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Polarized nature of taurine transport in LLC-PK1 and MDCK cells: Further characterization of divergent transport models*

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Summary. Taurine transport was measured in cultured epithelial cells-LLC-PK1 and MDCK-grown on permeable membrane supports. Taurine transport by LLC-PK1 cells was greater on the apical surface compared to the basolateral surface. MDCK cells exhibited greater taurine uptake from the basolateral side. Transepithelial taurine flux was in the direction of apical to basolateral in the LLC-PK1 monolayers. There was no net transepithelial movement of taurine in the MDCK monolayers. Efflux of taurine from the apical and the basolateral membrane surfaces of LLC-PK1 cell monolayers was stimulated by external β-alanine but not L-alanine. Efflux of taurine from MDCK cell monolayers was stimulated by β-alanine on the basolateral surface. While the competitive inhibitor guainidinoeithane sulfonate (GES) competitively inhibited taurine uptake to a similar degree on the apical and basolateral surface of LLC-PK1 cell monolayers, GES had a more potent inhibitory effect on the basolateral taurine uptake in MDCK cells when compared to its inhibition of apical taurine transport. We conclude that there are characteristic differences in transport of taurine by apical and basolateral surfaces of LLC-PK1 and MDCK cells which may be the consequence of asymmetric distribution or unique structural properties of the taurine transporter.

Keywords: Amino acids – Amino acid transport – Taurine – MDCK – LLC-PK

Introduction

Taurine is a β-amino acid, or sulfonic acid, which is postulated to function as an intracellular osmolyte and a cytoprotectant (Chesney et al., 1985). In addition,

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taurine is vital to normal development of the central nervous system and retina (Chesney et al., 1985). In mammals, taurine is reabsorbed in the proximal tubule by a specific, NaCl-dependent, active transport mechanism (Chesney et al., 1985). The proximal reabsorption of taurine serves to maintain the total body content or homeostasis of taurine. In the event of reduced dietary intake of taurine or its metabolic precursors, urinary taurine excretion decreases as the direct result of enhanced proximal tubular reabsorption by the β-specific transporter located on the brush border membrane (Chesney et al., 1983). Although not well characterized, mechanisms for amino acid transport are also present in distal tubule (Silbernagl, 1988). Transport of taurine in distal tubular segments is postulated to achieve cellular accumulation of the osmolyte (Uchida et al., 1990).

We have previously described β-specific, active transport of taurine in two continuous renal epithelial cell lines, the LLC-PK1 and MDCK cells (Jones et al., 1990). The β-amino acid transporter in these cell lines has similar characteristics to that described for the mouse and rat renal brush border membranes. Transport of taurine by both LLC-PK1 and MDCK cells requires sodium and chloride, and is regulated by the availability of substrate (medium taurine concentration). Taurine transporter activity increases when cells are exposed to taurine-free medium for 24 hours; conversely, taurine transport activity decreases when cells are exposed to relatively high extracellular taurine concentrations for 24 hours. In contrast, taurine transport is greatly influenced by medium osmolality in the MDCK cells and much less so in the proximally derived LLC-PK1 cells (Jones et al., 1990). We have speculated that the transporter for taurine in the proximal tubule is distinct from that located in the distal tubule, and question whether apical and basolateral systems are also distinct. For this purpose, we have continued studies of the nature of taurine transport by LLC-PK1 and MDCK cells.

Materials and methods

Cell culture methods

LLC-PK1 and MDCK cell lines were obtained from American Type Culture Collection (Rockville, MA) and maintained in 5% CO2, 95% air. Standard medium consisting of Dulbecco's Modified Eagle's medium (1000mg/L glucose, 584 mg/L L-glutamine, and 110 mg/L sodium pyruvate) in a 1:1 mixture with Ham's F12 Nutrient Mixture, plus 10% fetal bovine serum and penicillin (100U/ml) and streptomycin (100 μg/ml) was used for routine cell carriage. Cells were subcultured by trypsinization and seeded onto 0.4 μm polycarbonate filter supports (Costar, transwell) (Boerner et al., 1986). Prior to experiments, medium was replaced with a hormonally defined, serum-free formulation consisting of DMEM/F 12 with Insulin (5 ug/ml), Transferrin (5 ug/ml), Prostaglandin E1 (2.5×10^{-5} mg/ml), Hydrocortisone (5×10^{-8} M) and thyroxin (5×10^{-12} M).

