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Interactions of Cephradine and Cefaclor with the Intestinal Absorption of D-Galactose

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Abstract

Oral cephalosporins are frequently prescribed β-lactam antibiotics. Although it has been well established that cephalosporins compete with dipeptides for absorption in the intestine, using the same transport mechanism, little is known about the action of the drugs on the absorption of other nutrients. In this work the effect of cephradine and cefaclor on the absorption of D-galactose has been studied. Intestinal sugar uptake was measured in-vitro in pieces of intestine (50 mg) and brush-border membrane vesicles, and in-vivo in intestinal loops.

Galactose uptake was inhibited by cephalosporins in a dose-related, time-dependent manner. In-vivo the inhibition appeared when the antibiotics were on the luminal side of the enterocyte and when they reached the gut from the basolateral side. Only the active transport of the sugar was modified; passive transfer did not change in the presence of cephalosporins. In brush-border membrane vesicles, cephradine and cefaclor did not alter sugar uptake in either sodium or potassium gradients. Both antibiotics non-competitively inhibited basolateral Na^+,K^+-ATPase activity.

These findings show that cephradine and cefaclor inhibit the active-transport component of galactose absorption because they reduce the activity of the basolateral Na^+,K^+-ATPase.

The interactions between drugs and nutrients is important to the pharmacological and nutritional implications of drug therapy and safety as well as to nutrient availability (Roe 1989). Drugs administered orally are mainly absorbed in the small intestine; it is, therefore, possible that interactions between drugs and food components may arise there. Whereas the effects of nutrients on drug absorption are well known (Krause & Mahan 1992), few studies have examined the influence of drugs on the transport of nutrients. A recent paper from our laboratory has shown that the anti-depressant fluoxetine inhibits the intestinal absorption of D-galactose (Monteiro et al 1993). In relation to antibiotics frequently used in therapeutics and sometimes associated with adverse gastrointestinal reactions such as nausea, vomiting, abdominal pain and diarrhoea, we have observed that amoxicillin and tetracycline also reduce sugar absorption (Barcina et al 1986; Alcalde et al 1987). Cephalosporins such as cefatrizine, cephaloglycine and cefroxadine interact with the intestinal transport of L-leucine (Mendizábal et al 1990, 1991). Cephradine and cefaclor, like other aminocephalosporins, are absorbed efficiently from the small intestine (Dantzig et al 1992; Sugawara et al 1992). Even though they are ionized at a physiological pH and have very low lipid solubility, they quickly disappear from the intestinal tract as they are actively transported by a carrier system (Nakashima et al 1984; Tsuji et al 1987). The aim of this study was to investigate the effect of these cephalosporins on the intestinal absorption of D-galactose, a sugar that is poorly metabolized by the small intestine (Berman et al 1976).

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Materials and Methods

Chemicals

Cephradine (Squibb Barcelona, Spain) and Cefaclor (Ely Lilly Indiana Madrid, Spain) were kindly donated. D-[1-^{14}C]-Galactose (sp. act. 50–60 mCi mmol^{-1}) was purchased from Amersham Radiochemical Centre (UK). D-Galactose, phlorhizin, ouabain, mannitol, imidazole, Triton X-100, bovine serum albumin, ATP and Percoll were purchased from Sigma Chemical Co. (USA). Ammonium molybdate tetrahydrate and 1-amino-2-naphthol-4-sulphonic acid were from Fluka (Buchs, Switzerland). Scintillators Formula 989 (for liquid samples) and Optiphase "Hisafe" 3 (for solid samples) were from Du Pont de Nemours (Belgium) and LKB (UK), respectively. Cellulose nitrate filters (type HAWP 0.45 μm, 25 mm diam.) were from Millipore (USA). All other chemicals were from commercial sources and were of analytical purity.

Animals

Male Wistar rats, 180–200 g, obtained from the Centre of Applied Pharmacobiology CIFA (Spain), were fasted overnight before the experiment; drinking water was freely available.

