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# Nicotinic Acid Transport Mediated by pH-dependent Anion Antiporter and Proton Cotransporter in Rabbit Intestinal Brush-border Membrane

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## Abstract

In order to determine whether the vitamin nicotinic acid is absorbed via an anion antiporter, intestinal epithelial cell membrane transport mechanisms for nicotinic acid were characterized using isolated rabbit jejunal brush-border membrane vesicles.

The uptake of nicotinic acid by the membrane vesicles showed an overshoot phenomenon in the presence of an outwardly directed bicarbonate gradient or an inwardly directed proton gradient and the uptakes were two times and six times greater, respectively, than that in the absence of any ion gradient. The bicarbonate-dependent initial uptake of nicotinic acid was increased at acidic pH, showing pH-dependent transport activity. An inhibitor of anion transport, 4,4′-diisothiocyanostilbene-2,2′-disulphonic acid, specifically reduced bicarbonate-dependent transport of nicotinic acid. The initial uptakes of nicotinic acid via the anion antiporter and the proton cotransporter were specifically inhibited by monocarboxylic acids such as acetic acid, benzoic acid, D- and L-lactic acid, pravastatin and valproic acid, but not by di- or tricarboxylic acids, bile acids or amino acids. Nicotinic acid uptake activity was, furthermore, expressed in a *Xenopus laevis* oocyte system after injection of messenger RNA (mRNA) derived from rabbit intestinal epithelial cells.

These observations demonstrate that nicotinic acid is absorbed by two independent active transport mechanisms from small intestine, i.e. a proton cotransporter and an anion antiporter. The pH-dependence observed in the intestinal absorption of nicotinic acid might, therefore, be ascribed partly to pH-sensitive and partly to carrier-mediated transport mechanisms in the brush-border membrane.

Nicotinic acid (niacin) is an essential water-soluble vitamin with one monocarboxyl group, $pK_a$ 4·84, which appears to be absorbed from the small intestine in a pH-dependent manner. Although simple diffusion according to pH partition theory has been suggested for the intestinal absorption of nicotinic acid (Henderson & Gross 1979; Elbert et al 1986; Rose 1988), it seems unlikely that such a charged compound would permeate the intestinal epithelial barrier at the prevailing luminal pH. Sadoogh-Abasian & Evered (1980) suggested the existence of carrier-mediated facilitated diffusion at lower concentrations of nicotinic acid, which was masked by simple diffusion at higher concentrations (approximately 10 mM). A specialized transport process was also observed in a study using Ussing's flux chambers on the bullfrog intestine (Fox & Hogben 1974). We have, furthermore, clearly demonstrated that nicotinic acid is transported by a carrier-mediated transport mechanism utilizing a proton gradient as the driving force in intestinal brush-border membrane vesicles (BBMVs) in rats (Simanjuntak et al 1990). The failure to detect carrier-mediated transport in some previous studies might be ascribed to inadequate experimental conditions for demonstrating carrier-mediated transport, including pH and concentration of nicotinic acid. Carrier-mediated intestinal transport of various monocarboxylic acids shows pH-dependence and is thought to play an important role in the intestinal absorption of charged compounds at physiological pH (Ganapathy & Leibach 1985; Tsuji et al 1990, 1994; Takanaga et al 1994). Anion antiport, in parallel with proton-coupled transport, has also been demonstrated as an additional specific transport mechanism for weak organic acids such as short-chain fatty acids (Titus & Ahearn 1988; Harig et al 1991; Simanjuntak et al 1991). Interestingly, such an anion antiport seems to demonstrate pH-dependence, with higher activity at acidic pH than at neutral pH. Anion antiport and proton cotransport might, therefore, both contribute to the apparent pH-dependent absorption of nicotinic acid from the small intestine. It is, however, still unknown whether or not nicotinic acid is absorbed via an anion antiporter. The purpose of this study was to investigate whether nicotinic acid is absorbed via a pH-dependent anion antiport system in addition to a proton-cotransport mechanism, by comparing the absorption characteristics with those of the proton-cotransport mechanism using rabbit jejunal BBMVs.

