Synthesis and Characterization of High Affinity Inhibitors of the H⁺/Peptide Transporter PEPT2*

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In this study, we describe the rational synthesis and functional analysis of novel high affinity inhibitors for the mammalian peptide transporter PEPT2. Moreover, we demonstrate which structural properties convert a transported compound into a non-translocated inhibitor. Starting from Lys[Z(No2)]-Pro (where Z is benzyl-oxycarbonyl), which we recently identified as the first competitive high affinity inhibitor of the intestinal peptide transporter PEPT1, a series of different lysine-containing dipeptide derivatives was synthesized and studied for interaction with PEPT2 based on transport competition assays in Pichia pastoris yeast cells expressing PEPT2 heterologously and in renal SKPT cells expressing PEPT2. In addition, the two-electrode voltage clamp technique in Xenopus laevis oocytes expressing PEPT2 was used to determine whether the compounds are transported electrogenically or block the uptake of dipeptides. Synthesis and functional analysis of Lys-Lys derivatives containing benzyloxy carbonyl or 4-nitrobenzoxycarbonyl side chain protections provided a set of inhibitors that reversibly inhibited the uptake of dipeptides by PEPT2 with Kᵢ values as low as 10 ± 1 nM. This is the highest affinity of a ligand of PEPT2 ever reported. Moreover, based on the structure-function relationship, we conclude that the spatial location of the side chain amino protecting group in a dipeptide containing a dianimocarbonic acid and its intramolecular distance from the Co atom are key factors for the transformation of a substrate into an inhibitor of PEPT2.

The mammalian H⁺/peptide cotransporter PEPT2 was initially identified in the brush border membrane of renal proximal tubular cells as the high affinity subtype of the mammalian proton-coupled di- and tripeptide transporters (1). In kidney, PEPT2 is mainly responsible for the rapid and efficient uptake of a large number of different di- and tripeptides as well as various peptidomimetics from the tubular fluids into the cell. As recent studies show, PEPT2 is also expressed in a variety of other tissues such as lung and the central nervous system (2, 3), but its primary physiological function in these organs is still not known. Specific inhibitors have been extremely useful in the identification of the function and structure of numerous receptors, transporters, and enzymes, but so far no inhibitors of PEPT2 with the required specificity and affinity have been found. Recently, we identified Lys[Z(No2)]-Pro¹ as the first reversible and competitive inhibitor of the intestinal peptide transporter PEPT1 with a high apparent affinity constant (5–10 μM) (4). As PEPT2 is known to have similar but not identical structural requirements for substrate recognition and transport, this study was initiated to analyze whether Lys[Z(No2)]-Pro also inhibits PEPT2 or whether even more effective inhibitors can be obtained by alterations in the structure and hydrophobicity of this compound. Varying lysine-containing dipeptide derivatives were synthesized and submitted to structure-function analysis in three different expression systems employing competitive uptake studies with the radio-labeled dipeptides D-Phe-Ala and Gly-Sar and two-electrode voltage clamp measurements of transport-generated currents. This procedure led to a new class of high affinity inhibitors for PEPT2. It also allowed the identification of some structural features that turn a Lys-containing dipeptide substrate of PEPT2 into an inhibitor.

EXPERIMENTAL PROCEDURES

Materials—The renal cell line SKPT-0193 Cl.2 established from isolated cells of rat proximal tubules (5) was provided by U. Hopfer (Case Western Reserve University, Cleveland, OH). Glycine-1-¹⁴C Gly-Sar (specific radioactivity 53 mCi/mmol) was custom-synthesized by American Biosciences, Inc. Custom-synthesized [alanine-2,3-³H]D-Phe-Ala (specific radioactivity 40 mCi/mmol) was obtained from Biorent (Cologne, Germany). EDTA, dexamethasone, apotransferrin, Gly-Gln, and Gly-Sar were from Sigma; D-Phe-Ala was purchased from Bachem (Heidelberg, Germany). Culture media and supplements, fetal bovine serum, and trypsin solution were purchased from Invitrogen. Collagenase A was from Roche Molecular Biochemicals. Substrates and precursors were purchased from Sigma.