Sugar uptake in isolated jejunum

After the animals had been anaesthetized with sodium pentothal (60 mg kg^{-1}, s.c.), a portion of the jejunum about 20 cm long was quickly excised and rinsed with an ice-cold saline solution containing (mM) 140 NaCl, 10 $KHCO_3$, 0·4 KH_2PO_4, 2.4 K_2HPO_4, 1·2 $CaCl_2$ and 1·2 $MgCl_2$ (pH 7.4). Two or three pieces of intestine weighing about 50 mg were incubated with continuous oxygenation with 95% O_2–5% CO_2 in the already

described saline solution with D-galactose (0·5 mM) and radioactive D-galactose (0·1 μCi/10 mL) for 15, 30, 45 and 60 min. Cephalosporins were added to the incubation solution at 0·5, 1, and 2 mg mL^{-1}. At the end of the incubation the tissues were washed in ice-cold saline solution, blotted carefully to remove excess moisture, weighed wet and extracted in HNO_3 (100 mM; 15 h; 4–8°C). Radioactivity was determined by liquid scintillation counting in a Wallac 1409 Pharmacia instrument. Values are expressed in μmol D-galactose (g wet tissue)$^{-1}$.

In-situ recirculation perfusion method

The procedure of successive absorptions in a closed circuit was as described by Ponz et al (1979). Briefly, a 15-cm jejunum loop (starting 5 cm distal to the ligament of Treitz) was isolated between two glass cannulae, replaced into the abdomen and connected to a perfusion system equipped with a constant-flow electric pump (5 mL min^{-1}, Microperpex, model 2123 LKB Produkter, Sweden). The saline solution used in sugar uptake experiments was also employed here. The loop was pre-washed with saline (50 mL) and then perfused for seven successive periods of 15 min each, with or without cephalosporins, with the saline solution containing D-galactose (2 mM) and D-[1-^{14}C]galactose (0·1 μCi mL^{-1}). In a different set of experiments the saline solution and D-galactose (2 mM) were perfused for seven successive periods to determine the galactose absorption under our control conditions. The volume perfused was 10 mL. Between perfusion periods, the intestine was washed with saline for 5 min to remove all traces of luminal galactose. All solutions were kept at 37°C. Galactose absorption was estimated as the difference between the sugar in the solution before and after perfusion. Results are in μmol galactose cm^{-1}/15 min. Phlorhizin (0·5 mM) was used to evaluate mediated transport and diffusion.

Preparation of brush-border membrane vesicles

Brush-border membrane vesicles were prepared by an Mg^{2+} precipitation method (Shirazi-Beechey et al 1990). The small intestine was everted and a segment of jejunum similar to that used in perfusion experiments was employed. All steps of preparation of the brush-border membrane vesicles were performed at 0–4°C. The jejunum segment was suspended in a buffer containing mannitol (100 mM) and Tris-HCl (2 mM; pH 7·4). The brush-border cells were removed from the intestine by means of a Vibromixer (model E-1, Omnimix, Sorvall) used at top speed for 3 min. After several centrifugations magnesium chloride was added to the suspension at 10 mM to obtain a preparation rich in brush-border membrane. The final pellet of the vesicle preparation was suspended in the desired volume of mannitol (300 mM), $MgSO_4$ (0·1 mM) and Tris-HEPES buffer (10 mM; pH 7·4), using a 27 gauge needle, with a final protein concentration between 8 and 10 mg mL^{-1}. Vesicles were frozen in liquid nitrogen. The enrichment of the specific activity of the brush-border marker enzyme sucrase (EC 3.2.1.48) was approximately tenfold, measured as described by Dahlqvist (1964). Protein was determined according to Bradford (1976), with bovine albumin as standard.

Uptake by brush-border membrane vesicles

The uptake of D-galactose was measured at 37°C by means of the rapid filtration technique of Hopfer et al (1975) with some modifications. The uptake was initiated by addition of buffer (1 mM D-galactose, 100 mM NaSCN or KSCN, 100 mM mannitol, 0·1 mM $MgSO_4$, 10 mM HEPES (pH 7·4) and 2 μCi mL^{-1} D-[1-^{14}C]galactose; 45 μL) to membrane suspension (5 μL). At the stated times, the incubation was stopped by addition of ice-cold stop solution (5 mL) containing KSCN (150 mM), phlorhizin (0.25 μM) and Tris-HEPES (10 mM; pH 7·4). The suspension was immediately poured on to a Millipore filter; the filter was then washed once with ice-cold stop (1 mL) solution and then dissolved in Hisafe 3 scintillator (5 mL) and counted.

