Metabolism of Leukotriene C4 in \(\gamma\)-Glutamyl Transpeptidase-deficient Mice

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We have investigated the metabolism of leukotriene C4 (LTC4) in \(\gamma\)-glutamyl transpeptidase (GGT)-deficient mice (Lieberman, M. W., Wiseman, A. L., Shi, Z.-Z., Carter, B. Z., Barrios, R., Ou, C.-N., Chevez-Barrios, P., Wang, Y., Habib, G. M., Goodman, J. C., Huang, S. L., Lebovitz, R. M., and Matzuk, M. M. (1996) Proc. Natl. Acad. Sci. U. S. A. 93, 7923–7926) and have found substantial conversion of LTC4 to leukotriene D4 by high performance liquid chromatography and continuous flow fast atom bombardment-tandem mass spectrometric analyses. LTC4-converting activity has a tissue distribution different from GGT with highest activity in spleen followed by small intestine, kidney, and pancreas and lower activity in liver and lung. The activity is membrane-bound and is inhibited by acivicin, a known inhibitor of GGT. The enzyme was partially purified from the small intestine of GGT-deficient mice by papain treatment and gel filtration chromatography. The partially purified fragment released by papain has an apparent molecular mass of 85–70 kDa and the same substrate specificity as the tissue homogenate. In addition to LTC4, S-decyl-GSH is also cleaved. GSH itself, oxidized GSH, and the synthetic substrates used to analyze GGT activity (\(\gamma\)-glutamyl-p-nitroanilide and \(\gamma\)-glutamyl-4-methoxy-2-naphthylamide) are not substrates for this newly discovered enzyme. These data demonstrate that in addition to GGT at least one other enzyme cleaves LTC4 in mice. To reflect this enzyme's preferred substrate, we suggest that it be named \(\gamma\)-glutamyl leukotrienase.

Peptidyl leukotrienes, cysteine-containing derivatives of arachidonic acid, are potent inducers of airway constriction, vasconstriction, smooth muscle contraction, edema, and inflammation (1–4). LTC4 is formed by conjugation of leukotriene A4 with GSH (5) and is known to be cleaved by GGT, which removes the glutamyl moiety to form LTD4 (6). LTC4 conversion to LTD4 has long been thought to be mediated solely by GGT (7, 8). Recently, however, the existence of an activity termed GGT-rel has been identified in humans (9). GGT-rel shares an overall 40% amino acid sequence identity with human GGT and is capable of cleaving the \(\gamma\)-glutamyl linkage of LTC4, but it is unable to hydrolyze synthetic substrates that are commonly used for assaying GGT. This activity has been reported to be absent in mice (9).

The role of GGT in leukotriene metabolism is of interest because of the great potency of these compounds in responses to injury. However, the distribution of GGT activity and the sites of peptidyl leukotriene actions are not concordant. In the mouse, GGT tends to be expressed at very high levels in epithelia concerned with catabolism of GSH and reabsorption of its constituent amino acids (kidney and small intestine) and other ductular and secretory epithelia (pancreas and seminal vesicles) (7, 10–12). It is characteristically low in organs in which leukotrienes may play a role in responses to injury (e.g. lung, heart, and lymphoid tissue (spleen)). In addition, the types of responses mediated by the peptidyl leukotrienes (vasoconstriction, bronchoconstriction, increases in vascular permeability, and mucus formation) do not occur in close proximity to sites where GGT is most abundant (13). Although there are reports of GGT activity in endothelium (14–16), the discordance between peptidyl leukotriene targets and GGT activity raises the possibility that there are other LTC4-cleaving enzymes in the mouse.

We have recently used homologous recombination to inactivate GGT in the mouse (12). Mice homozygous for this mutation are completely GGT-deficient and have the expected phenotype (glutathionemia and massive glutathionuria). Thus, they represent a useful model to evaluate the conversion of LTC4 to LTD4 in the absence of GGT. In this paper we report the results of our initial experiments in which we demonstrate the presence of an additional LTC4/LTD4-converting enzyme in the mouse.