Synthesis of Dipeptide Derivatives—All non-commercially available dipeptide derivatives were synthesized according to laboratory standard procedures. Briefly, from Boc-Ala-OH, Boc-Val-OH and N-Boc-N-(X-Lys)-OH, and N-Boc-N-(X-Orn-OH and N-Boc-N-(X-Dab-OH (with X = Z(No2), Z, Ac, where Dab is diaminobutyric acid), respectively, we prepared the respective N-hydroxysuccinimid esters (ONSu). The activated amino acid derivatives were coupled with 1.5-fold excess of the aminos to form the desired dipeptides. The acti

1 The abbreviations used are: Z, benzyloxycarbonyl; Z(No2), 4-nitrobenzoxycarbonyl; Boc, tert-butyloxycarbonyl; Dab, diaminobutyric acid; D-Phe-Ala, D-phenylalanylalanine; Gly-Sar, glycylsarcosine; LNA, lysyl(Z[No2])-alanine; LNZ, lysyl(Z[No2])-valine; ALZN, alanyl-lysine[Z(No2)]; VLZN, valyl-lysine[Z(No2)]; LNZLZN, lysyl(Z[Ly-lysine][Z(No2)]; LNZLNZ, lysyl[Z(No2)]-lysine[Z(No2)]; PPβ3, potassium phosphate buffer; MES, 4-morpholinoethanesulfonic acid.
The crude products were purified by flash chromatography on silica gel. After removal of the Boc groups by treatment with concentrated formic acid at room temperature, the resulting dipeptide derivatives were characterized as formates. In the case of Lys[Boc]-Ala, the Z-Lys[Boc]-ONsu was coupled with alanine, and the Z-protecting group was removed by catalytic hydrogenation. The purity of the final products was evaluated by analytical reversed phase-high pressure liquid chromatography, mass spectrometry, and capillary electrophoresis, and it was found to exceed 98% in all cases. The dipeptide derivatives shown in Tables 1 and 3 were dissolved at high concentrations in dimethyl sulfoxide before preparing the respective uptake buffers.

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Interaction of Lys[Z(NO2)] Dipeptide Derivatives with PEPT2—We first determined the affinity of Lys[Z(NO2)]-Pro (LZN) and three related dipeptide derivatives containing the N-terminal Lys[Z(NO2)] moiety but varying C-terminal amino acids (Ala, Val, Sar). Using competition assays based on Lys[Z(NO2)]-Xaa derivatives, the uptake rate measured in the presence of inhibitors (260 ± 19 pmol x 15 min x 10^6 x OD^-1) was taken as 100%. n = 3, B, steady-state I-V relationships were measured by the two-electrode voltage clamp technique in oocytes expressing PEPT2 superfused with modified Barth solution at pH 6.5 and 0.2 mM Gly-Gln in the absence or presence of increasing concentrations (0–200 μM) of Lys[Z(NO2)]-Xaa derivatives. The uptake rate measured in the absence of inhibitors (260 ± 19 pmol x 15 min x 10^6 x OD^-1) was taken as 100%. n = 3, B, steady-state I-V relationships were measured by the two-electrode voltage clamp technique in oocytes expressing PEPT2 superfused with modified Barth solution at pH 6.5 and 0.2 mM Gly-Gln in the absence or presence of increasing concentrations (0–200 μM) of LZN. The membrane potential was stepped symmetrically to the test potentials shown, and substrate-dependent current responses were recorded as the difference measured in the absence and presence of substrates.

RESULTS AND DISCUSSION

Interaction of Lys[Z(NO2)] Dipeptide Derivatives with PEPT2—We first determined the affinity of Lys[Z(NO2)]-Pro (LZN) and three related dipeptide derivatives containing the N-terminal Lys[Z(NO2)] moiety but varying C-terminal amino acids (Ala, Val, Sar). Using competition assays based on PEPT2-expressing P. pastoris yeast cells and the renal cell line SKPT constitutively expressing PEPT2, it became obvious that the four dipeptide derivatives compete with radiolabeled D-Phe-Ala and Gly-Sar competitively in dose-dependent manners (Fig. 1A and Table 1). The obtained K_i values varied from 0.1 to 3.5 μM showing that Lys[Z(NO2)]-Pro as well as the other tested derivates interacted with PEPT2 with high affinities. Whether these compounds are still substrates or indeed inhibitors was analyzed by the two-electrode voltage clamp technique in PEPT2-expressing X. laevis oocytes. As shown for...
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TABLE I

| Compound                   | P. pastoris | SKPT | \(K_i\) | \(K_i\) |
|----------------------------|-------------|------|--------|--------|
| Lys(Z(NO₂))-Pro (LZNP)     | 2.3 ± 0.6   | 0.7 ± 0.1 | 1.7 ± 0.1 | 0.1 ± 0.01 |
| Lys(Z(NO₂))-Val (LZNV)     | 1.7 ± 0.6   | 0.1 ± 0.01 | 0.7 ± 0.1 | 0.1 ± 0.01 |
| Lys(Z(NO₂))-Ala (LZNA)     | 0.7 ± 0.1   | 0.7 ± 0.1 | 3.5 ± 0.3 | 0.9 ± 0.1 |
| Lys(Z(NO₂))-Ser (LZNS)     | 3.5 ± 0.3   | 0.9 ± 0.1 | 3.5 ± 0.3 | 0.9 ± 0.1 |