Measurement of basolateral Na^+,K^+-ATPase activity (EC 3.6.1.37)

A fraction enriched in basolateral membrane was obtained by the method of Del Castillo & Robinson (1982). Briefly, a jejunum segment 30 cm long was removed and opened longitudinally. The mucosa was scraped off and homogenized in a solution of sucrose (250 mM) in Tris-HEPES (2 mM; pH 7·2). The suspension was centrifuged at 1500 *g* for 10 min, then the precipitate was resuspended in sucrose (2 M) and centrifuged once more at 12 500 *g* for 10 min. The supernatant diluted with seven volumes of distilled water, was centrifuged at 35 000 *g* for 15 min and the precipitate was mixed with a solution of Percoll (11.67%), sucrose (2 M) and Tris (2 mM; pH 7·2) and centrifuged at 50 800 *g* for 1 h. The Percoll fraction was centrifuged at 50 800 *g* for another hour and the final pellet was resuspended in the required volume of sucrose (2 M) and Tris-HEPES (2 mM; pH 7·2) to obtain a protein concentration of 4–6 mg mL^{-1}. The enrichment of Na^+,K^+-ATPase was approximately elevenfold.

The ATPase activity was determined by the method of Jorgensen (1975) as modified by Hardcastle et al (1986). First the basolateral membrane was preincubated with Triton X-100, to expose all ATPase sites, and then this suspension (25 μL) was added to a solution (1 mL; pH 7·4) containing imidazole (60 mM), NaCl (120 mM), KCl (20 mM), $MgCl_2$ (10 mM), Tris (60 mM), EDTA (1 mM) and ATP (3 mM). The mixture was incubated for 30 min at 37°C with or without cephalosporins (2 mg mL^{-1}) and the reaction was stopped with trichloroacetic acid. After centrifugation at 12 500 *g* the free phosphate liberated during the incubation was measured. The values of the Na^+,K^+-ATPase activity were determined indirectly by the difference between ATPase activity without and with ouabain (3 mM). Results are expressed in μmol Pi (mg protein)$^{-1}$ h^{-1}.

Statistics

Data were analysed statistically using the one-way analysis of variance followed by a Fisher PSLD test. Differences were considered significant if $P < 0 \cdot 05$.

Results

Galactose uptake in isolated jejunum

Cephradine and cefaclor inhibited intestinal galactose uptake (Table 1); the inhibition was time-dependent. For the highest concentration of antibiotics tested (2 mg mL^{-1}) and 15-min incubation, inhibitions of 16 and 19% were observed, whereas for 60 min incubation 31% ($P < 0·001$) and 36% ($P < 0·001$) reductions were found for cephradine and cefaclor, respectively. Cephradine at 2 and 1 mg mL^{-1} caused a significant reduction of sugar uptake at all times assayed; the

Table 1. Effect of cephradine and cefaclor on the uptake of D-galactose into jejunum.

Time (min)	D-Galactose uptake (μmol g^{-1})			
	Control	Cephradine 2 mg mL^{-1}	1 mg mL^{-1}	0·5 mg mL^{-1}
15	0·79 ± 0·03	0·66 ± 0·02*	0·66 ± 0·02*	0·77 ± 0·02
30	1·08 ± 0·05	0·83 ± 0·02*	0·83 ± 0·02*	1·01 ± 0·02
45	1·20 ● 0·04	0·86 ± 0·02*	0·91 ± 0·02*	1·04 ± 0·04*++
60	1·29 ± 0·03	0·89 ± 0·02*	0·92 ± 0·03*	1·06 ± 0·03*++
	Control	Cefaclor 2 mg mL^{-1}	1 mg mL^{-1}	0·5 mg mL^{-1}
15	0·78 ± 0·02	0·63 ± 0·02*	0·67 ± 0·03*	0·74 ± 0·03
30	1·06 ± 0·06	0·77 ± 0·02*	0·87 ± 0·02*+	0·99 ± 0·03
45	1·21 ± 0·02	0·81 ± 0·03*	0·92 ± 0·03*++	1·02 ± 0·02*+
60	1·29 ± 0·02	0·83 ± 0·03*	0·94 ± 0·02*++	1·05 ± 0·02*++

