Rapid Elimination of Cefaclor from the Cerebrospinal Fluid Is Mediated by a Benzylpenicillin-Sensitive Mechanism Distinct from Organic Anion Transporter 3

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ABSTRACT

The purpose of this study was to investigate the carrier-mediated elimination of cephalosporins from the cerebrospinal fluid (CSF) via the choroid plexus. Cefaclor and cefalexin are structural analogs with similar lipophilicity, differing by only one functional group (cefaclor, –Cl; cephalexin, –CH₃), and they are substrates of rat peptide transporter PEPT2 with similar transport activities. However, cefaclor was cleared from the CSF more rapidly than cefalexin after intracerebroventricular administration (the elimination rate constants were 0.11 and 0.050 min⁻¹, respectively). The elimination of cefaclor from the CSF was inhibited by benzylpenicillin, but not by glycylsarcosine (GlySar), whereas GlySar, but not benzylpenicillin, had an inhibitory effect on the elimination of cefalexin from the CSF. The uptake of cefaclor by the freshly isolated rat choroid plexus was saturable, with a Kₘ value of 250 μM, and the uptake clearance corresponding to saturable components accounts for the major part of the in vivo clearance from the CSF (17 versus 26 μl/min, respectively). The uptake of cefaclor by the choroid plexus was inhibited by benzylpenicillin, but not by GlySar. However, the inhibitory effect of benzylpenicillin was weaker than expected from its own Kₘ value, and furthermore, organic anion transporter (Oat)3 substrates (cimetidine or p-aminohippurate) had no effect. These results suggest that cefaclor and cefalexin are eliminated from the CSF by different transporters, and rapid elimination of cefaclor from the CSF is accounted for by a benzylpenicillin-sensitive mechanism distinct from Oat3. A slight modification of a single chemical group of cephalosporins can greatly affect the contribution of the transporters involved, and their duration in the CSF.

The β-lactam antibiotics display a broad spectrum of antibacterial activity with a relatively low risk of allergic and toxic reactions, and cephalosporin antibiotics are prescribed widely throughout the world for the treatment of various infections, including bacterial meningitis (Dancer, 2001). Despite the availability of effective antimicrobial therapy, the morbidity and mortality associated with bacterial meningitis still remain significantly high, especially in developing countries (Tunkel and Scheld, 1997). As in other body sites, the bactericidal activity of cephalosporins in cerebrospinal fluid (CSF) predominantly depends on the length of time during which their concentrations exceed the minimum bactericidal concentrations of the infecting organisms. After intravenous administration, despite the similarity in their structures, various β-lactam antibiotics exhibit a noticeable difference in their distribution, which cannot be explained by their physicochemical properties.

Two major factors are known to determine the pharmacokinetics of β-lactam antibiotics in the CSF. One is their ability to cross the barriers of the central nervous system, which may be influenced by molecular size, their degree of plasma protein binding, and ionization (Levin, 1980; Spector, 1987). Another factor is their rate of efflux from the CSF via an active transport system in the choroid plexus, a leaf-like, highly vascularized organ that protrudes into the ventricles and is comprised of fenestrated capillaries surrounded by a tightly joined monolayer of epithelial cells (Spector, 1990; Suzuki et al., 1997). Quantitative studies of the distribution of β-lactam antibiotics in the CSF, using cefodizime (Nohjoh et al., 1989) and imipenem (Suzuki et al., 1989b) in comparison with benzylpenicillin, have also indicated that the CSF concentration of β-lactam antibiotics is greatly affected by their active elimination via the choroid plexus.

Recent progress in molecular cloning of transporter genes has identified the transporters involved in the elimination of

