Amino Acids (1993) 5: 77–89

Amino
Acids
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Printed in Austria

The components of taurine transport across the rat small intestine A kinetic study

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Accepted September 17, 1992

Summary. The transport of taurine across adult Sprague-Dawley rat small intestine was studied in vitro using small intestinal strips. The kinetics of the transport mechanism were investigated under both steady-state and influx conditions. Our findings were compatible with the presence of two distinct transport mechanisms; a linear non-carrier mediated component and a saturable carrier mediated component, with almost equal contribution from each. The mediated component was found to be largely Na^+-dependent and exhibited marked inhibition by B-alanine and structurally related sulfur amino acids.

Keywords: Amino acids Taurine – B-amino acids – Transport – Intestine – Nutrition

Introduction

Taurine, 2-aminoethanesulfonic acid, is an end product of the metabolism of sulfur amino acids in mammals (Jacobsen and Smith, 1968). Taurine is present in very high concentrations in many mammalian tissues and body fluids including the brain, retina, myocardium, skeletal muscle, platelets, lymphocytes, cerebrospinal fluid and breast milk (Chesney, 1985). Taurine concentrations are especially high in developing mammals, with it being the most concentrated free amino acid in the neonatal brain, three to four times its concentration in the mature brain (Sturman, 1988).

The past two decades have witnessed an increasing recognition of the biologic importance of taurine. Among many other putative functions, taurine seems to play an important role in the development and integrity of the nervous system (Sturman et al., 1978). The developing brain is capable of achieving much higher taurine concentrations more rapidly as compared to the mature brain (Sturman et al., 1977; Sturman, 1979; Sturman et al., 1980). Perhaps the best evidence for the role of taurine in the integrity of neural tissue is the resulting

retinal degeneration and blindness in kitten fed a low taurine diet (Wen et al., 1979). In humans, the description of retinopathy secondary to taurine deficiency was illustrated in infants on chronic total parenteral nutrition who demonstrated electroretinographic as well as fundoscopic retinal degenerative changes (Vinton et al., 1987). The importance of taurine in the nervous system development was recently demonstrated by breeding taurine deficient female cats (Sturman et al., 1985). The experiment resulted in a high rate of fetal wastage and a high rate of central nervous system malformations in the aborted fetuses (Sturman et al., 1987). The live kitten were also found to have severely depressed taurine concentration, poor survival rate and slow growth rate.

The only identifiable sources for endogenous biosynthesis of taurine are the liver and the brain (Chesney, 1985). In neonatal animals, the demand for taurine by developing neural tissue is at its highest, at a time when the liver capacity for taurine biosynthesis is at its lowest (Sturman et al., 1978). Concomitantly, there is a profound requirement imposed by expanding muscle mass, especially in species with high postnatal growth rate, like the rat (Hayes and Sturman, 1982).

Although the main dietary source for taurine is meat in adult animals (Jacobsen and Smith, 1968; Sturman and Rassin, 1979), maternal milk is the most important source in the neonates (Rassin et al., 1978; Sturman, 1981; Huxtable and Lippincott, 1983). Even in the developing rat, which has considerable taurine biosynthetic capacity in the liver, a sizable part of taurine body pool is derived from maternal milk (Sturman, 1981). In humans, taurine biosynthetic activity in the liver is negligible (Swan, 1964). As a result, taurine is currently regarded as a conditionally essential amino acid for human infants, children and possibly adults (Gaull, 1986; Laidlaw and Kopple, 1987).

Efficient intestinal absorption appears to be an important tool for conserving dietary taurine, especially in humans and neonatal animals in general. Hepatocytic membranes from neonatal rats displayed a higher uptake of taurine as compared to adult (Bucuvalas et al., 1980). Numerous reports suggested the presence of a high affinity, energy requiring, carrier-mediated transport mechanism for taurine across the small intestine of rodents (Buffoni et al., 1978; Kim, 1983; Barnard et al., 1988). The authors have compared the intestinal absorption of taurine in the adult and suckling rats (Sharafuddin et al., 1988). Suckling rat intestinal mucosa exhibited notably enhanced capacity to concentrate taurine, and significantly higher uptake, maximum velocity and affinity as compared to adult rats. The present work studies the contribution of active and passive mechanisms to the transport of taurine in adult rat small intestine and analyzes the kinetics of the transporter.

