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Characterization of the oral absorption of several aminopenicillins: Determination of intrinsic membrane absorption parameters in the rat intestine in situ

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Summary

The absorption mechanism of several penicillins was characterized using in situ single-pass intestinal perfusion in the rat. The intrinsic membrane absorption parameters were determined using a modified boundary layer model (fitted value ± S.E.): $J^*_{max} = 11.78 \pm 1.88$ mM, $K_m = 15.80 \pm 2.92$ mM, $P^*_m = 0$, $P^*_c = 0.75 \pm 0.04$ for ampicillin; $J^*_{max} = 0.044 \pm 0.018$ mM, $K_m = 0.058 \pm 0.026$ mM, $P^*_m = 0.558 \pm 0.051$, $P^*_c = 0.757 \pm 0.088$ for amoxicillin; and $J^*_{max} = 16.30 \pm 3.40$ mM, $K_m = 14.00 \pm 3.30$ mM, $P^*_m = 0$, $P^*_c = 1.14 \pm 0.05$ for cyclacillin. All of the aminopenicillins studied demonstrated saturable absorption kinetics as indicated by their concentration-dependent wall permeabilities. Inhibition studies were performed to confirm the existence of a nonpassive absorption mechanism. The intrinsic wall permeability (P^*_w) of 0.01 mM ampicillin was significantly lowered by 1 mM amoxicillin and the P^*_w of 0.01 mM amoxicillin was reduced by 2 mM cephradine consistent with competitive inhibition.

Introduction

The wall permeability, which is determined from steady-state perfusion experiments in the rat intestine, has been shown to be a key variable controlling oral drug absorption (Amidon et al., 1988). It was found that there is a good correlation between the fraction dose absorbed in humans and the dimensionless wall permeability (P^*_w), irrespective of the mechanism of absorption, and that P^*_w might be useful for estimating oral drug absorption.

A modified boundary layer analysis has been developed by Johnson and Amidon (1988) in order to estimate the intrinsic membrane absorption parameters. To characterize the absorption mechanism of various β-lactam antibiotics, an in situ single-pass intestinal perfusion technique in rats was used and the intrinsic membrane parameters of some cephalosporins were determined (Hu et al., 1988; Sinko and Amidon, 1988).

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The β-lactam aminopenicillins, such as ampicillin, amoxicillin, and cyclacillin, are relatively well absorbed from the small intestine. Since they are ionized at the physiological pH and have low partition coefficients, it has been suggested that the mechanism of intestinal absorption of the aminopenicillins may be a saturable absorption process in the rat (Dixon and Mizen, 1977; Tsuji et al., 1977, 1978, 1981a,b; Kimura et al., 1978, 1983; Shindo et al., 1978; Iseki et al., 1984; Nakashima et al., 1984). However, there are conflicting reports in the literature on the absorption mechanism. Some investigators reported the passive absorption of ampicillin (Penzotti and Poole, 1974; Dixon and Mizen, 1977; Miyazaki et al., 1977; Kimura et al., 1978; Tsuji et al., 1981a; Iseki et al., 1984), amoxicillin (Dixon and Mizen, 1977; Miyazaki et al., 1977), and cyclacillin (Penzotti and Poole, 1974). Recently, human oral absorption data have suggested the existence of a capacity-limited transport system for aminopenicillins (Sjövall, 1985a).

In this report, the intrinsic parameters of some aminopenicillins were determined by carrying out single-pass perfusion experiments in rats. Inhibition studies were performed to confirm the existence of carrier-mediated absorption of aminopenicillins including ampicillin.

Experimental

Materials

Ampicillin, amoxicillin, and urethane were purchased from Sigma Chemical Co. (St. Louis, MO). Cyclacillin was supplied by Wyeth-Ayerst (Philadelphia, PA). Polyethylene glycol (PEG) 3350 was obtained from Fisher Scientific (Fair Lawn, NJ), and [^{14}C]PEG 4000 from New England Nuclear (Boston, MA). Citric acid and sodium chloride were purchased from Mallinckrodt, Inc. (Paris, KY). Monobasic potassium phosphate, acetonitrile, and dibasic sodium phosphate were obtained from J.T. Baker Chemical Co. (Phillipsburg, NJ). All chemicals were analytical or HPLC grades. Ecolite (+), a liquid scintillation cocktail, was supplied by ICN Biomedicals, Inc. (Cleveland, OH).