Small pieces of intestine were incubated with continuous gassing in a solution of 0.5 mM D-galactose with or without cephalosporins. Each value represents the mean of 20 results ± s.e. obtained from seven animals. *$P < 0.001$ compared with its respective control. +$P < 0.05$, ++$P < 0.01$ comparing cephalosporin 2 with1 mg mL^{-1} and 1 with 0·5 mg mL^{-1}.

different concentrations did not have a statistically different effect on the percentage inhibition. For 0·5 mg mL^{-1} cephradine the effect was lower and appeared after incubation for 45 min. The behaviour of cefaclor was similar to that of cephradine, although the concentration of 2 mg mL^{-1} resulted in slightly greater inhibition than that of 1 mg mL^{-1}.

Sugar absorption in-vivo

Seven successive perfusion periods of 15 min were performed in the same animal. In periods 1, 3, 5 and 7, a solution containing 2 mM D-galactose only was perfused; in periods 2, 4 and 6, a solution containing D-galactose plus either cephradine or cefaclor was perfused. Between one absorption period and the next the intestine was rinsed with saline. As was also observed in-vitro, cephradine and cefaclor also reduced sugar absorption in-vivo (Fig. 1). Once the antibiotic was present in the intestinal loop, galactose absorption did not reach the value obtained in the first perfusion period although the drug was washed away from the loop. As the time of exposure of the intestine to the drug increased, sugar absorption further decreased, reaching plateau for the last two periods. When the concentration of the cephalosporins was 2 and 1 mg mL^{-1}, inhibition appeared after 15 min perfusion; at 0·5 mg mL^{-1} the effect was smaller and appeared later.

The intestinal absorption of galactose in-vivo has at least two components, a Na^+-dependent mechanism upon which is superimposed a diffusive process. To investigate which of the two mechanisms involved in intestinal sugar absorption was altered by the cephalosporins, the effect of the antibiotics on sugar absorption was tested in the presence of phlorhizin, a classical competitive inhibitor of the Na^+-dependent transporter SGLT1. The active transport was calculated as the difference of total absorption minus diffusion. The antibiotics affected the Na^+-dependent transport system only; the diffusion process was not modified (Fig. 2).

Systemic effect on intestinal galactose absorption

These experiments used a double-loop perfusion model. Two adjacent intestinal loops were simultaneously perfused. In one loop saline (control) or cephalosporins, either cephradine or cefaclor (2 mg mL^{-1}), were continuously perfused for 2 h. In a contiguous loop (the test loop) D-galactose (2 mM) was perfused. D-Galactose absorption was tested before starting drug perfusion through the other loop (time 0) and after 15, 45, 75 and 105 min of perfusion. Under these conditions, allowing the drugs to reach systemic circulation, cephalosporins reduced D-galactose absorption (Table 2). The effect was detectable after 45 min for both cephalosporins.

D-Galactose uptake by brush-border membrane vesicles

To characterize the effect of cephalosporins on D-galactose absorption, brush-border membrane vesicles, preincubated for 30 min with antibiotics (2 mg mL^{-1}), were incubated in a solution of galactose with and without a sodium gradient. In the presence of a sodium gradient the uptake of D-galactose after 5 s was eighteen times that at equilibrium (10 min), this uptake was not modified by the antibiotics. In the absence of a sodium gradient neither cephradine nor cefaclor changed the uptake of D-galactose (Fig. 3).

Effect of cephradine and cefaclor on Na^+,K^+-ATPase activity

Active sugar transport requires suitable transmembrane Na^+ gradients which are maintained by the basolateral Na^+,K^+-ATPase. The effect of cephradine and cefaclor on the enzyme was studied in a preparation of basolateral membrane. Na^+,K^+-ATPase activity was measured indirectly using a specific inhibitor (ouabain). Both cephalosporins reduced Na^+,K^+-ATPase activity. For cephradine the inhibition was 48·8% and for cefaclor 52·7% (Fig. 4).

