Activity of Guinea Pig Liver Transglutaminase toward Ester Analogs of Amide Substrates*

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SUMMARY

Calcium-activated guinea pig liver transglutaminase catalyzes the hydrolysis and aminolysis of γ-glutamyl methyl and ethyl ester analogs of a specific amide substrate, benzoylcarbonyl(Z)-L-glutaminylglycine. Kinetic comparisons of amine incorporation into the γ-N-methylamide, and the γ-methyl and ethyl esters of Z-L-glutamylglycine indicate that the same acyl-enzyme intermediate is formed from each of these substrates. The differences in catalytic efficiency toward these substrates are due to differences in rates of formation of this intermediate, and may be a consequence of different orientations of the leaving groups (−OR and −NHR) at the catalytic site of the enzyme. An aliphatic ester, methyl acetate, and its amide analog, N-methylacetamide, are about equally effective, although poor substrates for transglutaminase. This, together with the fact that the acyl-enzyme intermediate is formed from the γ-methyl ester of Z-L-glutamylglycine and from its γ-N-methylamide at approximately the same rate, is strong evidence that C−O and C−N bonds are about equally susceptible to cleavage by transglutaminase.

The ability of an alcohol to function as an acyl acceptor in a transglutaminase-catalyzed amide transfer reaction and the reversibility of the ester to amide conversion have been demonstrated with the use of a fluorescent-labeled alcohol derivative, N-(5-dimethylaminonaphthalenesulfonyl)-5-amino-1-pentanol.

Guinea pig liver transglutaminase catalyzes hydrolysis and aminolysis of the carboxamide group of peptide-bound glutamine residues (for review see Ref. 1). Certain aliphatic amides (2) and p-nitrophenyl esters (active esters) (3-5) are also substrates. Chemical and kinetic studies (4-6) support an hypothesis that these reactions proceed through the formation of acyl-enzyme intermediates, probably thiol esters, formed between an essential sulfhydryl group in the Ca2+-activated enzyme and the acyl portion of substrates. The kinetic data of hydrolysis and amine transfer (5, 6) conform to Mechanism I, in which an acyl-enzyme, F, is partitioned between water and another acceptor nucleophile.

* This communication is the ninth paper in the series “Mechanism of Action of Guinea Pig Liver Transglutaminase.” The preceding paper is Ref. 7.
bonds to cleavage by the enzyme. The finding that an alcohol may be enzymatically incorporated in place of the —NH₂ at the carboxamide group of peptide-bond glutamine residues is a clear demonstration that alcohols, like primary amines, may function as acceptor nucleophiles (Substrate B in Mechanism 1) in transglutaminase-catalyzed reactions.

**Experimental Procedure**

**Materials**

Transglutaminase was prepared from guinea pig liver by a published procedure (9). The enzyme exhibited 95 ± 5% of the reported specific activity when assayed by hydroxamate formation with the substrate benzoyloxycarbonyl-L-glutaminylglycine (10).

An extinction coefficient of $E_{280} = 15.8$ and a molecular weight of 90,000 were used to determine enzyme concentration (10).

[14C]Methylamine·HCl (6.17 mCi per mmole) was purchased from New England Nuclear, N-(5-aminopentanyl)-5-dimethylaminol-naphthalene sulfonamide (monodansylcadaverine) from Cyclo. Cellulose phosphate paper assay strips (7) were prepared on a custom basis by Reeve Angel.

Z-L-glutamyl(γ-ethyl ester)glycine, Z-L-glutamyl(γ-methyl ester)glycine and Z-L-aspartyl(β-ethyl ester)glycine were prepared by a procedure similar to that used by Miller and Waelsch (11) for preparation of Z-L-glutamyl(γ-ethyl ester)glycine. An ω-methyl- or ethyl ester of the dicarboxylic amino acid was converted to its Z-derivative and coupled by means of a mixed anhydride procedure (isobutylchloroformate and triethylamine in dioxane) with glycine benzyl ester. The Z-ω-methyl- or ethyl ester dipeptide benzyl ester was hydrogenated in 95% ethanol with a palladium black catalyst. The resultant dipeptide benzyl ester was finally converted to the Z-derivative with benzyloxycarbonyl chloride under mild alkaline conditions.