Transport studies

Uptake studies were performed on confluent monolayers 10–14 days after seeding. Briefly, cells were washed with Earle's Balanced Salt Solution (EBSS) at 37°C. Uptake was initiated by the addition of EBSS with or without sodium, pH 7.4, with 50 μM taurine (0.5 μCi ^{3}H-taurine) at 37°C (Boerner et al., 1986; Jones et al., 1990). Uptake was terminated by the removal of uptake solution followed by three rapid washes with cold EBSS. The uptake

solution contained 14C-inulin (0.1 μCi/ml) in addition to ^{3}H-taurine. Luminal uptake was measured by addition of uptake solution on the upper surface of the monolayer with an equal volume of EBSS on the lower chamber. For basolateral uptake, the uptake solution was added to the lower chamber and the EBSS with or without sodium to the upper chamber. The contralateral solution was sampled for contamination with ^{14}C-inulin as a measure of monolayer integrity as well as contamination by the extracellular space. Monolayers were considered to be intact if the inulin leakage was less than 1%. Cells were solubilized in 1% SDS in 0.2 N NaOH. An aliquot was dispersed into Optifluor, and then radioactivity counted in a Packard Tricarb 2000-CA Liquid Scintillation Analyzer (Packard, Downer's Grove, IL). Total cell protein was measured by the Lowry method. Uptake was expressed as picomoles taurine per mg cell protein.

Effect of sodium concentration on taurine uptake

The concentration of sodium or chloride in the uptake solution was varied between 0 and 200 mM while holding the concentration of chloride constant at 126 mM.

Measurement of taurine efflux in cell monolayers

Confluent monolayers were incubated for 2 hours in the presence of EBSS plus 50μM taurine (3H-taurine), followed by two rapid washes at 4°C. Both chambers were filled with EBSS (37°C). Buffer was sampled over time for radioactivity and efflux was calculated as percent radioactivity in the bath using total dpm (cell dpm + buffer dpm).

Materials

Media, penicillin/streptomycin, trypsin, and fetal bovine serum were purchased from Gibco (Grand Island, NY). Radiolabeled taurine and inulin were purchased from New England Nuclear Corporation (Boston, MA). Insulin, hydrocortisone, thyroxin, prostaglandin E1, Earle's Balanced Salt Solution (EBSS), choline chloride, choline bicarbonate. and other chemicals were from Sigma Chemical Company (St. Louis, MO) and transferrin from Calbiochem (LaJolla, CA).

Data analysis

Data comparisons were made with the Student t test for independent data and linear regression analysis by the least squares method, with assistance from the computer program STATVIEW 512+, (Brainpower, Inc., Calabasas, CA)

Results

Sodium dependence of taurine uptake

Taurine uptake into LLC-PK1 cell monolayers was minimal in the absence of external sodium and increased as the sodium concentration increased reaching maximum uptake at approximately 120 mM. As can be seen from Fig. 1 a, the magnitude of taurine uptake was greater from the apical side compared to the basolateral surface, although both membrane surfaces are characterized by high degree of sodium dependence. In the MDCK cells, taurine uptake was also minimal in the absence of sodium and increased to maximum uptake at an external sodium concentration between 100 and 150 mM on both the apical and the basolateral surfaces. In contrast to the LLC-PK1 cells, the uptake from the basolateral cell surface by MDCK cells was greater than from the apical side.

