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UNCOUPLING OF Na+-DEPENDENT SOLUTE TRANSPORT IN RENAL BRUSH BORDER MEMBRANES OF MALEATE-TREATED RATS**

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The effect of maleate on the Na+-dependent transport of glucose, phenylalanine and phosphate in the renal brush border membranes (BBM) was studied. It was found that maleate as such had no effect on the isolated BBM vesicles. In BBM isolated from kidney cortex slices which were incubated with maleate, as well as in BBM isolated from the kidneys of maleate-treated rats, an inhibition of the Na+-dependent glucose and phenylalanine transport was observed, whereas the Na+-dependent phosphate transport was stimulated. In kidney slices these effects were prevented by the simultaneous addition of acetate to the incubation medium. The permeability to Na+ ions was increased in the brush border membranes isolated from maleate-treated renal tissue. Cyclic AMP level was decreased nearly by half in the kidneys of maleate-treated rats. It is concluded that the formation of maleyl-CoA, which is prevented by acetate, is a prerequisite for the effects of maleate on the BBM. The data suggest that the inhibition of Na+-dependent glucose and phenylalanine transport results from the uncoupling of Na+ and solute transport, due to increased permeability of the BBM to Na+. The stimulation of the phosphate transport system results probably from a decrease of cell cyclic AMP level. It is suggested that the uncoupling of Na+ and solute transport in the BBM is responsible for the generalized impairment by maleate of solute reabsorption in the renal proximal tubules.

Administration of maleate to experimental animals results in an increased excretion in urine of bicarbonate, phosphate, glucose, amino acids, organic acids and calcium (Berliner et al., 1950; Angielski et al., 1958; Rosenberg & Segal, 1964; Szczepańska & Angielski, 1980). These effects are attributed to impaired reabsorption of solutes in the proximal tubules (Rosen et al., 1973) as well as in the distal

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parts of the nephron (Bergeron et al., 1976). In recent years considerable evidence has been accumulated to prove that the transport of glucose, phosphate, amino acids and bicarbonate in the proximal tubule was catalysed by specific Na⁺-dependent transport systems located in the brush border membranes (Kinne, 1975; Ullrich, 1975). Changes in the activities of the brush border transport systems were suggested to be involved in the regulation of phosphate reabsorption in proximal tubules by parathyroid hormone (Ullrich, 1975; Evers et al., 1978). Within the scope of this model, the inhibition by maleate of glucose, phosphate and amino acid reabsorption might result either from inhibition of the brush border transport systems or from diminished driving forces, i.e. a decreased Na⁺ electrochemical potential gradient between the tubule lumen and the cell. The former possibility is investigated in this paper.

Selective renal toxicity of maleate depends on two basic phenomena: (i) high accumulation of maleate in the kidney as compared to other tissues (Angielski, 1963) and (ii) metabolism of maleate in a succinyl-CoA transferase (EC 2.8.3.5) reaction (Angielski & Rogulski, 1975; Rogulski & Pacanis, 1978; Angielski, 1981):

\[
\text{succinyl-CoA + maleate} \rightarrow \text{maleyl-CoA + succinate}.
\]

The activated double bond of maleyl moiety in maleyl-CoA can react with free SH groups of CoA-SH, glutathione and proteins to form respective addition products (Pacanis & Rogulski, 1981). Maleylation of protein NH₂ groups by maleyl-CoA via the acyl transfer reaction was also observed (Mohuczy, unpublished). Acetoacetate, which is a physiological substrate of succinyl-CoA transferase, can compete with maleate and prevent formation of maleyl-CoA. Acetoacetate prevented in vitro inhibitory effects of maleate in several oxidation reactions in isolated kidney mitochondria (Rogulski et al., 1974). The infusion of acetoacetate in vivo to rats prevented the maleate-induced ketoaciduria, bicarbonate diuresis, glucosuria and phosphaturia (Szczepańska & Angielski, 1980). These observations made it clear that maleyl-CoA is responsible for most, if not all, renal effects of maleate. The present work was undertaken to see whether the brush border membrane transport systems responsible for the reabsorption of glucose, phosphate and amino acids are affected by maleate or its metabolites.