Z-L-glutamyl(γ-ethyl ester)glycine was recrystallized from water (m.p. 55-56°; value found in the literature, 54° (11)). Z-L-glutamyl(γ-methyl ester)glycine was recrystallized from water (m.p. 115-117°).

**Methods**

Rate studies were conducted at 30° in 0.1 M Tris-chloride buffer, pH 7.0, containing 1 mm EDTA, 50 mM CaCl₂, and 30 mM NaCl. Measurement of [14C]methylamine incorporation was carried out by means of a cellulose phosphate paper strip ion exchange procedure (7). The enzymatic methylamine incorporation reactions were terminated in the incubation tubes by making solutions 20 mM in iodoacetamide. Hydroxylamine incorporation was measured by the use of the calorimetric FeCl₃ procedure as described previously (10). An extinction coefficient of 340 M⁻¹ cm⁻¹ at 525 nm for the product, Z-L-glutamyl(γ-N-hydroxamido)glycine, was determined by the use of synthetic material.

Stock solutions of peptide derivatives (about 0.2 m) were prepared by dissolving weighed amounts of the materials in appropriate volumes of 0.2 M NaOH. These solutions were adjusted to pH 7.0. The exact concentrations were determined on aliquots by amino acid analysis after acid hydrolysis (8).

For kinetic experiments, conditions were adjusted such that no more than 10% of the substrate of the lowest concentration was consumed during the reaction period. The nomenclature is, in general, that of Cleland (12). For clarity, the definitions of certain kinetic constants that have been previously defined (6) are given in the footnote to Table I. The kinetic constant $k$ designates an inhibitor or dissociation constant, $K$ the Michaelis constant for hydrolysis, and the Michaelis constant for transfer.

Reciprocal velocities were plotted graphically against reciprocals of substrate concentration. The data were fitted to Equation 1 assuming equal variance for the velocities. Final estimates of certain kinetic constants were made by fitting the data points to Equation 2, that for amine incorporation in Mechanism 1. All fits were performed by the use of an interactive curve-fitting program, MLAB, developed at the National Institutes of Health and running on a PDP-10 digital computer (13).

A sensitive procedure (14), utilizing the thin layer chromatographic separation of fluorescent amine and the fluorescent product of amine incorporation, was employed for comparison of rates of hydroxamate formation between the standard and the sample.

$$v = \frac{V}{K + A}$$

$$v = \frac{V_{0}AB}{K_{s}K_{u} + K_{s}B + K_{u}A + AB}$$

1 The abbreviation used is: Z-, benzoyloxycarbonyl. This extract was found to contain four fluorescent components resolved by chromatography on silica gel (Eastman chromatogram sheets) with 10% (v/v) methanol in benzene. The mixture of reaction products was applied to a column (2.5 x 63 cm) of silica gel (0.05 to 0.2 mm, Brinkmann) which had been equilibrated with benzene. Following a wash with 1 liter of benzene, elution was carried out using 2% methanol (v/v) in benzene. The product emerged from the column between 1.8 and 1.9 liters of eluant. The fractions containing the product were combined and the solvents were removed under vacuum. The resulting oil crystallized on standing; yield was 0.9 g (70%). It was recrystallized from aqueous ethanol (m.p. 77.5°), R₈ of 0.5 in the above chromatography system.

C₁₇H₂₄N₂O₅S (336.5)

Calculated: C 60.7, H 7.2, N 8.3

Found: C 61.0, H 7.3, N 8.2

Other materials and reagents are described in earlier publications (2, 7, 8).

