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Permeation and Systemic Absorption of R- and S-Baclofen across the Nasal Mucosa

Hefei Zhang, Mark Schmidt, Daryl J. Murry, and Maureen D. Donovan

Division of Pharmaceutics and Translational Therapeutics, College of Pharmacy, University of Iowa, Iowa City, Iowa 52242

Abstract

Baclofen, an antispasmodic agent that acts as a GABA_B agonist, resembles phenylalanine in structure and has been reported to be a substrate of the large amino acid transporter, LAT-1. The objective of this study was to investigate the absorption of baclofen across the nasal mucosa both *in vitro* and *in vivo*. Baclofen transport was measured across excised bovine olfactory and respiratory mucosae to investigate site-specific uptake of baclofen, and the intranasal bioavailability of R- and S- baclofen was determined in rats. Increasing flux with increasing baclofen donor concentration and the absence of polarized transport was observed *in vitro* and similar distribution profiles were observed for both enantiomers following intranasal administration in rats. The absence of stereospecificity in nasal absorption indicates limited involvement of the amino acid or other transporters in the nasal absorption of baclofen.

Keywords

nasal absorption; nasal drug delivery; permeability; transporters; bioavailability; pharmacokinetics

INTRODUCTION

Baclofen is a muscle relaxant whose primary activity is in the central nervous system (CNS).¹ Despite its unfavorable physicochemical properties (zwitterionic at physiological pH values), baclofen is therapeutically active following oral administration. Its low lipophilicity yet good oral bioavailability and CNS efficacy suggests that it crosses the GI epithelium and the blood-brain barrier (BBB) utilizing uptake carrier systems. The mechanisms of baclofen transport have been investigated in cultured bovine blood-brain barrier (BBB) microvessel endothelial cells, and both a concentration and temperature dependence of baclofen transport was observed.² Based on the calculated K_m and V_{max} values obtained from these studies (58.5 μ M and 0.23 nmol/min), the large amino acid transporter (LAT) was proposed to be the carrier responsible for baclofen uptake. Baclofen has a similar chemical structure and physicochemical properties to phenylalanine and tyrosine, and competitive inhibition of baclofen absorption by phenylalanine has been reported during its intestinal absorption in rats,³ suggesting that these two compounds share the same uptake transporter. While carrier mediated transport of baclofen in the gastrointestinal tract has been reported in several *in vitro* and *in vivo* investigations,^{4–6} Balerio and Rubio,⁷ reported the concentration-independent transport of baclofen across

mouse duodenal sacs, suggesting that there are regional differences in the expression of transporters capable of transporting baclofen across the gastrointestinal mucosa.

Baclofen is a chiral compound; R-baclofen is reported to have more potent pharmacological effects on the patellar, flexor and linguo-mandibular reflexes than the S-enantiomer.⁸ The stereospecificity of baclofen distribution was investigated by Wuis et al. who compared the pharmacokinetics of racemic baclofen and its two enantiomers following intravenous administration to dogs.⁹ The half-life of R-baclofen (4.5 hr) was slightly longer than the racemic mixture (3.8 hr) and much longer than S-baclofen (2.9 hr). These findings suggest the existence of stereoselective renal elimination pathways.

The nasal absorption of amino acids or amino acid-like compounds has been previously reported.^{10,11} Transport of tyrosine and phenylalanine across rat nasal mucosa was suggested to be via an active, saturable, stereo-specific and energy-dependent uptake process, and competitive inhibition between these two amino acids was also observed.¹¹ L-phenylalanine transport across a human nasal primary cell culture system was also studied,¹⁰ and the influence of temperature, concentration and presence of other amino acids on L-phenylalanine transport were investigated. The amino acid was shown to cross the human nasal epithelium by a polarized, saturable ($K_m = 1.23$ mM; $V_{max} = 805.1$ nmol/mg protein/min) and sodium dependent process. L-phenylalanine permeation was significantly reduced in the presence of cationic, small and large neutral amino acids, ouabain and at reduced temperature. These results suggest the presence of uptake carrier(s) within the nasal mucosa that are responsible for the transport of these two amino acids.

The objective of the current study was to identify the intranasal transport characteristics of baclofen, a drug compound reported to utilize amino acid uptake carrier systems, using excised bovine nasal mucosal tissues. In addition, the pharmacokinetic distribution of R- and S- baclofen following intra-arterial and intranasal administration was also studied to investigate the stereospecificity of absorption and to determine the functional role of the carrier system(s) within the nasal mucosa on baclofen transport.

