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Short communication

Thiodipeptides targeting the intestinal oligopeptide transporter as a general approach to improving oral drug delivery

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ABSTRACT

The broad substrate capacity of the intestinal oligopeptide transporter, PepT1, has made it a key target of research into drug delivery. Whilst the substrate capacity of this transporter is broad, studies have largely been limited to small peptides and peptide-like drugs. Here, we demonstrate for the first time that a diverse range of drugs can be targeted towards transport by PepT1 using a hydrolysis resistant carrier. Eleven prodrugs were synthesized by conjugating modified dipeptides containing a thioamide bond to the approved drugs ibuprofen, gabapentin, propofol, aspirin, acyclovir, nabumetone, atenolol, zanamivir, baclofen and mycophenolate. Except for the aspirin and acyclovir prodrugs, which were unstable in the assay conditions and were not further studied, the prodrugs were tested for affinity and transport by PepT1 expressed in *Xenopus laevis* oocytes: binding affinities ranged from approximately 0.1 to 2 mM. Compounds which showed robust transport in an oocyte *trans*-stimulation assay were then tested for transcellular transport in Caco-2 cell monolayers: all five tested prodrugs showed significant PepT1-mediated transcellular uptake. Finally, the ibuprofen and propofol prodrugs were tested for absorption in rats: following oral dosing the intact prodrugs and free ibuprofen were measured in the plasma. This provides proof-of-concept for the idea of targeting poorly bioavailable drugs towards PepT1 transport as a general means of improving oral permeability.

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1. Introduction

The oral bioavailability of a compound is a crucial factor in its success or failure as a therapeutic agent, particularly given the convenience of this route of administration. There are two main mechanisms of absorption from the GI tract: passive diffusion [1] and carrier mediated transport [2]. The oral bioavailability of poorly absorbed drugs can be improved either by modifying their physicochemical properties to aid passive diffusion and/or by targeting of the compounds towards carrier mediated transport [3–5].

PepT1 is a proton coupled oligopeptide transporter expressed principally in the small intestine and the proximal tubule of the kidney [6]. It has a broad substrate specificity including most di- and tripeptides, β-lactam antibiotics and ACE inhibitors [7].

There are many examples of targeting PepT1 to improve the oral bioavailability of pharmacologically active compounds, usually by modifying them so that they resemble the natural di- or tripeptide substrates [8–13]. We have patented [14] a set of thiodipeptide substrates (such as **A** and **B**) that we hope can act as "carriers" for drug transport by PepT1 generally, and have previously published our work on model systems demonstrating that a variety of linkers can be employed [15,16]. The basic premise is illustrated in Fig. 1 in which drugs are conjugated directly or by a linker to our thiodipeptides, converting them into prodrugs that are PepT1 substrates.

In this paper, we apply the results of our previously reported

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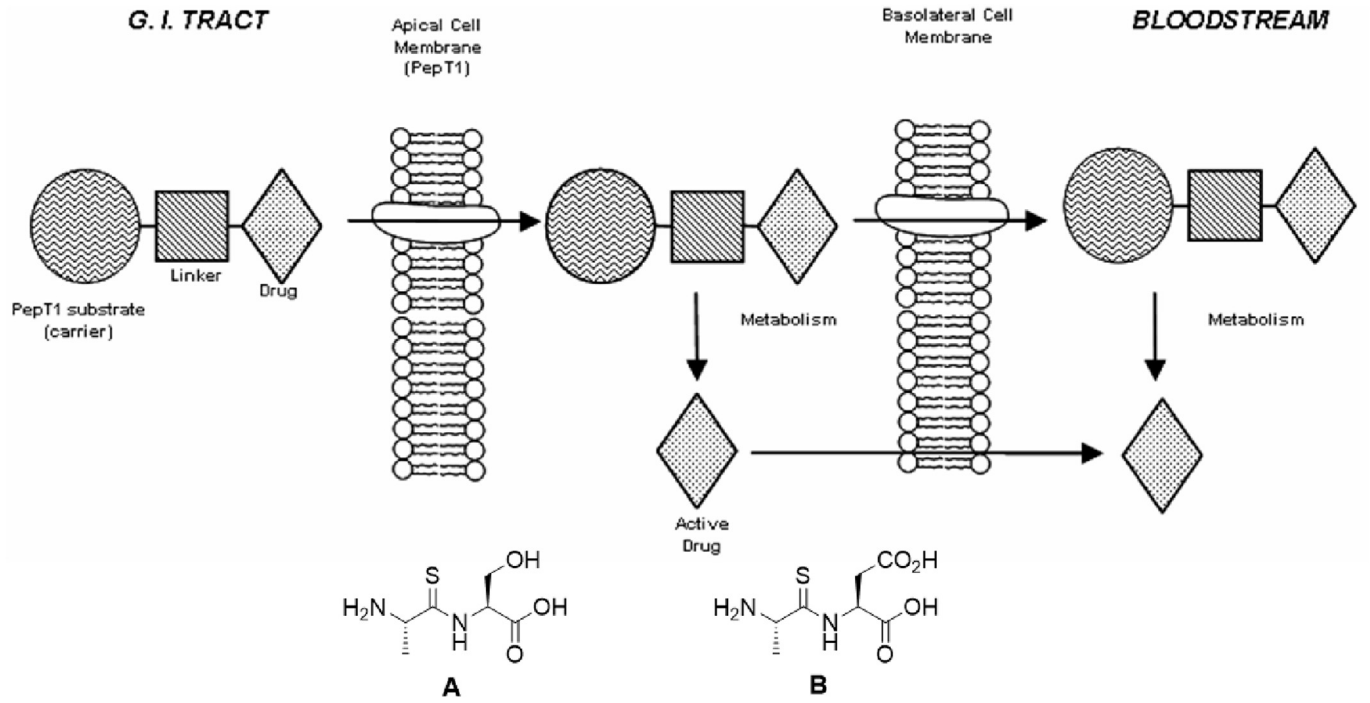

