound. A partial sequence around this labeled lysine, as presented by these authors, in comparison with that of the pyridoxal-5'-P-labeled hexadecapeptide isolated by us is shown in Fig. 5. It is evident that the two peptides resemble one another. Examination of our sequence data for the entire polypeptide chain of the dehydrogenase leads us to believe that the sequence given by Holbrook and Jeckel (11) is incorrect, since there is no other region of the molecule which could accommodate the partial sequence deduced by them. Thus, we conclude that pyridoxal phosphate and the substituted maleimide react with the same lysyl residue of the dehydrogenase.

The differences between the two sequences (Fig. 5) can probably be attributed in part to an incorrect amino acid analysis for the maleimide substituted peptide. Thus, proline, which gives a low color yield with ninhydrin (6), was presumably overlooked or considered to be negligible in quantity. Also, cysteine was not detected in their study, but an extra residue of aspartic acid was reported in their analysis (11). It is conceivable that during reaction with the maleimide or in the subsequent handling cysteine was oxidized (or modified in another manner) to yield a product chromatographically similar to aspartic acid. Since the bovine glutamate dehydrogenase used in both studies was obtained from the same supplier, there appears to be no other reasonable explanation for the differences in composition, nor is there any obvious explanation for the difference in sequence proposed for the 2 residues NH₂-terminal to the labeled lysyl residue.

### DISCUSSION

<table>
<thead>
<tr>
<th>Composition (yield, 16%)</th>
<th>Acidic hydrolysis</th>
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<tbody>
<tr>
<td></td>
<td>Cm-Cys, 0.43(1); Ala, 2.06(2); Val, 2.88⁶ (3); Asp, 1.10(1); Pro, 1.01(1); Phe, 0.98(1); Gly, 2.20(2); Lys, 0.96(1)</td>
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<td>16 hrs: Cm-Cys, 0.95(1); Ala, 2.06(2); Val, 2.98(3); Asp, 1.00(1); Pro, 0.95(1); Phe, 0.95(1); Gly, 2.06(2); Lys, 1.05(1)</td>
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<tr>
<td>Aminopeptidase M</td>
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<td>Edman degradation</td>
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<td>Step 1</td>
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<td></td>
<td>Residue: Cm-Cys, 0.00(0); Ala, 2.00(2); Val, 2.62⁶ (3); Asp, 1.04(1); Pro, 1.04(1); Phe, 0.92(1); Gly, 2.04(2); Lys(1)⁷</td>
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<tr>
<td>Step 2</td>
<td>PTH-Ala</td>
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<td>Step 3</td>
<td>PTH-Val; residue: Cm-Cys, 0.00(0); Ala, 1.17(1); Val, 2.03(2); Asp, 0.97(1); Pro, 1.03(1); Phe, 0.83(1); Gly, 2.20(2); Lys(1)⁷</td>
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<tr>
<td>Step 4</td>
<td>PTH-Val</td>
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<td>Step 5</td>
<td>PTH-Asp; residue: Cm-Cys, 0.00(0); Ala, 1.30(1); Val, 1.52(1); Asp, 0.59(0); Pro, 0.99(1); Phe, 0.88(1); Gly, 2.14(2); Lys(1)⁷</td>
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<td>Carboxypeptidases A and B</td>
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<td>Chymotryptic peptides</td>
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<tr>
<td>C-1 (yield, 49%)</td>
<td>PTH-Gly</td>
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<tr>
<td>Carboxypeptidase A</td>
<td>PTH-Gly; residue: Gly, 0.35(0); Ala, 1.00(1); Lys (1)⁸</td>
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<td>C-2 (yield, 69%)</td>
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<tr>
<td>Edman degradation</td>
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<td>Step 1</td>
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<td>Step 2</td>
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<td>Carboxypeptidases A and B</td>
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⁶ Hydrolysis for 72 hours.
⁷ Hydrolysis for 24 hours only: Val-Val bond was not completely hydrolyzed.
⁸ Not determined.
⁹ Identified by paper chromatography with 1-butanol-glacial acetic acid-water (200:30:75, by volume) as the solvent system.

**Table I**

Amino acid sequence of Peptide GDH-T1

**Fig. 5.** Comparison of the sequences of the pyridoxal-5'-P-hexadecapeptide determined in this investigation and that given by Holbrook and Jeckel (11) for a peptide labeled with a maleimide derivative (ASPM). SCMC, S-carboxymethylcysteine; PLP, pyridoxal-5'-P.
a lysyl residue. Colman and Frieden (12) have shown that
acetic anhydride at low concentration reacts with one amino
group per subunit chain to cause inactivation. Similarly,
2,4,6-trinitrobenzenesulfonic acid (13) and carbamyl phosphate
(14) inactivate the enzyme by reacting with approximately one
lysine ε-amino group per subunit chain. In view of the specific
reactions of pyridoxal-5'-P and N-(N'-acetyl-4-sulfamoylphenyl)
-maleimide with the enzyme, one may reasonably expect all of
these reagents to inactivate glutamate dehydrogenase by covalently bonding to the ε-amino group of the lysyl residue tenta-
tively assigned to position 97.

It should be recalled that glutamate dehydrogenase is one of
the few enzymes involved in amino acid metabolism that does
not require pyridoxal-5'-P as a cofactor. The participation of
pyridoxal-5'-P-dependent enzymes in other pathways for the
metabolism of glutamic acid suggests that the reaction of pyri-
doxal-5'-P with the dehydrogenase may function physiologically
as a regulatory effector in amino acid metabolism. Before the
nature and significance of this inhibitory reaction can be fully
appraised, however, a thorough study is required of the effect of
this substance in relation to substrates and other effectors. Such
an investigation is now in progress.

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McNall for performing the amino acid analyses and Mr. Larry
Tabata for his technical assistance.

REFERENCES

Bovine Liver Glutamate Dehydrogenase: SEQUENCE OF A HEXADECAPETIDE CONTAINING A LYSYL RESIDUE REACTIVE WITH PYRIDOXAL 5'-PHOSPHATE
Dennis Piszkiewicz, Michael Landon and Emil L. Smith


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