An appropriate amount of the compound to be studied was dissolved in a citric acid-dibasic sodium phosphate buffer, of which the pH was adjusted to 6.5 (Beckman pH meter, Fullerton, CA) and the osmolality to 300 ± 5 mosM/kg (Wescor Model 5500 vapor pressure osmometer, Logan, UT). PEG 3550 (0.01% w/v) with a trace amount of [^{14}C]PEG 4000 was added to the perfusion solution.

In situ single-pass rat perfusion experiments

Male Charles River rats (250–420 g, age 60–90 days) were fasted for 15–18 h prior to each experiment. Water was given ad libitum. Anesthesia was induced by an intraperitoneal injection of a 50% (w/v) urethane solution (1.6 g/kg). The jejunum was cannulated at 2–4 cm below the ligament of Treitz and about 10 cm distal to the first incision. The intestinal segment was perfused using a constant infusion pump (Harvard Apparatus, Model 931, South Natick, MA) for 2 h. The perfusate was maintained at 37 ± 1°C by a water bath (Tek-Pro, American Dade, Miami, FL). During the experiment the rat was kept on a Precision slide warmer (GCA Co., Chicago, IL), and the abdomen was covered with a saline-wetted paper towel and a piece of Parafilm (American Can Co., Greenwich, CT). The perfusion flow rate was 0.123 or 0.191 ml/min. Steady state was achieved in approx. 30 min, after which six samples were taken at 15-min intervals. After the last sample was taken, the length of the intestine was measured by placing a piece of string along the intestine and measuring the string with a ruler.

For the inhibition studies, two segments of the rat jejunum were perfused simultaneously to serve as a control. The second segment was distal to the first segment. The data are reported as means ($\pm$S.E.) from three to five rats with two to five determinations per rat.

Analytical methods

For the water flux measurement, 0.5 ml of the sample was mixed with 15 ml of scintillation cocktail. The samples were counted on a Beckman LS-9000 counter (Beckman Instruments Inc., Fullerton, CA).

The samples were analyzed by high-performance liquid chromatography (HPLC). The HPLC instrumentation consisted of a pump (Spectroflow 400, Kratos Analytical Instruments, Ramsey, NJ), an automatic injector (Waters 712 WISP, Millipore Co., Milford, MA), a reverse-phase column (Partisil 10-ODS, 25 cm, Whatman Inc., Clifton, NJ), a UV detector (Spectroflow 783 or 773, Kratos Analytic Instruments, Ramsey, NJ), and an integrator (Model 3390A, Hewlett-Packard Co., Avondale, PA). The mobile phase consisted of acetonitrile and 0.01 M monobasic potassium phosphate (pH 6.1) in the ratio of 10:90 and 5:95 for ampicillin and amoxicillin, respectively, and acetonitrile, methanol, and monobasic potassium phosphate in the ratio of 19:11:70 for cyclacillin. The flow rate was 1.2 ml/min, and the UV wavelength was 215 nm for ampicillin and 225 nm for amoxicillin and cyclacillin. The concentration was determined from the peak height.

Data Analysis

Water transport

Assuming that [^{14}C]PEG 4000 will not be absorbed from the intestine, the percentage of water transport per centimeter length perfused for each sample was calculated from

$$\%\ \text{water transport/cm} = \frac{100}{L} \cdot \frac{(A_o - A_b) - (A_m - A_b)}{A_m - A_b} \tag{1}$$

where A_o, A_m, and A_b represent the disintegrations per min (dpm) of the inlet, outlet, and blank samples, respectively.

Water transport below 0.5%/cm of intestinal length was considered normal and experiments at higher rates of water transport were not used for the determination of the permeability parameters. The perfusate outlet concentrations were corrected using Eqn 1.