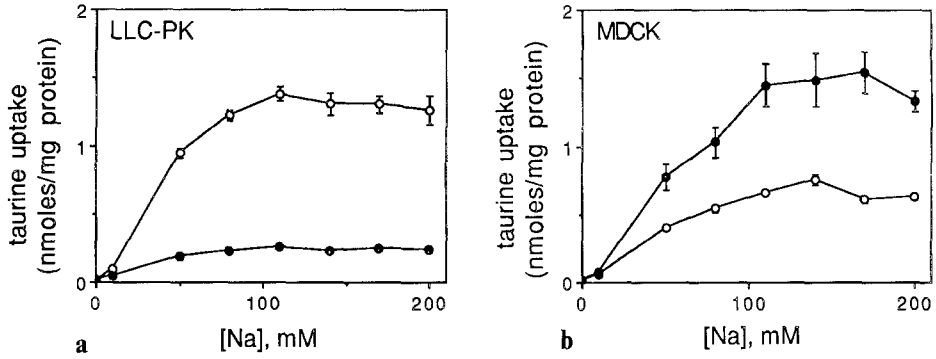

Fig. 1. Sodium dependence of taurine uptake into LLC-PK1 and MDCK cells. Confluent cell monolayers were incubated in Earle's balanced salt solution containing 0–200 mM sodium, 0–200 mM choline, and constant, 126 mM chloride plus 50 μM taurine (^{3}H-Taurine, 0.5 μCi) and apical (open circles) or basolateral (closed circles) uptake was measured at 15 minutes in LLC-PK1 cells, (**a**) or 20 minutes in MDCK cells (**b**). Values represent the mean ± SEM for 4 filters

Chloride dependence of taurine uptake

A similar pattern was observed for taurine transport at various concentrations of external chloride as was seen for sodium (Fig. 2). At low external chloride concentrations, the uptake of taurine was concentration-dependent, and was less at low chloride concentrations compared to uptake in the presence of chloride in a physiologic range, although taurine uptake at lower external chloride concentrations was greater than at a comparable sodium concentration.

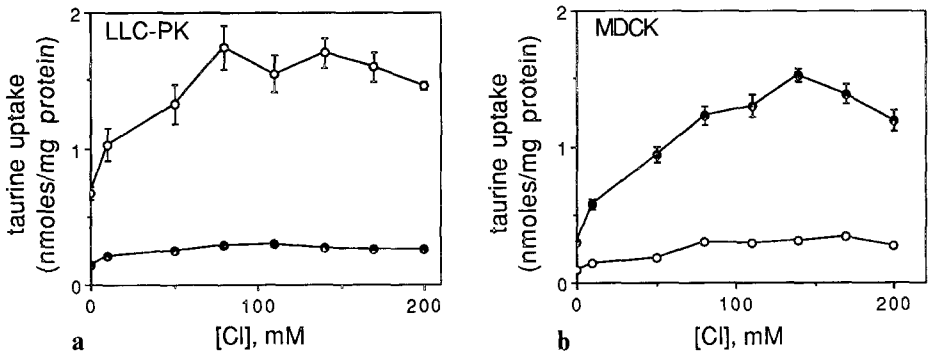

Fig. 2. Chloride dependence of taurine uptake into LLC-PK1 and MDCK cells. Confluent cell monolayers were incubated in Earle's balanced salt solution containing 0–200 mM chloride, 0–200 mM gluconate, and constant, 130 μM sodium plus 50 μM taurine (^{3}H-Taurine, 0.5 μCi) and apical (open circles) or basolateral (closed circles) uptake was measured at 15 minutes in (**a**) LLC-PK1 cells, or 20 minutes in (**b**) MDCK cells. Values represent the mean ± SEM for 4 filters

Transepithelial movement of taurine

LLC-PK1 cell accumulation of taurine was much greater from the apical cell membrane compared to the basolateral membrane over 180 minutes incubation.

The appearance of taurine in the contralateral bathing solution was measured. As can be seen from Fig. 3b, in the presence of sodium, apical to basolateral taurine movement was greater than basolateral to apical movement. However, in the absence of sodium, the movement from apical to basolateral was essentially identical to the basolateral to apical movement. As can be seen from Fig. 3a, the cellular accumulation of taurine in the absence of sodium is minimal, therefore one might logically conclude that the sodium independent transepithelial flux is paracellular.

