Active Alanine Transport in Isolated Brush Border Membranes*

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Uptake of L-alanine against a concentration gradient has been shown to occur with isolated brush border membranes from rat small intestine. An alanine transport system, displaying the following characteristics, was shown: (a) L-alanine was taken up and released faster than D-alanine; (b) Na⁺ as well as Li⁺ stimulated the uptake of both stereoisomers; (c) the uptake of L- and D-alanine showed saturation kinetics; (d) countertransport of L-alanine was shown; (e) other neutral amino acids inhibited L-alanine but not D-alanine entry when an electrochemical Na⁺ gradient across the membrane was present initially during incubation. No inhibition occurred in the absence of a Na⁺ gradient.

The electrogenicity of L-alanine transport was established by three types of experiments: (a) Gradients of Na⁺ salts across the vesicle membrane (medium concentration > intravesicular concentration) supported a transient uptake of L-alanine above equilibrium level, and the lipophilic anion SCN⁻ was the most effective counterion. (b) A gradient of K⁺ across the membrane (vesicle > medium) likewise supported active transport of L-alanine into the vesicles provided the K⁺ conductance of the membrane was increased with valinomycin. (c) Similarly, a proton gradient (vesicle > medium) in the presence of carbonyl cyanide p-trifluoromethoxyphenylhydrazone, an agent known to increase the proton conductance of membranes, produced an overshooting L-alanine uptake. A consideration of the possible forces, existing under the experimental conditions, suggests that the gradients of SCN⁻, K⁺ in the presence of valinomycin, and H⁺ in the presence of carbonyl cyanide p-trifluoromethoxyphenylhydrazone contribute to the driving force for L-alanine transport by creating a diffusion potential. Since the presence of Na⁺ was required in all experiments with active L-alanine transport these results support the existence of a transport system in the brush border membrane which catalyzes the co-transport of Na⁺ and L-alanine across this membrane.

Much research, utilizing a wide variety of techniques, has been carried out on the intestinal transport of amino acids (for references on the subject see Refs. 1–3). Many observations, sometimes conflicting, regarding stereospecificity, saturability, competition, and the Na⁺ dependency of transport processes have been reported. Because of the many complicating factors inherent in the methods used to date to study amino acid transport, we have chosen to utilize isolated enterocyte brush border membranes for our studies.

Intact glucose and fructose transport systems have been demonstrated in the vesiculated membrane preparation (4, 5). Furthermore, it has been shown that the Na⁺-coupled D-glucose transfer across the brush border membrane occurs by an electrogenic process (6). With the sugar transport systems well characterized, we have now turned our attention to another class of nutritionally important non-electrolytes, amino acids. Using L-alanine as a neutral amino acid prototype, we have demonstrated the electrogenicity of its transport and shown in a purified mammalian plasma membrane system accumulation against a concentration gradient. Throughout this paper the term “active transport” will be used synonymous with concentrative uptake.

METHODS AND MATERIALS

Membrane Isolation—Membranes were prepared from rat small intestine by the procedure of Schmitz et al. (7) as modified by Storrelli et al. In essence, mucosal scrapings were homogenized in hypotonic medium; after addition of CaCl₂, the brush border membranes were purified by differential centrifugation. The membranes were then treated according to the method of Hopfer et al. (4) starting with their Step 3. For some experiments 100 mM D-mannitol were replaced by 500 mM D-mannitol, in others by 100 mM D-sorbitol or 100 mM cellobiose through the procedure.

Sucrase (EC 3.2.1.48), an enzyme marker for the intestinal brush border membrane, was enriched in the final membrane 30-fold over the homogenate while the specific activity of CaCl₂, the brush border membranes were purified by differential centrifugation. The membranes were then treated according to the method of Hopfer et al. (4) starting with their Step 3. For some experiments 100 mM D-mannitol were replaced by 500 mM D-mannitol, in others by 100 mM D-sorbitol or 100 mM cellobiose through the procedure.

