Apparent Inhibition of Active Non-Electrolyte Transport by an Increased Sodium Permeability of the Plasma Membrane

MECHANISM OF ACTION OF p-CHLOROMERCURIBENZENE SULFONATE

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Sodium-dependent amino acid and sugar uptake by intact cells and tissues is reduced by p-chloromercuribenzenzene sulfonate. This inhibition is believed to be specific for neutral amino acids as the uptake of other amino acids and sugars is affected to a lesser extent. Since p-chloromercuribenzenzene sulfonate is known to increase the sodium conductance of biological membranes, the inhibition of amino acid transport by jejunal brush border membrane vesicles was examined to determine if the inhibition was at the carrier level or involved the electrochemical sodium gradient. The uptake rate of L-valine is the same in control and treated vesicles. However, the sodium gradient energized overshoot of L-valine is eliminated by pretreatment with p-chloromercuribenzenzene sulfonate. Since the overshoot of D-glucose is also eliminated, the effect of p-chloromercuribenzenzene sulfonate is due to an increased dissipation of the sodium gradient which energizes sodium-dependent solute transport.

Treatment of membrane vesicles with reagent grade p-chloromercuribenzenzene sulfonate abolishes the activity of sucrase and reduces the intravesicular space accessible to D-glucose or L-valine. The former effect is due to contaminating mercury. The latter effect, and the effect on the sodium gradient-driven overshoot, are also caused by purified inhibitor and can be reversed by subsequent treatment of the vesicles with dithiothreitol. These effects are due to the sulfhydryl actions of this compound.

Sulfhydryl reagents have long been known to influence ion, water, and non-electrolyte uptake by various cells and tissues (1-6). Many sulfhydryl reagents, such as N-ethylmaleimide or p-chloromercuribenzenzene, readily permeate cell membranes (7, 8) with the result that they inhibit intracellular enzymes and cellular metabolism (7-9). The latter effects are often difficult to distinguish from direct interactions with membrane components (8). It was rationalized that polar derivatives of sulfhydryl reagents would be confined to the extracellular space and therefore their actions may be more specific for extracellular membrane functions such as those involving transport. Subsequently, it was found that pCMBS\(^1\) is taken up very slowly by human erythrocytes and platelets (1, 7, 8) yet still inhibits glucose uptake and increases potassium efflux and sodium uptake (2, 3, 5, 7, 9). As the inhibition by pCMBS of amino acid uptake by mouse embryo cells and by the rabbit small intestinal epithelial cells appeared to be specific for certain amino acids, e.g. phenylalanine and alanine, it was concluded that in these cells pCMBS was a specific inhibitor of the sodium-dependent neutral amino acid transport system (10-12).

The objective of this study was to examine more closely the effects of pCMBS on neutral amino acid transport using isolated intestinal brush border membrane vesicles. The use of plasma membrane vesicles is an accepted method of studying amino acid transport (13, 14) and enables transport to be studied under a variety of conditions not feasible with intact cells or tissues (15). The results indicate that pCMBS does not specifically interact with the neutral amino acid carrier, but increases the sodium conductance of the membrane. The latter effect of pCMBS is well known (2, 3); however, the implications relating to non-electrolyte transport are not widely understood or well documented. The increased sodium conductance provides a pathway for uncoupled sodium flow which lowers the driving force for all solutes absorbed via sodium-coupled transport systems. The presence of a sodium conductance pathway thus results in an apparent inhibition of transport energized by an electrochemical sodium gradient. A preliminary report of these results has been published (16).

EXPERIMENTAL PROCEDURES

Membrane Vesicle Preparation—Brush border membrane vesicles were prepared from the jejenum of Sprague-Dawley rats (strain number HEA/SD, Hilltop Lab Animals, Inc.). The general method has been described (13, 17); however, recent changes necessitate a detailed description.