Kinetic studies were performed to clarify the type of inhibitory effect of cephalosporins on the basolateral Na^+,K^+-ATPase activity. The enzyme activity was measured in the presence of various concentrations of cephalosporins (0·5–2 mg mL^{-1}). As shown in Fig. 5, Lineweaver-Burk plot analysis demonstrated that cephalosporins inhibited Na^+,K^+-ATPase activity non-competitively. The apparent K_i values calculated from the re-plots of slopes of the Lineweaver-Burk plots were 4·9 mM (1·71 mg mL^{-1}) for cephradine and 4·1 mM (1·51 mg mL^{-1}) for cefaclor.

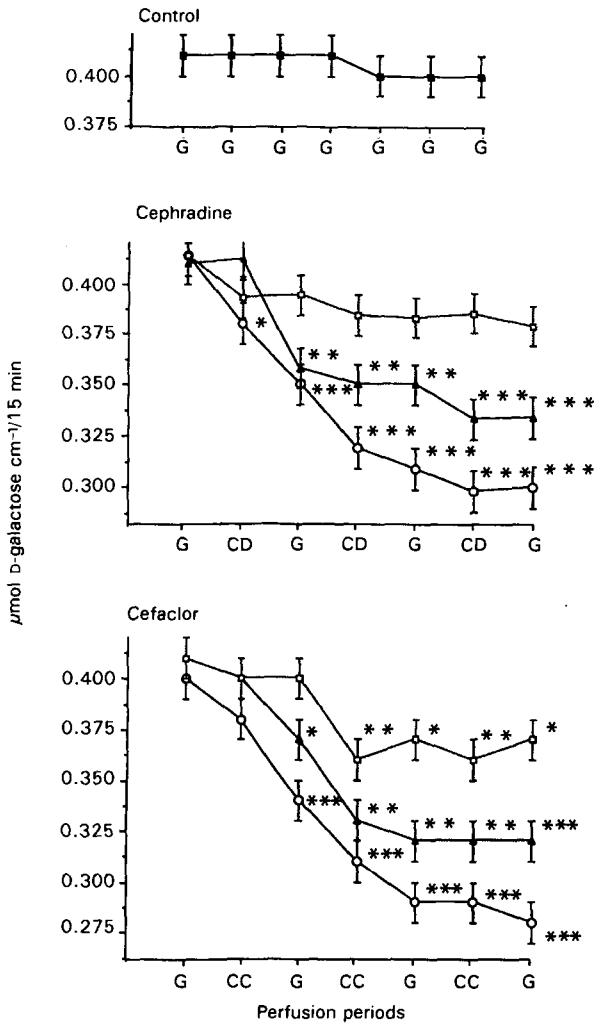

FIG. 1. In-vivo effect of cephalosporins on intestinal absorption of D-galactose. Seven successive perfusion periods of 15 min were performed on the same animal. For control, D-galactose (G; 2 mM) was perfused. For cephradine and cefaclor, either D-galactose (G; 2 mM) or D-galactose (2 mM) plus either cephradine (CD) or cefaclor (CC) were perfused. Between perfusion periods the intestine was rinsed with saline solution. Values are expressed in μmol D-galactose cm^{-1}/15 min. Each value is the mean ± s.e. of eight animals. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$ compared with the respective controls. □ 0.5, ▲ 1, ○ 2 mg mL^{-1}.

