Inactivation of Avian Myeloblastosis Virus DNA Polymerase by Specific Binding of Pyridoxal 5'-Phosphate to Deoxynucleoside Triphosphate Binding Site

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Avian myeloblastosis virus (AMV) DNA polymerase is inactivated by preincubation with pyridoxal 5'-phosphate. This inactivation is relatively specific since various pyridoxal-5'-P analogs cause no inactivation. This effect is reversible but can be made irreversible by reduction with sodium borohydride; the reduced pyridoxal-5'-P adduct exhibits a new absorbance maximum at 325 nm and a fluorescence emission at 392 nm when excited at 325 nm. The evidence presented suggests the formation of a Schiff base between pyridoxal-5'-P and a nucleophilic residue of AMV DNA polymerase. The presence of a deoxynucleoside 5'-triphosphate (dTTP) protected the enzyme from inactivation. Reduction of the pyridoxal-5'-P enzyme complex in the presence or absence of a deoxynucleoside 5'-triphosphate showed that the α subunit possesses five reactive amino groups, one of which is essential for catalytic activity; the β subunit has three reactive amino groups which are not involved in the deoxynucleoside binding site.

Pyridoxal 5'-phosphate serves as a prosthetic group for a variety of enzymes including aminotransferases, deaminases, and other enzymes concerned with reactions involving amino acids (1); it is also an essential constituent of phosphorylase (2, 3). In these enzymes it is present as a Schiff base linked to the ε-amino acid group of a lysine residue (4, 5). Aside from its normal functions in enzyme catalysis, pyridoxal-5'-P, with its active aldehyde also combines with lysine residues of a number of enzymes even in cases where it is not required for catalytic activity (6-10).

In order to gain more information on the nature of the active site of avian myeloblastosis virus DNA polymerase we selected pyridoxal-5'-P as an active site-directed reagent. This reagent is useful because it possesses a phosphate group which can direct it to a triphosphate binding site in the active center of the DNA polymerase and also a reactive aldehyde group which can form an adduct with the ε-amino group of lysine (7, 10).

In this report we present the results of an examination of the effects of pyridoxal-5'-P on AMV DNA polymerase. This study includes a characterization of the inactivation of the enzyme by pyridoxal-5'-P which occurs through apparent reaction to the deoxynucleoside triphosphate binding site. A preliminary report of these results has appeared (11).

EXPERIMENTAL PROCEDURES

Materials—Unlabeled and labeled triphosphates were obtained from Schwarz/Mann BioResearch, specific activities (Curies/mmol) were: [γ-32P]ATP, 17.3; ATP, 13; dGTP, 8.5. Whatman phosphocellulose P-11 was from H. Reeve Angel, Inc. All synthetic polynucleotides used were obtained from Collaborative Research. Pyridoxal-5'-P, pyridoxal, and pyridoxamine-5'-P were purchased from Sigma Chemical Co.; pyridoxine was obtained from Schwarz/Mann; pyridoxamine and pyridoxine-5'-P were purchased from Nutritional Biochemical Corp.; sodium borohydride (NaBH₄) was obtained from Fisher Scientific; Hepes buffer was purchased from Calbiochem.

Virus—Avian myeloblastosis virus was obtained from the plasma of infected chicks provided through Contract NO1CP33291 within the Virus Cancer Program of the National Cancer Institute. The virus was concentrated and purified as described (12).