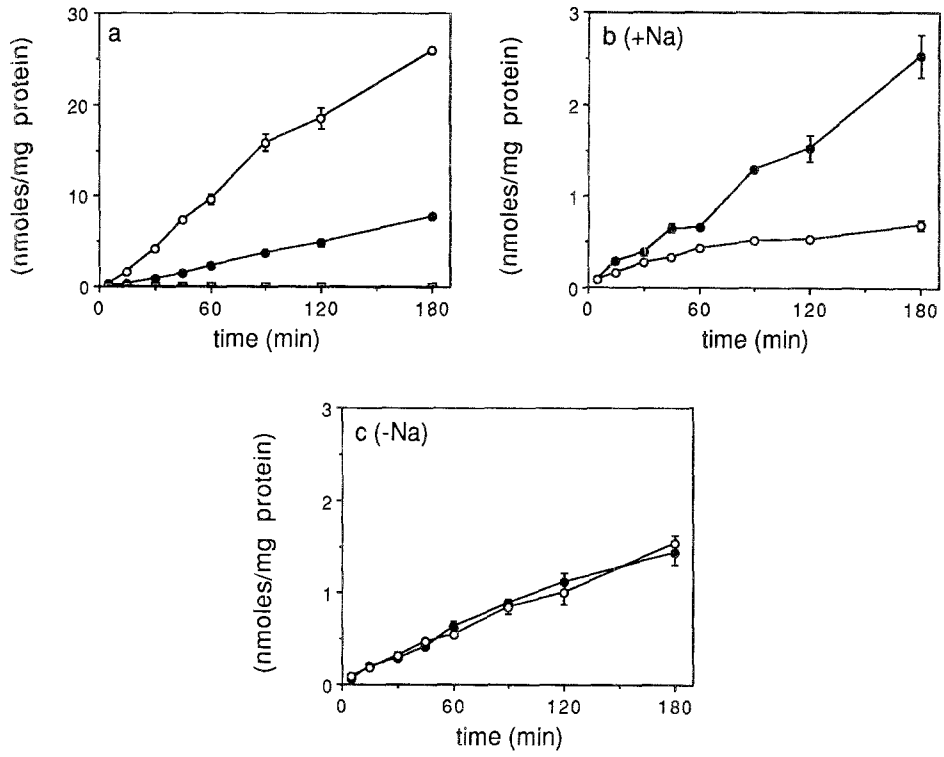

Fig. 3. Time course of transepithelial taurine flux in LLC-PK1 cells. Either the apical or the basolateral surface of confluent cell monolayers were incubated in EBSS containing radiolabeled taurine (50 μM); taurine-free buffer was added to the contralateral chamber. Appearance of contralateral taurine was measured over time in addition to cellular uptake. **a** Time course of taurine uptake from the apical in the presence of sodium (•) and the basolateral surface in the presence of sodium (o). Uptake in the absence of sodium is represented by **b** apical to basolateral taurine flux (•) and basolateral to apical flux (o) in the presence of sodium. **c** Apical to basolateral taurine flux (•) and basolateral to apical flux (o) in the absence of sodium. Values represent the mean of four filters ± SEM

In the MDCK cell monolayers, the time dependent accumulation of taurine proved to be greater from the basolateral surface, as previously noted, with neglible cell uptake in the absence of sodium. Despite the preferable accumulation from the basolateral surface, the apical to basolateral taurine flux was equal to the basolateral to apical flux in the presence of sodium in contrast to the LLC-PK1 cell monolayers. Transepithelial taurine movement was greater in the

absence of sodium compared to that observed with sodium in the external medium.

Polarity and specificity of taurine efflux

Cell monolayers were loaded with radiolabeled taurine over a 2 hour period in the presence of sodium containing EBSS. The external medium was then changed to an amino acid free EBSS and the appearance of radiolabeled taurine in both the apical and the basolateral chamber was measured over time. In addition, 500 μM of β-alanine or L-alanine was added to the buffer. Efflux is expressed as percent of the total counts which were associated with the medium. As seen in Fig. 5, apical and basolateral efflux of taurine was approximately 8% at 45 minutes, and was significantly enhanced by the addition of external β-alanine. The apical efflux was not altered by the addition of L-alanine, however, the basolateral efflux of taurine was slightly enhanced by presence of