Lys(Z(NO₂))-Val (LZNV) (Fig. 1B), no substrate-evoked inward current could be recorded. Moreover, LZNV was able to inhibit the inward current evoked by 0.2 mM of the dipeptide Gly-Gln. This was also the case for the other Lys(Z(NO₂)) dipeptide derivatives (data not shown). The inhibition of Gly-Gln-evoked inward current by Lys(Z(NO₂))-Val was found to be dose-dependent and reversible, suggesting a competitive mode of action at the substrate binding site of PEPT2 (Fig. 1B). To demonstrate this, we investigated the kinetics of the inhibition of Gly-Sar uptake in SKPT cells caused by LZNV. Gly-Sar uptake was measured over the concentration range of 0.02–5 mM in the absence or presence of LZNV at a concentration of 200 mM. In the absence of the inhibitor, the Michaelis-Menten constant, \(K_i\), for Gly-Sar was 108 ± 17 μM, and the maximal velocity, \(V_{max}\), was 5.4 ± 0.8 nmol × mg of protein⁻¹ per 10 min. The corresponding kinetic constants obtained in the presence of LZNV were \(K_i\) = 168 ± 14 μM and \(V_{max}\) = 4.5 ± 0.4 nmol × mg of protein⁻¹ per 10 min. Thus, the presence of the inhibitor at a concentration close to its \(K_i\) value increased the \(K_i\) value for Gly-Sar with the \(V_{max}\) not altered significantly. This confirmed that Lys(Z(NO₂))-Val inhibits PEPT2-mediated Gly-Sar uptake into SKPT cells in a competitive manner. The same experiment was performed in Xenopus oocytes expressing PEPT2. In this system, the \(K_i\) value for Gly-Gln transport was increased from 92 to 353 μM in the presence of LZNV (10 μM). The \(V_{max}\) values were affected only insignificantly (control, 118 nA; LZNV, 106 nA). Moreover, we determined the inhibition constant (\(K_i\)) for LZNV in a Dixon type experiment by measuring current in oocytes at two different Gly-Gln concentrations in the presence of increasing concentrations of LZNV (0–50 μM). The results revealed linearity at all Gly-Gln concentrations with lines intersecting above the abscissa in the fourth quadrant, as expected for a competitive inhibitor. A \(K_i\) value of 2.1 ± 0.1 μM was calculated from the point of intersection.

By moving the Lys(Z(NO₂)) moiety into the C-terminal position with either an N-terminal Ala or Val residue attached, two compounds (ALZN and VLZN) that also inhibited dipeptide influx in the Ficha and SKPT competition assays with apparent \(K_i\) values of 10 ± 4 and 3.7 ± 0.1 μM (ALZN) and 13 ± 1 μM and 0.5 ± 0.2 μM (VLZN) were obtained. However, in contrast to LZNA, which did not show any electrogenic transport in oocytes, the reversed peptide sequence ALZN produced an inward current of 11 nA, 46% as high as that generated by Gly-Gln (24 nA) at a membrane potential of −100 mV (Fig. 2). Moreover, whereas LZNA could completely block Gly-Gln-induced inward currents in oocytes, ALZN failed to cause the full inhibition of Gly-Gln-generated transport currents (Fig. 2). Similar results were obtained for VLZN (data not shown). These data demonstrate that the Lys(Z(NO₂)) residue provides a potent inhibitor only when present in the N-terminal position of a dipeptide.

Influence of the Physicochemical Properties and the Position of Protecting Groups on Inhibition of PEPT2—To understand why the Lys(Z(NO₂)) moiety when present in the N-terminal position of a dipeptide is able to block dipeptide transport activity, we synthesized a set of dipeptide derivatives differing in the structure and spatial position of the ω-amino protecting group. As shown in Table II, the dipeptide derivatives Lys(Z)-Ala, Lys(Boc)-Ala, and Lys(Ac)-Ala competed for uptake of radioactively labeled β-Pha-Ala in yeast cells with affinities of 23 ± 6, 26 ± 8, and 64 ± 7 μM and for uptake of radiolabeled Gly-Sar in SKPT cells with affinities of 0.9 ± 0.1, 3.2 ± 0.2, and 16 ± 2 μM, respectively. Whereas 5 mM Lys(Z)-Ala did not produce any inward current in oocytes, it inhibited the current evoked by 5 mM Gly-Gln in oocytes almost completely by 98% (data not shown). Lys(Boc)-Ala displayed the same characteristics as Lys(Z)-Ala with no transport currents when provided alone, but the dose-dependent inhibition of Gly-Gln generated currents. In contrast, 5 mM Lys(AC)-Ala showed electrogenic transport with inward currents as high as that of the dipeptide (102% \(I_{Gly-Gln}\)) but failed to inhibit Gly-Gln currents when both compounds were perfused together. The rather hydrophobic Z and Boc functions can therefore, similarly to the Z(NO₂) group,