EXPERIMENTAL PROCEDURES

Materials—GGT-deficient mice were developed in our laboratory (12). All mice used in this study were 6–7 weeks old. \(\text{glycine}-2^\text{15}\text{N}\)GSH was purchased from DuPont NEN. Bathophenanthroline disulfonic acid was obtained from GPS Chemicals (Columbus, OH), and HPLC grade methanol from Baxter Healthcare Corp. (McGaw Park, IL). LTC4, LTD4, LTE4, GSH, S-decyl-GSH, \(\gamma\)-glutamyl-p-nitroanilide, papain, and other chemicals were purchased from Sigma unless otherwise indicated.

LTC4 Conversion—Total homogenates from different tissues of both wild type and GGT-deficient female mice and the partially purified enzyme from the small intestine of GGT-deficient mice (see below) were incubated with 5 \(\mu\)M LTC4 in a total of 0.2 ml of 0.1 M Tris-HCl buffer, pH 8.0, at 37 °C for a preset time. The reaction was terminated by adding 0.8 ml of methanol and then centrifuged. The supernatant was adjusted to 13% methanol with water, and the solution was loaded onto a 3-ml octadecyl disposable extraction column (J. T. Baker Inc., Phillipsburg, NJ) conditioned as recommended by the manufacturer. The column was washed with water followed by 10% methanol to remove proteins and other impurities. LTC4 and its conversion products were eluted with methanol, dried by Speedvac, and separated by HPLC on a C18 reversed-phase column (Customsil ODS, 4.6 \(x\) 150 mm, 3-\(\mu\)m
Assay for GGT Activity—Various tissues from both wild type and GGT-deficient female mice were homogenized with a Polytron Tissue-mizer in 0.1 M Tris-HCl buffer, pH 8.0. GGT activity was assayed by incubating the homogenates from various tissues with γ-glutamyl-p-nitroanilide and Gly-Gly for a preset time at 37 °C as described (12). The specific activity is expressed as μmol of p-nitroanilide released/min/mg of protein.

GSH Metabolism—Tissue homogenates from either wild type mouse kidney or GGT-deficient mouse spleen were incubated with 0.2 mM GSH, 0.2 mM Gly-Gly, and 0.2 mM dithiothreitol in a total volume of 0.5 ml of 0.1 M Tris-HCl buffer, pH 8.0, at 37 °C for various lengths of time. In some experiments, 1 μl of lyophilized-2-HGSH (43.8 Ci/mmol, 1 μCi/μl) was added to the reaction. The reaction was stopped by adding 100 μl of 70% perchloric acid, 50 μl of 15 mM bathophenanthroline disulfonic acid, and 50 μl of 2.5 mM γ-Glu-Glu as an internal standard. Following derivatization with 2,4-dinitrofluorobenzene, the reaction was analyzed by a reversed-phase ion exchange HPLC using a 3-amino propyl column (14.6 × 200 mm, 5-μm particles; Cel Associates, Houston, TX) as described (19). The column effluent was monitored at 356 nm. The fractions were collected and counted using a Beckman LS scintillation counter.

FAB-MS/MS Analysis of LTC4 Conversion—LTC4, LTD4, and LTE4 standards and preparations from incubations of LTC4 and homogenates from both wild type and GGT-deficient mice were analyzed by reversed-phase HPLC as described above. The fractions corresponding to retention times of LTC4, LTD4, and LTE4 were collected, dried, and subjected to FAB-MS/MS analysis. Tandem mass spectrometric analyses were performed using a VG ZAB-SEQ (VG Analytical, Manchester, UK) hybrid mass spectrometer of BEqQ configuration (B, magnetic sector; E, electric sector; q, radio frequency-only quadrupole; Q, quadrupole mass filter), equipped with a VG 11−250 data system. The methods employed were similar to those previously described (20, 21). Briefly, ionization was accomplished by continuous flow FAB using xenon atoms (8 keV) for the primary atom beam. Delivery of solvent (wateracetonitrile (50:50) containing 1% saturated aqueous oxalic acid and 1% 2,2-dithiodiethanol) was via a fused silica capillary (50 μm inner diameter). Flow rate was maintained at 4.5 μl/min using a Waters prototypye syringe pump controlled by the modified output of a Waters model 680 gradient controller. Samples (10 μl) were injected using a Rheodyne model 7125 injector. The accelerating voltage was 10 kV and the ion source temperature was 70 °C. Narrow range parent ion scanning analyses were obtained by operating the instrument under hardware control. For LTC4, the instrument was set to detect parents of ions with a mass-to-charge ratio (m/z) of 308; similarly, the instrument was set to detect parents of m/z 319 for LTD4 and LTE4.