Uptake Method—Details of the method to measure uptake of labeled compounds by brush border membranes were reported elsewhere (4). All experiments were carried out at 25°C. Unless otherwise indicated, the membranes were incubated in a buffer containing 100

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1. C. Storrelli, M. Kessler, M. Mueller, H. Murer, C. Joss, and G. Semenza, manuscript in preparation.
2. H. Murer, and U. Hopfer, unpublished observation.
Membranes—The collected membranes were rinsed once with 4 ml of buffer of the same composition as the dilution buffer except for omission of isotope. The isotope in the solution used for dilution, served as a correction for the membrane preparation and during incubation. No difference in the amounts of substrate uptake varied up to 5-fold with different washing. Usually, this correction was negligible. The filters were dissolved and counted in a liquid scintillation fluid as described previously (4).

Analytical Procedures—Identification of L- and D-alanine was performed by thin layer chromatography on cellulose-coated plates. Samples of membranes (collected on the filters) containing transients were dissolved in l-cm strips from the origin to the solvent front. Reference compounds were sprayed with the ninhydrin reagent. The chromatogram was then separated into l-cm strips from the origin to the solvent front. These strips were eluted with 30% ethanol, the eluate concentrated and run on a thin layer chromatography. The extracted amino acids as well as the labeled amino acids employed in the incubation medium were chromatographed in the following solvent system: pyridine/isoamyl alcohol/water (7/7/6). Reference compounds were identified as alanine and no conversion to other compounds could be detected.

Materials—L-[^3-H]Alanine, D-[^1-"C]alanine, D-[^1-3H]glucose, and D-[1-14C]mannitol, and D-[1-14C]mannitol were purchased from New England Nuclear, Boston, Mass. 2"Na" was from the Radioclinical Centre, Amersham, England. Vainfominin was obtained from Sigma Chemical Co., St. Louis, Mo. Monacin was a gift from Ciba-Geigy, A.G., Basel, Switzerland, and CF-CCP was kindly given to us by Dr. Hexton, DuPont de Nemours and Co., Wilmington, Del. All chemicals were of highest purity available.

RESULTS

Uptake of D- and L-Alanine by Isolated Brush Border Membrane—When the two stereoisomers of alanine were incubated with the isolated membrane a differential time course of uptake was obtained (Fig. 1). L-Alanine entry was much more rapid than that of D-alanine. In this experiment the incubation medium contained NaSCN. Interestingly, L-alanine, but not D-alanine transport was dependent on the timely NaSCN addition to the membrane. Initial L-alanine transport was enhanced when the membranes were exposed simultaneously to substrate and NaSCN (Fig. 1, upper curve) rather than first to NaSCN and then to substrate (Fig. 1, middle curve). Hence, the difference between D- and L-alanine was especially pronounced under the former conditions. As D-alanine was not noticeably affected by the timing of the salt addition its uptake is shown only under one experimental condition (Fig. 1, lower curve). It is noteworthy that the D and L isomer of alanine reached the same equilibrium values, regardless of incubation conditions.

Fig. 2 demonstrates the reversibility of both L-alanine and D-alanine uptake. When membranes pre-equilibrated with either L- or D-alanine were diluted into a medium without either amino acid, both were released. The efflux of L-alanine was faster than that of D-alanine. After 10 s 35% of L-alanine had been released into the medium in comparison to 18% of D-alanine.

That transport of the amino acids into an intravesicular membrane space and not binding to the membranes occurred is indicated by the data of Fig. 3. Here, the equilibrium uptake of L-alanine was measured as a function of increasing medium osmolality, altered by the addition of the impermeant solute cellobiose. An inverse proportionality was observed. Extrapolation to infinite medium osmolality (zero on the osmolality scale Fig. 3) indicated that no uptake would take place. Thus, the observed relationship between uptake and medium osmolality corresponds to the expectations when L-alanine is transported into an osmotically active space, the membrane vesicles. Fig. 3 thus demonstrates that all the amino acid uptake can be accounted for by transport into membrane vesicles.