Materials and methods

Experimental procedure

Male Sprague-Dawley rats, weighing 150–200 grams were anesthetized by sodium pentobarbital injected intraperitoneally (0.05 mg/g body weight). Segments from the mid-intestine weighed 50–80 mg were cut and slit open along their mesenteric border. Incubation media contained 20 ml of phosphate buffered saline (0.14 M NaCl, 0.01 M K_2HPO_4, pH adjusted to 7.4 by KH_2PO_4), 11 μCi of ^{14}C-labeled taurine and various concentrations of non-labeled

amino acids depending on the type of the study. Sodium-free buffer solution was prepared by replacing NaCl with choline chloride. All incubation media were continuously saturated with O_2 and kept at 37°C in a water bath set to shake at 70 strokes per minute. After removal from the incubation medium, strips were immersed in ice-cold isotonic mannitol, blotted on filter paper and immediately weighed on a Sartorius balance. Each tissue was then extracted in 2ml of 0.1 N HNO_3 for at least 5 hours. Aliquots from tissue extracts and incubation media were counted for their ^{14}C content in a liquid scintillation counter. Tissue residues were thereafter dried in an oven at 90°C and their dry weights (DW) were determined.

Time course of taurine accumulation

To determine the time needed for taurine transport to reach steady-state, intestinal strips were incubated in media containing 11 μCi of ^{14}C-taurine in 20 ml of PBS solution for 2, 5, 15, 30, 120 min after which the tissues were removed and treated as described above. Accumulation of taurine was determined as the isotopic distribution ratio and plotted versus time (IN/OUT ratio; counts per minute (cpm)/ml intacellular fluid to cpm/ml extracellular fluid). Correction for extracellular space was made according to Hajjar and Bitar (1977).

Steady state kinetics of taurine transport

Concentration dependence

Tissues were incubated in media containing 20 ml of PBS solution, 10 μCi of ^{14}C-taurine and unlabeled taurine in concentrations ranging from 0.05 to 0.75 mM. The strips were incubated for at least 60 min after which they were removed and treated as described previously. The intracellular concentration of taurine was determined in nmole/mg DW and plotted versus concentration in the incubation medium.

Carrier-mediated and non-carrier-mediated components

The non-mediated component of taurine steady-state was estimated by a modification of the inhibition method of Inui and Christensen (1966). When the transport of ^{14}C-labeled taurine is studied in the presence of unlabeled taurine as the inhibitor, the following relationship is expected:

$$1/(1 - R) = 1 + (K_t + S)/I$$

R being the ratio of the inhibited to the uninhibited uptake of substrate concentration S in the presence of inhibitor concentration I.

Uninhibited taurine uptake was obtained in cpm/mg DW after one hour incubation in media containing ^{14}C-taurine without unlabeled taurine. The inhibited uptake was obtained in media containing, in addition to ^{14}C-taurine, unlabeled taurine at inhibitory concentrations I ranging from 0.05 to 0.75 mM. $1/R$ was plotted versus $1/I$ and a straight line was fitted by linear regression analysis. This line was extrapolated to zero abscissa yielding the value of R at infinite inhibitor concentration. This value, R, approximates the ratio of non-mediated transport to total transport of taurine (R = Non-mediated Transport/Total Transport).

Since this relationship was obtained for low taurine concentrations (11 μCi), then it was considered to correspond to the initial low concentration part of the concentration study curve (<0.2 mM) which was nearly linear. The non-mediated taurine transport was then plotted versus concentration as a non-intercept straight line with a slope equal to the slope of the initial linear part of the concentration study multiplied by R. The carrier-mediated component of taurine uptake was calculated by subtracting the non-mediated component from the total transport. Curves for the mediated uptake were then plotted and kinetic constants were determined.

Initial rate kinetics of taurine transport

Intestinal strips were mounted on Lucite chambers in a way that covers their serosal surface and exposes only the mucosal membrane to the bathing solution. Incubation media contained 20 ml PBS, 11 μCi of ^{14}C-labeled taurine and unlabeled taurine in concentrations 0.05, 0.1, 0.5 and 0.75 mM. A preliminary set of experiments was conducted to study ^{14}C-taurine accumulation by the mucosal border versus time in the first minute of incubation. The results described a straight line that passed through the origin, indicating the predominance of influx and absence of an adsorption component. As a result, 60 seconds of incubation was used to study influx, which was calculated in nmole/min.mg DW.