Rats were killed by cervical dislocation, the intestines were removed immediately and rinsed out with cold mammalian saline. The intestines were everted and the brush borders were removed by scraping with glass microscope slides on a cold glass surface. The scrapings were homogenized in 20 to 25 volumes of 0.05 M n-mannitol and 1 mM Tris/Hepes, pH 7.5, for 4 min with a Sorvall Omnimix at full speed. Calcium or magnesium chloride was added to a final concentration of 10 mM to precipitate intracellular and basal-lateral membranes and the homogenate was stirred at a moderate speed for 20 min in the cold. The homogenate was centrifuged as described in the flow scheme. Centrifugations were performed with the Sorvall RC-2B centrifuge at 0-4°C using either the SS-34 or the GSA rotors; with the latter rotor using 300-ml bottles, the centrifugation times should be increased by 3 min. The homogenization following the

\(^1\) The abbreviations used are: pCMBS, sodium p-chloromercuribenzenzene sulfonate; Heps, 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid.
White rabbits (obtained locally) were prepared in the same manner as described above except that the animals were killed with 90 mg/kg and 1 mM Tris/Hepes, pH 7.5 (uptake medium), prior to use in membrane vesicle transport experiments. Membrane vesicles were used for transport measurements without the addition of any driving force (see "Experimental Procedures"). Rates calculated in this manner minimize problems related to vesicle heterogeneity and experimental difficulties in estimating initial rates (15, 24). Uptake energized by a sodium gradient was initiated by adding membranes to uptake buffer containing 0.1 mM sodium chloride or sodium thiocyanate and the labeled solute.

The uptake of 

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NaCl was measured in the same manner except that the resolution termination contained 0.15 M d-mannitol, 0.1 M magnesium chloride, 1 mM D-glucose, and 10 mM Tris/Hepes, pH 7.5. This is illustrated in Fig. 1 by a lack of the "overshooting" peak observed in the absence of any driving force (see "Experimental Procedures").

Mercury Analysis—The inorganic mercury content of pCMBS solutions or the sodium salt was measured with dithizone using mercuric chloride as the standard (25). Free mercury ions in solutions of pCMBS were removed with a column (0.7 × 3.8 cm) of Dowex chelating resin, with the pCMBS eluted with water and measured by its absorbance at 265 nm (ε = 611 M⁻¹ cm⁻¹ at pH 7.5).

Electron Microscopy—Membrane vesicles were fixed for 45 min in 2% glutaraldehyde in uptake buffer, then washed with 0.5% nitricelulose-coated grids, and stained with 1% phosphotungstic acid, pH 6.5 (26). The negatively stained images were examined with a Zeiss EM 9A electron microscope and photographs of representative fields were taken. The size of individual vesicles was estimated from the final magnification (× 62,900) and the diameter of the vesicle image.

Materials—ICN Pharmaceuticals Inc. supplied the L-[U-¹⁴C]glucose and the L-[2,3-³H]valine. n-[¹⁴C]Glucose and "NaCl were obtained from the New England Nuclear Corp. Unlabeled d-glucose was purchased from the J. T. Baker Chemical Co. Unlabeled L-valine, pCMBS, Tris, dithiothreitol, Hepes, and Dowex chelating resin were bought from the Sigma Chemical Co. Reagent grade toluene, Triton X-100, and scintillation grade Preblend 2a70 were obtained from Research Products International Corp. All other chemicals were certified ACS reagent grade.

RESULTS

Sodium-dependent amino acid or glucose uptake by intact cells or membrane vesicles is driven by an electrochemical sodium gradient (13, 14, 23, 27-33). Pretreatment of brush border membrane vesicles with as little as 0.1 mM pCMBS results in an inhibition of concentrative non-electrolyte transport energized by a sodium thiochyanate or sodium chloride gradient. This is illustrated in Fig. 1 by a lack of the "overshooting" part of the amino acid or glucose uptake. These observations are similar to those of pCMBS effects with intact epithelia (10).

To determine whether the inhibition of energized glucose and valine transport is due to an inhibition of the carriers or to a faster dissipation of the energy, sodium-dependent solute transport was measured under equilibrating conditions in the absence of any driving force (see "Experimental Procedures"). The results in Table I demonstrate that pCMBS does not...
inhibit the rate of L-valine uptake by rat or rabbit brush border membrane vesicles. Similar results were obtained with D-glucose (Table I). In both control and pCMBS-pretreated membranes, L-valine was transported by a carrier-mediated process as shown by the inhibitory effect of 70 mM L-methionine (Table II). A similar argument can be made for D-glucose since 0.27 mM phlorizin inhibited the rate of D-glucose uptake by more than 65% in pCMBS-pretreated rat membranes.