The transport of L- and D-alanine showed saturability (Fig. 4). The rate of L-alanine uptake leveled off between 10 to 20 mM. Likewise, D-alanine transport could be saturated between 20 to 50 mM. D-Mannitol uptake, measured over the same concentration range, served as correction for diffusive entry and was subtracted from each of the amino acid uptake points. Preloading the membranes with 15 mM unlabeled L-alanine accelerated the subsequent entry of labeled L-alanine in comparison to D-mannitol-preloaded vesicles (Fig. 5).

Effect of Various Salts on L- and D-Alanine Transport—In Table I the effects of various salts on the amino acid transport can be seen. L- and D-alanine uptake were measured after 10 s of incubation. Na⁺, both the chloride and the thiocyanate salt, stimulated not only L-alanine, but also D-alanine entry. The

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*The abbreviations used are: Hesper, N-2-hydroxyethylpiperezaine; N'-2-ethanesulfonic acid; Mes, 2-(N-morpholino)ethanesulfonic acid; CF-CCP, carbonyl cyanide p-trifluoromethoxyphenylhydrazone.

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Fig. 1. Time course of L- and D-alanine uptake by brush border membranes. The uptake was initiated either by the addition of membranes to the complete incubation medium (NaSCN gradient present at zero time); L-alanine; D-alanine; Δt, by the addition of L-[3-3H]alanine after membranes had been preincubated for 10 min with the complete medium except for L-alanine (abolition of the NaSCN gradient) (L-alanine: □). Additions (final concentrations): NaSCN (100 mM) and L-[3-3H]alanine (1 mM) or D-[1-14C]alanine (1 mM), respectively.
nature of the accompanying anion strikingly influenced the amino acid uptake. Thiocyanate was the most effective anion in raising the uptake. K\(^+\), in the form of KCl and KSCN, did not elevate the transport of either alanine isomer above control levels measured in the presence of D-mannitol. Interestingly, LiSCN was able to stimulate transport of both isomers to the same extent as NaCl. The equilibrium uptake of D- or L-alanine was the same regardless of the nature of the salt in the incubation medium (data not shown).

**Effect of NaSCN Gradient on L-Alanine Uptake**—The effect of the timing of NaSCN addition was reported above in the context of differences in D- and L-alanine uptake. However, information about the forces determining L-alanine flow can be obtained from a consideration of the time curve of L-alanine uptake alone. As shown in the upper curve of Fig. 1, L-alanine exhibited an overshooting uptake when the membranes were exposed simultaneously to substrate and NaSCN and, hence, a NaSCN gradient existed between medium and the membrane vesicles at early time points. Preincubation of the membrane with NaSCN abolished the overshoot phenomenon (Fig. 1, middle curve). The effect of NaSCN addition after L-alanine had equilibrated is shown in Fig. 6. Membranes were first preincubated for 60 min with L-alanine. The amino acid equilibrated during this time between medium and intravesicular space as evidenced by constant uptake values during the last 30 min of the preincubation period. The subsequent addition of NaSCN produced a further uptake of L-alanine before a new, slightly lower equilibrium was reached. The addition of the same concentration of KSCN to another aliquot of the preincubated membranes resulted in a drop of L-alanine uptake to the same equilibrium level as observed with NaSCN. Concentrations of NaSCN below 0.1 M gave
FIG. 5. Uptake of L-[3-3H]alanine by preloaded (○) and control (□) membranes. Brush border membranes were preloaded with unlabeled L-alanine by taking one aliquot of the homogenized intestinal scrapings through the final steps of membrane preparation (beginning with Step 3 of Ref. 4) in a buffer containing 85 mM D-mannitol, 15 mM L-alanine, 1 mM Tris-Hepes, and 0.1 mM MgSO₄. In the control D-mannitol replaced L-alanine during preparation. L-[3-3H]Alanine uptake was initiated by 8-fold dilution of the membranes into a medium containing the additions: NaSCN (100 mM), and L-[3-3H]alanine (1 mM).