Estimate of the non-mediated component of taurine influx was calculated in the same way as for steady-state uptake, and was subtracted from the total influx to yield the carrier-mediated component of taurine influx.

The kinetics of taurine were investigated in sodium-free incubation media, at both steady-state and influx conditions.

Inhibition studies were performed at both steady-state and influx conditions. The mediated component of taurine transport was determined in the presence of B-alanine, cysteine, methionine and L-alanine at concentrations 10 times higher than taurine (5.0 mM). In addition, the steady-state mediated uptake of taurine was calculated in incubation media containing B-alanine in concentrations ranging from 0.1 to 20.0 mM.

Results

Time course of taurine accumulation

The time course of taurine accumulation by the rat small intestine was determined as the IN/OUT distribution ratio over a period of 2 hours (Fig. 1). The uptake was linear up to 5 min, indicating the predominance of the influx component over the other components. The accumulation of taurine reached steady-state at 60 min, with no significant difference between 60 min and 90 min ($P > 0.2$). Accordingly, at least 1 hour was chosen as the duration for subsequent tissue incubations under steady-state conditions. The IN/OUT distribution ratio reached a maximum value of 1.46, which speaks for a transport system capable of accumulating taurine against a concentration gradient. The IN/OUT

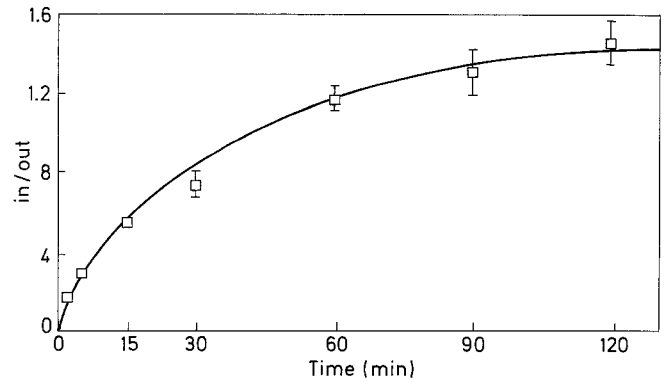

Fig. 1. Time course of taurine uptake by mucosal strips of rat small intestine. The incubation media contained 11 μCi ^{14}C-taurine. Each point is the mean of at least 6 determinations from 3 rats. The bars represent $\pm$ standard error of the mean (SE)

ratio was also calculated in the absence of Na^+ and found to be 0.85, significantly lower than in the presence of Na^+ ($P < 0.001$).

Concentration dependence at steady state

Total uptake

Intracellular taurine at steady-state was determined as a function of increasing taurine concentration in the incubation medium. The results are plotted in Fig. 2. The results show an intial linear increase in uptake with higher concentrations, with a tendency towards saturation between 0.25 and 0.5 mM where the relationship became curvilinear.