Analysis of S-decyl-GSH-cleaving Activity of GGT-deficient Mice—Homogenates from either wild type mouse kidney or GGT-deficient mouse spleen were incubated with 0.2 mM S-decyl-GSH and 0.2 mM Gly-Gly in a final volume of 0.2 ml of 0.1 M Tris-HCl buffer, pH 8.0, at 37 °C for a preset time. The reactions were stopped by adding 100 μl of 70% perchloric acid, 50 μl of 50 mM bathophenanthroline disulfonic acid, and 50 μl of 2.5 mM γ-Glu-Glu as an internal standard. Following derivatization with 2,4-dinitrofluorobenzene, the reaction was analyzed by a reversed-phase ion exchange HPLC using a 3-amino propyl column (14.6 × 200 mm, 5-μm particles; Cel Associates, Houston, TX) as described (19). The column effluent was monitored at 356 nm. The fractions were collected and counted using a Beckman LS scintillation counter.

RESULTS

Cleavage of Substrates Used to Assay GGT by GGT-deficient Mice—γ-Glutamyl-p-nitroanilide is the standard substrate used to assay GGT activity in mammalian tissues (22). As shown in Table I, GGT-deficient mice fail to cleave this substrate, while in wild type mice GGT levels are high in kidney, pancreas, and small intestine and low in spleen, lung, and liver (see also Ref. 12). These data indicate not only that GGT is absent from these mutant mice but also that no other enzyme in mice cleaves this substrate. Similarly, γ-glutamyl 4-methyx-2-naphthylamide, the usual histochemical substrate for GGT (23), was inactive as a histochemical substrate in GGT-deficient mice (data not shown), and thus, like γ-glutamyl-p-nitroanilide, it is not cleaved by other enzymes in mice.

Cleavage of LTC4 in GGT-deficient Mice—Since our previous studies did not detect any GGT activity in the GGT-deficient mice (12), we hypothesized that tissues from these mice would be unable to cleave LTC4. Our initial experiments with LTC4 were performed on wild type kidney as a positive control. When we examined homogenates of wild type kidney for the ability to metabolize LTC4, we found, as expected, that LTC4 was readily cleaved to LTD4; homogenates containing 50 μg of protein cleaved 39% of LTC4 (0.39 nmol) in 1 min with the appearance of a peak corresponding to LTD4 (Fig. 1A). Under similar conditions we were unable to detect degradation of LTC4 in homogenates of GGT-deficient kidney (not shown); however, longer incubation times (over 1 h) revealed conversion of LTC4 to LTD4 (Fig. 1B). This result indicates that LTC4-converting activity other than GGT exists in mice.

Next we surveyed a variety of tissues from GGT-deficient mice to determine the tissue distribution of this newly detected activity. We started by assaying mouse tissues that normally express little or no GGT activity such as spleen, adult liver, and lung for LTC4 metabolism (Fig. 2). We found that incubation of LTC4 with homogenates from these tissues resulted in a decrease in LTC4 (peaks 1) and the appearance of products having the same retention times as LTD4 (peaks 2) and LTE4 (peaks 3).
pears to result from this enzyme activity rather than from other processes. Under the same conditions, homogenates from wild type mouse spleen, liver, and lung also cleave LTC₄ (Fig. 2, right). Further, the cleavage of LTC₄ by homogenates from GGT-deficient mice occurs at rates comparable with those seen in preparations from wild type mice. In many tissues, we observed two new peaks following incubation, one corresponding to the retention time for LTD₄ and the other to that for LTE₄. The latter product is the result of the conversion of LTD₄ to LTE₄ by dipeptidase activity present in some tissues (2, 24).