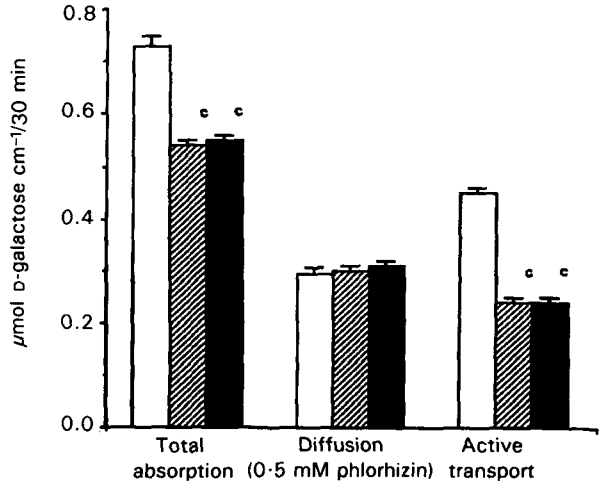

FIG. 2. In-vivo effect of cephalosporins on the diffusion and active transport-component of D-galactose absorption. Animals were perfused for 30 min with a solution of D-galactose (2 mM) with or without antibiotics (2 mg mL^{-1}). Phlorhizin (0·5 mM) was used to measure diffusion. Active transport was calculated as the difference between total absorption and diffusion. Each value is the mean ± s.e. of eight animals. *$P < 0.001$ compared with control. □ Control, ▨

Table 2. Effect of cephradine and cefaclor perfused in a loop adjacent to that used for D-galactose absorption.

Time (min)	D-Galactose absorption (test loop) (μmol cm^{-1}/15 min)		
	Control	Cephradine	Cefaclor
0	0·41 ± 0·01	0·40 ± 0·01	0·39 ± 0·01
15	0·41 ± 0·01	0·38 ± 0·01	0·38 ± 0·01
45	0·40 ± 0·01	0·37 ± 0·01*	0·37 ± 0·01*
75	0·40 ± 0·01	0·33 ± 0·01**	0·35 ± 0·01**
105	0·40 ± 0·01	0·32 ± 0·01**	0·35 ± 0·01**

Two adjacent intestinal loops were simultaneously perfused. In one loop saline (control) or solutions of cephradine or cefaclor (2 mg mL^{-1}) were continuously perfused for 120 min. In the other (test loop) D-galactose (2 mM) was perfused. Galactose absorption was measured in the test loop before and after starting drug perfusion through the other loop. Each value represents the mean ± s.e. of seven or eight animals. *$P < 0.05$, **$P < 0.001$ compared with respective controls.

Discussion

Cephalosporins are frequently prescribed β-lactam antibiotics (Carton et al 1993). Despite their very low lipid solubility, they quickly disappear from the intestine. In the last ten years extensive investigations have been performed on the intestinal absorption of cephalosporins and there is much evidence that aminocephalosporins and dipeptides share the dipeptide transport system (Nakashima et al 1984; Okano et al 1986; Kato et al 1989), which is a proton-dependent carrier (Ganapathy & Leibach 1985). Both types of molecule have in common certain structural features such as a peptide bond with an α-amino group and a terminal carboxylic acid group. Although the competitive inhibition of cephalosporin absorption by dipeptides has been well described (Sugawara et al 1994), little is known about the effect of these antibiotics on the absorption of other nutrients.

In-vitro experiments showed that cephradine and cefaclor inhibited the uptake of D-galactose in rats (Table 1). In-vivo, successive perfusions in the same intestinal loop also showed a reduction of the absorption of galactose, whereas the transport defect did not revert on cessation of the drugs (Fig. 1). The greatest inhibitory effects found at the maximum perfusion time and dose of antibiotics were 29% for cephradine and 33% for cefaclor. This similar effect could be related to their similar stabilities and rates of absorption (Schwinghammer et al 1990; Satterwhite et al 1992). In earlier reports, we showed that amoxicillin (Alcalde et al 1987) and tetracycline (Barcina et al 1986) also caused a reduction in sugar absorption in a dose-related, time-dependent manner. For other antibiotics, such as neomycin, opposite results have been described and it seems that the effect is species-specific; for rabbits and rats an increase in sugar absorption, related to changes in the permeability of the intestinal epithelia, has been observed (Lemaire et al 1982;