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## Materials and Methods

### *Chemicals*

[Carboxyl-$^{14}$C]nicotinic acid (2·0 GBq (mmol)$^{-1}$) and valinomycin were purchased from Sigma (St Louis, MO, USA). Unlabelled nicotinic acid and 4,4′-diisothiocyanostilbene-2,2′-disulphonic acid were obtained from Wako Pure Chemical Industries (Osaka, Japan). Pravastatin was a generous gift from Sankyo (Tokyo, Japan). All other chemicals were of reagent grade or of the highest purity available.

### *Membrane vesicle preparation and uptake study*

The study was performed according to the Guidelines for the Care and Use of Laboratory Animals in Takara-machi Campus

of Kanazawa University and was approved by the Committee on Animal Experimentation of Kanazawa University, Takaramachi Campus. Jejunal BBMVs of male rabbits, 2·5–3 kg (Japan SLC, Hamamatsu, Japan) were isolated by a modification of the magnesium precipitation method (Burckhardt et al 1983) and used on the day of preparation. Briefly, jejunum was removed and washed with saline and the mucosa was scraped off. A Waring blender was used to homogenize the mucosa in 20 times the mucosal volume of Tris-HCl (2·4 mM, pH 7·1) containing 60 mM mannitol and 1 mM ethylene glycol bis(β-aminoethyl ether)-*N,N,N′,N′*-tetraacetic acid. The homogenate was reacted with 10 mM $MgCl_2$ for 20 min before centrifugation at 3000 *g* for 15 min. The supernatant was then centrifuged at 27 000 *g* for 30 min. The resulting pellet was suspended in 60 mM mannitol, 5 mM ethylene glycol bis(β-aminoethyl ether)-*N,N,N′,N′*-tetraacetic acid, 12 mM Tris-HCl, pH 7·1, and homogenized by 20 strokes in a Potter–Elvehjem homogenizer at 900 rev $min^{-1}$ using a tightly fitting Teflon pestle. The magnesium precipitation was repeated. The homogenate was then centrifuged at 47 000 *g* for 30 min and the resulting pellet was suspended in the medium specified in each figure legend or table footnote to give a membrane protein concentration of 28·9 ± 3·74 mg $mL^{-1}$ (n = 10, mean ± s.e.m.). The purified membrane preparation showed an alkaline phosphatase enrichment of 10·0 ± 0·77-fold compared with the crude mucosal homogenate (n = 10, mean ± s.e.m.). The $Na^+$,$K^+$-ATPase activity, on the other hand, was not concentrated.

Uptake measurements were performed by a rapid filtration technique as described previously (Simanjuntak et al 1990). All media containing bicarbonate were aerated for 1 h with 95% $N_2$–5% $CO_2$ and the pH was adjusted immediately before experiments. Other media were aerated with 100% $N_2$ as a control for non-specific effects of gassing. Uptake was initiated by adding a 90-μL volume of incubation medium containing [$^{14}$C]nicotinic acid to a 10-μL volume of BBMV suspension in the appropriate suspension medium. Uptake of [$^{14}$C]nicotinic acid was determined at 37°C and was terminated by addition of ice-cold stop solution (1 mL), then immediate filtration through a 0·45 μm filter (HAWP; Millipore, Bedford, MA, USA). Initial uptake was evaluated as the uptake at 10 s. The filter was washed twice with ice-cold stop solution (25 mM 2-[4-(2-hydroxyethyl)-1-piperazinyl]ethanesulphonic acid (HEPES)-Tris buffer, pH 7·5, 30 mM potassium gluconate and the appropriate concentration of mannitol to make the solution equi-osmolar with the incubation medium; 4 mL).