METHODS

Three types of experiments were performed:

1) The Na⁺-dependent transport of glucose, phenylalanine and phosphate was measured in brush border membrane vesicles isolated from kidney cortex of normal rats. The vesicles were incubated with 5 mM-maleate for 10 min prior to transport measurements.

2) Kidney cortex slices were incubated for 30 min in the Ringer-Krebs bicarbonate medium to which 5 mM-maleate, 10 mM-acetoacetate or both were added. Upon termination of the incubation, brush border membrane vesicles were isolated from the slices, and the Na⁺-dependent transport of glucose, phenylalanine and phosphate was measured.
3) Rats were injected intraperitoneally with sodium maleate, 200 mg per kg body weight. After 30 min the animals were killed and the brush border membrane vesicles were isolated from the kidney cortex for measurements of Na⁺-dependent transport of glucose, phenylalanine and phosphate.

**Isolation of brush border membrane vesicles.** The vesicles were isolated from the outermost kidney cortex by the magnesium precipitation method, as described by Booth & Kenny (1974). The purity of the isolated brush border fraction was checked by measurements of the marker enzyme activities: maltase for brush border membranes, Na,K-ATPase for basal-lateral plasma membranes and NADH-cytochrome c reductase for mitochondria. As shown in Table 1, the separation obtained in our laboratory was similar to that obtained by other workers (Kinne *et al.*, 1975; Turner & Silverman, 1977).

**Table 1**

*Marker enzyme activities in the isolated brush border membrane fraction*

Values are means ±S.E.M. from the number of experiments indicated in parentheses.

<table>
<thead>
<tr>
<th></th>
<th>Homogenate</th>
<th>Brush border</th>
<th>Enrichment</th>
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<tr>
<td></td>
<td>Specific activity (nmol/mg protein × min)</td>
<td></td>
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<tr>
<td>Amylomaltase</td>
<td>231 ± 21</td>
<td>2957 ± 140</td>
<td>12.9</td>
</tr>
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<td>(9)</td>
<td></td>
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<tr>
<td>Na,K-ATPase</td>
<td>113 ± 8</td>
<td>202 ± 33</td>
<td>1.78</td>
</tr>
<tr>
<td>(5)</td>
<td></td>
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<tr>
<td>NADH-cytochrome c reductase</td>
<td>6.2 ± 2.0</td>
<td>1.6 ± 0.5</td>
<td>0.26</td>
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<td>(9)</td>
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**Incubation of kidney cortex slices.** Thin slices of the outer cortex of rat kidneys were cut off with a razor blade. The slices were incubated in a 50 ml plexiglass chamber at 25°C in the Ringer-Krebs bicarbonate medium (120 mm-NaCl, 5 mm-KCl, 15 mm-NaHCO₃, 0.6 mm-NaH₂PO₄, 2.5 mm-MgSO₄, 1.3 mm-Ca(OH)₂, and 5 mm-glucose); 200 ml of the medium was recirculated through the incubation chamber and an oxygenator, connected in series, at 160 ml/min. The medium was saturated with 95% O₂/5% CO₂ gas mixture in the oxygenator before being pumped into the incubation chamber. About 2 g of the slices were used for each incubation. After 30 min of incubation the slices were transferred to ice-cold homogenization medium and the brush border membrane vesicles were isolated. Where indicated, maleate and acetacetate (sodium salts) were added to the incubation medium at 5 mm and 10 mm final concentration, respectively.

**Transport measurements.** Na⁺-dependent glucose transport was measured in isolated brush border membrane vesicles by the Millipore filtration technique as described by Kinne *et al.* (1975). The incubation medium contained 100 mm-mannitol, 20 mm-Hepes-Tris buffer, pH 7.6, 100 mm-NaCl and 2 mm-[¹⁴C]glucose
The uptake reaction was started by adding 20 μl of membrane suspension, containing about 100 μg membrane protein, to 100 μl of the incubation medium in an Eppendorf tube at 25°C. The reaction was terminated by transferring an 20 μl sample of the membrane suspension to 1 ml of ice-cold "stop solution", which contained 150 mm-mannitol, 150 mm-NaCl and 20 mm-Hepes-Tris buffer, pH 7.6. The suspension was rapidly mixed on a vortex mixer and filtered through Millipore HAWP filters (0.45 μm pore diameter). The filters were washed once with 5 ml of the same ice-cold "stop solution". The radioactivity retained on the filters was measured by liquid scintillation counting in a Beckman LS-330 counter. In blank samples no membranes were added to the incubation medium.