MATERIALS AND METHODS

Materials

R- and S- baclofen, and 4-chloro-L-phenylalanine were purchased from Sigma Chemical Co. (St. Louis, MO). Oasis MCX cartridges were purchased from Waters Co. (Milford, MA). Kreb's Ringer's buffer (KRB) salts, HPLC solvents and all other reagents were obtained from Fisher Scientific (Chicago, IL). A Navicyte® vertical diffusion apparatus was obtained from Harvard Apparatus (Holliston, MA), and a Lauda RM6 circulating water bath (Brunkmann Instruments Co. New York, NY) was connected to the diffusion apparatus. KRB containing 1.67 mM MgCl₂, 4.56 mM KCl, 119 mM NaCl, 1.5 mM NaH₂PO₄, 0.83 mM Na₂HPO₄ and 10 mM D-glucose, 15 mM NaHCO₃ and 1.2 mM CaCl₂ was prepared by dissolving the salts in deionized water at room temperature.

Bovine Nasal Tissues

Excised bovine nasal mucosa was obtained from Bud's Custom Meats Co. (Riverside, IA). Nasal turbinate mucosa was retrieved by opening the nasal cavity along the septal midline and removing the turbinates from the lateral wall. The ethmoturbinates, covered by olfactory mucosa, and the maxilloturbinates, covered by respiratory mucosa, were harvested carefully and transported in ice-cold KRB.

Transport Studies

The flux of R- and S-baclofen was measured across excised bovine olfactory and respiratory mucosa using Navicyte® diffusion chambers (Harvard Apparatus, Holliston, MA). Donor concentrations of 50–200 μM were studied across the olfactory explants and, due to the increased thickness of the respiratory tissues, concentrations of 50–500 μM were investigated in these tissues. The diffusional cross-sectional area for the mounted olfactory tissues was 0.64 cm^2 , and the volume of each cell was 1 mL. For the respiratory mucosa, chambers with a 1.13 cm^2 cross-sectional area and 4 ml cell volumes were used. Flux in both the mucosal-to-submucosal (m-s) and submucosal-to-mucosal (s-m) directions was measured.

The inhibitory effect of L-phenylalanine on baclofen transport at 100 μM donor concentration was examined by adding L-phenylalanine (500 μM) in both the donor and receiver chambers for an initial 30 min equilibration period. These solutions were replaced with donor and KRB solutions, respectively, for the remainder of the transport experiment.

Transepithelial Electrical Resistance (TEER)

The mucosal integrity of the tissues was checked by measuring the transepithelial electrical resistance (TEER) using an EVOM volt-ohmmeter (World Precision Instruments, Inc, Sarasota, FL). At various times during the experiment, a potential difference (PD) of 0.1 mV was applied across the nasal mucosa and the membrane resistance (R_m) was monitored. Typical TEER values were in the range of $165\text{--}200\ \Omega\cdot\text{cm}^2$ for respiratory mucosa and $100\text{--}160\ \Omega\cdot\text{cm}^2$ for olfactory mucosa.

Analysis of Transport Samples Using HPLC

A modification of the method of Balero and Rubio⁷ was used to analyze the baclofen transport samples. Chemical analysis was carried out on a chromatographic system consisting of an LC-600 liquid chromatograph, SPD-6A UV spectrophotometric detector (Shimadzu Scientific Instruments, Columbia, MD) and a Waters 712 WISP auto sampler (Waters, Inc, Milford, MA). The detector response was collected using a SpectraSYSTEM SN4000 data relay system and archived on an HP computer using PC1000 software (Thermo Separation Products, Freemont, CA). A Phenomenex Luna, $250\times 4.6\text{ mm}$, 5 μM , C-18 column (Phenomenex Inc., Torrance, CA) was used with a mobile phase consisting of phosphate buffer [H_3PO_4 (3.9 mM) and NaH_2PO_4 (6 mM)] and acetonitrile (90:10); pH was adjusted to 2.4 using 1N HCL or NaOH, and the flow rate was 1ml/min. The wavelength of UV detection was 220 nm, and the retention time for baclofen was 8.6 minutes.

Permeability Calculation

Flux values were calculated using Equation 1 according to Fick's First Law under steady-state conditions.

$$J_{m-s} \text{ or } J_{s-m} = (dQ/dt)/(A) \quad (1)$$

Where J_{m-s} is the flux of baclofen in mucosal-to-submucosal direction; J_{s-m} is the flux of baclofen in submucosal-to-mucosal direction; dQ/dt is the cumulative amount of drug transported versus time; and A is the diffusional cross-sectional area of the mucosal membrane (0.64 cm^2). The cumulative amount of baclofen permeated versus time was plotted and a linear regression of the data was performed using GraphPad Prism 5.0 software (GraphPad Software Inc., San Diego, CA). The flux was determined from the slope of the resulting line.