*Heterologous gene expression in* Xenopus laevis *oocytes*

RNA was isolated from small intestinal epithelial cells of rabbits by a routine guadinium thiocyanate-cesium chloride procedure. Messenger RNA (mRNA) was isolated by affinity chromatography on an oligo(dT)-cellulose column (Pharmacia, Tokyo, Japan).

*Xenopus laevis* oocytes were injected with mRNA solution (1·0 μg $\mu L^{-1}$; 50 nL) or water and cultured in Barth's solution at 18°C for 3 days as described previously (Tamai et al 1995a). Two oocytes were incubated in HEPES-Tris-buffered saline (50 μL) containing 150 mM NaCl, 5 mM KCl, 1 mM $MgCl_2$, 1 mM $CaCl_2$, 10 mM HEPES-Tris (pH 7·5) or 10 mM 2-(*N*-morpholino)ethanesulphonic acid-Tris (pH 6·0) and test compound at 25°C. Uptake was terminated by washing the oocytes with ice-cold HEPES-Tris-buffered saline at pH 7·5 (3 × 15 mL). Washed oocytes were transferred to vials containing sodium dodecylsulphate (5%; 0·5 mL), for solubilization, and the associated radioactivity was measured.

*Analytical method*

The amount of [$^{14}$C]nicotinic acid taken up was determined by measuring the radioactivity. The filters trapping [$^{14}$C]nicotinic acid were transferred to counting vials, dissolved in Clear-sol I scintillation fluid (Nacalai Tesque, Kyoto, Japan; 4 mL), and counted by means of an LSC-1000 (Aloka, Tokyo, Japan) liquid scintillation counter. The specific activity of alkaline phosphatase was measured according to the method of Walter & Schutt (1974). Protein was measured by the method of Bradford (1976) using a Bio-Rad protein assay kit (Bio-Rad, Richmond, CA, USA) with bovine serum albumin as the standard.

*Data analysis*

Uptake was represented as uptake coefficient (μL (mg protein)$^{-1}$/10 s), uptake rate (pmol (mg protein)$^{-1}$/10 s) or vesicle : medium ratio obtained by dividing the uptake amount by the concentration of nicotinic acid in the incubation medium (μL (mg protein)$^{-1}$).

The kinetic parameters for the uptake of nicotinic acid by BBMVs were estimated by solving the following equation, consisting of both a saturable term and an apparently non-saturable linear term, using the non-linear least-squares regression analysis program MULTI (Yamaoka et al 1981):

$$V = V_{max} \times [S]/(K_m + [S]) + k_d \cdot [S] \quad (1)$$

where V and [S] represent the apparent uptake rate and the concentration of nicotinic acid, respectively, $V_{max}$ and $K_m$ are the maximum uptake rate and the apparent Michaelis constant for the carrier-mediated process, respectively, and $k_d$ is the first-order rate constant for the apparently non-saturable component; this was estimated from the uptake determined in the absence of a bicarbonate gradient at pH 7·5.

## Results

*Effect of bicarbonate and proton-gradients on nicotinic acid uptake*

Fig. 1 shows the time-courses of the uptake of [$^{14}$C]nicotinic acid in the presence or absence of proton or bicarbonate gradient, or both. In the presence of an inwardly directed proton gradient or an outwardly directed bicarbonate gradient, uptake of [$^{14}$C]nicotinic acid showed an overshoot phenomenon, whereas in the absence of any ion gradient, no significant uptake was observed. The simultaneous imposition of the two ion-gradients, bicarbonate and proton gradient, induced very efficient uptake, with a 10-fold increased transient overshoot uptake over the equilibrium value. The initial uptake measured at 10 s (9·4 μL (mg protein)$^{-1}$) was larger than the sum of the uptakes obtained with proton or and bicarbonate gradients alone (1·5 and 4·5 μL (mg protein)$^{-1}$, respectively).