Estimation of intrinsic membrane parameters

The intrinsic membrane absorption parameters were estimated using a modified boundary model approach developed by Johnson and Amidon (1988). Assuming that the difference between the rate of mass flowing into and out of the intestine is equal to the rate of mass absorbed, the dimensionless * effective wall permeability, P^*_{eff}, is calculated from the steady-state perfusion results:

$$P^*_{eff} = \frac{1 - (C_m/C_o)}{4Gz} \tag{2}$$

where C_o and C_m represent the inlet and outlet perfusate concentrations, respectively, and the Graetz number **, Gz, is defined as

$$Gz = \frac{\pi DL}{2Q}, \tag{3}$$

where D denotes the diffusion coefficient, L is the length of the intestine perfused, and Q represents the fluid flow rate. The dimensionless aqueous permeability, P^*_{aq}, is estimated from the film model approximation to the boundary layer results:

$$P^*_{aq} = \frac{1}{A \cdot Gz^{1/3}}, \tag{4}$$

where

$$A = \begin{cases} 10.00Gz + 1.010 & 0.004 \leqslant Gz \leqslant 0.01 \\ 4.50Gz + 1.065 & 0.010 \leqslant Gz \leqslant 0.03 \\ 2.50Gz + 1.125 & 0.030 \leqslant Gz \end{cases} \tag{5}$$

The wall concentration, C_w, and the dimensionless wall permeability, P^*_w, are then calculated as follows:

$$C_w = C_o\left(1 - \frac{P^*_{eff}}{P^*_{aq}}\right) \tag{6}$$

$$P^*_w = \frac{P^*_{eff}}{\left(1 - \frac{P^*_{eff}}{P^*_{aq}}\right)}. \tag{7}$$

* The multiplication of the parameter by R/D results in the dimensionless parameter where R is the radius of the intestine and D denotes the diffusion coefficient.

** In the engineering literature Gz is traditionally defined as the inverse of Eqn 3.

The dimensionless flux at steady state, J_{ss}^*, is expressed as:

$$J_{ss}^* = P_w^* \cdot C_w, \tag{8}$$

and for a combination of carrier and passive transport mechanisms P_w^* is assumed to be of the form:

$$P_w^* = \frac{J_{max}^*}{K_m + C_w} + P_m^*, \tag{9}$$

where J_{max}^* and K_m are the maximal flux and the intrinsic Michaelis constant for the carrier transport, respectively, and P_m^* represents the intrinsic passive membrane permeability. The dimensionless carrier permeability, P_c^* is defined as

$$P_c^* = \frac{J_{max}^*}{K_m}. \tag{10}$$

From Eqns 9 and 10,

$$P_w^* = \frac{P_c^*}{\left(1 + \frac{C_w}{K_m}\right)} + P_m^*. \tag{11}$$

The corrected concentration ratio (C_m/C_o) was kept between 0.85 and 0.95 to estimate the permeability parameters (Johnson and Amidon, 1988).

Estimation of the aqueous diffusion coefficients

The diffusion coefficients used in the evaluation of the permeabilities were calculated according to the Hayduk-Laudie expression (Reid et al., 1977):