Carrier activity can also be assessed by countertransport or tracer exchange experiments. As shown by the open triangles in Fig. 2, A and B, preloading of membrane vesicles with 40 mM L-valine can be used to drive the transport of labeled D-glucose or labeled L-valine against their respective concentration gradients (the latter in terms of isotope concentration). This ability is expressed in Fig. 2, A and B as “overshooting” uptake. In contrast, loading the vesicles with fructose, which is transported by a sodium-independent system (34), does not stimulate L-valine uptake (Fig. 2A, open circles). Pretreatment of membranes with pCMBS abolishes the “overshoot” for D-glucose but not for labeled L-valine (Fig. 2, A and B, filled triangles). The differential effects of pCMBS on D-glucose and L-valine uptake can be explained on the basis of the different nature of the coupling between L-valine efflux and the uptake of labeled D-glucose and labeled L-valine. Countertransport between neutral amino acids and D-glucose has been shown in intestinal membranes to result from the sodium and electrical charge movements coupled to non-electrolyte fluxes and the requirement for overall electroneutrality (14). This type of interaction is sensitive to the presence of other parallel conductance pathways in the membrane, especially those for sodium. For example, the overshoot of labeled D-glucose driven by unlabeled L-valine efflux is abolished by monactin (Fig. 2B, open squares and Ref. 14). In contrast, the overshooting tracer exchange in Fig. 2A is due to carrier-mediated coupling of unlabeled and labeled L-valine fluxes.

**Table I**
The effect of pCMBS on the rate of valine and sodium chloride uptake by brush border membrane vesicles

| Animal species | Transported solute | pCMBS concentration (mM) | Uptake rate (min⁻¹) |
|---------------|-------------------|--------------------------|---------------------|
| Rat           | L-Valine          | 0.1                      | 4.0 ± 0.6 (6)       |
| Rat           | L-Valine          | 1.0                      | 2.9 ± 1.0 (4)       |
| Rat           | NaCl              | 0.1                      | 5.4 ± 0.7 (4)       |
| Rabbit        | L-Valine          | 5.0                      | 2.1 ± 0.7 (3)       |
| Rabbit        | D-Glucose         | 3.9                      | 5.2 ± 1.6 (5)       |

**Table II**
Effect of methionine on valine transport by brush border membrane vesicles

| Animal species | Pretreatment | Transport rate (min⁻¹) | Inhibition |
|---------------|--------------|------------------------|------------|
|               |              | 0.1 mM Val             | 0.1 mM Val + 70 mM Met |
| Rat           | Control      | 2.22 ± 0.44 (3)        | 1.05 ± 0.24 (4)* | 53 |
| Rat           | 1 mM pCMBS   | 2.05 ± 0.27 (3)        | 1.00 ± 0.17 (4)* | 51 |
| Rabbit        | Control      | 1.67 ± 0.33 (3)        | 0.12 ± 0.06 (4)* | 93 |
| Rabbit        | 5 mM pCMBS   | 2.31 ± 0.87 (3)        | 0.31 ± 0.09 (4)* | 87 |
Plasma Membrane Effects of p-Chloromercuribenzenesulfonate

Spherical shape dropped to 72% of the control vesicles (from 0.0022 μm² to 0.0016 μm²) after treatment with 1 mM pCMBS. However, this cannot account for the change in the equilibrium space, as for the same membrane preparation the glucose accessible volume of the pCMBS-pretreated vesicles was 29% of the control vesicles. Since dithiothreitol at 1 mM reversed the pCMBS effect (Fig. 6) changes in vesicle shape, such as from spherical to oblate spheroid, are the most likely explanation for the equilibrium effect. The loss of the sodium gradient-energized overshoot (Fig. 1) is not due to the same effect which reduces the equilibration space because the concentrations required for the two effects are very different (see Figs. 3 and 4). For example, pretreatment of rat membranes with 0.1 mM pCMBS abolishes the sodium gradient-driven L-valine overshoot (Fig. 3) while the equilibration space is reduced by only 20% (Fig. 4).

In preliminary experiments, the sucrase activity of brush border membranes treated with pCMBS was abolished with the rat enzyme more sensitive than the rabbit enzyme (Fig.