We evaluated homogenates of pancreas and small intestine for the ability to cleave LTC₄ and found results similar to those from kidney: homogenates from GGT-deficient mice cleaved LTC₄ at much reduced rates compared with pancreas and small intestine homogenates from wild type mice (Fig. 3).

Results from these and similar experiments were used to calculate the specific activity of LTC₄ conversion for various tissues of GGT-deficient and wild type mice (Table I). In GGT-deficient mice, the highest level of this new activity is found in spleen, kidney, small intestine, and pancreas have activity levels that are about 30–40% that of spleen, while liver and lung have somewhat lower levels. In contrast, in wild type mice the highest level is found in kidney, followed by pancreas and then small intestine. This order of activity is similar to that of GGT when assayed by glycine-γ-nitroanilide (Table I; see also Ref. 12). It is of interest, however, that in tissues with low activity, monitored by HPLC, the activity could also be detected spectrophotometrically.

Evaluation of GSH and GSSG Cleavage by LTC₄-converting Activity—GGT is believed to be the major enzyme responsible for the cleavage of GSH. We were curious to know if the newly identified LTC₄-converting activity in GGT-deficient mice could also metabolize GSH. This question was examined by two approaches. The first involved monitoring the disappearance of GSH enzymatically from homogenates of spleens of GGT-deficient mice (25). We were unable to demonstrate any loss of GSH using this method (data not shown).

The second method involved HPLC and was adapted from Heisterkamp et al. (9). These investigators identified an enzyme from human material termed GGT-rel (GGT-related) that cleaved LTC₄ and suggested that it might cleave the γ-glutamyl moiety from GSH. We modified the assay conditions of Heisterkamp et al. and used nonradioactive GSH and glycine-2-3H/GSH in the incubation mixtures to improve assay sensitivity. We also added 0.2 mM dithiothreitol in the reaction to prevent the conversion of GSH to GSSG. We monitored the appearance of products (Cys-Gly, Cys, and Gly) and the disappearance of GSH spectrophotometrically or by liquid scintillation counting of HPLC effluent. No metabolism of GSH was observed with either method in the absence of homogenate (Fig. 4, A1 and B1), while kidney homogenates from wild type mice readily cleaved GSH (positive control; Fig. 4, A2 and B2). Fig. 4, A3 and B3, illustrates profiles of homogenates of spleen from GGT-deficient mice in which no loss of GSH or appearance of Cys-Gly, Cys, or Gly was detected spectrophotometrically or by liquid scintillation counting even after a 3-h incubation.

To confirm our results, we also used a partially purified enzyme preparation (see “Experimental Procedures”) to assay for the hydrolysis of GSH. We standardized conditions so that a kidney homogenate from wild type (GGT-positive) mouse and...
our partially purified preparation catalyzed the same amount of LTC₄ to LTD₄ conversion and used these to assay for GSH cleavage. We could not detect any GSH cleavage with the partially purified enzyme from the small intestine of GGT-deficient mice, while under the same conditions, the wild type kidney homogenate cleaved 13.5% (6.75 nmol) of GSH. Thus, the newly identified LTC₄-converting enzyme does not metabolize GSH or does so at a negligible rate.

Cleavage of GSSG was also evaluated. It is likely that the dipeptidase (membrane-bound dipeptidase, renal dipeptidase) that cleaves Cys-Gly generated by the action of GGT actually uses Cys-bis-Gly rather than Cys-Gly as a substrate (26). Thus, we modified both the enzymatic approach and the nonradioactive HPLC approach described above to determine if our LTC₄-cleaving activity could metabolize GSSG. In GGT-deficient mouse spleen homogenates, we could not detect cleavage of GSSG; however, when we used homogenates of wild type kidney as a positive control, GSSG cleavage was detected (data not shown). Thus, unlike GGT, the activity we have detected in GGT-deficient mice cleaves LTC₄ and does not cleave GSH or GSSG. To reflect the substrate specificity of this enzyme, we suggest that the newly identified LTC₄-converting enzyme be designated \( \gamma \)-glutamyl leukotrienase (GGL).