TABLE I
Effect of various salts on D- and L-alanine uptake by isolated membrane vesicles

| Addition   | Alanine uptake | mM | pmol/mg protein |
|------------|----------------|----|-----------------|
|            | L-Alanine      |     |                 |
| D-Mannitol, 200 | 1110  | 640  |
| NaCl, 100    | 1874  | 752  |
| NaSCN, 100   | 3800  | 1200 |
| KCl, 100     | 1109  | 643  |
| KSCN, 100    | 1131  | 650  |
| LiSCN, 100   | 1900  | 722  |

|            | d-Alanine      |     |                 |
|------------|----------------|----|-----------------|
| D-Mannitol, 200 | 1060  | 564  |
| NaCl, 100    | 1923  | 712  |
| NaSCN, 100   | 3659  | 1200 |
| KCl, 100     | 1109  | 643  |
| KSCN, 100    | 1131  | 650  |
| LiSCN, 100   | 1900  | 722  |

*Time of incubation: 10 s.

The concentration of L-[3-3H]alanine or of D-[1-3H]alanine was 1 mM.

similar, but less pronounced effects with respect to L-alanine uptake.

The results of the experiments in Figs. 1 and 6 suggested that the presence of a NaSCN gradient was related to the enhanced uptake of L-alanine. In order to measure directly the dissipation of the salt gradient, established by the addition of NaSCN to membranes without Na⁺, the uptake of labeled Na⁺, L-alanine, and d-glucose was measured with the same membranes under identical conditions (Fig. 7). The results show that NaSCN equilibrates across the brush border membrane within about 2 min. Furthermore, the experiment shows that the two non-electrolytes are taken up to approximately the same membrane space as Na⁺.

**Effect of Ionophores on L-Alanine Transport**—Fig. 8 presents the results of L-alanine uptake into membrane vesicles under conditions of a K⁺ concentration gradient (inside > outside).

The membranes were preloaded with 50 mM K₂SO₄ by osmotic shock, then diluted with a K⁺-free, Na⁺-containing medium. The addition of valinomycin, an ionophore specific for K⁺ (rather than Na⁺), produced an overshoot in the L-alanine uptake of 2 times that at equilibrium. The equilibrated uptake values of both the control and the valinomycin-containing membranes were identical. Valinomycin when added to K⁺-free membranes exerted no effect on L-alanine transport.

An analogous experiment with H⁺ instead of K⁺ is depicted in Fig. 9. Here the membranes were preloaded with a Tris-Mes buffer, pH 7.5, and then incubated in the usual medium, pH 7.5, with Na₂SO₄ present. When CF-CCP, known to increase specifically the H⁺ conductance of biological membranes, was added L-alanine uptake rose transiently to 3 times above equilibrium level. L-Alanine was not accumulated above equilibrium when either the pH gradient or CF-CCP were omitted.

**Influence of Other Neutral Amino Acids on L- and D-Alanine Uptake**—Table II shows the inhibitory effect that a number of neutral amino acids have on L- and D-alanine transport. All of the neutral amino acids tested inhibited L-alanine entry while D-alanine transport remained largely uninfluenced. Only glycine was able to inhibit D-alanine to any significant extent. This experiment was designed such that initially a NaSCN gradient (medium concentration > vesicle concentration) existed. However, when NaSCN was added 10 min before the substrate plus the test-inhibitor, L-alanine uptake was not inhibited by any of the compounds given in Table II. The equilibrium value of L- and D-alanine uptake was not influenced by any of the inhibitors, i.e. only the rate, but not the
FIG. 8. Effect of valinomycin on L-alanine transport in K+-preloaded membranes. The membranes were prepared, preloaded, and resuspended similarly as described for Fig. 6 but with 500 mM n-mannitol buffer instead of 100 mM. They were preloaded with K₂SO₄ by suspending 1 volume of membranes in 6 volumes of buffer containing 50 mM K₂SO₄, 1 mM Tris-Hepes (pH 7.5), and 0.1 mM MgSO₄. The membranes were collected by centrifugation and resuspended in 50 mM K₂SO₄, 100 mM n-mannitol, 1 mM Tris-Hepes (pH 7.5), and 0.1 mM MgSO₄. L-Alanine uptake was initiated by adding 1 volume of the K⁺-preloaded membranes to 8 volumes of incubation medium with Na₂SO₄ (50 mM) instead of K₂SO₄ and L-[3-³H]alanine (1 mM) as substrate. Valinomycin, when present, was 8 µg/mg of membrane protein.