Enzymes—AMV DNA polymerase was assayed essentially as described (13). The reaction mixture contained in a final volume of 0.1 ml: 50 mM Hepes (pH 8.3), 6 mM MgCl₂, 0.4 mM dithiothreitol, 50 mM KCl, 0.2 mM each of dATP, dGTP, dCTP, and 0.125 mM [3H]dTTP (80 to 300 cpm/pmol). Reactions were incubated at 37°C for 30 min and stopped by transfer to 4°C. To each reaction 0.2 mg of bovine serum albumin, 0.2 mg of yeast RNA, and 10 μmol of pyrophosphate were added followed by cold trichloroacetic acid to final concentration of 10%. After allowing the reaction mixtures to incubate for 10 min at 4°C, acid-insoluble material was collected on Whatman GF/C filters. Filters were washed with 10% trichloroacetic acid and the radioactivity was counted. AMV DNA polymerase was purified as described by Kacian et al. (14). Isolation and purification of the α subunit was performed according to the procedure described by Papas et al. (15). The purified fraction of AMV DNA polymerase showed two distinct bands on sodium dodecyl sulfate gel electrophoresis (Fig. 1), representing the two subunits β and α of Mr = 97,000 and 63,000.

Protein Measurements—Protein was determined by measuring the relative intensity of fluorescence upon excitation at 375 nm and emission at 490 nm as described by Bohlen et al. (16).

Enzyme Inactivation—Treatment of DNA polymerase with pyridoxal-5'-P was carried out in the dark. When the enzyme was assayed after reacting with pyridoxal-5'-P the assay mixture contained the same concentration of pyridoxal-5'-P as the precipitation mixture; these conditions prevented dissociation of the complex.

Reduction with Sodium Borohydride—The enzyme (88 μg/ml) was incubated with 1 mM pyridoxal-5'-P at room temperature for 30 min in the dark. The solution was cooled to 0°C and brought to pH 4.5 by addition of 1 M acetic acid. Octyl alcohol was added in order to avoid foaming. A freshly prepared solution of sodium borohydride, dissolved in 0.1 M sodium hydroxide to avoid acid-catalyzed decomposition, was added in 10-fold excess with respect to pyridoxal-5'-P. During the reduction, the pH was maintained at 4.5 by addition of 1 M acetic acid. The reaction was completed within 10 min. The reduced complex was then dialyzed overnight against 10 mM potassium phosphate buffer, pH 8.0. Absorption spectra of the dialyzed complex
were added sequentially 25 ~1 of 1 N acetic acid to bring the pH to 4.5, proceed for 30 min in the dark at 25°C. To the solutions cooled in ice sodium lauryl sulfate. The amount of tritium label present in the (Y and 6 subunits was estimated by fractionating the gel in a Gilson electrophoretically in 8% polyacrylamide gels in the presence of serum albumin as a carrier. Tritium-labeled enzyme was analyzed tritium incorporation into foreign products present in dialysis sacks, against 10 mM sodium phosphate buffer, pH 8. In order to avoid the dialysis tubing was boiled for 20 min in 0.2 N Na2CO3 containing cold and the excess of reactants was removed by extensive dialysis water, cold water, 0.5 mM HCl, and finally by cold water. 0.01% NaBH4. The treated membranes were washed with boiling water, cold water, 0.5 mM HCl, and finally by cold water.

The incorporation of tritium label into the polymerase was measured in the trichloroacetic acid-precipitable material, using 70 μg of serum albumin as a carrier. Tritium-labeled enzyme was analyzed electrophoretically in 8% polyacrylamide gels in the presence of sodium lauryl sulfate. The amount of tritium label present in the α and β subunits was estimated by fractionating the gel in a Gilson Aliquogel fractionator and counting the radioactivity of the individual sections.

Polyacrylamide Gel Electrophoresis − Polyacrylamide gel electrophoresis in the presence of sodium dodecyl sulfate and molecular weight determinations were performed as described by Dunker and Rueckert (18). Molecular weight markers used for the calibration curve were: β-lactoglobulin (18,400), ovalbumin (45,000), bovine serum albumin (68,000), phosphorylase a (95,000), and β-galactosidase (130,000). Staining of the protein bands was accomplished as described elsewhere using Coomassie blue (18). Protein samples labeled with 13C by reductive alkylation (19) were subjected to electrophoresis in acrylamide gels using N,N'-diallyltartadiamide as cross-linking agent (20). After electrophoresis, gels were fractionated in the Gilson Aliquogel fractionator and dissolved with 2% periodic acid, and the radioactivity was measured.