**Calculation**

Calculated: C 54.7, H 6.0, N 12.0

Found: C 54.7, H 5.7, N 11.7

NH₂-(5-Dimethylaminonaphthalenesulfonyl)-5-aminol-1-pentanol (5-dansylaminol-1-pentanol)—To a solution of 1.5 g of 5-aminopentanol (Albrieh) and 0.53 ml of triethylamine in 5 ml of water was added 1 g of dansyl chloride (Pierce) and 5 ml of ether. This reaction mixture was stirred vigorously in a glass-stoppered tube at room temperature for 16 hours. The ether was removed by evaporation in a stream of nitrogen and the resulting water-insoluble oil was extracted into benzene. The benzene extract was dried over anhydrous Na₂SO₄ and examined by thin layer chromatography.

**Note**

Z-L-glutamyl(γ-N-hydroxamido)glycine was prepared in a manner similar to that described here for the γ-N-methyamide derivative. Z-L-glutamyl(γ-ethyl ester)glycine was converted to the hydroxamate during 18 hours at pH 9 in 2 M NaH₂O₆. The product was purified by ion exchange chromatography using a 3.2-liter linear gradient from 1.0 to 2.6 mM in acetic acid. The product which was eluted between 1.7 and 2 liters was crystallized from water and recrystallized from aqueous acetic acid. This material was obtained in 60% yield and melted at 127°. It showed satisfactory values upon elemental analysis.
of monodansyleadaverine incorporation into amide and ester substrates. In this case measurement of monodansyleadaverine incorporation was made on developed chromatographic plates by the use of a Zeiss spectrophurometer equipped with a chromatogram scanning device. The excitation wavelength was 365 nm and a FC 46 emission filter was used. Incorporation of the fluorescent alcohol, 5-dansylamino-1-pentanol, was measured in the same manner. The fluorescent ester (RF ~ 0.1) and the fluorescent ester product (RF = 0) were separated on polyamide sheets using 1% pyridine in water adjusted to pH 5.6 with acetic acid (14).

RESULTS

That Z-L-glutamyl-γ-N-methylamido)glycine acts as a substrate for transglutaminase in the [14C]methylamine incorporation reaction (Table I) was as expected. This is an example of an isotope exchange reaction, several of which have already been shown to be catalyzed by the enzyme (5, 6). We did not anticipate that Z-L-glutamyl(γ-ethyl ester)glycine and Z-L-glutamyl(γ-methyl ester)glycine, the ester analog of the γ-N-methylamide, would function as substrates. In fact, it was concluded from an early survey of transglutaminase-catalyzed hydroxamate formation that the γ-ethyl ester acted as an inhibitor, but not as a substrate, for the enzyme (15). This incorrect conclusion is understandable in light of the poor substrate properties of this ester compared to Z-L-glutaminylglycine (Table I) and the insensitive assay used.

When the initial velocities of methylamine incorporation into the γ-methyl and γ-ethyl esters of Z-L-glutaminylglycine were measured at several concentrations of [14C]methylamine and the data were plotted in the usual fashion (for example, see Ref. 6), interesting patterns were obtained that were consistent with the steady state equation (Equation 2) for formation of Q, radioactive product, in Mechanism I. The kinetic constants, estimated from these data, together with those obtained for the glutamine substrate and for the γ-N-methylamide substrate, are given in Table I. Also given in Table I are the $K_m$ values and maximum velocities for hydroxamate formation with these substrates obtained at a high level of hydroxylamine.

The question arises, is the activity of transglutaminase toward the two esters listed in Table I manifest as a consequence of their structural similarity to glutamine (and γ-N-substituted glutamine) substrate? There is substantial evidence that straight chain aliphatic amides, such as acetamide, function as substrates for transglutaminase because of their structural relationship to the side chain portion of peptide-bound glutamine residues, i.e. that these aliphatic amides bind at the glutamine side chain binding site in the enzyme (2). Since the γ-N-methyl derivative of Z-L-glutaminylglycine and its ester analog are substrates (Table I), one would anticipate that N-methyl acetamide and its ester analog, methyl acetate, would also act as substrates. Indeed, this proved to be the case. Curves 4 and 5 of Fig. 1 show the slow, but similar, rates of monodansyleadaverine incorporation into the two compounds. The rates of fluorescent amine incorporation into acetamide (Curve 3) and into Z-L-glutaminylglycine (Curve 1) under the same experimental conditions are shown in this figure for comparative purposes.