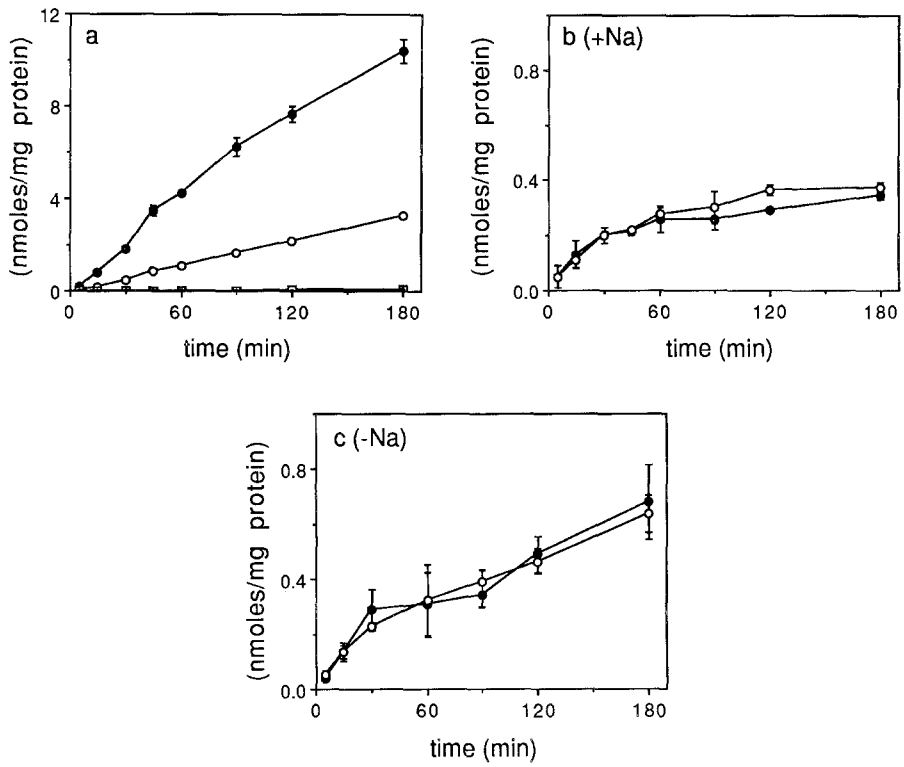

Fig. 4. Time course of transepithelial taurine flux in MDCK cells. Either the apical or the basolateral surface of confluent cell monolayers were incubated in EBSS containing radiolabeled taurine (50μM); taurine-free buffer was added to the contralateral chamber. Appearance of contralateral taurine was measured over time in addition to cellular uptake. **a** Time course of taurine uptake from the apical in the presence of sodium (o) and the basolateral surface in the presence of sodium (●). Uptake in the absence of sodium is represented by Ú (□) for the apical and (●) for the basolateral surface. **b** Apical to basolateral taurine flux (o) and basolateral to apical flux (o) in the presence of sodium. **c** Apical to basolateral taurine flux (●) and basolateral to apical flux (o) in the absence of sodium. Values represent the mean of four filters ± SEM

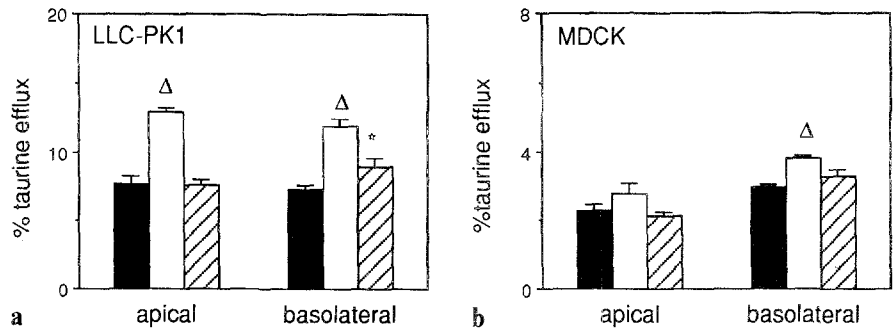

Fig. 5. Taurine efflux at 45 minutes was measured in LLC-PK1 (**a**) and MDCK (**b**) cell monolayers following a 2 hour loading period with EBSS plus 50 μM ^{3}H-Taurine, 1.0 μCi/ml. Uptake medium was replaced with amino acid-free buffer (shaded bars) or in buffer containing 500 μM β-alanine (open bars) or 500 μML-alanine (hatched bars). Appearance of taurine in the apical and the basolateral medium was measured in addition to cellular taurine. Efflux is expressed as percent of total counts appearing in the medium. Values present the mean of 8–10 filters. $\Delta = p < .001$, $* = p \leq .01$

L-alanine in the buffer. In the MDCK cell monolayers, taurine efflux was less than that seen in the LLC-PK1 cells, or 3% of total taurine accumulated. Addition of β-alanine to the external medium increased taurine efflux from the apical surface, but not significantly so. Taurine efflux from the basolateral surface of the MDCK cells was significantly increased by medium β-alanine but not L-alanine (Fig. 5b).