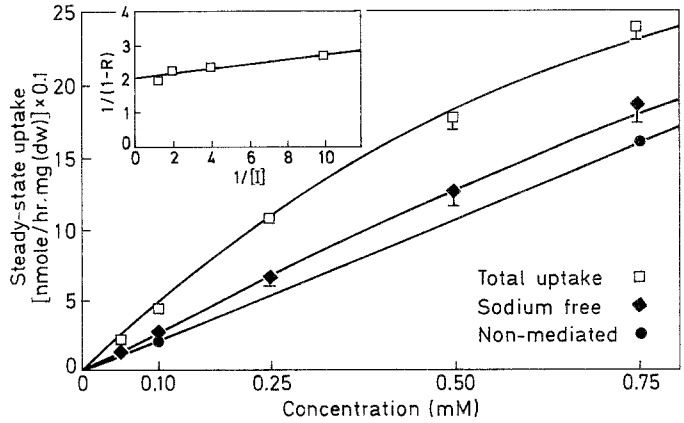

Fig. 2. Concentration of taurine total uptake at steady state in the presence of: 140 mM NaCl (□—□) and 140 mM choline chloride (◆—◆). Note that the total uptake is linear at high concentrations. Each point is the mean of 8–15 determinations from 3–5 animals. The bars represent ±SE. The calculated non-mediated component of taurine transport at steady state (●—●) was considered to be linearly related to concentration with a slope of 2.17 nmole/hr.mgDW.mM. Insert. Inhibition of ^{14}C-taurine at steady state by unlabeled taurine. R is the ratio of inhibited to uninhibited uptake. $1/I$ is the reciprocal of inhibitor concentration. Each point is the mean of at least 6 determinations from 3 animals. The regression line intercepts the ordinate axis at 2.02. This indicates that, at low taurine concentrations, 49.5% of taurine total uptake is susceptible to inhibition, i.e. carrier mediated

Mediated and non-mediated components

The inhibition of ^{14}C-taurine uptake by unlabeled taurine was studied. A plot of $1/(1 - R)$ versus $1/I$ is shown in Fig. 2. Extrapolation of the best fit line to infinite concentration gave an R of 2.02, which is different from unity. This indicated that an alternate uptake process is present which is not accessible to inhibition, i.e. is not carrier-mediated. The non-mediated component was then assumed linearly related to taurine concentration in the medium and was calculated to be 2.17 nmole/hr.mgDW.mM (Fig. 2). The carrier-mediated component of taurine steady-state uptake was determined by subtracting the non-mediated component from the total steady-state uptake. A good hyperbolic relationship which can be well described by Michaelis-Menten kinetics was obtained (Fig. 3).

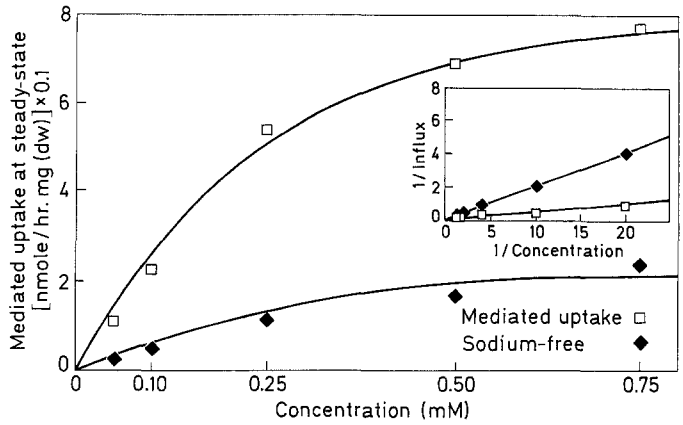

Fig. 3. Concentration dependence of taurine mediated uptake at steady state in the presence (□—□) and absence (◆—◆) of Na^+. Values for mediated uptake were obtained by subtracting the non-mediated component from the total uptake (Fig. 2). Saturation is now evident for both curves. Insert. Corresponding Lineweaver-Burk double reciprocal plots. The kinetic constants were calculated in the presence of Na^+ (V_s = 2.25 nmole/hr.mgDW, K_t = 0.97 mM) and in the absence of Na^+ (V_s = 0.79 nmole/hr.mgDW, K_t = 1.57 mM)

Uptake in the absence of sodium

Steady-state uptake of taurine in the absence of Na^+ ions is shown in Figs. 2 and 3. The contribution of taurine transport by Na^+ dependent mechanisms was also determined (Fig. 4). At taurine concentration of 0.5 mM, about 71% of steady-state mediated uptake was Na^+-dependent.

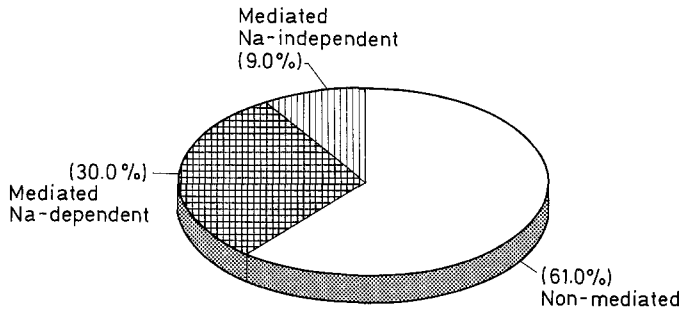

Fig. 4. Components of taurine steady-state uptake at taurine concentration 0.5 mM. 61% of the total taurine was non-mediated, 30% was carrier-mediated-Na^+-dependent and 9% was carrier-mediated-Na^+-independent. Hence, 71% of the carrier-mediated taurine uptake is Na^+-dependent