Fig. 3. Effect of various concentrations of pCMBS on the sodium gradient-dependent uptake of L-valine by brush border membrane vesicles. Membrane vesicles were pretreated for 5 min at 25°C with various concentrations of pCMBS. Active uptake of 0.1 mM L-valine (driven by a 0.1 M sodium thiocyanate gradient) was defined as: (10⁻⁸ valine uptake by buffer-treated vesicles − 10⁻⁸ valine uptake by 0.1 M potassium thiocyanate-treated vesicles) + (10⁻⁸ valine uptake by control vesicles − 10⁻⁸ valine uptake by 0.1 M potassium thiocyanate-treated vesicles) × 100. Open symbols indicate results obtained with purified pCMBS and filled symbols represent results obtained with the same lot of pCMBS before purification. Rabbit membranes, △; rat membranes, ○.

Fig. 4. Effect of pCMBS on the intravesicular space accessible to L-valine. Membrane vesicles were pretreated for 5 min at 25°C with various concentrations of pCMBS. Uptake of 0.1 mM L-valine was measured at equilibrium (25-min rat or 75-min rabbit). Open symbols indicate results obtained with purified pCMBS and filled symbols represent results obtained with the same lot of pCMBS before purification. Membranes: rabbit, △; rat, ○.

L-valine and d-glucose and does not change from 15 to 60 min after the addition of the solute (results not shown). The rat membranes are more sensitive to this equilibrium space effect of pCMBS than the rabbit membranes (Fig. 4). The observed decrease in equilibrium space per mg of protein can arise from fragmentation of vesicles, changes in vesicle shape to yield higher surface area to volume ratios (e.g., sphere to ellipsoid at fixed surface area), or conversion of membrane vesicles to membrane sheets. A small decrease in the average vesicle size was detected in electron micrographs of negatively stained vesicles (Fig. 5). The calculated mean volume (assuming spherical shape) dropped to 72% of the control vesicles (from 0.0022 μm² to 0.0016 μm²) after treatment with 1 mM pCMBS.

Fig. 5. Size distribution of control and pCMBS-pretreated rat brush border membrane vesicles. Vesicle size distribution of 172 control vesicles from six fields (A) and 188 vesicles pretreated with 1 mM pCMBS from five fields (B). The control vesicles had a diameter (mean ± 6.D.) of 161 ± 70 nm and the pCMBS-pretreated vesicles had a diameter of 146 ± 71 nm with p < 0.05 (unpaired Student’s t test (two-tailed)).

Fig. 6. Reversal of pCMBS effects of dithiothreitol. Rat membranes were pretreated with either buffer or 1 mM pCMBS, washed, and treated with either buffer or 1 mM dithiothreitol. After a final wash, the uptake of 1.0 mM D-glucose was measured in the presence of a 0.1 M sodium thiocyanate gradient as described under “Experimental Procedures.” Control, ○; pCMBS, ●; and pCMBS + dithiothreitol, △.
FIG. 7. Effect of pCMBS on the sucrase activity of brush border membrane vesicles. Purified membranes were treated with pCMBS and washed, and the sucrase activity was measured as described in "Experimental Procedures." The control membranes had a specific activity of 1.44 units/mg of protein for the rat and 0.80 units/mg of protein for the rabbit. Untreated pCMBS, •; purified pCMBS, □, ○; rabbit membranes, △; rat membranes, †; △; L-valine not shown. 

7). Sucrase does not require a sulfhydryl group for activity; therefore, we suspected that the inhibition was due to the presence of trace amounts of inorganic mercury in the pCMBS, as sucrose is very sensitive to mercury (37). Subsequent analysis demonstrated that ≈1.5% (by weight) of the pCMBS was mercury. Contrary to previous results (1), pCMBS is not unstable in solution, the mercury content of pCMBS solutions was the same as that of the anhydrous salt (results not shown). Solutions of pCMBS freed of mercury (see "Experimental Procedures") did not inhibit sucrose (Fig. 7); however, the equilibrium space for L-valine was still reduced (Fig. 4, open symbols) and the sodium thiocyanate driven L-valine or D-glucose overshoot was still abolished (Fig. 1). The latter two effects are evidently not due to mercury contamination of the pCMBS. 

The effects of pCMBS on the equilibrium space for L-valine and D-glucose can be completely reversed by treatment with dithiothreitol (Fig. 6; L-valine not shown). The sodium thiocyanate driven D-glucose overshoot was partially restored by dithiothreitol (Fig. 6). Both effects are therefore due to the sulfhydryl blocking action of pCMBS.