FIG. 9. Effect of CF-CCP on L-alanine transport in H⁺-preloaded membranes. The membranes were prepared, preloaded, and resuspended similarly as described for Fig. 6 but with 50 mM Tris-Mes buffer (pH 5.0) replacing K₂SO₄ and Tris-Hepes. The reaction was initiated by the addition of 1 volume of the H⁺-preloaded membranes to 8 volumes of incubation medium containing (end concentration) Na₂SO₄ (50 mM), Tris-Hepes, pH 7.5, (50 mM), as buffer, and L-[³H]alanine (1 mM) as substrate. CF-CCP, when present, was 8.7 µM.

The presented data describe the transport of the two isomers of a neutral amino acid in isolated brush border membrane vesicles. Several observations indicate that the measured D- and L-alanine uptake represents transport into membrane vesicles and not membrane binding. (a) The equilibrium uptake of the amino acids decreased with increasing medium osmolarity as predicted for osmotically active vesicles. (b) Both amino acids were taken up to the same extent as D-glucose and Na⁺ when based on the same medium concentration. (c) L-Alanine exhibited overshooting uptake under some conditions. (d) Preloading the membranes with unlabelled L-alanine enhanced the subsequent uptake of labeled L-alanine. (e) The uptake of both amino acids was reversible.

D- and L-alanine transport show some of the general properties that have been reported in intact tissue (1, 8): saturation, stereospecificity, Na⁺-stimulation, and countertransport.

The role of Na⁺ in amino acid translocation is one of the most fascinating aspects of transport. Two widely different models have been proposed to account for the fact that Na⁺ is a required factor in intestinal amino acid transport. Both Csaky (9) and Tucker and Kimmich (10) have suggested that a direct input of metabolic energy is required for Na⁺-dependent transport, e.g. via ATP hydrolysis by a Na⁺-stimulated ATPase. A second model, the Na⁺ gradient hypothesis (11, 13).
envisions a mechanism where Na⁺ movement down a concentration difference provides the driving force for active amino acid transport. The presented data show that L-alanine transport was stimulated by Na⁺ in the absence of ATP as an energy source and in membrane vesicles which are virtually free of (Na⁺, K⁺)-ATPase (sodium and potassium ion-activated ATPase) (14, 15). These results therefore are not consistent with any hypothesis assuming a direct input of metabolic energy into active transport of amino acids. On the contrary, they support the Na⁺ gradient mechanism.

The membrane vesicles have several properties which facilitate interpretation of transport experiments. For example, they are metabolically inert toward the investigated amino acids and sugars (4, 5). The composition of the intravesicular buffer is known at the beginning and the end of any experiment where uptake is followed to equilibrium. Furthermore, the vesicles are osmotically active and stable for more than 2 hours at room temperature as evidenced by constant electrolyte and non-electrolyte uptake. Since at equilibrium the intravesicular concentration of a neutral, permeant solute equals the medium concentration, the overshooting part of L-alanine uptake after perturbation of the electrochemical Na⁺ gradient (Figs. 1 and 6 to 9), is due to either active amino acid transport or swelling and shrinking of the membranes. The latter explanation can be ruled out since in all pertinent experiments the medium osmolality either remained equal or was increased when the Na⁺ gradient was established. Thus, only the former explanation appears reasonable. The energy for the concentrative uptake of L-alanine could only be derived from the salt or pH gradients across the membrane of the vesicles. Consistent with this view is the transient nature of the active transport as the energy content of ion gradients is small in comparison to chemical energy and is easily dissipated as shown in Fig. 7.