RESULTS

Inhibition of AMV DNA Polymerase by Pyridoxal-5'-P−DNA polymerase was inactivated by preincubation with pyridoxal-5'-P. To study this effect, the enzyme was preincubated with pyridoxal-5'-P and then analyzed in assay mixtures that also contained the reagent. It was necessary to add pyridoxal-5'-P to the assay mixture to avoid dissociation of enzyme-reagent complexes. The inhibition of DNA polymerase activity was dependent on the concentration of pyridoxal-5'-P (Fig. 2); 50% inhibition was obtained at a concentration of 0.2 mM pyridoxal-5'-P and complete inhibition at 1 mM.

Effect of Analogs of Pyridoxal-5'-P on AMV DNA Polymerase Activity − Analogs were tested for their effect on the enzyme activity at a concentration of 1 mM (Table I). In each case, complete inhibition was observed only with pyridoxal-5'-P, therefore, both the aldehyde and the phosphate groups were required for complete inhibition.

Effect of Primary Amino Groups on Pyridoxal-5'-P Inhibition of AMV DNA Polymerase − Complete inhibition of the enzyme by pyridoxal-5'-P was regularly observed except when the buffer system contained primary amino groups, as in the case of Tris, when only partial inhibition was observed. In the presence of high concentrations of Tris (known to react reversibly with the aldehyde group of pyridoxal 5'-phosphate) the enzyme was inhibited by only 54%. Since the enzyme is capable of reacting with free pyridoxal 5'-phosphate obtained from the dissociation of the pyridoxal 5'-phosphate−Tris complex, it appears that the enzyme has a high affinity for pyridoxal 5'-
The document discusses the binding of pyridoxal 5'-phosphate (PLP) to AMV DNA polymerase. It includes experimental procedures, results, and tables detailing the effects of various compounds on the enzyme's activity.

### Table I

**Effect of pyridoxal-5'-P analogs on activity of AMV DNA polymerase as tested by different template-primers**

| Analog tested | Remaining activity (Poly[d(A-T)]) | Remaining activity (PolyA-dTTP) | Remaining activity (PolyC-dGTP) |
|---------------|-----------------------------------|---------------------------------|---------------------------------|
| None          | 23.2 ± 0.10                      | 63.70 ± 1.00                    | 238.5 ± 0.05                    |
| Pyridoxal     | 24.1 ± 0.10                      | 61.20 ± 1.00                    | 234.1 ± 0.10                    |
| Pyridoxal-5'-P| 0.1 ± 0.4                        | 1.1 ± 1.0                       | 1.41 ± 0.7                      |
| Pyridoxine    | 25.2 ± 0.10                      | 59.8 ± 0.9                      | 241.3 ± 1.0                     |
| Pyridoxine-5'-P| 22.5 ± 0.10                     | 66.3 ± 1.0                      | 228.1 ± 0.9                     |
| Pyridoxamine  | 23.5 ± 0.10                      | 64.2 ± 0.9                      | 218.8 ± 1.0                     |
| Pyridoxamine-5'-P| 26.4 ± 0.10                | 66.5 ± 0.9                      | 231.7 ± 0.9                     |

### Table II

**Effect of Tris/HCl on pyridoxal-5'-P inhibition of AMV DNA polymerase**

| Buffer               | Remaining activity (pmol) | Remaining activity (%) |
|----------------------|---------------------------|------------------------|
| Tris/HCl             | 92.85 ± 0.05              | 100.0                  |
| Tris/HCl + pyridoxal-5'-P | 38.18 ± 0.05             | 46.0                   |
| Heps                 | 94.81 ± 0.05              | 100.0                  |
| Heps + pyridoxal-5'-P| 0.34 ± 0.05               | 0.3                    |