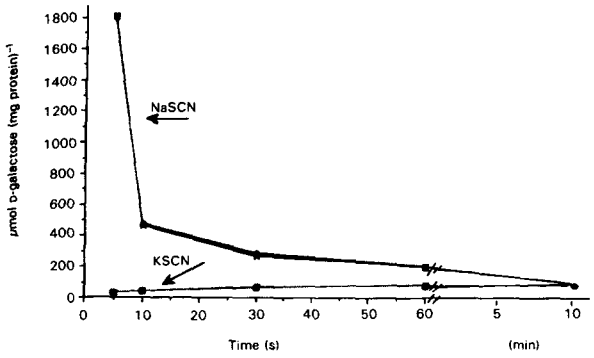

FIG. 3. Time course of D-galactose uptake by brush-border membrane vesicles in the presence of cephradine and cefaclor. Vesicles were preincubated for 30 min without (■) or with cephradine (2 mg mL^{-1}, ●) or cefaclor (2 mg mL^{-1}, ⋈). Uptake studies were performed at 37°C, in a medium of D-galactose (1 mM) with NaSCN (100 mM) or KSCN (100 mM). Each value is the mean of ten results obtained from three different membrane preparations.

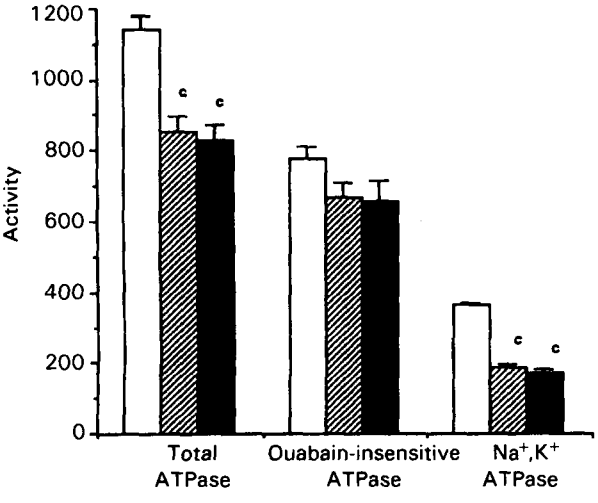

FIG. 4. Effect of cephradine and cefaclor on the activity of the basolateral ATPase of jejunum. A fraction enriched in basolateral membrane was incubated for 30 min at 37°C with cephalosporins (2 mg mL^{-1}). Ouabain (3 mM) was used for the inhibition of Na^+,K^+-ATPase. Na^+,K^+-ATPase was calculated as the difference between total ATPase and ouabain-insensitive ATPase. Activity is expressed in μmol Pi (mg protein)$^{-1}$ h^{-1}. Values are the mean ± s.e. of twelve results. *$P < 0.001$ compared with control. □ Control, ▨ cephradine, ■ cefaclor.