Na⁺-dependent phenylalanine and phosphate uptakes were measured in media of similar composition but with 1 mm-[¹⁴C]phenylalanine (30 - 40 μCi/ml) or 0.2 mm-NaH₂¹³²PO₄ (30 - 40 μCi/ml). The phosphate "stop solution" contained 300 mm-NaCl, 20 mm-Hepes-Tris buffer, pH 7.4, and 1 mm-Na₂AsO₄ (Hoffman et al., 1976). The procedure was the same as described above.

Sodium uptake by the brush border membrane vesicles was measured as described by Will & Hopfer (1979). The incubation medium contained 100 mm-mannitol, 50 mm-Hepes-Tris buffer, pH 7.5, and 0.25 mm-²²Na₂SO₄ (50 μCi). The "stop solution" contained 150 mm-MgCl₂, 100 mm-mannitol and 10 mm-Hepes-Tris buffer, pH 7.5. The procedure was the same as in the measurement of the glucose uptake.

Each transport measurement was done in triplicate. The number of experiments is given in the legends to Figures and Tables.

Analytical methods. Amylomaltase activity was measured by the method of Wiesmeyer (1962), Na,K-ATPase activity by the enzymatic method of Schoner et al. (1967) as modified by Berner & Kinne (1976), NADH-cytochrome c reductase activity by the spectrophotometric method described by Hatef & Rieske (1967). Protein was determined by the biuret method using crystalline bovine serum albumin as a standard. Cyclic AMP in kidney cortex was measured by radioimmunoassay as described by Gilman (1970).

RESULTS

Effect of maleate on isolated brush border membranes. The effect of maleate on transport properties of the brush border membranes was investigated in vitro in order to see whether maleate could react directly with the components of the membrane and thereby affect its transport properties. The results are shown in Fig. 1. In control experiments, when the vesicles were exposed to an NaCl-containing medium which created a gradient of Na⁺ concentration (higher outside) across the membranes, a typical transient concentrative uptake (an "overshoot") of glucose, phenylalanine and phosphate was observed. Then, the intravesicular concentrations of the measured solutes declined gradually towards equilibrium as the Na⁺ gradient was dissipated by diffusion. No such overshoot was observed in a KCl medium. These phenomena are indicative of Na⁺ gradient dependence of glucose, phenyl-
alanine and phosphate transport in the brush border membrane (Kinne, 1975; Sigrist-Nelson et al., 1975). The addition of 5 mM-maleate to the incubation medium had no effect on the transport of any measured solute. These data indicate that maleate has no direct effect on the transport properties of the brush border membrane.

**Effect of maleate on the brush border membranes in the intact cells.** The negative results of the first series of experiments did not exclude the possibility that the products of intracellular maleate metabolism, namely maleyl-CoA, might affect the transport properties of the brush border membrane. To check this possibility, kidney cortex slices were incubated with or without maleate and then the brush border membranes were isolated from the slices. The results are shown in Fig. 2. Preincubation of the kidney cortex slices with 5 mM-maleate for 30 min resulted in an inhibition of Na⁺-dependent glucose uptake. Interestingly, the initial rate of glucose uptake, measured after 15 s of incubation of the vesicles, was not significantly decreased, whereas the magnitude of the overshoot was significantly smaller than in the control. This might suggest that the transport of sodium, rather than of glucose itself, was affected in these vesicles.

Na⁺-dependent phenylalanine transport was also inhibited by preincubation of the slices with maleate, but to a smaller extent than the glucose transport. However, the transport of this amino acid was much slower than that of glucose and secondary effects, e.g. due to increased sodium permeability of the vesicles, might not occur in this type of the experiment.
The Na\(^+\)-dependent phosphate transport was, rather unexpectedly, considerably stimulated by the preincubation of kidney slices with maleate. Both the initial rate and the overshoot of phosphate uptake were significantly increased. This effect is apparently inconsistent with the in vivo data which show that phosphaturia is an early and sensitive index of maleate intoxication (Szczepańska & Angielski, 1980).