![Image](https://example.com/image.png)
render the natural dipeptide Lys-Ala into an inhibitor. That the blocked ε-amino group of the lysine residue has to be in the N-terminal position for the inhibition of PEPT2 could be confirmed by comparing Lys(Z)-Ala with Ala-Lys(Z). The latter showed an affinity in the yeast transport competition assay of 9 ± 2 μM and 1.7 ± 0.3 μM using SKPT cells and was transported in oocytes with maximal currents of 82% of that induced by 5 mM Gly-Gln. Employing this series of derivatives, we therefore established that a hydrophobic blocking group at the

![Structural formulas of Lys(Z)-Lys[Z(NO₂)] and Lys[Z(NO₂)]-Lys[Z(NO₂)].](https://example.com/structural-formulas)

N*-amino function of lysine is required for the generation of a transport inhibitor and simultaneously confirmed that this side chain construct only works as an inhibitor when present at the N terminus of a dipeptide.

Next, we synthesized ornithine derivatives with the side chain blocked by a Z(NO₂) or a Z group and an alanine residue in the C-terminal position. Orn(Z(NO₂)) has proved to be a slightly weaker inhibitor for PEPT2 than the corresponding Lys derivative with affinities of 2.0 ± 0.8 (yeast) and 1.7 ± 0.04 μM (SKPT), respectively. The affinity of Orn(Z)-Ala in the competition assays was almost identical to that of Lys(Z)-Ala (yeast, 26 ± 10 versus 23 ± 6 μM; SKPT, 1.9 ± 0.2 versus 0.9 ± 0.1 μM), too. However, in contrast to the Lys derivative, which also clearly was an inhibitor, Orn(Z)-Ala failed to inhibit Gly-Gln-evoked transport currents in oocytes but generated transport currents when perfused alone at 5 mM that reached 65% of currents of 5 mM of Gly-Gln in the same oocytes. In this special case, shortening the side chain with the protecting group just by one CH₂ unit (Orn versus Lys) prevents the inhibition of PEPT2 and maintains the compound's capability for transport. That the distance between Ca and the protecting group of the side chain of the N-terminal amino acid is indeed a key factor in rendering a compound into an inhibitor was further confirmed by the dipeptide derivatives Dab(Z)-Ala and Dab(Z(NO₂))-Ala. They contain a Dab residue instead of an ornithine or lysine residue with the protecting group in N. When provided at a concentration of 5 mM, Dab(Z)-Ala is electrogenically transported by PEPT2 with inward currents of 97% of that evoked by 5 mM Gly-Gln. Again, adding a NO₂ group renders the substrate into an inhibitor. Dab(Z(NO₂))-Ala does not generate inward current. This observation suggests that both the structure as well as the spatial position of the N-protecting group within the substrate binding domain of PEPT2 is crucial for the ability of a compound to block the transport cycle.