ABBREVIATIONS: CSF, cerebrospinal fluid; OAT/Oat, organic anion transporter; PEPT, peptide transporter; GlySar, glycylsarcosine; HPLC, high-performance liquid chromatography.
drugs from the CSF, namely, organic anion transporters [Oat3/Slc22a8 (Nagata et al., 2002) and Oatp1a5/Slc28a5 (Kusuhara et al., 2003)] and a peptide transporter (PEPT2/Slc15a2) (Novotny et al., 2000). Both Oat3 and Oatp1a5 are characterized by their broad substrate specificity; Oat3 accepts amphipathic and hydrophilic organic anions as well as H2 receptor antagonists as substrates (Kusuhara et al., 1999; Nagata et al., 2002, 2004a,b), whereas Oatp1a5 accepts amphipathic organic anions as substrates. Kinetic studies using Oat3 substrates and inhibitors suggest that Oat3 plays a major role in the uptake of hydrophilic organic anions such as benzylpenicillin, p-aminobiphenyl, and 2,4-dichlorophenoxyacetate (Nagata et al., 2002, 2004b) as well as cationic drugs; H2 receptor antagonists (Nagata et al., 2004a) via the isolated rat choroid plexus; but not an amphipathic organic anion, estradiol 17β glucuronide, the uptake of which is mainly accounted for by Oatp1a5 (Kusuhara et al., 2003). PEPT2 has been reported to recognize various di- and tripeptides as well as peptide-mimetic drugs, including some β-lactam antibiotics, that contain an α-amino group in their structures, such as cefadroxil and cefalexin (Ganapathy et al., 1995; Daniel and Kottra, 2004; Smith et al., 2004). Using PEPT2 knockout mice, cefadroxil uptake by the freshly isolated choroid plexus has been shown to be mainly mediated by PEPT2 and partly by Oat3 (Ocheltree et al., 2004). Therefore, Oat3 and PEPT2 play important roles in regulating the CSF concentration of β-lactam antibiotics.

We found that after intracerebroventricular administration, cefalexin and cefaclor were eliminated from the CSF with different rate constants, even though they are structurally analogous with similar lipophilicity (their apparent isobutylalcohol-buffer partition coefficients at pH 7.3 are 0.129 and 0.08 for cefaclor and cefalexin, respectively; Suzuki et al., 1987), differing by only one functional group (cefaclor, –Cl; cefalexin, –CH3) (Fig. 1). The present study is aimed at characterizing the transport mechanisms accounting for the difference in the efflux rates of cefalexin and cefaclor. An inhibition study was carried out using benzylpenicillin and GlySar and showed that their inhibitory effect differed for the elimination of cefalexin and cefaclor, suggesting that different pathways were involved in the elimination of cefalexin and cefaclor from the CSF.

**Materials and Methods**

**Materials.** [14C]Mannitol (56.0 mCi/mmol) was purchased from Amersham Biosciences UK, Ltd. (Little Chalfont, Buckinghamshire, UK), and [3H]GlySar (4 Ci/mmol) was purchased from Moravek Biochemicals (Brea, CA). Unlabeled benzylpenicillin and cefalexin were purchased from Wako Pure Chemicals (Osaka, Japan), and other cephalosporins were obtained from Sigma-Aldrich (St. Louis, MO). All other chemicals and reagents were of analytical grade and were readily available from commercial sources. All cell culture media and reagents were purchased from Invitrogen (Carlsbad, CA), except for fetal bovine serum, which was obtained from Sigma-Aldrich.

**Animals.** Male Sprague-Dawley rats, weighing 220 to 240 g, were obtained from Japan SLC (Shizuoka, Japan), and experiments were carried out according to the guidelines provided by the Institutional Animal Care Committee (Graduate School of Pharmaceutical Sciences, University of Tokyo, Tokyo, Japan).

**Construction of the LLC-PK1 Cell Line Stably Expressing Rat PEPT2 (PEPT2-LLC).** Full-length PEPT2 cDNA was isolated from rat kidney mRNA and, after ligation into T vector (Promega, Madison, WI), was subcloned into pcDNA3.1 vector (Invitrogen) using NotI, SpeI, and XbaI. The construct was introduced into LLC-PK1 cells by LipofectAMINE (Invitrogen) according to the manufacturer’s protocol, and stably transfected cells were selected by adding G418 sulfate (Invitrogen) to the culture medium. Five weeks after transfection, different clones were seeded on 12-well culture plates, and the transport activity was tested for positive clones.

**Cell Culture.** LLC-PK1 cells expressing rat Oat3 (Oat3-LLC) have been established previously (Sugiyama et al., 2001). Oat3- and newly established PEPT2-LLC were cultured on culture dishes in M199 (Invitrogen) supplemented with 10% fetal bovine serum, 100 U/ml penicillin, 100 µg/ml streptomycin, and 400 µg/ml G418 sulfate at 37°C with 5% CO2 and 95% humidity. LLC-PK1 cells between passages 5 and 22 were used.

**Transport Studies in cDNA-Transfected LLC-PK1 Cells.** Cells were seeded in 12-well plates at a density of 1.2 × 105 cells/well for the transport studies. Twenty-four hours before beginning the assay, the cell culture medium was replaced with that containing 5 mM sodium butyrate to induce the expression of Oat3 and PEPT2.