### Table III

**Effect of primary amino groups on pyridoxal-5'-P inhibition of AMV DNA polymerase**

| Additions                  | Remaining activity (pmol) | Remaining activity (%) |
|---------------------------|---------------------------|------------------------|
| Complete                  | 79.97 ± 0.05              | 100.0                  |
| + Cycloserine             | 112.56 ± 0.05             | 141.0                  |
| + Pyridoxal-5'-P         | 1.78 ± 0.05               | 2.0                    |
| + Pyridoxal-5'-P + cycloserine | 73.03 ± 0.05           | 92.0                   |

The high affinity of pyridoxal 5'-phosphate for the enzyme results from the interaction between the phosphate moiety of pyridoxal 5'-phosphate and the active site of the enzyme. This interaction stabilizes the enzyme in the presence of pyridoxal-5'-P and protects it against inhibition by other compounds.

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Binding of Pyridoxal 5'-Phosphate to AMV DNA Polymerase

Fig. 3. Absorption spectra of unreduced and reduced pyridoxal-5'-P enzyme complex. A, absorption spectra of pyridoxal-5'-P enzyme unreduced complex. DNA polymerase (88 µg/ml) was incubated with excess pyridoxal-5'-P at room temperature for 30 min in the dark. This was read against an identical sample without enzyme. A 6-fold dilution of each was performed prior to reading. B, absorption spectra of sodium borohydride reduced pyridoxal-5'-P enzyme complex. DNA polymerase (88 µg/ml) was incubated with excess pyridoxal-5'-P at room temperature in the dark. After 30 min, the mixture was cooled to 0°C, reduced, and dialyzed as described under "Experimental Procedures." The reference was a sample treated identically but without pyridoxal-5'-P.

Fig. 4. Fluorescent spectra of sodium borohydride-reduced pyridoxal-5'-P enzyme complex. The fluorescence of the reduced sample from Fig. 3D was measured upon excitation at 325 nm. ∆, reduced aldolase-pyridoxal-5'-P complex (positive control); ○, reduced AMV DNA polymerase-pyridoxal-5'-P complex; □, AMV DNA polymerase alone.

Fig. 5. Lineweaver-Burk plots of AMV DNA polymerase activity as a function of template and deoxynucleoside triphosphate concentration in the presence of pyridoxal-5'-P. ○——○, absence of pyridoxal-5'-P; △——△, presence of 1 mM pyridoxal 5'-P; □——□, presence of 3 mM pyridoxal-5'-P.

Table IV

| Preincubation mixtures** | Remaining activity |
|-------------------------|--------------------|
|                         | RNA-dependent†     | DNA-dependent†     |
| Enzyme                  | 100.0              | 100.0              |
| + Pyridoxal-5'-P        | 80.0               | 40.0               |
| + dTTP                  | 105.0              | 105.0              |
| + Poly(A)-dT_{12-18}    | 28.0               | 28.0               |
| + Poly(d(A-T))          | 36.0               | 36.0               |

** DNA polymerase (0.58 µg) was incubated at room temperature for 10 min, where indicated 0.05 mM pyridoxal phosphate, 0.04 mM dTTP, 20 µg/ml of poly(A)-dT_{12-18}, 20 µg/ml of poly(d(A-T)). After 10 min aliquots were removed and assayed for enzymatic activity in the presence of 1 mM pyridoxal 5'-P.

† Poly(A)-dT_{12-18} was used as the template at 20 µg/ml.

and β band in electrophoresis, the relative distribution of radioactivity in the α and β subunit was calculated (Table VI). From the relative distribution number and the total number of pyridoxal phosphate groups in the αβ dimer, obtained from spectrophotometric studies (Table V), it was possible to calculate the absolute number of pyridoxal phosphate groups incor-
Polymerase. Approximately 6000 cpm of H bound to protein were
estimated using a value of 8,300 for the extinction coefficient at 325 nm.