*pH-Dependence of nicotinic acid uptake*

The pH-dependence of nicotinic acid uptake in the presence and absence of intravesicular bicarbonate ion is shown in Fig. 2. At acidic extravesicular pH the uptake of [$^{14}$C]nicotinic acid

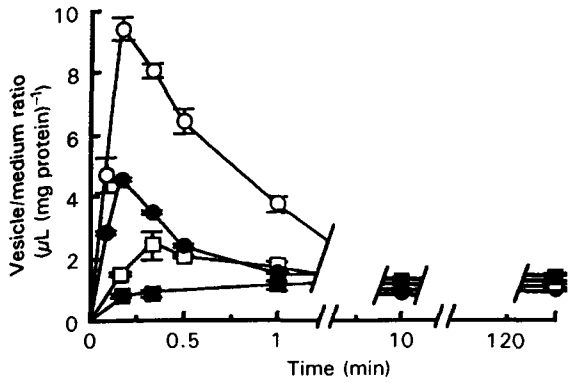


FIG. 1. Time-courses of [$^{14}$C]nicotinic acid uptake by rabbit jejunal BBMVs. BBMVs were pre-loaded with 25 mM HEPES-Tris buffer (pH 7·5), containing either potassium gluconate (30 mM; closed symbols) or $KHCO_3$ (30 mM; open symbols). The uptake of [$^{14}$C]nicotinic acid (50 μM) was examined at 37°C in either 2-(*N*-morpholino)ethanesulphonic acid (25 mM)-Tris buffer (pH 6·0; ○ ●), or HEPES-Tris buffer (pH 7·5; □ ■) containing potassium gluconate (30 mM). Each solution contained an appropriate concentration of mannitol to make it isotonic. All experiments were performed in medium containing valinomycin (10 μM) and ethanol (1%) (final concentration). Each point represents the mean ± s.e.m. of three or four experiments.

was increased both in the presence and in the absence of an outwardly directed bicarbonate gradient. To examine the pH-dependence of bicarbonate-dependent nicotinic acid uptake, we defined uptake as the difference between the uptake coefficients in the presence and absence of bicarbonate ions. The uptake increased markedly on reduction of the extravesicular pH. In the absence of proton and bicarbonate gradients, the pH-dependence of [$^{14}$C]nicotinic acid uptake was negligible.

*Concentration-dependence of nicotinic acid uptake*

The dependence of the saturation kinetics of initial uptake of nicotinic acid (50 μM to 50 mM) on bicarbonate or proton gradient, or both, were examined. A single saturable process was, apparently, involved in each case. Non-linear least-squares analysis of the results yielded an apparent $K_m$ of 3·93 ± 0·19 mM and $V_{max}$ of 38·8 ± 0·67 nmol (mg protein)$^{-1}$/10 s for uptake in the presence of both proton and bicarbonate gradients; the values were 3·52 ± 0·43 mM and 11·3 ± 0·55 nmol (mg protein)$^{-1}$/10 s for uptake in the presence of a the proton gradient alone and 17·0 ± 0·42 mM and 6·85 ± 0·95 nmol (mg protein)$^{-1}$/10 s for uptake in the presence of a bicarbonate gradient alone. The non-saturable uptake rate, $k_d$, estimated in the absence of a bicarbonate gradient at pH 7·5 was 0·32 ± 0·02 μL (mg protein)$^{-1}$/10 s.