Transport studies were carried out as described previously (Nagata et al., 2002). After cells were washed twice and preincubated with Krebs-Henseleit buffer at 37°C for 15 min, uptake was initiated by adding medium containing 1 µM unlabeled benzylpenicillin or GlySar in addition to 0.1 µCi of [3H]benzylpenicillin or [3H]GlySar. The Krebs-Henseleit buffer consisted of 118 mM NaCl, 23.8 mM NaHCO3, 4.83 mM KCl, 0.96 mM KH2PO4, 1.20 mM MgSO4, 12.5 mM HEPES, 5 mM glucose, and 1.53 mM CaCl2, adjusted to pH 7.4. The uptake was terminated at designated time points by washing the cells twice with 1 ml of ice-cold Krebs-Henseleit buffer after removal of the incubation buffer. The cells were kept in 500 µl of 0.2 N NaOH overnight to allow lysis. After adding 100 µl of 1 N HCl, aliquots (400 µl) were transferred to scintillation vials containing 2 ml of scintillation fluid. The radioactivity associated with the cells and an aliquot of the incubation medium was determined using a liquid scintillation spectrophotometer (Amersham Biosciences, Inc., Piscataway, NJ) after the addition of scintillation fluid (Nacalai Tesque, Kyoto, Japan). Then, 50 µl of cell lysate was used to determine the protein concentration in each sample by the method of Lowry with bovine serum albumin as a standard.

Ligand uptake was given as the cell-to-medium concentration ratio determined as the amount of ligand accumulated in the cells divided by the medium concentration. Specific uptake was obtained by subtracting the uptake by vector-transfected cells from the uptake by cDNA-transfected cells. Inhibition studies were carried out by adding the desired concentrations of unlabeled inhibitors to the incubation medium.

Kinetic parameters were obtained using the following equation:

\[ v = V_{\text{max}} \times S / (K_m + S) \]  

where \( v \) is the uptake velocity of the substrate (picomoles per minute per milligram of protein), \( S \) is the substrate concentration in the medium (in micromolar), \( K_m \) is the Michaelis-Menten constant (in micromolar), and \( V_{\text{max}} \) is the maximum uptake rate (picomoles per minute per milligram of protein).
Inhibition constants ($K_i$) values of a series of compounds were obtained by examining their inhibitory effects on the Oat3- and PEPT2-mediated uptake. The substrate concentration was below the $K_m$ values; thus, the inhibition constants can be obtained from the following equation, irrespective to the nature of the inhibition.

$$CL_{int} = CL(1 + I/K_i)$$  \hspace{1cm} (2)

where $CL$ is the uptake clearance, $I$ is the concentration of inhibitor (in micromolar), and the subscript (+I) represents the value in the presence of inhibitor. Fitting was performed by the nonlinear least-squares method using a MULTI program (Yamaoka et al., 1981), and the Damping Gauss Newton Method algorithm was used for fitting.

**Liquid Chromatography-Mass Spectrometry Analysis.** The cellular accumulation of cefalexin and cefaclor by the cells and the medium concentration (45–55 μM) were quantified using liquid chromatography-mass spectrometry. Cefalexin and cefaclor in cell lysate were analyzed by liquid chromatography/mass spectrometry. The HPLC system consisted of a Separation Module (Waters 2695; Waters, Tokyo, Japan) connected to a Micromass ZQ with a ZSpray system (Waters). The system was controlled by version 3.5 of the Masslynx software. Chromatography was performed on a Capcell Pak C18 column (3 μm, 75 × 4.5 mm i.d.; Shiseido, Tokyo, Japan) protected by the same material. A gradient was applied using water (A) and acetonitrile (B), each containing 0.05% formic acid. The gradient conditions were as follows: initiate gradient with 100% A, ramp over 4 min to 30% A and 70% B, ramp over 1 min to 20% A and 80% B, hold for 0.5 min, and ramp over 0.1 min to 100% A to re-equilibrate the system. The total run time was 10 min. The compounds were eluted at a flow rate of 0.8 ml/min and allowed to pass into the electrospray source. The Micromass ZQ was operated in the atmospheric pressure chemical ionization-mass spectrometry positive ion mode with a corona current of 0.3 μA, cone voltage of 20 V, extractor voltage of 2.20 V, RF lens voltage of 0.3 V, source temperature of 100°C, cone temperature of 20°C, and desolvation temperature of 350°C. High-purity nitrogen gas was used as the desolvation gas at 300 ml/min, and the cone gas flow was 50 ml/min.

