

Role and relevance of PEPT2 on the pharmacokinetics, renal tubular reabsorption and brain penetration of cefadroxil: studies in wild-type and PEPT2 knockout mice

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Abstract. The in vivo significance of PEPT2 was investigated in wild-type and PEPT2 null mice following intravenous and intracerebroventricular doses of cefadroxil. We found that renal PEPT2 was almost entirely responsible for the reabsorption of cefadroxil in kidney and that choroid plexus PEPT2 limits the exposure of cefadroxil in cerebrospinal fluid (CSF). (www.actabiomedica.it)

Key words: PEPT2; cefadroxil; kidney; brain

Introduction

PEPT2, a proton-coupled oligopeptide transporter (POT) of the SLC15 family, is believed to function in the reclamation of peptide/mimetic from glomerular filtrate in kidney and in the maintenance of neuropeptide homeostasis in brain (1-4). Moreover, PEPT2 is thought to play an important role in the exposure and therapeutic outcome of some drugs in the central nervous system (5). However, the contribution of multiple transport systems and overlapping substrate specificities may lead to difficulty in defining the function of PEPT2 and its significance in relation to other possible proteins present in the tissue or organ of interest. Therefore, the aim of this study was to examine the role of PEPT2 on the disposition of cefadroxil in the body, particularly the kidney and brain.

Material and methods

Pharmacokinetic, tissue distribution and renal clearance studies were performed for cefadroxil after intravenous bolus administration of radiolabeled drug at 1,

12.5, 50 and 100 nmol/g body weight, as described previously for glycylsarcosine (6). Studies were also performed in the absence and presence of probenecid and quinine. Cefadroxil disposition in brain was further evaluated after injecting 1 μ l of radiolabeled drug (dissolved in artificial CSF) into the right lateral ventricle.

Outcomes

Cefadroxil disposition kinetics was clearly nonlinear over the dose range studied (1-100 nmol/g), which was attributed to both saturable renal tubular secretion and reabsorption of the antibiotic. Following an intravenous bolus dose of 1 nmol/g cefadroxil, PEPT2 null mice exhibited a 3-fold greater total clearance compared to wild-type animals (0.92 ± 0.09 mL/min vs. 0.30 ± 0.02 mL/min, $p < 0.001$). As a result, lower systemic concentrations of cefadroxil were observed in PEPT2 null mice (AUC: 21.7 ± 2.7 min $\cdot\mu$ mol/L vs. 67.4 ± 8.7 min $\cdot\mu$ mol/L, $p < 0.001$). Renal clearance studies further demonstrated that the renal reabsorption of cefadroxil was almost completely abolished in PEPT2 null mice compared to wild-type animals ($3 \pm 3\%$ vs. $70 \pm 3\%$,

$p < 0.001$). Out of the 70% of cefadroxil reabsorbed in wild-type mice, PEPT2 accounted for 95% and PEPT1 accounted for 5% of reabsorbed substrate. Tissue distribution studies indicated that PEPT2 had a dramatic effect on cefadroxil tissue exposure, especially in brain where the CSF-to-blood concentration ratio of cefadroxil was 6-fold greater in PEPT2 null mice compared to wild-type animals. Using intracerebroventricular injection, we found that the CSF efflux of cefadroxil in PEPT2 null mice was much slower than that of wild-type animals (half-life of 188 min vs. 46 min, respectively).

Conclusions

These findings demonstrate that renal PEPT2 is almost entirely responsible for the reabsorption of cefadroxil in kidney and that choroid plexus PEPT2 limits the exposure of cefadroxil (and perhaps other aminocephalosporins) in CSF.

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