The cyclic AMP level was decreased nearly by half in the kidney cortex of maleate-treated rats (cf Table 4). The stimulation of phosphate transport by maleate can be explained in terms of cyclic AMP-dependent phosphorylation - dephosphorylation hypothesis.

In the course of these experiments it was observed that the amount of all the measured solutes at equilibrium was significantly smaller in the maleate series than in control. This is shown in Table 2. Since glucose is not bound by the membrane to any appreciable extent, its amount at equilibrium is a good measure of intravesicular volume (Kinne et al., 1975). Thus, the data shown in Table 2 suggest that the brush border membrane vesicles obtained from kidney slices incubated with maleate are consistently smaller than the control vesicles, despite the identical isolation procedure. The basis of this effect is obscure. It only suggests that some structural changes may occur in the brush border membranes of kidney cells exposed to maleate.
Table 2

Uptake at equilibrium of glucose, phenylalanine and phosphate by the brush border membrane vesicles incubated with maleate

Kidney cortex slices were incubated for 30 min at 25°C in the Ringer-Krebs bicarbonate buffer with or without 5 mM-maleate. Solute uptake was measured in the brush border membrane vesicles, as described under "Methods", after 30 min incubation of the vesicles with glucose and phenylalanine, and 60 min incubation with phosphate. Data are means ±S.E.M. from 4 experiments in each series.

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Maleate</th>
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<tr>
<td></td>
<td>solute uptake (nmol/mg protein)</td>
<td></td>
</tr>
<tr>
<td>Glucose</td>
<td>0.91±0.01</td>
<td>0.81±0.02</td>
</tr>
<tr>
<td>Phenylalanine</td>
<td>0.81±0.03</td>
<td>0.64±0.04</td>
</tr>
<tr>
<td>Phosphate</td>
<td>1.18±0.17</td>
<td>0.93±0.11</td>
</tr>
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Reversal of the effect of maleate by acetoacetate. As it was mentioned earlier (Angielski & Rogulski, 1975), acetoacetate can compete with maleate in the succinyl-CoA transferase reaction, thereby preventing the formation of maleyl-CoA. The use of acetoacetate allows for an identification of those effects which are produced by maleyl-CoA. Therefore, the kidney cortex slices were incubated with maleate and acetoacetate, and the transport properties of the brush border membranes isolated were investigated (Fig. 3). Acetoacetate reversed both the inhibition

![Graph showing glucose and phosphate uptake (Fig. 3).](image)

Fig. 3. Na⁺-dependent glucose and phosphate transport in the brush border membrane vesicles isolated from kidney cortex slices incubated with maleate and acetoacetate. Experimental conditions as in Fig. 2. ■, Control (no additions); □, 5 mM-maleate and 10 mM-acetoacetate added to the incubation medium. Each point represents a mean ±S.E.M. from 4 experiments.
of glucose uptake, the stimulation of phosphate uptake and the changes in the intravesicular volume which were normally produced by maleate. These results demonstrate that the effect of maleate on the brush border membrane level, like the effect in vivo (Szczepańska & Angielski, 1980), is produced by maleyl-CoA rather than by maleate itself.

**In vivo treatment.** In this series of experiments rats were injected intraperitoneally with sodium maleate, 200 mg per kg body weight. After 30 min the animals were killed and brush border membranes were isolated from the kidney cortex. In Fig. 4 the Na⁺-dependent transport of glucose, phenylalanine and phosphate in these membranes is shown. The pattern is the same as that observed in kidney slices incubated with maleate: glucose and, to a smaller extent, phenylalanine transport is inhibited, whereas phosphate transport is stimulated. These experiments show that the effects of maleate in the intact animal are the same as in the kidney cortex slices incubated with maleate *in vitro*.