Inhibition studies

Increasing the concentration of B-alanine in the incubation medium resulted in a hyperbolic decrease in the mediated component of taurine steady-state uptake (Fig. 5). A plot of $1/(1 - R)$ versus $1/I$ gave an intercept of 1.03 which indicates a nearly complete inhibition. The inhibitory effects of B-alanine, cysteine, methionine and L-alanine, present in 10-fold excess in the incubation medium, on the

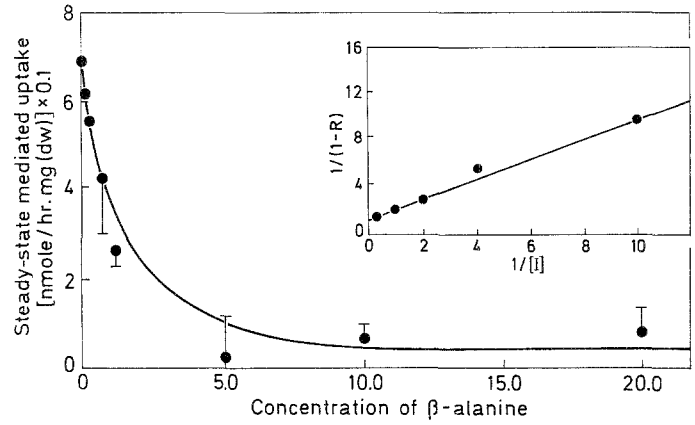

Fig. 5. Inhibition of the mediated component of taurine uptake at steady state by increasing concentrations of B-alanine. Each point is the mean of at least 6 determinations from 3 animals. Bars represent ±SE. Insert. R is the ratio of inhibited to uninhibited uptake, $1/I$ is the reciprocal of the inhibitor concentration. This line was fitted by regression analysis with an intercept of 1.03. This indicates that B-alanine is a potential substrate for this transport system

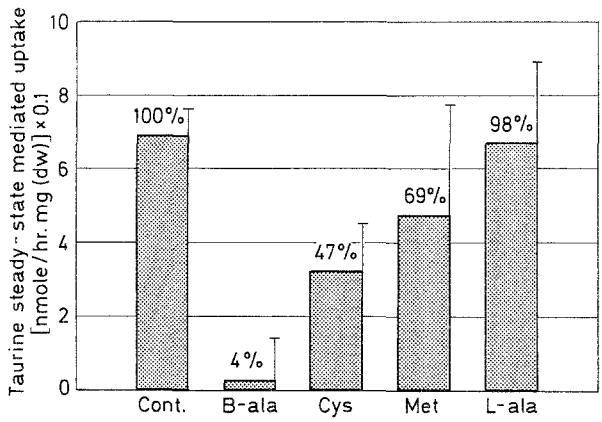

Fig. 6. Steady-state mediated uptake of taurine (0.5 mM) in the presence of 10 times higher concentrations of inhibitor amino acids. Values are the means of at least 6 determinations from 3 animals. Bars represent ±SE. B-alanine and cysteine produced significant inhibition ($p < 0.001$ and $p < 0.01$) while methionine and L-alanine did not ($p > 0.3$ and $p > 0.9$)

mediated component of taurine uptake at steady-state are shown in Fig. 6, B-alanine caused a significant inhibition equivalent to 96% ($P < 0.001$). Cysteine significantly inhibited the uptake by 53% ($P < 0.01$), whereas methionine and L-alanine failed to show a significant inhibition ($P > 0.03$ and $P > 0.9$).