**Intracerebroventricular Administration.** The efflux of [3H]GlySar after intracerebroventricular administration was studied using the method described previously in detail (Suzuki et al., 1989; Ogawa et al., 1994). Rats were anesthetized with ketamine (60 mg/rat) and xylazine (0.984 mg/rat), and their heads were fixed in a stereotaxic apparatus. A hole was drilled in the skull, 1.5 mm to the left and 0.5 mm posterior to the bregma, into which a needle was fixed as a cannula for injection. An intracerebroventricular dose of [3H]GlySar (20 nCi/rat) and [14C]mannitol (0.4 nCi/rat), dissolved in 10 μl of artificial CSF, was administered to the left lateral ventricle. The prepared artificial CSF consisted of 122 mM NaCl, 25 mM NaHCO3, 10 mM glucose, 3 mM KCl, 1.4 mM CaCl2, 1.2 mM MgSO4, 0.4 mM K2HPO4, and 10 mM HEPES, adjusted to pH 7.3. For inhibition studies, unlabeled inhibitors of desired concentrations ranging from 10 μM to 10 mM, and the effects of benzylpenicillin, GlySar, cimetidine, and $p$-aminopheniprazine were investigated at designated concentrations.

**HPLC Assay.** Concentrations of cefalexin and cefaclor in CSF and in the choroid plexus were analyzed by HPLC. The HPLC system included a pump (L-6200 intelligent pump; Hitachi, Ibaraki, Japan), a YMC-Pack Pro C18 column (5 μm, 250 × 4.6 mm; YMC, Tokyo, Japan) protected by the same material, a column oven (L-7300; Hitachi) set at 40°C, and a UV detector (L-4200 UV-VIS detector; Hitachi) operated at 260 nm. The system was controlled by an L-7200 autosampler (Hitachi). The mobile phase consisted of 0.01 M acetic acid, pH 4.7/methanol/2-propanol (80/10/1). The compounds were eluted at a flow rate of 1.0 ml/min.

**Statistical Analysis.** Statistical analysis of the effect of inhibitors on the uptake of cefaclor by the freshly isolated rat choroid plexus was performed by one-way analysis of variance followed by Fisher’s t test to identify significant differences.

**Results**

**Uptake of GlySar, Cefalexin, and Cefaclor by PEPT2-LLC.** Transfection of rat PEPT2 cDNA increased the uptake of GlySar, a typical substrate of PEPT2 (Fig. 2A). The concentration dependence of the uptake of GlySar by PEPT2 was determined after a 3-min incubation. Nonlinear regression analysis yielded $K_m$ and $V_{max}$ values of 172 ± 21 μM and 2340 ± 240 pmol/min/mg protein, respectively (Fig. 2B).

Figure 2C shows the time profiles of the uptake of cefaclor and cefalexin by PEPT2. As for GlySar, the uptake of cefaclor and cefalexin was significantly greater in PEPT2-LLC than in vector-LLC. The $K_i$ values of cefalexin for GlySar uptake by PEPT2 were determined to be 171 ± 27 μM (Fig. 2D).

**Effect of Cefaclor, Cefadroxil, and Cefalexin on Benzylpenicillin Uptake by Oat3-LLC.** The uptake of benzylpenicillin by Oat3- and vector-LLC for 5 min was 27.5 ± 2.1 and 5.32 ± 0.30 μM/g protein, respectively. The uptake of cefaclor was determined in Oat3- and vector-LLC. It was found that they were comparable, and no specific uptake of cefaclor was detected by Oat3 (data not shown). The inhibitory effect of cefaclor, cephalaxin, and cefadroxil on the uptake of benzylpenicillin by Oat3-LLC for 5 min was examined (Fig. 3). Cefaclor showed moderate potency, whereas cefalexin and cefadroxil showed weak potency. The $K_i$ values of cefaclor, cephalaxin, and cefadroxil were determined to be 105 ± 24, 677 ± 143, and 1060 ± 210 μM, respectively.