![Graph showing glucose, phenylalanine, and phosphate transport](image_url)

*Fig. 4. Na⁺-dependent glucose, phenylalanine and phosphate transport in the brush border membrane vesicles isolated from the kidneys of maleate-treated rats. Rats were injected intraperitoneally with sodium maleate, 200 mg per kg body weight, 30 min prior to the sacrifice. Control rats received an equal volume of isotonic saline. ●, Control; ○, maleate-treated rats. Each point represents a mean ± S.E.M. from 5 experiments.*

**Effect of maleate on permeability to Na⁺ of the brush border membranes.** The inhibition by maleate of Na⁺-dependent glucose transport in the brush border membranes might result either from the inhibition of glucose transport system itself or from an increased permeability of the vesicles to sodium. In the latter case
Table 3

Effect of maleate on the initial rate of $^{22}\text{Na}^+$ uptake by the brush border membrane vesicles

In the *in vivo* experiments the brush border membrane vesicles were isolated from kidney cortex 30 min after intraperitoneal injection of 200 mg/kg sodium maleate. Control rats received isotonic saline. Kidney cortex slices were incubated for 30 min at 25°C with the additions listed in the Table. Brush border membrane vesicles were isolated from the slices for measurements of $^{22}\text{Na}^+$ uptake as described under "Methods". Values are means ±S.E.M. from 4 experiments in each series.

<table>
<thead>
<tr>
<th>In vivo treatment</th>
<th>$^{22}\text{Na}^+$ uptake (nmol/mg protein $\times$ 10 s)</th>
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<tbody>
<tr>
<td>Control</td>
<td>0.72±0.08</td>
</tr>
<tr>
<td>Maleate, 200 mg/kg</td>
<td>1.03±0.09</td>
</tr>
<tr>
<td>Kidney cortex slices</td>
<td></td>
</tr>
<tr>
<td>Control (no additions)</td>
<td>0.65±0.05</td>
</tr>
<tr>
<td>Acetoacetate, 10 mm</td>
<td>0.67±0.06</td>
</tr>
<tr>
<td>Maleate, 5 mm</td>
<td>0.92±0.07</td>
</tr>
<tr>
<td>Acetoacetate + maleate</td>
<td>0.69±0.06</td>
</tr>
</tbody>
</table>

the transport of sodium and glucose would become uncoupled. To distinguish between these two possibilities the effects of maleate on sodium transport in the brush border membrane vesicles were investigated both after *in vivo* treatment and in kidney cortex slices. The results are shown in Table 3. The initial rate of $^{22}\text{Na}^+$ uptake was significantly higher in the brush border membrane vesicles obtained from kidneys of maleate-treated rats than in control. Since the measurements were made in a medium which contained no permeant anions, these results suggest a higher permeability of these vesicles to sodium. Like the inhibition of glucose uptake, the stimulation of sodium uptake was also prevented by acetoacetate.

Table 4

Effect of maleate administration *in vivo* on cyclic 3',5'-AMP level in rat kidney cortex

Experimental rats were given sodium maleate, 200 mg per kg body weight intraperitoneally. Kidneys were removed 30 min later for cyclic AMP determination. Control rats received an equal volume of isotonic saline. Data are means ±S.E.M. from 11 experiments.

<table>
<thead>
<tr>
<th></th>
<th>Cyclic 3',5'-AMP (nmol/g wet weight)</th>
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<tbody>
<tr>
<td>Control rats</td>
<td>0.98±0.15</td>
</tr>
<tr>
<td>Maleate-treated rats</td>
<td>0.51±0.10</td>
</tr>
</tbody>
</table>

Cyclic 3',5'-AMP level in the kidneys of maleate-treated rats. The activity of phosphate transport system in the brush border membrane is regulated by cyclic AMP-dependent phosphorylation catalysed by brush border protein kinase; phos-
phorylation of the membrane results in an inhibition of the phosphate transport system (Evers et al., 1978). Maleate-induced stimulation of the phosphate transport in the brush border membranes (Figs. 2 and 4) might thus result from a decrease of cellular cyclic AMP level. As it is shown in Table 4, the level of cyclic 3',5'-AMP is indeed decreased considerably in the kidneys of maleate-treated rats.