Concentration dependence at initial rate

Total influx

Concentration dependence of taurine total influx across the mucosal membrane is shown in Fig. 7. A linear increase was observed up to a medium concentration

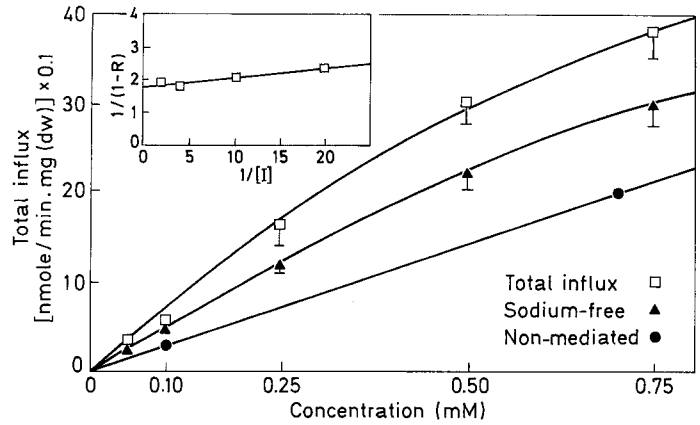

Fig. 7. Taurine influx across the mucosal membrane in the presence of 140 mM NaCl (□—□) and 140 mM choline chloride (▲—▲). Each point is the mean of at least 6 determinations from 3 rats. Bars represent ±SE. The non-mediated component (●—●) of the total influx was considered to be linearly related to concentration, with a slope of 2.81 nmole/hr.mgDW.mM. Insert. Inhibition of ^{14}C-taurine influx by unlabeled taurine. R is the ratio of inhibited to uninhibited influx. $1/I$ is the reciprocal of inhibitor concentration. Each point is the mean of 4 determinations. The regression line intercepts the ordinate axis at 1.79. This indicates that, at low taurine concentrations, 56% of taurine total influx is carrier-mediated

of 0.25 mM, followed by curvilinear increase. However, the influx failed to reach saturation in the concentration range of the study; influx rates at the 0.5 and 0.75 mM points were significantly different ($P < 0.05$).

Components of total influx

The non-mediated and mediated components of total taurine influx were determined in the same way as for the steady-state uptake. The inhibition of ^{14}C-taurine by unlabeled taurine was studied. A plot of $1/(1 - R)$ versus $1/I$ gave an intercept of 1.79 (Fig. 7), and the non-mediated component was determined as a straight line with a slope of 2.81 nmole/min.mgDW.mM (Fig. 7). The carrier-mediated component of taurine influx was then calculated by subtracting the non-mediated component from the net influx and, when plotted versus concentration, displayed a hyperbolic relationship which conformed to the Michaelis-Menten type of kinetics (Fig. 8).

Influx in sodium free conditions

The concentration dependence taurine influx across the mucosal border was studied in the absence of Na^+ (Fig. 7). The mediated component was then calculated (Fig. 8). About 47% of taurine carrier-mediated influx was found to be Na^+-dependent, at taurine concentration of 0.5 mM (Fig. 9).

Inhibition studies

Influx of 0.5 mM taurine was measured in the presence of B-alanine, cysteine, methionine and L-alanine, in 10-fold excess (Fig. 10). Among these amino acids,

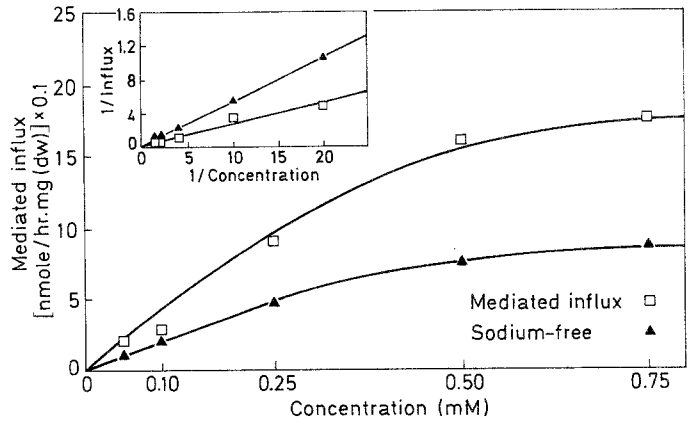

Fig. 8. Effect of taurine concentration on taurine mediated influx in the presence (□—□) and absence (▲—▲) of sodium ions. Values for mediated influx were calculated by subtracting the non-mediated component from the total influx (Fig. 7). Insert. Corresponding Lineweaver-Burk double reciprocal plots. The kinetic constants were calculated in the presence of Na^+ (V_{max} = 3.48 nmole/hr.mgDw, k_t = 0.88 mM) and in the absence of Na^+ (V_{max} = 3.12 nmole/hr.mgDW, K_t = 1.61 mM)