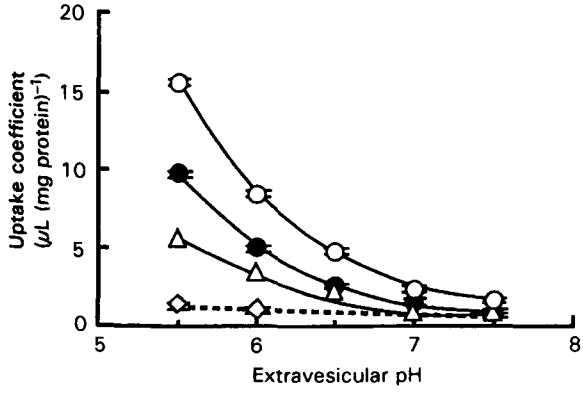


FIG. 2. Extravesicular pH-dependence of [$^{14}$C]nicotinic acid uptake by rabbit jejunal BBMVs. BBMVs were pre-loaded with 25 mM HEPES-Tris buffer (pH 7·5), containing $KHCO_3$ (30 mM; ○) or potassium gluconate (30 mM; ●). For the uptake study in the absence of a proton gradient, vesicles were loaded with 25 mM HEPES-Tris buffer (pH 7·5) or 2-(*N*-morpholino)ethanesulphonic acid-Tris buffer (pH 5·5, 6·0), containing potassium gluconate (30 mM; ◇). The uptake was performed under conditions identical to those described in the legend of Fig. 1. The uptake shown by triangles is the bicarbonate-dependent uptake obtained as the difference between the uptakes in the presence and in the absence of a bicarbonate gradient. Each point represents the mean ± s.e.m. of three or four experiments.

*Effect of anion transport inhibitor on nicotinic acid uptake*

The effect of an anion exchange inhibitor, 4,4′-diisothiocyanostilbene-2,2′-disulphonic acid, on the bicarbonate or proton gradient-dependent uptake of [$^{14}$C]nicotinic acid was examined. In the presence of a bicarbonate gradient, 4,4′-diisothiocyanostilbene-2,2′-disulphonic acid showed a concentration-dependent inhibitory effect on [$^{14}$C]nicotinic acid uptake of 61·2 ± 14, 42·5 ± 2·6 and 35·0 ± 0·63% of control in the presence of 0·1, 1 and 10 mM 4,4′-diisothiocyanostilbene-2,2′-disulphonic acid, respectively, whereas no significant effect was observed in the absence of bicarbonate ion.

*Substrate specificity of bicarbonate antiport and proton cotransport systems*

Table 1 shows the inhibitory effects of various compounds on proton or bicarbonate gradient-dependent uptake of nicotinic acid. Both proton and bicarbonate gradient-dependent uptakes were inhibited by all of the monocarboxylic acids examined, including acetic acid, benzoic acid, D- and L-lactic acids, pravastatin and valproic acid. A structural analogue (nicotinamide), di- and tricarboxylic acids (phthalic acid, succinic acid and citric acid), an amino acid (phenylalanine) and

Table 1. Inhibitory effects of various compounds on [$^{14}$C]nicotinic acid uptake by rabbit jejunal BBMVs.

| Inhibitor | Relative uptake (% of control) | |
|---|---|---|
| | Bicarbonate gradient | Proton gradient |
| Acetic acid | 15·4 ± 4·0* | 20·2 ± 0·87* |
| Benzoic acid | n.d.* | 16·9 ± 1·3* |
| D-Lactic acid | 37·1 ± 2·1* | 28·4 ± 7·6* |
| L-Lactic acid | 55·3 ± 3·5* | 31·1 ± 1·4* |
| Pravastatin | 48·1 ± 4·0* | 9·72 ± 0·66* |
| Valproic acid | 2·6 ± 2·2* | 10·4 ± 0·4* |
| Citric acid | 97·9 ± 3·5 | 103·4 ± 1·5 |
| Nicotinamide | 87·8 ± 5·1 | 97·4 ± 4·0 |
| Phenylalanine | 97·9 ± 6·6 | 104·7 ± 2·6 |
| Phthalic acid | 100·4 ± 7·5 | 96·0 ± 5·6 |
| Succinic acid | 97·3 ± 8·9 | 103·6 ± 5·5 |
| Taurocholic acid | 85·1 ± 4·0 | 101·7 ± 5·7 |

All experiments were performed under conditions identical to those described in the legend of Fig. 1. n.d., not detected. The concentration of each inhibitor was 20 mM except for taurocholic acid, 0·1 mM. Each point represents the mean ± s.e.m. of three or four experiments as the percentage of the control uptake. Uptake coefficients of the control studies for bicarbonate antiport and proton cotransport, that were corrected with no gradient, were 1·29 ± 0·11 and 4·80 ± 0·11 (μL (mg protein)$^{-1}$/10 s; mean ± s.e.m.), respectively. *$P < 0·05$ compared with the control value.

taurocholic acid, however, had no inhibitory effect on the uptake of nicotinic acid.