**Elimination of GlySar, Cefalexin, and Cefaclor from CSF after Intracerebroventricular Administration.** Figure 4 shows the CSF concentration of GlySar, cephalaxin, or cefadroxil and mannitol after intracerebroventricular ad-
administration as a function of time. GlySar was eliminated from the CSF with a greater rate constant than mannitol, a reference compound for CSF turnover and diffusion into the brain interstitial space through the ependyma surface, with a rate constant of 0.073 min⁻¹. The elimination clearance of GlySar from the CSF (18 μl/min) was 2.5-fold greater than that of mannitol (7.23 ± 2.49 μl/min). The elimination of GlySar was saturated at the concentration examined (3 mM), whereas simultaneous injection of benzylpenicillin had no effect at a concentration sufficiently high to saturate its own elimination (Ogawa et al., 1994) (Fig. 5A).

Cefalexin was eliminated from the CSF with a rate constant of 0.0504 ± 0.0228 min⁻¹ after intracerebroventricular administration (Fig. 4B), whereas cefaclor was more rapidly eliminated from the CSF with an elimination rate constant of 0.105 ± 0.002 min⁻¹ (Fig. 4C). The elimination clearances of cefalexin and cefaclor were 13.0 ± 5.7 and 26.3 ± 0.5 μl/min, respectively. The elimination of both cephalosporins from the CSF was saturable, suggesting the involvement of a transporter (Fig. 5). Furthermore, the elimination of cefalexin was inhibited by GlySar, but it was not significantly affected by benzylpenicillin (Fig. 5B). Conversely, the elimination of cefaclor was inhibited by benzylpenicillin, but not by GlySar (Fig. 5C).

Uptake of Cefaclor by Isolated Rat Choroid Plexus.

The uptake of cefaclor by freshly isolated rat choroid plexus was determined (Fig. 6A). The accumulation of cefaclor in the choroid plexus increased linearly for up to 5 min of incubation.
tion; therefore, further studies were carried out at 5 min. Kinetic analyses based on Akaike’s information criteria revealed that the $K_m$ and $V_{max}$ values for cefaclor uptake by rat isolated choroid plexus were $251 \pm 31 \mu M$ and $722 \pm 62$ pmol/min/$\mu l$ tissue, respectively, and the clearance corresponding to the nonsaturable component was $0.0242 \pm 0.0099$ µl/min/$\mu l$ tissue (Fig. 6B). Inhibition studies were carried out to characterize the uptake of cefaclor by freshly isolated rat choroid plexus. Benzylpenicillin exhibited a significant inhibitory effect on the uptake in a concentration-dependent manner, and 3 mM benzylpenicillin had a significant effect (Fig. 7). In contrast, GlySar, cimetidine or p-aminohippurate had no significant inhibitory effect (Fig. 7).

**Discussion**

The efflux mechanisms in the choroid plexus have been shown to be an important factor governing the CSF concentration of $\beta$-lactam antibiotics and their therapeutic efficacy in bacterial meningitis. Regarding the efflux transport of $\beta$-lactam antibiotics from the CSF, Oat3 has been suggested to be responsible for the elimination of benzylpenicillin from the CSF and partly of the cephalosporin cefadroxil (Nagata et al., 2002; Ocheltree et al., 2004), whereas PEPT2 has been suggested to play a role in the elimination of cephalosporins with an $\alpha$-amino group (Smith et al., 2004). In the present study, the elimination profiles of the analogs cefalexin and cefaclor from the CSF were compared after intracerebroventricular administration, and the uptake of cefaclor by the freshly isolated rat choroid plexus was characterized. Transport studies using the PEPT2-cDNA transfectant showed that both cefaclor and cefalexin are substrates of PEPT2 with...
similar transport activities (Fig. 2). For Oat3, although the cephalosporins had a moderate or weak inhibitory effect (Fig. 3), no specific uptake of cefaclor by Oat3 could be detected (data not shown).

After intracerebroventricular administration, the elimination rates of cefalexin and cefaclor from the CSF were different. The elimination clearance of cefaclor from the CSF was 2-fold greater than that of cefalexin. Taking into consideration the clearance by nonspecific elimination pathways, such as a convective flow associated with CSF turnover and diffusion into the brain parenchyma across the ependyma surface, there was a 3-fold difference in the efflux clearance across the choroid plexus between cefaclor and cefalexin. To characterize the efflux transport, an in vivo inhibition study was carried out using benzylpenicillin and GlySar as inhibitors. It was found that there was a clear difference in the inhibition potencies of these inhibitors for the elimination of cefalexin and cefaclor from the CSF (Fig. 5), suggesting a difference in the contribution of the transporters responsible, despite their analogous chemical structures.