**General Properties of GGL**—GGL is a membrane-bound enzyme. After centrifugation of spleen homogenates from GGT-deficient mice at 45,000 \( g \) for 30 min, we recovered all of the GGL activity in the pellet. Treatment of similar homogenates with papain prior to centrifugation (22) released more than 90% of the GGL activity into the supernatant. The papain-cleaved enzyme has an apparent molecular mass of \( \sim 65 \text{ kDa} \) by gel filtration chromatography on Sephadex G-150 and 65–70 kDa by sedimentation velocity centrifugation using linear 5–20% sucrose gradient (27). Incubation at 60 °C for 5 min completely inactivated cleavage of LTC₄, but at 37 °C the enzyme was active for as long as 5 h. Acivicin, a commonly used inhibitor of GGT (28, 29), also inhibited GGL (data not shown).

We determined the \( K_m \) of LTC₄ to LTD₄ conversion by GGL to be \( 2.2 \times 10^{-6} \text{ M} \). In contrast, the \( K_m \) for this conversion by GGT was found to be an order of magnitude higher (\( 2.0 \times 10^{-5} \text{ M} \)). Inclusion of Gly-Gly, a \( \gamma \)-glutamyl acceptor, in the incubation mixture did not significantly enhance the conversion of LTC₄ to LTD₄ (data not shown). GSH does not appear to be a competitive inhibitor of GGL, since even an 80-fold molar excess of GSH in the reaction mixture does not alter the rate of cleavage of LTC₄ by GGL (data not shown).

Studies from Goffinet and Nguyen (30) demonstrated that...
mouse brain LTC₄ binding sites are also S-alkyl-GSH binding sites. S-Decyl-GSH has the strongest binding among all of the S-alkyl-GSH analyzed and had binding activity similar to LTC₄. We hypothesized that S-decyl-GSH might be a substrate for GGL and examined the cleavage of S-decyl-GSH by GGL. Our results indicated that, like GGT, GGL indeed hydrolyzes S-decyl-GSH (results not shown). We compared the $K_m$ of GGL using S-decyl-GSH as a substrate with the value we obtained when LTC₄ was used as a substrate. We found that the $K_m$ for S-decyl-GSH is about $3.0 \times 10^{-5}$ M, more than an order of magnitude higher than the value of $2.2 \times 10^{-6}$ M we found for LTC₄. The fact that GGL cleaves LTC₄ and S-decyl-GSH but not GSH, GSSG, $\gamma$-glutamyl-$\beta$-nitratoxilide, and $\gamma$-glutamyl-4-methoxy-2-naphthylamide suggests that GGL prefers hydrophobic GSH conjugates.

**DISCUSSION**

Using transgenic mice that lack GGT, we have detected an enzyme that cleaves the $\gamma$-glutamyl group from LTC₄ and generates LTD₄. The activity is highest in spleen followed by small intestine and kidney. Relatively high levels are also found in liver and lung, organs in which GGT activity is less than 1% of that seen in kidney (Table I). GGL cleaves LTC₄, but GSH and GSSG, which are the major substrates for GGT in organs such as kidney, do not appear to be cleaved by GGL. Support for this conclusion also comes from our work with GGT-deficient mice: urine levels of GSH in GGT-deficient mice are $\sim 15$ mm compared with urine levels of $\sim 6$ mM in wild type mice (12), suggesting that GGL metabolizes little, if any, of the GSH filtered or secreted by the kidney. The fact that the $K_m$ of GGL (2.2 $\times 10^{-6}$ M) is an order of magnitude lower than that of GGT (2.0 $\times 10^{-5}$ M) indicates that GGL has higher affinity for LTC₄ than GGT. Thus, LTC₄ is likely to be a physiologically significant substrate for GGL. Several possibilities may explain why the level of GGL activity is low under our assay conditions. First, the expression of GGL may be confined to certain cell types within organs, and analysis of GGL activity from homogenates of whole organs may underestimate GGL activity. Second, the GGL activity may be constitutively low, but inducible under appropriate conditions including responses to physiological stimuli or injury. Third, we cannot exclude the possibility that compounds other than LTC₄ may be better substrates for GGL.