Permeability was calculated according to Equation 2.

$$P_{m-s} \text{ or } P_{s-m} = J_{m-s} \text{ or } J_{s-m} / C_0 \quad (2)$$

Where P_{m-s} or P_{s-m} is the permeability of baclofen in the mucosal-to-submucosal (m-s) or submucosal-to-mucosal (s-m) direction and C_0 is the initial donor concentration.

Animal Preparation for Nasal Absorption Studies

Male Sprague-Dawley rats weighing 250–350 g were used. The animal experiments adhered to the "Principles of Laboratory Animal Care" and were approved by the University of Iowa Committee on the Use and Care of Animals (approval No.1006120). Prior to the surgery, each rat was anesthetized using a combination of subcutaneous ketamine (60 mg/kg) and xylazine (7.5 mg/kg) as preoperative agents along with ketamine (40 mg/kg) and xylazine (5 mg/kg) intraperitoneally as intraoperative agents. Supplemental anesthesia was re-administered as needed throughout the experiment. The anesthetized animals were placed ventrally on a warming blanket, and incisions were made to expose the femoral artery. A polyethylene cannula (PE-50) was placed into the artery and held securely with suture. For intra-arterial administration, the opposite femoral artery was also cannulated to administer the baclofen solution.

For nasal administration, another vertical incision was made in the neck to expose the esophagus and trachea. The esophagus was ligated using sutures tied approximately 1 cm apart and then severed. This step assured that the drug solution did not pass from the nasal cavity into the gastrointestinal tract. A small incision was made in the trachea, and a loop of suture was placed around one of the tracheal rings. The trachea was then severed, and the suture loop was grasped using forceps to exteriorize the lower tracheal segment, thus providing a patent airway. Baclofen solution (10mg/ml; 50 μ l) was placed into each nostril. Serial blood samples (3–4 drops; ~200 μ l) were obtained from the femoral cannula at regular intervals. The initial 2 drops of blood were discarded to minimize dilution by the heparinized-saline present in the cannula, and approximately the same volume of

heparinized (10 U/ml) normal saline was used to replace volume lost following each sample collection. The animals were euthanized after the last sample collection.

Blood samples were centrifuged immediately after collection at 3000 rpm for 5 min (IEC Micro-MB, Needham Height, MA). Plasma aliquots (50 μ l) were frozen and stored at 20°C until assayed.

Analysis of Baclofen in Plasma

4-chloro-L-phenylalanine (14 μ g/ml, 10 μ l) was added to the samples (50 μ l) as an internal standard. The samples (60 μ l) were acidified with the same volume of 0.1 N HCl. Solid phase extraction was conducted using 1 mL MCX cartridges (Waters Corporation, Milford, MA). The cartridges were pre-treated using 1 mL of methanol followed by 1 mL of 0.1 N HCl. The acidified samples (400 μ l) were loaded onto the cartridges followed by washing with 1 mL 0.1 N HCl followed by 1 mL of methanol. A combination of NH_4OH (75%) and methanol (10:90) was used as the elution solution. The eluates were dried under nitrogen and reconstituted with 75 μ l of the mobile phase consisting of formic acid solution (0.1% formic acid in water): methanol (85:15).

LCMS Analysis

The LC-MS instrumentation system consisted of a Shimadzu LCMS-2010A mass spectrometer operated using atmospheric pressure chemical ionization (APCI) in positive-ion detection mode controlled using LabSolutions LCMSolution software (version 2.04, Shimadzu, Columbia, MD). The APCI temperature was 425°C, the curved desolvation line temperature was 200°C, and the block temperature was 200°C. Data were collected in the selected ion monitoring mode at 214.1 (baclofen) and 200.1 amu (4-chloro-L-phenylalanine). The analytical column was a CROWNPAK CR (+) (5 μ m, 150 $\times$ 4 mm) (Daicel Chemical Industries, Ltd., Japan) preceded by a Security Guard CROWNPAK CR (+) (2 $\times$ 4 mm) column. Separation conditions were as follows: sample temperature, 4°C; column temperature, 48°C; and sample injection volume, 25 μ l. The flow rate was 1 mL/min. The mobile phase was 0.1% formic acid/water: methanol (85: 15). The total run time for LCMS analysis was 12.5 minutes with retention times of 6.8 min for the R-enantiomer and 7.4 min for the S-enantiomer.