The fractionation of the gels applied in 1% 2-mercaptoethanol and 1% sodium dodecyl sulfate over a 8% acrylamide gel using N,N'-diallyltartadiamide as the cross-linking agent. Electrophoresis was carried out at 7 mA/gel until the bromophenol blue marker reached 8 cm. The fractionation of the gels and measurements of radioactivity were carried out as described in the text. A, H-labeled polymerase in the absence of dTTP; B, H-labeled polymerase labeled in the presence of 10 mM dTTP.

FIG. 6. Sodium dodecyl sulfate-polyacrylamide gel electrophoresis of pyridoxal phosphate/tritium borohydride-labeled AMV DNA polymerase. Approximately 6000 cpm of H bound to protein were applied in 1% 2-mercaptoethanol and 1% sodium dodecyl sulfate over a 8% acrylamide gel using N,N'-diallyltartadiamide as the cross-linking agent. Electrophoresis was carried out at 7 mA/gel until the bromophenol blue marker reached 8 cm. The fractionation of the gels and measurements of radioactivity were carried out as described in the text. A, H-labeled polymerase in the absence of dTTP; B, H-labeled polymerase labeled in the presence of 10 mM dTTP.

Table V

| Enzyme form | Inactivation* | Absorbance/ml | Moles of pyridoxal-5'-P bound/mol of enzyme |
|-------------|--------------|---------------|---------------------------------------------|
| α           | 98.0         | 0.99 ± 0.03   | 8.98 ± 0.23                                 |
| α + dTTP    | 100.0        | 0.37 ± 0.01   | 8.21 ± 0.11                                 |
| αβ + dTTP   | 0.0          | 0.33 ± 0.01   | 7.20 ± 0.20                                 |

* The percentage of inactivation represents the degree of inhibition of the unreduced pyridoxal-5'-P enzyme complex. Assays were performed as described under "Experimental Procedures.

Purified α subunit (880 µg/ml) and native enzyme αβ(880 µg/ml) were incubated for 10 min at room temperature in the presence or absence of 10 mM TTP. Then 1 mM pyridoxal-5'-P was added and the incubation was continued for 30 min in the dark. The solutions were cooled to 0°C, and the pH adjusted to 4.5 with 1 M acetic acid. Freshly prepared NaBH₄ was added to a final concentration of 10 mM and the pH was readjusted to 4.5. The reaction was completed within 10 min and the reaction mixture was dialyzed overnight against 10 mM potassium phosphate buffer, pH 8.0. The quantity of pyridoxal-5'-P bound/mol of protein was estimated spectrophotometrically using a value of 8,300 for the extinction coefficient at 325 nm. Molecular weights of α and αβ were 63,000 and 160,000, respectively.

Table VI

| Enzyme conditions | [H]α | Reactive NH₄ |
|-------------------|------|--------------|
|                   | [H]β | αβ | α' | β' |
| 0 mM TTP          | 1.78 | 8 | 5 | 3 |
| 10 mM TTP         | 1.45 | 7 | 4 | 3 |

* Ratio of H label in α and β subunits as determined from sodium dodecyl sulfate polyacrylamide gel electrophoresis analysis (Fig. 6).

Number of amino groups reactive toward pyridoxal-5'-P. Determined from spectrophotometric studies (Table V).

DISCUSSION

Reverse transcriptase is involved in the replicative cycle of RNA tumor viruses (22, 23). The enzyme transcribes its high molecular weight RNA genomic into DNA, a process known to be essential in the infectious process of these viruses. AMV DNA polymerase copies heteropolymeric regions of poly(A) containing RNAs and under certain conditions it can make a complete cDNA copy (24). The enzyme requires both a template-primer and deoxynucleoside triphosphates and is unable to initiate DNA chain synthesis de novo in the absence of a primer containing a 3'-OH terminus. The biological importance of this enzyme as well as its usefulness as an analytical tool, prompted us to study both its mechanism of action and chemical structure (13, 15, 25, 26).