It was not possible, because of their very limited water solubility, to test the substrate properties of branched chain aliphatic esters, such as methyl isobutyrate and methyl isovalerate. These esters are analogous of the N-methyl derivatives of those branched chain amides that do not act as substrates, i.e. α-methylpropionamide and β-methylbutyramide, respectively (2). Therefore, Z-L-aspartyl (β-ethyl ester) glycine was tested. This compound is the ester analog of the N-methyl derivative of Z-L-asparaginylglycine. The asparagine peptide derivative is not a substrate for transglutaminase (5, 16). Z-L-Aspartyl (β-ethyl ester) glycine did not act as a substrate (Curve 6, Fig. 1). No incorporation of fluorescent amine was found even after 24 hours of incubation under conditions of Fig. 1.

Formamide is not a substrate for transglutaminase (2). It has been suggested that this is the case because this amide has no hydrophobic attraction to the glutamine side chain binding site of the enzyme. We tested methyl formate, the ester analog

| $V_v$, $V_{av}$, and $V_{max}$, the maximum velocities for hydrolysis, for transfer with methylamine and for transfer with hydroxylamine, respectively, are expressed in micromoles per min (per mole of enzyme). |
|---|---|---|---|
| $K_{cat}$ (nm) | $k_3 + k_8$ | $k_8 + k_3$ |
| $K_{cat}$ (nm) | $k_3 + k_8$ | $k_8 + k_3$ |
| $K_{cat}$ (nm) | $k_3 + k_8$ | $k_8 + k_3$ |
| $K_{cat}$ (nm) | $k_3 + k_8$ | $k_8 + k_3$ |
| $v_0 = \frac{k_3 \beta E_0}{k_3 + k_3}$ |
| $V_{max}$ (nm) | $K_{cat}$ (nm) | $K_{cat}$ (nm) |
| $V_{max}$ (nm) | $K_{cat}$ (nm) | $K_{cat}$ (nm) |
| $V_{max}$ (nm) | $K_{cat}$ (nm) | $K_{cat}$ (nm) |
| $V_{max}$ (nm) | $K_{cat}$ (nm) | $K_{cat}$ (nm) |
| $v_0 = \frac{k_3 \beta E_0}{k_3 + k_3}$ |
| $V_{max}$ (nm) | $K_{cat}$ (nm) | $K_{cat}$ (nm) |
| $V_{max}$ (nm) | $K_{cat}$ (nm) | $K_{cat}$ (nm) |
| $V_{max}$ (nm) | $K_{cat}$ (nm) | $K_{cat}$ (nm) |
| $V_{max}$ (nm) | $K_{cat}$ (nm) | $K_{cat}$ (nm) |
| $v_0 = \frac{k_3 \beta E_0}{k_3 + k_3}$ |
| $V_{max}$ (nm) | $K_{cat}$ (nm) | $K_{cat}$ (nm) |
| $V_{max}$ (nm) | $K_{cat}$ (nm) | $K_{cat}$ (nm) |
| $V_{max}$ (nm) | $K_{cat}$ (nm) | $K_{cat}$ (nm) |