Fig. 1. PepT1 as a drug delivery target. Drugs are attached to the side-chains of the seryl (**A**) or aspartyl (**B**) thiodipeptide carriers, directly or *via* linkers, forming prodrug substrates of PepT1.

characterisation of the structure-transport relationships for PepT1 [15] to drug delivery challenges and report proof-of-concept studies that validate the use of our thiodipeptide carriers as a general approach for targeting a variety of drugs towards PepT1 mediated transport. We focused on two major areas that we felt could benefit from our thiodipeptide drug delivery technology:

i) *Drugs with GI side effects*. A common class of such drugs are the NSAIDs, as exemplified by aspirin and ibuprofen [17]. Whilst these drugs have high oral bioavailability, they also can cause severe gastric side effects. If a prodrug strategy could be developed so that bioavailability was retained, but active drug was not released close to the GI tract, such side effects might be significantly reduced. Prodrugs **1**, **4** and **6**–**7** of ibuprofen, aspirin and nabumetone respectively (Fig. 2) were synthesized to explore this area.

ii) *Drugs with poor oral bioavailability*. This is a major challenge in drug development. A search of ChEMBL [18] identified several marketed drugs with low, highly variable or no oral bioavailability [17]: gabapentin (an anticonvulsant and analgesic); baclofen (a GABA receptor agonist); propofol (chemotherapeutic nausea and intractable migraine); zanamivir (treatment and prophylaxis of influenza) and mycophenolic acid (an immunosuppressant). Prodrugs **2**, **3**, **5**, and **8**–**11** (Fig. 2) were synthesized to prove our concept in this important area.

2. Chemistry

The synthesis of the protected serine and aspartate carrier thiodipeptides (**12** and **13**), nabumetone prodrugs **6**–**7** and ibuprofen prodrug **1** have been reported previously [15,16]. Our chosen drugs could readily be attached to the appropriate carrier using standard coupling reagents, except for the aspirin prodrug **4** (Table 1). This was synthesized by first using concentrated Mitsunobu conditions [19] with sonication to esterify the salicylic acid with triethylene glycol to give **22**, then coupling this glycol ester to the aspartate carrier using standard coupling conditions (Scheme 1) to give **23**. This indirect route was chosen because we were unable to accomplish direct esterification of aspirin with the serine carrier using a variety of coupling conditions. Deprotection was usually achieved in >85% yield using either a 33% solution of TFA in DCM or neat formic acid, except for **5**, for which decomposition was avoided by using phenol as solvent [20]. Since the NMR [15] of carriers **12** and **13** show no signs of epimerisation, and rotamers observed in the NMR of some final compounds have spectral characteristics consistent with *cis*/*trans* rotamers around the thioamide bond as we have previously reported [21], we do not believe epimerisation occurred during synthesis.

3. Results and discussion

The results of binding studies, *trans*-stimulation and Caco-2 monolayer assays are summarised in Table 2. The binding affinities of all prodrugs for PepT1 were determined by measuring the concentration at which they inhibit uptake of radiolabelled D-Phe-L-Gln in *Xenopus laevis* oocytes expressing rabbit PepT1. Inhibition constants were calculated from standard Michaelis-Menten kinetics [22,23]. PepT1 is a low affinity, high capacity transporter and compounds with an affinity <1 mM are generally classed as high affinity binders of the transporter. Fig. 3 shows the data for prodrugs **1** and **3**, which are representative of those determined for all the prodrugs. Prodrugs **4** and **5** had limited stability in the pH 5.5 assay buffer (multiple HPLC peaks), and so no reliable affinity or transport data could be generated.

As binding studies only show affinity for PepT1 and do not provide information as to whether the compound is a substrate or an inhibitor, further transport experiments were undertaken. *Trans*-stimulation assays were performed using radiolabelled [^{3}H]-D-Phe-L-Gln efflux from rabbit PepT1 expressing oocytes in the

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