When considering the coupled flows of electrolytes and non-electrolytes, a question arises as to the electrogenicity of the process. Two possibilities exist: (a) The positive charge associated with an envisioned cation-coupled amino acid flux in one direction may be compensated for by either a simultaneous anion flux in the same direction or a cation flux in the opposite direction via the same transfer agency, the amino acid "carrier." (b) An alternative to the aforementioned electroneutral transfer is an electrogenic translocation. In this mechanism the charge compensation is accomplished by transfer of an ion at a different site in the plasma membrane.

Several experiments were designed to distinguish the two possibilities. The results indicate that the latter, electrogenic mode of L-alanine transport exists in brush border membranes. The evidence for this comes from a consideration of the conditions under which active L-alanine transport was obtained. The overshooting L-alanine uptake can be correlated in all experiments with a high electrical membrane conductance for ions other than Na⁺. SCN⁻ is a permeant anion at pH 7.5 (16) and valinomycin and CF-CCP increase quite specifically the K⁺ and H⁺ conductance, respectively. The structure and mode of actions of these latter two agents with respect to modification of membrane properties are well understood (17–21) and make a reasonable interpretation of results possible. An enhancement of L-alanine uptake or even concentrative transport was always observed under conditions where the electrochemical Na⁺ potential was lower in the vesicles in comparison to the medium and the absolute value of the gradient was greater than in the control, due to higher electrical potentials. This last point follows from a consideration of the ion fluxes whose direction and relative magnitude can be predicted from the known initial concentration gradients of the salts and the relative permeability of the membrane to specific ions.

It is worthwhile to discuss the ion fluxes of the three experiments with active L-alanine transport (Figs. 1 and 6 to 9). For example, NaSCN gradients (medium > vesicle) produced active L-alanine uptake. In this case, diffusion of the lipophilic anion from the medium into the vesicles would make the inside electronegative with respect to the medium, thereby providing an additional impetus for an electrogenic cation-coupled L-alanine uptake. Under conditions of a K⁺ gradient (vesicle > medium) the addition of valinomycin would catalyze an additional outflow of K⁺. The result on the potential would be the same as in the previous experiment. Similarly, the proton-carryer CF-CCP mediates the outflow of protons from H⁺-preloaded membranes, again with identical electrical consequences. It is noteworthy, that in the last two instances active L-alanine transport did not occur either in the absence of added ion carriers, i.e. low membrane permeability to K⁺ or H⁺, or of a driving force in the form of a K⁺ or H⁺ gradient. The movement of anions can be neglected in the last two experiments, at least in the context of this discussion, as the membrane appeared to be relatively impermeable to sulfate, Hepes, and Mes.

In summary, the experiments with such structurally unrelated compounds as SCN⁻, valinomycin, and CF-CCP have in common that L-alanine was taken up against a concentration gradient when electrical fluxes occurred making the inside of the vesicles negative. In other words, the electrical potential difference served as driving force for L-alanine transport. In terms of a mechanism, this means that a transport system in the brush border membrane catalyzed the co-transport of L-alanine and a cation (or the countertransport of L-alanine and an anion). Since the presence of Na⁺ also was required for active transport these results support an electrogenic Na⁺-activated L-alanine co-translocation mechanism.

Using rabbit ileum, Rose and Schultz (22) have shown the cell interior to be electrically negative with respect to the mucosal solution by approximately 30 to 40 mV. Addition of L-alanine to the mucosal solution brought about a decrease in the electrical potential difference. Corresponding results have been reported for bullfrog small intestine (24). These findings also suggested an electrogenic entry of Na⁺ coupled to the amino acid across the brush border membrane.

Finally, when L-alanine uptake was studied in the presence of other neutral amino acids its transport was markedly reduced. With one exception, L-alanine uptake remained unaltered. The inhibition was only observed when a NaSCN gradient was present during the incubation. It appears that the membrane potential plays a yet unclearly defined role in amino acid competition. The role of the membrane potential in amino acid-sugar transport interaction will be explored in more depth in a subsequent paper.

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1. U. Hopfer, and H. Murer, unpublished observation.
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