$$D = 13.26 \times 10^{-5}\, \eta^{-1.4} V_A^{-0.589} \tag{12}$$

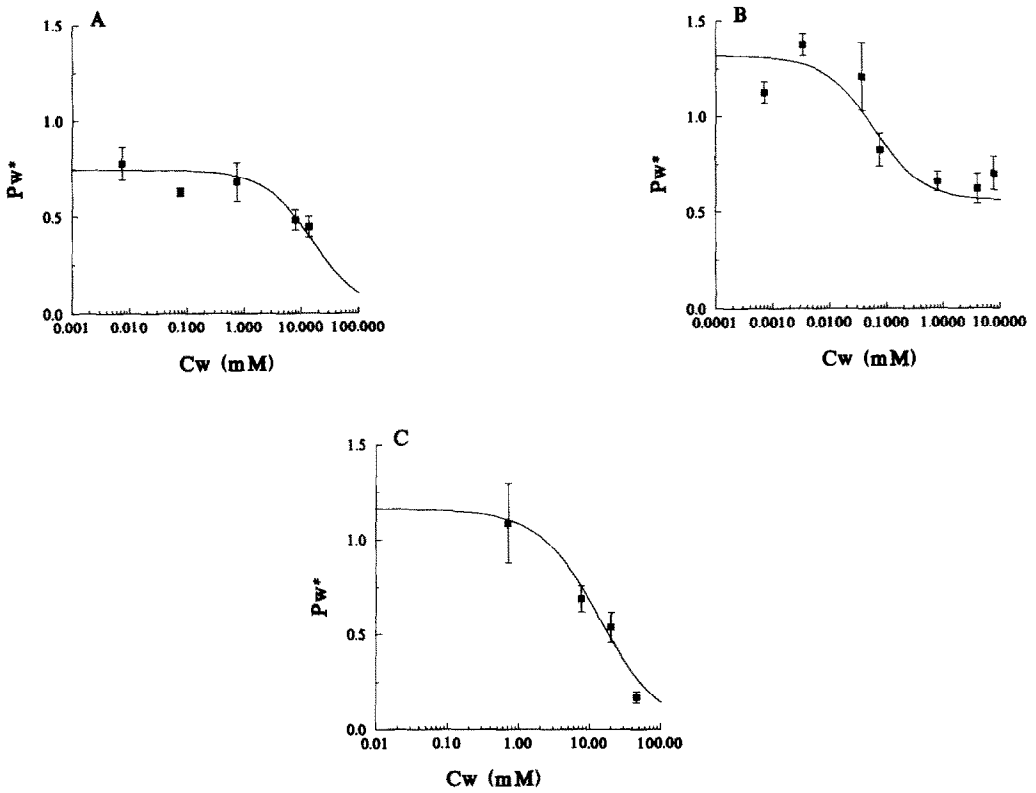

Fig. 1. Intrinsic wall permeability (P_w^*) vs wall concentration (C_w) of ampicillin (A), amoxicillin (B), and cyclacillin (C) in rat jejunum: (■) experimental data (mean ± S.E.) from three to five rats with two to five determinations per rat; (———) best fit line.

where η denotes the viscosity of water (0.6915 cP at 37°C), V_A is the solute molal volume at normal boiling point (cm^3/g per mol), and D denotes the binary diffusion coefficient at infinite dilution (cm^2/s). Molal volumes were estimated using Schroeder's additive method. The values of V_A and D are 315 and 0.00045 cm^2/min for ampicillin, 322 and 0.00044 cm^2/min for amoxicillin, and 315 and 0.00045 cm^2/min for cyclacillin, respectively.

Results and Discussion

Intrinsic wall permeabilities of ampicillin, amoxicillin, and cyclacillin show a dependence on concentration, suggesting the existence of a saturable absorption mechanism in rat jejunum (Fig. 1). The experimental data were fitted to Eqn 9 or 11 using a weighted nonlinear regression to obtain the absorption parameters (Sinko and Amidon, 1988). A summary of the intrinsic absorption parameters is given in Table 1. The intrinsic carrier permeabilities of ampicillin (0.75 ± 0.04) and amoxicillin (0.76 ± 0.09) are shown to be about the same, but less than that of cyclacillin (1.14 ± 0.05). The K_m of amoxicillin is several hundred times lower than that of ampicillin and cyclacillin, suggesting a higher affinity to the carrier transport system. A similar result for amoxicillin in rat intestine was reported by Nakashima et al. (1984). Amoxicillin exhibits significant passive transport in addition to the carrier-mediated pathway. A different experimental result for amoxicillin was reported (Sinko, 1988). It is not yet clear why the permeability profiles of ampicillin and amoxicillin are different even though their structures are similar.

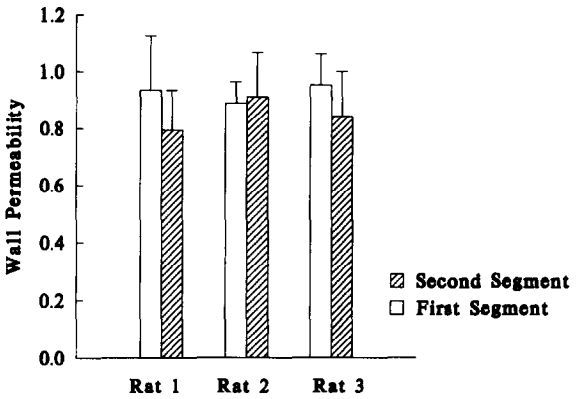

Fig. 2. Differences of the intrinsic wall permeabilities of 0.01 mM ampicillin between two rat jejunum segments (mean ± S.E. from two to five determinations). The p value from a paired t-test was 0.267.

There are few reports on carrier-mediated transport of ampicillin in rat intestine. Shindo et al. (1978) reported that the absorption of ampicillin in rat intestinal loop showed a tendency toward saturation at a dose above 3 mg per loop which was about 15 mM. It was shown that the intestinal absorption of cephradine and cephalexin was inhibited by ampicillin to some extent as well as by amoxicillin and cyclacillin (Miyazaki et al., 1982). The results of the present study indicate that the primary absorption mechanism of ampicillin in rat intestine is nonpassive.