* The constants are defined as (9):
mixtures were applied to polyamide sheets ("Methods"), quickly ethyl ester)glycine. At the times shown, 1-J aliquots of reaction Curve 2, 500 mM acetamide; Curve S, 60 mM Z-L-glutaminylglycine; 50 mM CaCl₂, 1 mM EDTA, and 1 mg of enzyme per ml. The levels pH 6, containing 0.2 mM fluorescent amine or fluorescent alcohol; The reactions were carried out at 37° in 0.1 M Tris-acetate buffer, of amides and esters were: Curve 1, 60 mM Z-L-glutaminylglycine; Curve 4, 500 mM methyl acetate; Curve 5, 500 mM N-methyl acetamide; Curve 6, 500 mM methyl formate or 60 mM Z-L-aspartyl(β-ethyl ester)glycine. At the times shown, 1-mg aliquots of reaction mixtures were applied to polyamide sheets ("Methods"), quickly dried in a stream of air, and chromatographed. The percentage of incorporation designates the percentage of the total amine or alcohol incorporated.

of the N-methyl derivative of formamide, and found that, indeed, this ester is not a substrate (Curve 6, Fig. 1).

The ability of an alcohol to act as an acceptor nucleophile in a transglutaminase-catalyzed reaction is demonstrated clearly in Curve 3 of Fig. 1. Here 5-dansylamino-1-pentanol, the alcohol analog of monodansylcadaverine, is incorporated in place of the -NH₂ at the carboxamide group of Z-L-glutaminylglycine. The slow rate of incorporation compared to that of monodansylcadaverine, is evident by comparison of Curves 1 and 8, Fig. 1.

The kinetic data for amine incorporation with the y-methyl amide and esters k₆, the rate of enzyme acylation limiting for both hydrolysis and transfer to amine, i.e. k₂ < k₇ and k₆. This follows from the facts that (a) V₃ = Vₑ₃ (Equations 4 and 5, respectively) for each substrate; (b) V₃ and Vₑ₃ = k₃E when k₃ < k₇ and k₆; and (c) these maximum velocities are significantly smaller than the Vₑ₃ value for Z-L-glutaminylglycine. With this glutamine substrate acylation is not the rate-controlling step for hydrolysis, i.e. k₃ > k₆. This has been pointed out earlier (5) and derives from the fact that the velocity for amine incorporation is significantly faster than that for hydrolysis, i.e. Vₑ₃ > V₆. It is not known whether k₃ is limiting for transfer with the glutamine substrate. It is, however, obvious that the rate of acylation, k₆, with this substrate is much faster than with the other substrates in Table I.

The maximum velocities for hydroxylamine incorporation recorded in Table I are larger than those for methylamine incorporation. It has been suggested that the normal enzymatic mechanism may be perturbed by the high concentration of hydroxylamine necessary in the assays (5). Inconsistencies with the acyl-enzyme theory observed with other enzymes in experiments with hydroxylamine have been assumed to be a result of mechanism perturbations caused by this strong nucleophile (17). Comparison of the Vₑ₃ and Vₑ₆ values in Table I suggests that the rates of enzyme acylation with the N-methylamide and esters are also rate-limiting for hydroxamate formation. The relative differences between the maximum velocities for transfer to methylamine and hydroxylamine are similar and the Vₑ₆ value for the glutamate substrate is much larger than those for the methylamide and esters. The fact that Z-L-glutamyl(γ,N-methylamido)glycine and its methyl ester analog display almost identical maximum velocities for both methylamine and hydroxylamine incorporation is strong evidence for approximately equal rates of enzyme acylation by these two compounds which differ only in the scissile bond, i.e. a C—N or a C—O bond. Thus, it may be concluded that these bonds are about equally susceptible to cleavage by transglutaminase. This is supported by the similar rates of monodansyleadaverine incorporation with N-methylacetamide and its ester analog, methyl acetate (Fig. 1). It is likely that enzyme acylation is also limiting with these acetyl derivatives, as appears to be the case with acetamide (2).

The chemical structure of the side chain portion, R, in the reactions of acyl-enzyme intermediate with water and added nucleophile, methylamine in this case. It is totally independent of the rate of formation of acyl-enzyme. Pronounced differences in Kₑ₆ values have been found for substrates that contain different acyl groups (5, 8), as well as for substrates that contain the same acyl group, but where different nucleophiles were added (5). The fact that the substrates of Table I show the same Kₑ₆ values with methylamine is further evidence in support of the acyl-enzyme mechanism.