RESULTS

Baclofen Flux

The flux across the olfactory and respiratory mucosa for R- and S- baclofen (Fig 1 (a-d)) was observed to increase in a linear fashion with increasing donor concentration in both the m-s and s-m directions. No statistically significant differences were observed when the m-s and s-m flux values were compared for each tissue type at each concentration except for a slight increase in R-baclofen flux across the olfactory mucosa (m-s) at 100 μ M. Differences in the flux values for the R- and S- enantiomer across the olfactory and respiratory tissues were apparent (Fig 1 (e and f)), with the R-enantiomer showing higher flux across the olfactory mucosa and the S-enantiomer having higher flux at high concentrations (400 μ M) across the respiratory mucosa. The permeability of both R- and S-baclofen across the

olfactory mucosa in the m-s direction were decreased ~30–50% in the presence of L-phenylalanine (Fig 2).

Drug Concentrations in Plasma following Intra-arterial (IA) Administration

The plasma concentrations of R- and S-baclofen following intra-arterial administration of single enantiomers are shown in Figure 3 (a and b). Both enantiomers exhibited rapidly decreasing plasma concentrations, and their concentrations remained low and nearly constant for all of the sampling times post-60 min. non-linear regression analysis was performed using GraphPad Prism 5 (GraphPad Software, Inc., La Jolla, CA), and baclofen distribution and elimination following intra-arterial administration can be well described by a biphasic decay function (Eqn 1; Table 1):

$$C_t = Ae^{-\alpha t} + Be^{-\beta t} \quad \text{Equation 1}$$

Where C_t is plasma concentration at time t ; α is the distribution rate constant and β is the elimination rate constant. The fitted equations from the regression analyses are shown in Table 1. The half lives for baclofen clearance have been reported to range between 2 to 5 hr in various experimental systems^{9,12} Most of these half-life values were estimated by calculating the terminal portion (relatively constant) of the drug distribution curve following intravenous administration. In this study, a two phase decay function was fit to the data and the half-life values were estimated from the slow elimination phase (β) (Table 1); most of these values fall within the reported 2 to 5 hr range, consistent with previous studies.

Nasal Absorption

Following administration of the individual enantiomers, R- and S- baclofen were well absorbed and baclofen was detected in the blood as early as 5 min. The $T_{\max}$ of both enantiomers was 2 hrs, and $C_{\max}$ values of 3.07 $\mu\text{g/ml}$ for R-baclofen and 2.36 $\mu\text{g/ml}$ for S-baclofen were measured (Figure 3). When the nasal absorption of the two enantiomers was compared, no statistically significant differences in plasma concentrations over the 3 hour time interval were observed. In particular, no differences in the early time points suggested no significant differences in the nasal absorption of the two enantiomers. Bioavailability was calculated by summing the areas of any two adjacent time points using the trapezoidal rule. The AUC values and bioavailability for both R- and S-baclofen are summarized in Table 1.

DISCUSSION

The observed concentration independent transport and the absence of polarized flux in the excised nasal tissues suggest that baclofen is primarily absorbed via simple passive diffusion across the bovine nasal tissues over the concentration ranges tested. These results are consistent with those reported by Balerio⁷ using mouse duodenal sacs but differ from other studies showing carrier-mediated uptake of baclofen in other regions of the intestine. The substrate concentrations used in these studies were selected based on the donor concentration reported by van Bree et al. for baclofen transport across bovine brain endothelial cell where these authors concluded that a carrier-mediated transport mechanism was responsible for baclofen transport across the BBB.² When combined with results

demonstrating baclofen's ability to inhibit leucine transport, that study's authors proposed that baclofen was likely transported by the large amino acid transporter.¹³ The absence of any concentration dependent flux in the current study suggests that LAT-1 or other carriers for baclofen transport are absent from the nasal mucosal tissues.

The expression of LAT-1 was evaluated using Western blotting during these investigations (data not shown).¹⁴ Bovine olfactory and respiratory mucosal tissues were probed with an LAT-1 specific antibody (non-species matched), but no confirmatory expression of LAT-1 was observed. This lends support to the possibility that LAT-1 is not expressed in the bovine nasal mucosa. Agu et al. also suggest that LAT-1 and LAT-2 are not expressed in the human nasal epithelium and additional amino acid transporters also appear to have limited expression.¹⁰ During their investigations, relatively high K_m values for phenylalanine uptake were determined, which also may be suggestive of the limited expression of amino acid transporters in these nasal epithelium.

The lack of observed saturable uptake may be the result of significant passive absorption in the nasal tissues. Since the nasal mucosa is capable of efficiently absorbing charged compounds, the rate of passive transport across the nasal mucosa may be relatively large compared to any carrier-mediated uptake present at the substrate concentrations investigated.¹⁵ The magnitude of the R- and S- baclofen permeabilities ($1-2 \times 10^{-6}$ cm/sec when inhibited by phenylalanine; see Fig 2) indicates that these compounds should still be well absorbed across the nasal mucosa, even when carrier activity is minimized.