The inter-rat variation can cause difficulty in estimating permeability when the compound has a relatively low P_w^*. To minimize this problem, two segments of rat jejunum were used to obtain

TABLE 1

Summary of the intrinsic wall permeability parameters for several penicillins in the rat intestine in situ

Compounds	J_{max}^* (mM)	K_m (mM)	P_m^*	P_c^*
Ampicillin	11.78 ± 1.88 [a]	15.80 ± 2.92	ND0 [b]	0.75 ± 0.04
Amoxicillin	0.044 ± 0.018	0.058 ± 0.026	0.558 ± 0.051	0.757 ± 0.088
Cyclacillin	16.30 ± 3.40	14.00 ± 3.30	ND0	1.14 ± 0.05

[a] Fitted value ± S.E.
[b] ND0 = not different from zero.

paired data. Fig. 2 shows that the difference of P_w^* of 0.01 mM ampicillin between two segments was not significant ($p = 0.267$), suggesting the homogeneous distribution of a transport system throughout the rat jejunum. Similarly, the permeabilities of amoxicillin and cyclacillin showed no differences between two segments. For inhibition studies two segments were used alternately for the compound alone and the compound with an inhibitor.

Mutual inhibition studies on the absorption of β-lactam antibiotics and/or some dipeptides have shown that they share at least one carrier-mediated system (Kimura et al., 1978; Miyazaki et al., 1982; Iseki et al., 1984; Nakashima et al., 1984; Inui et al., 1988; Sinko and Amidon, 1989).

The results of coperfusion of ampicillin and amoxicillin are presented in Table 2. The concentration of amoxicillin used as an inhibitor was 1 mM which is much higher than its K_m value. The P_w^* of 0.01 mM ampicillin was significantly lowered by amoxicillin ($p = 0.014$). Kimura et al. (1978) reported that the simultaneous perfusion of 0.1 or 1.0 mM amoxicillin did not inhibit the absorption of 0.1 mM ampicillin. However, the variability in P_w is high and the paired studies used in this report are more sensitive to differences. Table 3 shows that the P_w^* of 0.01 mM amoxicillin was significantly reduced by 2 mM cephradine. It has been reported by Iseki et al. (1984) that the absorption of amoxicillin is significantly inhibited by cyclacillin, cephradine, and cephalexin, and that the inhibitory tendency of ampicillin on amoxicillin absorption is also observed in the rat. Dose-dependent absorption of amoxicillin (Spyker et al., 1977; Sjövall et al., 1985b) and ampicillin (Magni et al., 1978; Sjövall, 1979) has been observed in the human and the interaction between aminopenicillins investigated (Sjövall et al., 1985). Their findings and our results support the contention that the β-lactam aminopenicillins are absorbed via a carrier-mediated process combined with a parallel passive process and that there exists a common carrier system for β-lactam antibiotics.

In summary, our results have shown that the wall permeabilities of ampicillin, amoxicillin, and cyclacillin are concentration-dependent in rat jejunum. For inhibition studies, two segments of rat jejunum were used for reducing inter-rat variations. Inhibition studies confirmed the existence of a carrier-mediated mechanism of aminopenicillins.

TABLE 2

Inhibition of wall permeability of ampicillin (0.01 mM) by co-perfusion with 1 mM amoxicillin in the rat jejunum

Rat	Wall permeability (P_w^*)		Difference [b]
	Without inhibitor	With inhibitor	
1	1.41 ± 0.17 [a]	1.10 ± 0.14	0.31
2	1.10 ± 0.03	0.82 ± 0.04	0.28
3	0.74 ± 0.09	0.63 ± 0.08	0.11
4	1.12 ± 0.21	0.91 ± 0.12	0.21

[a] Mean ± S.E. from two to five determinations.
[b] $p < 0.02$ by a paired t-test.

TABLE 3

Inhibition of wall permeability of amoxicillin (0.01 mM) by co-perfusion with 2 mM cephradine in the rat jejunum

Rat	Wall permeability (P_w^*)		Difference [b]
	Without inhibitor	With inhibitor	
1	1.37 ± 0.22 [a]	0.99 ± 0.14	0.38
2	1.27 ± 0.04	0.95 ± 0.17	0.32
3	1.45 ± 0.06	1.22 ± 0.14	0.23

[a] Mean ± S.E. from two to five determinations.
[b] $p < 0.02$ by a paired t-test.

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