Pyridoxal-5'-P, in addition to its catalytic function to certain enzyme systems (1, 3), has become a useful active site-directed reagent (27). The inactivation of AMV DNA polymerase is relatively specific for pyridoxal-5'-P since various analogs cannot inactivate the enzyme (Table I); the specificity of inhibition is therefore a result of both the aldehyde and phosphate groups. The interaction of pyridoxal-5'-P with the enzyme has been demonstrated to involve the formation of a Schiff base between the enzyme and amino groups of the protein. Studies with NaBH₄, reduction of pyridoxal-inactivated enzyme affords supporting evidence for a primary Schiff base formation in the inactivation process. The fluorescence emission band at 390 nm observed when the pyridoxal enzyme is excited at 325 nm is likewise characteristic of a Schiff base formation.

Preincubation of the enzyme with the substrate (dTTP) prevents the binding of pyridoxal-5'-P and results in the maintenance of catalytic activity; such protection cannot be obtained when the enzyme is preincubated in the presence of...
template-primer (Table IV). In addition, pyridoxal-5'-P is a competitive inhibitor of deoxynucleoside triphosphate (dTTP) but not of the template-primer (Fig. 5). Thus pyridoxal 5'-P appears to bind at or near the active site of the enzyme.

Borders et al. (28) have shown that AMV DNA polymerase is inactivated by butanedione, a reagent which selectively modifies arginyl residues. In their case, the enzymatic activity was protected by template-primer but not by deoxynucleoside triphosphate. They concluded that arginyl residues are essential for binding of template-primer to the active site. Comparison of their findings with those presented here suggest that the enzyme possesses two independent binding sites: the deoxytriphosphate site which involves a single essential amino group located in the α subunit of the enzyme and a template-primer binding site involving essential arginine residue(s). Early work by Papas et al. (13) showed that sequential addition of substrates resulted in a synergistic protection of the enzymatic activity against heat inactivation. This can be explained by a stabilization of the different regions of the active site as a result of interaction between the binding site and their respective ligands. The suggestion of independent binding sites obtained from heat inactivation (13) is now strongly supported by specific chemical modification with butanedione (28) and pyridoxal-5'-P.

Spectrophotometric studies of pyridoxal-5'-P enzyme formed in the presence or absence of dTTP shows that the αβ enzyme form possesses eight reactive groups, one of which is protected by dTTP. Under similar conditions the isolated α subunit possesses nine reactive groups, one of which is protected by dTTP. Reduction of pyridoxal-5'-P enzyme with [3H]NaBH₄, allows the incorporation of tritium label into the stable pyridoxal group of the complex. Electrophoretic analysis of labeled αβ enzyme prepared in the presence and absence of dTTP substrate allows a calculation of the relative distribution of the pyridoxal groups in the α and β subunits. The β subunit has three reactive groups, none of which is protected by dTTP, while the α subunit has five reactive groups, one of which is protected by dTTP and is therefore essential for catalytic activity. The single group which is essential for catalytic activity is located in the α subunit and is not buried during the interaction of the subunits. It is interesting to note that the β subunit of the αβ form does not have a binding site for deoxytriphosphate.

It is well documented that a precursor relationship exists between the β and α subunits (15, 29, 30). The larger β subunit contains a polypeptide with a molecular weight of 31,000 in addition to the α sequences (10). The presence of this peptide could induce changes in the tertiary structure of the sequences corresponding to the α region of the β subunit and alter the configuration of the deoxytriphosphate binding site. Alternatively, the absence of this site could be the result of steric hindrance in the region of α and β interactions. Lack of reliable procedures for the isolation of the β subunit has limited our efforts to test these possibilities.

We are presently concentrating our efforts on the isolation and sequencing of peptides containing the essential residue for the deoxytriphosphate binding site. These studies will be expanded to other oncornavirus polymerases available in our laboratory including those from fish (31), reptiles (32), and mammals in an effort to determine the degree of conservation of the primary amino acid sequences in the region of the deoxytriphosphate binding sites.

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T S Papas, T W Pry and D J Marciani

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