Effect of GES on taurine accumulation

Guanidinoethyl sulfonate, (GES) is a competive inhibitor of taurine transport. The effect of 0–1000 μM GES on taurine uptake was measured. In the LLC-PK1 cells, GES reduced apical and basolateral taurine uptake to 40% of control with approximately 50% inhibition at 500 μM GES. In the MDCK cells, addition of GES (1000μM)to the apical uptake solution reduced taurine accumulation to

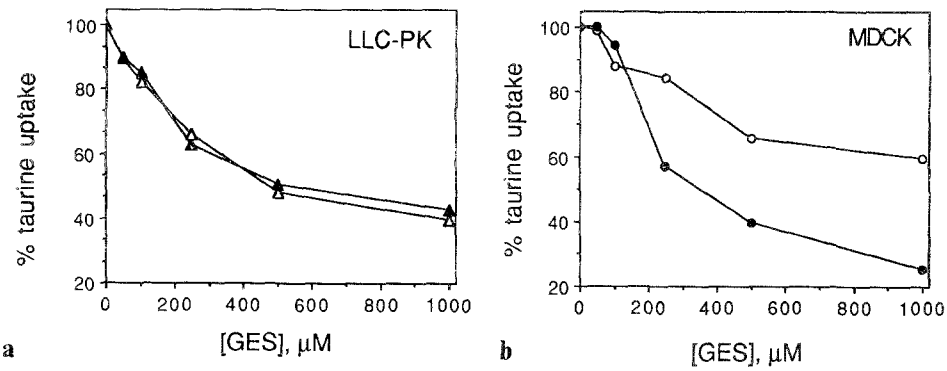

Fig. 6. Effect of GES on taurine uptake in LLC-PK1 and MDCK cells. Taurine uptake was measured in LLC-PK1 (**a**) and MDCK (**b**) cells in the standard uptake solution with 0–1000 μM GES. Values represent the mean of two filters and are expressed as percent of control for each concentration of GES

60% of control compared to almost 20% of control on the basolateral surface. Therefore the basolateral surface of the MDCK cells was more sensitive to inhibition by GES than the apical transport.

Discussion

Taurine transport by the proximally-derived LLC-PK1 cells was concentrated on the apical side of the cell monolayer; taurine transport is sodium and chloride dependent on both surfaces. In contrast, taurine transport was greater on the basolateral surface of MDCK cells, with similar characteristics of chloride and sodium dependence. The transport of taurine by brush border membrane vesicles from rabbit, rat and mouse as well as the basolateral membrane vesicles from mouse uniformly require sodium and chloride (Turner, 1986; Mandla et al., 1988; Zelikovic et al., 1989). In addition, all other epithelial cell plasma membrane systems (liver, intestinal, placental, retinal, and neuronal) are sodium-dependent (Bucuvalas et al., 1987, Hibbard et al., 1990; Meiners et al., 1980; Miyamoto et al., 1989; Scaleda, 1980). Only lysosomal taurine transport has been demonstated to be sodium independent (Vadgama et al., 1991).

Attempts to study the renal tubular basolateral transport system for taurine have lagged behind the extensive investigation of the luminal system(s), but in general have demonstated that the basolateral system is a lower capacity system with a higher Km when compared to the luminal system (Mandla et al., 1988). The magnitude of snake basolateral membrane vesicle taurine uptake was less than brush border membrane uptake and was not electrogenic (Benyajati et al., 1991).