In addition to its cleavage of LTC₄, GGL is capable of cleaving S-decyl-GSH. Although we have not tested S-GSH conjugates exhaustively, relatively long chain S-GSH conjugates of aliphatic (hydrophobic) moieties (LTC₄ and S-decyl-GSH) seem to be preferred substrates for GGL. GGL will not cleave GSH, GSSG, $\gamma$-glutamyl-nitroanilide, or $\gamma$-glutamyl-naphthylamide; all of them are good substrates for GGT. Thus, based on the substrates examined to date, GGL appears to have a more restricted substrate specificity than GGT and cleaves only some of the $\gamma$-glutamyl compounds that GGT metabolizes. At present, we have not found a compound that is a specific substrate for GGL.

In humans another enzyme, termed GGT-rel, that cleaves LTC₄ has been identified (9). It appears to be a different enzyme from GGL, since GGT-rel is not found in the mouse, and it may cleave GSH as well (9). However, at present neither GGT-rel nor GGL has been extensively characterized, and it is not inconceivable that they may represent the human and mouse counterparts of the same enzyme. Because we have not yet extensively purified GGL, it is conceivable that GGL represents more than one enzyme. However, we view this possibility as unlikely.

In addition to a partial overlap in substrate specificity, GGL and GGT share some properties. Both are membrane-bound and are inhibited by acivicin. The papain-released fragment of GGL from mouse small intestine has an apparent molecular mass of 65 kDa compared to 68 kDa for GGT from rat kidney (22). This observation must be viewed with some caution, since GGT at least is known to exist in many glycosylated forms. However, all of these observations suggest that like human GGT and GGT-rel, mouse GGT and GGL may be related. Nevertheless, GGL and GGT are clearly separate enzymes, as evidenced by the fact that we have characterized GGL in tissues of GGT-deficient mice. In addition, GGL and GGT have different substrate preferences and different tissue distributions.

The tissue distribution of the two enzymes raises several interesting questions about their functions. It is unclear, for example, why GGL is expressed in kidney, pancreas, and small intestine, where GGT is expressed at very high levels. One possibility is that GGL has other as yet unidentified functions; for example, it may cleave substrates that are not metabolized by GGT. Another possibility is that within these organs GGL and GGT have different cellular distributions. It is known, for example, that GGT is confined to the proximal tubular cells of the kidney and the villous epithelium of the small intestine (31, 32) and may function at these sites to initiate the degradation of circulating or biliary LTC₄ to LTD₄. However, much of the physiologic action of LTC₄/LTD₄ occurs at sites where responses to injury occur, such as the smooth muscle of vessels and bronchi/bronchioles, and in inflammatory exudates. GGL function may be related to these responses and occur at the sites of these responses. Thus, it is possible that in the kidney and the small intestine, for example, the metabolism of LTC₄ may be divided into two “compartments,” one concerned with physiologic function in these organs and the other with the clearance of peptidyl leukotrienes from the body. GGL activity accounts for 35–95% of the LTC₄-metabolizing activity in spleen, lung, and liver. It may be that the substrate specificity of GGL compared with GGT is an advantage in these organs. Because GSH/GSSG is not cleaved by GGL, the function of this enzyme may be important in environments in which the extracellular reducing capability of GSH is necessary but generation of LTD₄ is also required. Such conditions are met in the lung, in which GSH plays an important role in protection from oxidative injury and the generation of LTD₄ may be essential as part of the response to injury in this organ. All of the above considerations suggest that this newly identified enzyme may play a significant role in the metabolism of leukotrienes.

**Acknowledgments**—We thank Drs. Mark L. Entman, Hiram F. Gilbert, Richard N. Sifers, and Russell M. Lebovitz for helpful discussion, Yan Liu for helping with some experiments, and Cheryl L. Rognerud for technical assistance with HPLC.

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J. Biol. Chem. 1997, 272:12305-12310.
doi: 10.1074/jbc.272.19.12305

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