*Expression of nicotinic acid uptake in* Xenopus laevis *oocytes injected with rabbit intestinal mRNA*

Uptake of [$^{14}$C]nicotinic acid by the two transport systems was assessed by functional expression in *Xenopus laevis* oocytes. In the presence of an inwardly directed proton gradient or an outwardly directed bicarbonate gradient, the uptake of [$^{14}$C]nicotinic acid by *Xenopus laevis* oocytes injected with rabbit small intestinal mRNA was significantly increased compared with that by water-injected oocytes (Table 2).

## Discussion

In the presence of an inwardly directed proton gradient nicotinic acid uptake showed an overshoot phenomenon (Fig. 1), suggesting that nicotinic acid transport is coupled with transport of protons. In addition, nicotinic acid transport activity in oocytes injected with intestinal total mRNA was significantly stimulated by an inwardly directed proton gradient (Table 2). These results strongly suggest that the intestinal proton-nicotinic acid cotransporter functions in the intestinal epithelial cell membrane. Such proton cotransport of nicotinic acid is consistent with our previous finding in rats that nicotinic acid is cotransported with protons (Simanjuntak et al 1990). Accordingly, rabbits seem to have a transport mechanism similar to that of rats.

The imposition of an outwardly directed bicarbonate gradient also stimulated the uptake of nicotinic acid with an overshoot phenomenon (Fig. 1). Similar anion antiport of weak organic acids with bicarbonate is known for propionic acid and acetic acid (Titus & Ahearn 1988; Harig et al 1991; Simanjuntak et al 1991). The enhanced uptake of nicotinic acid induced by imposition of an outwardly directed bicarbonate gradient seems to be specific and cannot be ascribed to formation of an inwardly directed proton gradient by alkalinization owing to the presence of intravesicular bicarbonate ions, because carbonyl cyanide *p*-trifluoromethoxyphenylhydrazone, a protonophore, had no effect on the bicarbonate-dependent nicotinic acid uptake at the intra- and extravesicular pH of 7·5 (data not shown). Similarly enhanced uptake of nicotinic acid was, furthermore, observed upon imposition of a chloride ion gradient (55% increase compared with uptake in the absence of any ion gradient), but not a sulphate ion gradient. These observations suggest that the anion antiport mechanism functions for nicotinic acid uptake and that chloride ion and bicarbonate ion can be exchanged with nicotinic acid. The independence of anion antiport from proton cotransport is also supported by the inhibitory effect of a specific anion-exchange inhibitor, 4,4′-diisothiocyanostilbene-2,2′-disulphonic acid (Jennings & Adams-Lackey 1982). An interesting finding is that the anion antiport of nicotinic acid is activated at acidic pH. As is clearly shown in Fig. 2, the intravesicular bicarbonate-dependent uptake, obtained by subtraction of the proton gradient-dependent uptake from that in the presence of both bicarbonate and proton gradients, increased as the extravesicular pH was reduced. Apparent lack of pH-dependence in the absence of any ion gradient suggests that the increase of non-ionic diffusion or vesicular surface binding of nicotinic acid, or both, are negligible as contributing factors to the apparently increased uptake at acidic pH. Maximum uptake rate evaluated from the kinetic analysis at pH 6·0 in the presence of both bicarbonate and proton gradients (38·8 nmol (mg protein)$^{-1}$/10 s) was much greater than the sum (18·2) of the value of proton gradient-dependent uptake rate measured at pH 6·0 (11·3) and the value of bicarbonate gradient-dependent uptake rate at pH 7·5 (6·85). The difference might be explained by greater uptake via the anion antiporter at pH 6·0 than that at pH 7·5. It appears, therefore, that the anion antiporter for nicotinic acid is activated at acidic pH. Apparent single saturable kinetics for the concentration-dependence of nicotinic acid uptake in the presence of both bicarbonate and proton gradients might suggest that only a single mechanism functions, namely the proton cotransporter, is also dependent on bicarbonate ion. The anion antiporter seems, however, to be activated at acidic pH, as discussed above, and the apparent $K_m$ value for the anion antiporter might decrease from 17 mM at pH 7·5 to about 4 mM at pH 6·0, which would result in difficulty in distinguishing the two transport mechanisms at pH 6·0 by a concentration-dependence study only.