Accepting the evidence for a common acyl-enzyme intermediate formed from each substrate of Table I, one may conclude that, with the γ-N-methylamide and the γ-methyl and γ-ethyl esters k₆, the rate of enzyme acylation limiting for both hydrolysis and transfer to amine, i.e. k₂ < k₇ and k₆. This follows from the facts that (a) V₃ = Vₑ₃ (Equations 4 and 5, respectively) for each substrate; (b) V₃ and Vₑ₃ = k₃E when k₃ < k₇ and k₆; and (c) these maximum velocities are significantly smaller than the Vₑ₃ value for Z-L-glutaminylglycine. With this glutamine substrate acylation is not the rate-controlling step for hydrolysis, i.e. k₃ > k₆. This has been pointed out earlier (5) and derives from the fact that the velocity for amine incorporation is significantly faster than that for hydrolysis, i.e. Vₑ₃ > V₆. It is not known whether k₃ is limiting for transfer with the glutamine substrate. It is, however, obvious that the rate of acylation, k₆, with this substrate is much faster than with the other substrates in Table I.

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The chemical structure of the side chain portion, R, in the

\[ Kₑ₆ = \frac{k₃(k₄ + k₆)}{k₆} \]
leaving group (—OR or —NHR) of transglutaminase substrates has a notable influence upon the rate of enzyme acylation. This has been observed previously with amide substrates (5, 18) and glutaminylglycine and its N-methyl derivative. In this case substitution of a methyl for a hydrogen in the R position of the leaving group results in a large decrease in the rate of enzyme acylation. Comparison of the maximum velocities for the two ester substrates of Table I shows that a small change in the size of the leaving group results in a large decrease in the rate of enzyme acylation. These changes may be a consequence of different arrangements of the leaving groups in the active site of the enzyme. Dislocation of the amide or ester bond enough to change, but not to curtail, acylation could result.

When \( k_3 \) is rate-limiting, i.e. \( k_3 < k_1 \) and \( k_1 \), as in the case of the \( \gamma\-N\-methylamide and the esters of Table I, and one assumes \( k_2 > k_{\text{cat}} \), \( K_{\text{cat}} \) (Equation 6) reduces to \( K_m \) (Equation 7), the enzyme-substrate dissociation constant. The differences in \( K_{\text{cat}} \) values for these three substrates are not great. In the hydroxylamine incorporation reaction enzyme acylation may be rate-limiting with \( Z\-L\-glutamylglycine, as well as with the other substrates. If so, the recorded \( K_m \) values are comparable measures of enzyme substrate affinity under the conditions of this assay. That these values are essentially the same for all of the substrates is in agreement with earlier indications that hydrophobic interactions alone in the glutamine side chain binding region of the active site of the enzyme do not play the major role in the over-all binding of substrates (8). There is evidence that the amino acids (or other residues) surrounding the glutamine moiety make a significant contribution to this binding (8).

The \( p\)-nitrophenyl (active) ester hydrolysis and transfer reactions catalyzed by transglutaminase are consistent with Mechanism I (5). The isolation of a stable trimethylacetyl-enzyme (4) is strong support for an acyl-enzyme mechanism with the ester bond enough to change, but not to curtail, acylation could result. That an aliphatic alcohol derivative, 5-daiisylamino-1-panitol, functions as an acceptor for the acyl group in a transglutaminase-catalyzed amide reaction (Fig. 1) is consistent with the action of the enzyme on esters of aliphatic alcohols and clearly demonstrates the reversibility of the reaction. The slow rate of incorporation of this alcohol derivative compared to monodansylcadaverine, its amine analog (Curves 1 and 3, Fig. 1), probably results from its weaker nucleophilicity.

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