Our studies indicate that the net transepithelial movement of taurine in LLC-PK1 cells proceeds in the direction from apical to basolateral membrane surface, in a manner similar to the mammalian proximal tubule. Taurine flux in the MDCK cells does not proceed either apical to basolateral or basolateral to apical, despite the greater transport capacity found on the basolateral surface. It is of interest that in the flounder tubule, taurine is secreted so that net transepithelial movement is in the opposite direction than in the mammalian tubule (King et al., 1985). The opposing directions of transepithelial flux in the mammalian proximal tubule and the flounder tubule could be related to dissimilar polarity of membrane characteristics. For example, greater transporter density may exist on the apical side of the mammalian tubule, and at the basolateral surface of the flounder tubule, both of which would permit a high intracellular amino acid concentration which could participate in the creation of a net driving force in the direction of luminal to peritubular in the mammalian proximal tubule and peritubular to luminal in the marine tubule (Perlman et al., 1991). Some investigators have postulated that the efflux step might ultimately determine the directionality of transport. In the flounder, the net transepithelial flux of taurine is in the direction of secretion, and this was significantly inhibited by the presence of 10μM taurine in the external medium (Perlman et al., 1991). However, the presence of external taurine did not alter the luminal to peritubular flux. These results suggest functional (and possibly structural) differences in the

apical and basolateral taurine transport systems. In addition, the apical system was sensitive to inhibition by organic anions; however, the basolateral system was not. The flounder tubule did not secrete β-alanine at comparable intracellular concentrations, therefore passive efflux of amino acid across the membrane is probably not the only factor responsible for the direction of flux (Perlman et al., 1991). Taken together these results support the presence of two distinct carrier systems in the flounder tubule. As further suggestive evidence, apical but not basolateral taurine uptake was inhibited by organic anions in the snake tubule.

Efflux of taurine was similar on the both surfaces of the LLC-PK1 cell monolayers, and was stimulated by the presence of another β-amino acid, β-alanine, but not L-alanine, an α-amino acid, which indicates that the efflux step is carrier mediated with structural specificity. There was a small but significant stimulation of taurine efflux by L-alanine on the basolateral surface of LLC-PK1 cells which could be due to efflux of taurine via a neutral amino acid carrier. The magnitude of taurine efflux was slightly less in the MDCK cell monolayers compared to the LLC-PK and was equivalent from either apical or basolateral membrane surfaces. Basolateral efflux was significantly enhanced by the presence of β-alanine but not L-alanine in the external medium. Luminal efflux was not significantly affected by external alanine. In the snake tubule, taurine efflux was greater from the basolateral surface compared to the apical (Benyajati et al., 1993). Previous studies in BBMV from rat kidney failed to demonstate transtimulation of sodium-independent taurine efflux by other β-amino acids (Chesney et al., 1993), however, transtimulation of taurine efflux by external taurine (10 μM) was observed in cultured hepatocytes (Hardison and Weiner, 1980).

GES inhibited taurine transport equally on apical and basolateral surfaces of LLC-PK1 cells yet had a greater inhibitory effect on the basolateral surface of MDCK cells. This provides further evidence for subtle functional differences in the transport of taurine between the apical and basolateral systems of these two cell lines.

In summary, our studies demonstrate differences in the distribution and directionality of taurine transport in these two cultured renal epithelial cells. The LLC-PK1 cell exhibits greater taurine uptake from the apical surface while the MDCK cell monolayers accumulated taurine primarily from the basolateral side. Transepithelial transport of taurine occurs in the LLC-PK1 cell monolayers under the experimental conditions, and is in the direction of apical to basolateral. In contrast, there was no net transepithelial movement of taurine in the MDCK cells. The polarized characteristics of the LLC-PK cell is similar to the proximal renal tubule because of the greater transport capacity found on the apical membrane and the net lumenal to basolateral flux. Taurine efflux from the apical and the basolateral membranes was equivalent and exhibited transstimulation by the β-amino acid. In addition, taurine efflux from the basolateral surface was slightly enhanced in the presence of L-alanine. Both surfaces of the LLC-PK1 cell monolayers were equally inhibited by GES while the basolateral side of the MDCK monolayers was more sensitive to GES than the apical surface.

Differences in taurine handling by LLC-PK1 and MDCK cell monolayers may be related to distribution of transporters, as well as unique protein structures, post-translational modification, or other intracellular factors (Rabito and Karich, 1982). It is not possible to attribute these differences simply to the tubular site of cell origin because either differences in species of origin or changes in cell characteristics with culture could be implicated. However, because there are functional similarities between the LLC-PK1 and MDCK cells and proximal and distal tubules these cells provide potential model systems for the study of epithelial transporter polarity which might allow better understanding of factors which affect epithelial function.

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