It seems that both proton- and bicarbonate-dependent transporters are similarly specific to monocarboxylic acid compounds as judged from the inhibitory effects shown in Table 1. All the monocarboxylic acids examined showed significant inhibitory effects on nicotinic acid uptake mediated by both bicarbonate and proton gradients. Acetic acid has already been demonstrated to be transported by both a proton cotransporter and an anion antiporter (Tsuji et al 1990; Simanjuntak et al 1991). Benzoic acid, lactic acid and the monocarboxylic acid-type drug pravastatin, a 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor, are also transported by a proton cotransporter (Tsuji et al 1994; Takanaga et al 1995; Tamai et al 1995b, c). We have, furthermore, evidence that uptake of benzoic acid, lactic acid and valproic acid is enhanced by imposing a bicarbonate gradient in rabbit intestinal BBMVs (Tamai et al (1996)), whereas pravastatin uptake was not affected by a bicarbonate gradient (Tamai et al 1995c). These observations suggest that the proton cotransporter is independent of the anion antiporter. Di- and tricarboxylic acids, phenylalanine and taurocholic acid had no inhibitory effect. Because it is known that di- and tricarboxylic acids are absorbed via pH- and sodium-dependent carrier-mediated transport mechanisms (Wolffram et al 1992), the presence of

Table 2. Uptakes of nicotinic acid by *Xenopus laevis* oocytes microinjected with rabbit intestinal mRNA.

| Conditions | Uptake coefficient ($\mu$L h$^{-1}$ (oocyte)$^{-1}$) | |
|---|---|---|
| | Water injected | mRNA injected |
| pH 7·5 | 0·114 ± 0·0059 | 0·100 ± 0·0012 |
| pH 6·0 | 0·308 ± 0·016 | 0·598 ± 0·047* |
| Bicarbonate gradient (pH 7·5) | 0·160 ± 0·0086 | 0·230 ± 0·012* |

Oocytes were preincubated for 30 min in HEPES-Tris-buffered saline at pH 7·5 and uptake of [$^{14}$C]nicotinic acid (18 $\mu$M) was measured at 25°C for 1 h by incubating *Xenopus laevis* oocytes injected with mRNA or water in HEPES-Tris buffered saline at pH 6·0 and 7·5. Bicarbonate gradient was supplied by pre-incubating oocytes with HEPES-Tris buffered saline containing bicarbonate (30 mM) at pH 7·5. Each value represents the mean ± s.e.m. of 3–5 determinations. *$P < 0·05$ compared with the uptake by water-injected oocytes.

more than one carboxyl group might reduce the affinity for the nicotinic acid transporter.

In conclusion, these results suggest that the anion antiporter effects the transport of nicotinic acid across the intestinal brush-border membrane in parallel with a proton cotransporter. Because the intracellular bicarbonate and intestinal luminal protons are supplied by cytoplasmic carbonic anhydrase and by microclimate pH, owing to a sodium-proton antiporter (Knickelbein et al 1990), respectively, pH-dependent intestinal absorption of nicotinic acid is ascribed to pH-sensitive carrier-mediated transport mechanisms and to non-ionic simple diffusion according to pH partition theory. The inhibitory effects of various monocarboxylic acid compounds suggest, furthermore, the relevance of these carrier-mediated transporters to the intestinal absorption of some acidic drugs.

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