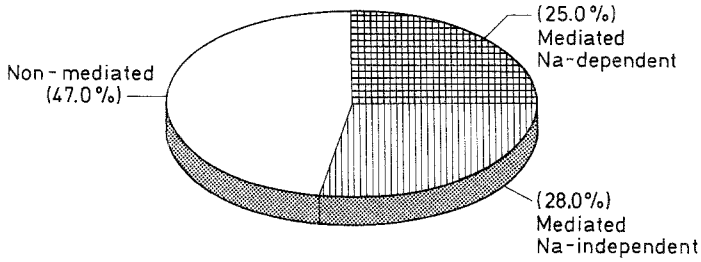

Fig. 9. Components of taurine influx across the mucosal membrane at a taurine concentration of 0.5 mM. 47% of total influx was mediated. 25% was non-mediated-sodium-dependent. 28% was carrier-mediated-Na^+-independent. It follows that about 47% of taurine carrier-mediated influx is Na^+-dependent

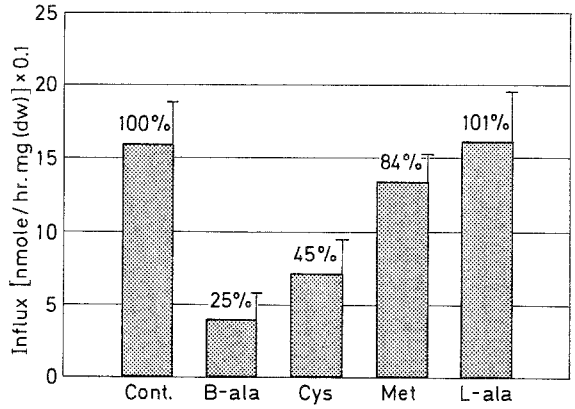

Fig. 10. Inhibition of taurine influx by other amino acids in 10-fold excess. Values are means of at least 6 determinations from 3 animals. Bars represent ±SE. B-alanine and cysteine showed significant inhibition ($p < 0.01$ and $p < 0.01$) whereas methionine and L-alanine did not ($p > 0.4$ and $p > 0.9$)

B-alanine was the most efficient in inhibiting the mediated component of taurine influx causing a significant decrease of 75% ($P < 0.1$). Cysteine also caused a significant inhibition of 55% ($P < 0.01$), whereas methionine and L-alanine failed to show a significant effect ($P > 0.4$ and $P > 0.9$).

Discussion

The non-saturable component of taurine was determined. At low taurine concentrations, it was found to account for 44% of influx and 50% of steady-state uptake (Figs. 2 and 7). The significant contribution by passive diffusion to taurine transport is not surprising; the intestinal mucosa has been considered unique among other membranes in that the uptake of B-amino acids is solely mediated by passive diffusion (Stevens et al., 1984). In addition, taurine, at physiological pH exists as a zwitterion (Jacobsen and Smith, 1968), which increases its permeability coefficient across lipid membranes.

The mediated components of taurine at steady-state and initial rate conditions were kinetically analyzed. Plots of taurine uptake versus taurine concentration described hyperbolic relationships which, when projected on Lineweaver-Burks plots, yielded straight lines with non-zero intercepts (Figs. 4 and 9). This, together with the steady-state IN/OUT ratio greater than unity, suggested that the saturable component of taurine uptake is due to an active, carrier-mediated transport process.

A common source of energy for active transport of amino acids is co-transport with Na^+ (Schell et al., 1983), whereby the transport of the amino acid is coupled to the flow of Na^+ in the same direction through the use of the same carrier. A high extracellular Na^+ concentration, which is maintained by the activity of the (Na^+-K^+) ATPase exchange pump, is thus necessary to drive the transport process at an IN/OUT ratio higher than one. Our results showed that, in the absence of Na^+ ions, the IN/OUT ratio decreased from 1.47 to 0.85, which indicates the failure of the intestinal cells to accumulate taurine against a concentration gradient in the absence of Na^+. At steady-state and influx conditions, respectively 71% and 47% of mediated taurine uptake were Na^+-dependent (Figs. 4 and 9). The absence of Na^+ decreased the maximum velocity at steady-state (V_s) from 2.25 to 0.79 nmole/hr.mg, and decreased the affinity ($1/K_t$) from 1.03 to 0.64 mM^{-1}. However, at initial rate conditions, the absence of Na^+ decreased the affinity ($1/K_t$) changing it from 1.14 to 0.62 while it only slightly decreased the maximum rate of influx (V_{max}) 3.12 as compared to 3.48 in the presence of Na^+. This observation indicates that the binding of Na^+ to the carrier contributes mainly by increasing the carrier's affinity for taurine (decreasing K_t) with only little effect on taurine maximal rate of influx.