Furthermore, the uptake of cefaclor by isolated rat choroid plexus was characterized. Time-dependent and saturable uptake of cefaclor was observed in the freshly isolated rat choroid plexus (Fig. 6). Taking the water space of the rat choroid plexus (6 μl/rat) into consideration (Ogawa et al., 1994), it would be expected that the uptake clearance corresponding to the saturable fraction would account for the major part of the elimination clearance from the CSF (17 versus 26 μl/min/rat, respectively). Consistent with the in vivo observation (Fig. 5), benzylpenicillin had a significant effect on the uptake of cefaclor by the freshly isolated rat choroid plexus, whereas GlySar had no significant effect (Fig. 7). The uptake of benzylpenicillin by the isolated rat choroid plexus has been shown to be carrier-mediated (Suzuki et al., 1987; Nagata et al., 2002). However, its inhibition of the uptake of cefaclor was lower than expected from its own K_m value [58 μM (Suzuki et al., 1987), 111 μM (Nagata et al., 2002)] (Fig. 7). Furthermore, p-aminohippurate and cimetidine had no effect (Fig. 7), even at a concentration sufficient to inhibit benzylpenicillin uptake in the choroid plexus (Nagata et al., 2002). These kinetic results suggest that benzylpenicillin and cefaclor do not share the same uptake mechanism at the choroid plexus.

Considering the previous result obtained using another analog, cefadroxil (Ocheltree et al., 2004), PEPT2 is one of the candidate transporters responsible for the uptake of cefalexin by the choroid plexus. Inhibition of its elimination from the CSF by GlySar supports this hypothesis. In contrast to these analogs, the absence of inhibitory effect of GlySar on the elimination of cefaclor suggests a minimal contribution from PEPT2. Instead, a benzylpenicillin-sensitive transporter, distinct from the classical transporter responsible for benzylpenicillin uptake in the choroid plexus, accounts for the uptake of cefaclor by the choroid plexus and the rapid elimination of cefaclor from the CSF.

The present study demonstrates that even a minor modification of a single chemical group can dramatically alter the CSF retention time. Changing the methyl group of cefalexin to chloride alters the contribution of the responsible transporters, resulting in a marked increase in the elimination clearance across the choroid plexus. As discussed by Ocheltree et al. (2004), several cephalosporins without an α-amino group can achieve clinically adequate CSF concentrations for the treatment of bacterial meningitis. These clinical observations suggest that the α-amino group is also required for substrate recognition by the benzylpenicillin-sensitive transporter. This should be investigated further in future studies to establish a rational strategy for chemical modification to regulate the CSF concentrations of cephalosporins.

In addition to the CSF, it has been found that the brain parenchyma is the target of β-lactam antibiotics to prevent glutamate neurotoxicity through induction of glutamate transporters (Rothstein et al., 2005). The delivery of β-lactam antibiotics to the brain will become more important in future as far as increasing their therapeutic efficacy is concerned. There is another barrier, the blood-brain barrier, formed by a tight monolayer of brain capillary endothelial cells, in the central nervous system that prevents the passage of drugs into the central nervous system from the circulating blood. It has been suggested that the uptake of benzylpenicillin and cefodizime by the brain from the blood is mediated by a transporter (Suzuki et al., 1989a; Matsushita et al., 1991). However, benzylpenicillin has been suggested to undergo efflux across the blood-brain barrier, presumably by Oat3 (Kikuchi et al., 2003). Since the concentration of cefodizime in the extracellular fluid of the brain is less than the unbound plasma concentration (Matsushita et al., 1991), it could be that the efflux system for cefodizime is located in the blood-brain barrier. Further studies are necessary to investigate these transport mechanisms and the structure-activity relationships of cephalosporins governing their transport across the blood-brain barrier.

In conclusion, despite their very similar chemical structures, the elimination clearances of cefalexin and cefaclor from the CSF are markedly different. The results of the present study suggest that this distinction is accounted for by a difference in the contribution of the transporter responsible. A benzylpenicillin-sensitive transporter distinct from Oat3 accounts for the rapid elimination of cefaclor from the CSF, whereas a GlySar-sensitive transporter, presumably PEPT2, accounts for the elimination of cefalexin.
Characterization of CSF Elimination of Cefaclor


References