DISCUSSION

The failure of high concentrations of pCMBS to inhibit the rate of nonenergized L-valine or D-glucose uptake by brush border membrane vesicles indicates that pCMBS has no direct effect on the carriers (Table 1). Both solutes are transported by carrier-mediated systems as shown by sensitivity of the L-valine uptake to L-methionine (Table II and Ref. 13), and by sensitivity of D-glucose uptake to phlorizin (23, 35). These results conflict with reports that pCMBS inhibits the uptake of glucose analogues (12, 38) and amino acids via sodium-dependent transport systems (10-12, 38). In all of the latter studies, solute uptake was measured into intact cells or tissues, therefore, other effects of pCMBS, such as a decrease in the energy supply for transport may have produced the apparent inhibition of transport (16). It should be stressed that our results on the sodium-dependent glucose transport do not have any bearing on the sodium-independent glucose transport system for which inhibition by sulfhydryl reagents is well established (1, 39).

It is well known that pCMBS increases the cation permeability of the plasma membrane (2, 3, 7, 8); indeed, pCMBS is often used to load cells with sodium (2, 40, 41). Detailed studies have established that pCMBS-induced sodium uptake occurs by a conductance pathway (3, 42, 43). Under energized steady state conditions, such as with intact cells or tissues, an electrochemical sodium gradient (greatest sodium concentration outside the cell and a negative electrical potential inside the cell) is present across the plasma membrane. This gradient accounts for "active" accumulation of amino acids and glucose which are co-transported with sodium (14, 27-33). In the vesicle system, an increased sodium conductance would reduce or abolish any experimentally established sodium gradient and would result in an inhibition of solute flux, often erroneously equated with an inhibition of the transport system. In an intact viable cell, the pCMBS-induced sodium conductance would allow a dissipative sodium flux, which would constitute an additional "load" on the sodium pump (the (Na" + K")-ATPase) and the metabolic reserves of the cell. The additional sodium flux induced by pCMBS may or may not produce a significant reduction of the electrochemical sodium gradient depending upon the total sodium and charge fluxes across the plasma membrane, and whether the reserve capacity of the sodium pump can handle the additional fluxes. Any change in the electrochemical sodium gradient would be reflected in the sodium-dependent non-electrolyte uptake rates. Therefore, it is conceivable that pCMBS could produce an apparently specific inhibition of amino acid transport (10-12). If the pCMBS-independent sodium fluxes (e.g. those associated with 3-O-methylglucose uptake in the small intestine) are not high, the additional pCMBS-induced load could be handled by the sodium pump. In contrast, in the presence of already high non-electrolyte-coupled sodium fluxes (e.g. in the presence of amino acids or D-galactose), the pCMBS-induced sodium flux could overload the pump, which would be expressed as an inhibition of sodium-dependent non-electrolyte transport. Unfortunately, it is experimentally not possible to circumvent the "load" problem in the intact tissue or cells by using "initial" uptake rates. The depolarization of the plasma membrane potential due to sodium fluxes via any type of conductance pathway occurs within seconds and before non-electrolyte fluxes could be measured, experimentally (44, 45). The apparent specificity of the pCMBS effect for certain amino acid transport systems in intact cells or tissues (10-12) may simply result from a specific dependency of the kinetic parameters on the electrical field and sodium concentrations. This dependency may differ for the various sodium-dependent transport systems (46).

The effect of pCMBS on the equilibrium space for either D-glucose or L-valine is thought to represent a different effect from that causing an increased sodium permeability as much higher concentrations are required (see Figs. 3 and 4). The decreased space is not caused by fragmentation of the vesicles because pCMBS did not sufficiently affect the vesicles' size, estimated from negatively stained images, to account for the large decrease in the intravesicular space (Fig. 5 and see "Results", and because the space can be restored to that of the control by treating the vesicles with dithiothreitol (Fig. 6).

Membrane vesicles probably behave in suspension as loose sacs with the membrane "sides" free to move. The solute accessible intravesicular space may be reduced by pCMBS-induced cross-linking of opposing pieces of membrane, perhaps through residual microfilament attachment sites.

The effects of pCMBS on sodium-energized solute transport and the intravesicular space accessible to solutes are due to pCMBS and not to contaminant mercury. However, the sensitivity of the membrane-bound sucrase to traces of mercury demonstrates that studies involving pCMBS should be undertaken with considerable care as mercury is a well known
inhibitor of many enzymes and transport systems (1, 9, 47, 48).

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