At steady-state, the contribution to taurine transport by the different components were: 61% through passive diffusion, 30% through Na^+-dependent-carrier-mediated uptake and 9% through Na^+-independent-carrier-mediated uptake. In the suckling rat, we previously showed that, in the absence of Na^+ ions, the bulk of taurine uptake was through passive diffusion with a higher permeability coefficient than in the adult (unpublished data). The increased taurine uptake in

the suckling rat could be due to an increase in Na^+-dependent carrier sites, as well as to increased permeability of the mucosal membrane to taurine. Leaky membranes are also reported in the renal tubules of neonatal rats, resulting in the physiologic taurinurea which later disappears with maturity (Chesney, 1985). A similar phenomenon could be occuring in the intestinal mucosa.

To characterize the structural specificity of the taurine transport system, inhibition by four other amino acids was studied. The inhibitory effect of B-alanine, a close relative of taurine, was studied by determining the mediated uptake of taurine over a wide range of B-alanine concentrations. The results described a hyperbolic relationship which, when analyzed by plotting $1/(1 - R)$ versus $1/I$, described a straight line with an intercept of 1.03 (Fig. 5). This indicated that B-alanine is capable of almost completely inhibiting the steady-state uptake of taurine. However, B-alanine, when present in 10-fold higher concentrations than taurine, inhibited only 75% of the mediated taurine influx (Fig. 10) as compared to 96% inhibition at steady-state (Fig. 6). Cysteine proved to be a fairly good inhibitor of taurine mediated transport in the rat intestine, reducing its steady-state uptake by 53% (Fig. 6) and influx by 55% (Fig. 10). Methionine and L-alanine failed to cause a significant decrease in both taurine influx and steady-state uptake (Figs. 6 and 10) which eliminates the possibility of transport via the NBB and PHE systems (Stevens et al., 1984).

Taurine and B-alnine have been reported to share the same process in several tissues. This system, namely the B-amino acid transport, was identified in Ehrlich tumor cells (Christensen, 1964), renal brush border (Chesney et al., 1985), heart (Franconi et al., 1981), liver (Hardison and Weiner, 1980), retina (Miller and Steinberg, 1979), nervous system (Meiner et al., 1980; Larsson et al., 1986) and in other tissues. Whether the B-system is also present in the intestine has been subject to controversy. Most investigators held that the transport of B-alanine in the intestine was not concentrative (Lin et al., 1962; Burril et al., 1976; Hama et al., 1976; Navab et al., 1984; Stevens et al., 1984). However, non of these observers studied the transport of taurine. Taurine is present at very high concentrations in the small intestine (Huxtable and Lippincott, 1982) and since it can not be synthesized locally, then the presence of a system capable of concentrating it against a concentration gradient is essential. Such system has been reported by various workers (Hayes and Sturman, 1982; Kim, 1983; Sharafuddin et al., 1988). The present study was also consistent with the presence of a carrier mediated taurine transport system in the rat intestine, with a high structural selectivity for B-amino acids. The carrier probably has two sites. The first site binds the B-NH_2 group (B-NH_2 of taurine and B-alanine, and a-NH_3 of cysteine). The second site binds the sulfonic acid and carboxylic acid groups with high affinity and, to a lesser extent, the sulfhydryl group (B-SH group of cysteine).

In conclusion, taurine transport across the adult rat small intestine was demonstrated to take place by two distinct mechanisms with almost equal contributions. The first mechanism is a carrier mediated transport system that was found to be largely dependent on Na^+, capable of actively accumulating taurine against a concentration gradient and exhibited a high degree of structural selectivity for B-amino acids. The other mechanism is a first order, non-

saturable transport process that is not sensitive to inhibition and does not depend on Na^+.

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Received April 30, 1992