The flux of S-baclofen across the respiratory mucosa was higher than across the olfactory mucosa in both the mucosal-to-submucosal and submucosal-to-mucosal directions while the flux of R-baclofen was higher than S-baclofen in the olfactory tissues (Fig 1 (e & f)). These results suggest a difference in the transport of S-baclofen in the respiratory mucosa as compared to the olfactory tissues, and further suggest that there is a stereospecific uptake or clearance process with activity in the nasal mucosa. The differences in flux did not result in an increased nasal absorption of one of the enantiomers, however. Instead, good absorption was observed for both enantiomers (Fig 3, Table 1), and there were no statistically significant differences between the concentrations of the enantiomers measured at each sampling time (Fig 3 (c)). While there was a significant difference between the calculated bioavailabilities of the enantiomers, the difference was primarily due to a much higher AUC for the S- form following iv administration than for the R-form. The differences in the calculated bioavailabilities of the enantiomers appear to be due primarily to differing clearance properties rather than due to differences in their absorption properties, and there is little evidence of transporter-mediated uptake from the nasal mucosa improving the bioavailability of either of the baclofen enantiomers.

CONCLUSIONS

Both the permeability and pharmacokinetic results indicate that the nasal absorption of baclofen is predominantly via simple passive diffusion. These results are similar to those reported by Wuis et al. who compared the pharmacokinetics of R- and S-baclofen in dogs and found no stereospecificity in the resulting drug distribution profiles.⁹ While previous

investigators have suggested that baclofen is a substrate for LAT-1, it does not appear that baclofen utilizes this transporter in its uptake across the nasal mucosa. The limited expression of relevant amino acid transporters in human nasal epithelium reported by Agu et al. also supports the conclusion that LAT-1, and likely other amino acid transporters, do not play a significant role in the absorption of baclofen administered intranasally.

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(a)

(b)

(c)

(d)

(e)

(f)

Figure 1.

Flux of R-baclofen (open symbols) across olfactory (a) and respiratory (b) mucosae and S-baclofen (closed symbols) across olfactory (c) and respiratory (d) mucosae in the mucosal-to-submucosal (○,●) and submucosal-to-mucosal (▲,) directions. Comparison of flux between R- and S-baclofen across olfactory (e) and respiratory (f) mucosae in the mucosal-to-submucosal direction. Flux was calculated from transport studies carried out for 150 minutes. Mean flux $\pm$ standard deviation values are shown; $n = 3-4$. * indicates statistically significant difference in flux between mucosal-to-submucosal and submucosal-to-mucosal directions (a-d), and significant difference in flux between olfactory and respiratory mucosae (e-f).

Figure 2. Comparison of permeability of R- (filled bars) and S-baclofen (open bars) across olfactory mucosa following exposure to L-phenylalanine. * indicates statistically significant difference in permeability between olfactory mucosa and L-phenylalanine exposed olfactory mucosa.

(a)

(b)

(c)

Figure 3.

Plasma concentration of R- ((a), open symbols) and S-baclofen ((b), closed symbols) following intranasal (▲,) and intra-arterial (○,●) administration of 1mg of individual enantiomers in rats (n=3). (c) Comparison of pharmacokinetics of R- (open symbols) and S-baclofen (closed symbols) following intranasal administration of 1 mg of individual enantiomers in rats.

Pharmacokinetic parameters of R- and S-baclofen distribution following intra-arterial (IA) and intranasal (IN) administration of individual enantiomers in rats (n=3).

Table 1

	C_{max-IN} ($\mu\text{g/ml}$)	T_{max-IN} (hr)	$t_{1/2elim}$ (hr)	AUC_{IN} ($\mu\text{g}\cdot\text{hr/ml}$) (0–180 min)	AUC_{IA} ($\mu\text{g}\cdot\text{hr/ml}$) (0–180 min)	$(AUC_{IN}/AUC_{IA})\times 100$ (0–180 min)	Biphasic Clearance Function (Figure 3) (r^2)
R-baclofen	3.07 ± 0.67	2	5.51 ± 0.08	5.80 ± 1.71	4.70 ± 2.10	123	$y = 7.95e^{-11.03x} + 0.09e^{-0.12x}$ (0.99)
S-baclofen	2.36 ± 0.38	2	5.14 ± 0.13	5.02 ± 0.57	8.15 ± 0.97	62	$y = 7.41e^{-5.14x} + 0.16e^{-0.13x}$ (0.97)