Optimizing the Lysine-Dipeptide Derivatives for Inhibition of PEPT2—The demonstration that the rather hydrophobic
dipeptides Lys(Z)-Ala and Ala-Lys(Z) displayed a higher affinity for PEPT2 than most of our earlier tested naturally occurring dipeptides led us to assume that an N\(^{\text{N}}\)-protected lysine derivative in both the N- and C-terminal position could be advantageous for obtaining more effective inhibitors. We therefore synthesized lysyl-lysine derivatives containing either a Z- or a Z(NO\(_2\)) group attached at the N\(^{\text{N}}\)-amino groups, resulting in Lys(Z)-Lys\([\text{Z(NO}_2]\)] (LZLZN) and Lys\([\text{Z(NO}_2]\]-Lys\([\text{Z(NO}_2]\]) (LZNLN). Fig. 3 shows an electrophysiological analysis of PEPT2 function in X. laevis oocytes with Lys\([\text{Z(NO}_2]\]-Lys\([\text{Z(NO}_2]\]) as the transport inhibitor. Table III summarizes the data obtained on the affinities of these compounds for PEPT2 in yeast as well as SKPT cells. As expected, adding a Z- or Z(NO\(_2\)) group to a Lys residue, resulting in a higher hydrophobicity of the corresponding dipeptide, increased its affinity for interaction with PEPT2 dramatically. The apparent affinity of Lys-Lys was 43\(\mu\)M (yeast cells) and 10\(\mu\)M (SKPT-cells) and could be gradually increased 7–54-fold for Lys(Z)-Lys and Lys\([\text{Z(NO}_2]\]-Lys and up to more than 4000-fold for Lys(Z)-Lys\([\text{Z(NO}_2]\)] and Lys\([\text{Z(NO}_2]\]-Lys\([\text{Z(NO}_2]\]) with resulting \(K\_i\) values of 10–40 nM in both assay systems. The structural formulas of LZLZN and LZNLN are presented in Fig. 4. When these dipeptide derivatives were analyzed for transport in oocytes expressing PEPT2 (Fig. 3A, shown for LZLZN), they did not produce any inward currents but were able to inhibit the current evoked by Gly-Gln completely but reversibly. Fig. 3B shows the dose-dependent inhibition of the Gly-Gln-mediated inward current by increasing concentrations of LZLZN in the current voltage relationship. To demonstrate unequivocally the competitive nature of the transport inhibition by LZLZN, we performed comparable experiments in both systems, the Xenopus oocyte assay and the SKPT cells. First, we investigated the kinetics of the inhibition of Gly-Sar uptake in SKPT cells caused by LZLZN. Gly-Sar uptake was measured over a concentration range of 0.02–5 mM in the absence or presence of LZLZN at a concentration of 20 nM. The Michaelis-Menten constant, \(K\_m\), for Gly-Sar uptake was 91 ± 20 \(\mu\)M in the absence of the inhibitor and 250 ± 40 \(\mu\)M in its presence. The \(V\_\text{max}\) values were not altered significantly. Second, we determined the inhibition constant (\(K\_i\)) of LZLZN by measuring [\(^{14}\)C]Gly-Sar uptake at two different Gly-Sar concentrations (25 and 70 \(\mu\)M) in the presence of increasing concentrations of LZLZN (0–500 nM). The results of the Dixon plot revealed linearity at both Gly-Sar concentrations with lines intersecting above the abscissa in the fourth quadrant and a \(K\_i\) value of 16.2 nM. Measuring Gly-Gln-elicited inward current in Xenopus oocytes in the presence of increasing concentrations of LZLZN (0–400 nM) resulted in a similar Dixon plot with lines intersecting in the fourth quadrant, as expected for a competitive inhibitor. A \(K\_i\) value of 190 ± 66 nM was calculated from the point of intersection. Thus, as has been shown for LZNV, LZLZN also inhibits PEPT2-mediated peptide uptake both in SKPT cells and in Xenopus oocytes expressing PEPT2 in a competitive manner.

In the present study, we demonstrate that lysine-containing dipeptides can be converted from transported substrates of PEPT2 into effective transport inhibitors by blocking the N\(^{\text{N}}\)-amino group of an N-terminal lysine residue with either a Boc, Z, or Z(NO\(_2\)) function. Moving such a modified Lys residue into the C-terminal position of a dipeptide structure surprisingly retains the compound’s capacity for electrogenic transport. This strongly suggests that two distinctly different pockets (N-terminal P1 and C-terminal P2 pocket) within the substrate binding domain of PEPT2 accommodate the side chains of dipeptides and derivatives. Although it has been shown that the physicochemical characteristics of the N- and C-terminal
residues of dipeptides differently affect their affinity for interaction with PEPT2 (11), the present data demonstrate for the first time that the specificity within the side chains can also discriminate between substrates and inhibitors. To obtain a high affinity inhibitor, a sufficiently long side chain spacer in the N-terminal position carrying a hydrophobic function like the Z or Z(NO2) groups must be provided for the proposed P1 pocket. Shortening the spacer by just one CH2 unit, as in the ornithine homologue with the Z-function, prevents the inhibition of PEPT2 and allows transport. This suggests that a definite amino acid side chain of the PEPT2 protein specifically interacts with the altered side chain structure in P1, preventing the conformational change of the protein in the initiation of the substrate translocation step. In contrast, the P2 site in PEPT2 appears to be less restrictive to all substrate side chain modifications for transport, although they clearly affect substrate affinity. Fig. 5 provides a model for the proposed asymmetry for binding and transport or inhibition by the modified lysyl-dipeptides. With LZLZ and LZN, we obtained substrates with the highest affinity (40 and 10 nM, respectively, in the yeast assay) reported so far for a ligand of PEPT2. These compounds should be very useful for probing the protein structure of PEPT2 as well as for identifying its biological role in the various cell types and tissues where the protein is expressed.

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