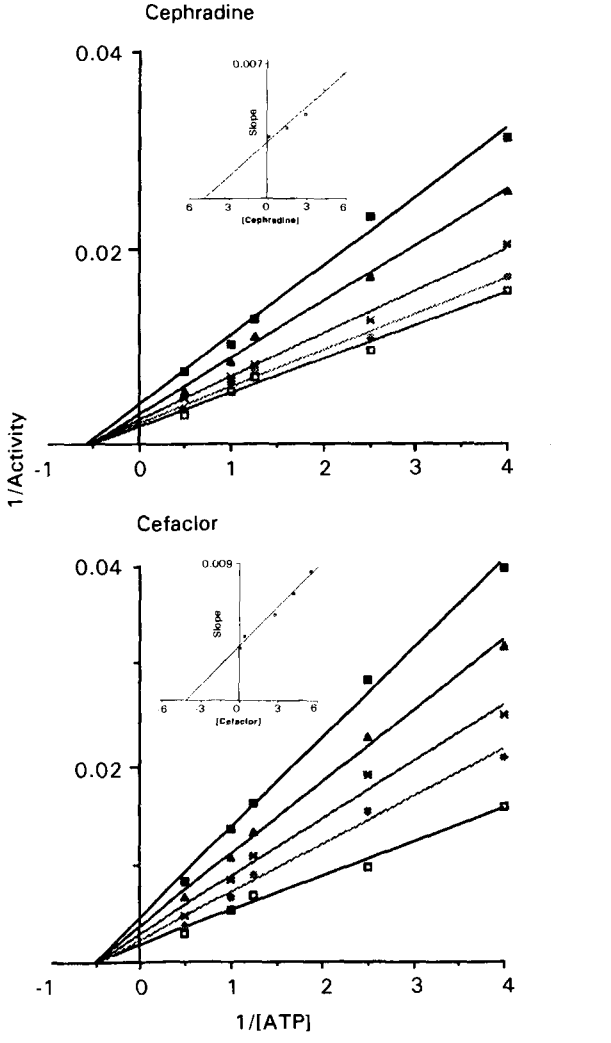

FIG. 5. Analysis of inhibition by cephalosporins on the basolateral Na^+,K^+-ATPase activity. Lineweaver-Burk plots. Na^+,K^+-ATPase activity was measured in the absence (control □) and presence of cephalosporins (0·5 ●, 1 ⋈, 1·5 ▲, and 2 mg mL^{-1} ■). Each point represents the mean of 10–12 measurements. ATP concentration in mM and activity values in μmol (mg protein)$^{-1}$ h^{-1}. Insets are replots of slopes of Lineweaver-Burk plots vs cephalosporins (mM).

Debnam & Thompson 1984), whereas in man a decrease, owing to intestinal mucosa disruption, has been reported (Keusch et al 1970).

The inhibition detected could not be a result of alteration of the metabolism of the transported sugar, since galactose is a hexose known to be poorly metabolized by enterocytes. It also appears unlikely that the observed effect was a result of intestinal mucosa disruption because microscopic examination failed to detect any effect of other cephalosporins on intestinal mucosa morphology (Barcina et al 1988). As only the active transport of galactose was altered (Fig. 2) and the action appeared early, after 15 min incubation in-vitro (Table 1) or immediately after the perfusion of the antibiotics in-vivo (Fig. 1), we suggest that there is interference between the drugs and carrier SGLT1, located at the brush-border membrane of the enterocyte, which mediates the transport of galactose (Turk et al 1991), even though galactose and cephalosporins are very different in structure. When brush-border membrane vesicles, preincubated with cephalosporins, were incubated in a sodium gradient (100 mM outside, 0 mM inside), the antibiotics did not affect the uptake of the sugar (Fig. 3) implying that the inhibition of the active transport was not a result of local action of the antibiotics on the carrier at the apical side of the enterocyte. As was shown in-vivo (Fig. 2), it also appears that the antibiotics did not modify passive sugar transfer in vesicles (potassium gradient 100 mM outside, 0 mM inside) (Fig. 3).

The occurrence of inhibition in successive perfusion periods, when the drug was absent from the intestinal lumen together with the systemic action of cephradine and cefaclor (Fig. 1),

altering sugar absorption when they reached the enterocyte from the blood (Table 2), suggested an effect on the basolateral membrane. This membrane has a very high Na^+,K^+-ATPase activity, and it is this enzyme which is responsible for maintenance of the sodium gradient necessary for active transport of sugars across the luminal membrane of intestinal epithelial cells (Dixon & Hokin 1980). Cephalosporins drastically reduced Na^+,K^+-ATPase activity (Fig 4). Lineweaver-Burk plots showed non-competitive inhibition (Fig. 5). For cephatrizine and cephaloglycine (Mendizábal et al 1990) and cefroxadine (Mendizábal et al 1991) we also observed inhibition of the Na^+,K^+-ATPase activity that caused a reduction in the absorption of leucine. A decrease in the absorption of sugars and inhibition of the basolateral Na^+,K^+-ATPase activity has also been described for dihydrostreptomycin (Gallucci et al 1985). The inhibition of this enzyme could account for the appearance of soft stools or diarrhoea when cephalosporins are prescribed, as many nutrients are transported by sodium-coupling, although other mechanisms including local irritation, changes of intestinal motility, intestinal mucosa or intestinal flora cannot be ruled out.

Our results indicate that cephradine and cefaclor cause inhibition of galactose absorption both in-vivo and in-vitro. This inhibition is not a result of the effect of the drugs on the luminal side of the enterocyte but to a reduction of the basolateral Na^+,K^+-ATPase activity responsible for the maintenance of Na^+ gradient necessary for the active transport of galactose, which is the only component of the absorption altered by cephradine and cefaclor.

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