DISCUSSION

Results of this investigation indicate that the functional integrity of the brush border membranes of renal tubular cells is impaired by maleate both in vivo and in isolated kidney cortex slices. This impairment is manifested by the inhibition of Na⁺-dependent transport of glucose and phenylalanine (Figs. 2 and 4). Direct measurements have shown an increased permeability of these membranes to sodium ions (Table 3). Taken together, these data suggest an uncoupling between sodium and glucose and amino acid transport rather than a direct inhibition of the respective transport systems. Such a mechanism would imply an inhibition by maleate of the transport of a wide variety of solutes which are co-transported with sodium. Indeed, in maleate-treated animals a decreased reabsorption of glucose, most amino acids, phosphate, bicarbonate, uric acid and several organic acids was observed (Angielski et al., 1958; Rosenberg & Segal, 1964; Gmaj et al., 1972).

The data accumulated during past few years suggest that the Na⁺ electrochemical potential across the brush border membranes of proximal tubular cells provides a major driving force for the reabsorption of a number of solutes in this part of the nephron. The results obtained with maleic acid are in full agreement with the predictions of the sodium gradient hypothesis: uncoupling between sodium transport and solute transport in the brush border membrane results in a generalized impairment of proximal solute reabsorption. The present results provide evidence for a new, hitherto undescribed, mechanism of renal transport lesion.

The behaviour of the phosphate transport presents a special case. The Na⁺-dependent transport of phosphate is stimulated in the brush border membranes obtained from kidneys of maleate-treated rats. It was shown earlier (Ullrich, 1978) that the phosphate transport system was regulated by the cyclic AMP-dependent protein kinase system, whereas glucose and phenylalanine transport systems were not subject to such regulation. Cyclic AMP-dependent phosphorylation of the brush border membrane resulted in an inhibition of Na⁺-dependent phosphate transport. The cyclic AMP level in kidney cortex of maleate-treated rats is decreased nearly by half (Table 4), which explains, in biochemical terms, the stimulation of phosphate transport in the brush border membrane. These results provide an extension of earlier observations (Kinne et al., 1975) that not only the parathyroid hormone-induced increase of the cell cyclic AMP level results in an inhibition of brush border phosphate transport, but also the maleate-induced decrease of cell cyclic AMP level results in a stimulation of the brush border phosphate transport. Apparently, the degree of uncoupling between the sodium and the phosphate transport is not high enough to alleviate the stimulation of the transport system itself.
Phosphaturia produced by maleate administration is, however, more difficult to explain. It must be taken account in this respect that the brush border transport systems which do not utilize ATP are symmetric. The direction of the net solute transport is imposed by the direction of the sodium gradient. The stimulation of the phosphate transport system would result in a stimulation of net phosphate reabsorption only if the magnitude of the sodium gradient remains unchanged. If, however, the intracellular sodium concentration were increased by maleate, the backflux of phosphate from the cell to the tubule lumen *via* the stimulated transporter might well result in a decreased net phosphate reabsorption. From these considerations it follows that the maleate-induced phosphaturia would be very difficult to explain without assuming an increase in the intracellular sodium concentration. Measurements made in the kidney cortex slices confirmed this supposition: addition of maleate to the incubation medium resulted in an increase of cell sodium concentration (Hong Que, 1980). In view of profound metabolic alterations produced in kidney cells by maleate, this is by no means a surprising finding.

Acetoacetate, which competes with maleate in a succinyl-CoA transferase reaction, also prevents the effects of maleate on the brush border membranes. This provides one more indication that maleyl-CoA rather than maleate itself is a potent toxic substrate.

The mechanism of action of maleyl-CoA on the brush border membrane is not clear. It has been reported that the SH-reactive mercurials increase the permeability of the brush border membranes to sodium (Will & Hopfer, 1979). It is possible that the SH-reactive maley-CoA may act in the same way, although indirect effects (*e.g.* *via* decreased ATP and cAMP levels or *via* intracellular Ca\(^{2+}\) redistribution) cannot be excluded at present.

The present experiments give some support to the "permeability hypothesis" of the transport defects in maleate-induced Fanconi syndrome (Bergeron *et al.*, 1976). However, since phosphaturia cannot be explained by altered brush border function alone, the energetic aspects of solute transport, and notably the magnitude of the sodium gradients, must be considered in the analysis of maleate-induced defects of renal tubular transport.

The authors are indebted to Dr. K. Drewnowska and Miss H. Dutkowska for the estimations of cyclic AMP.

REFERENCES


**ROZKOJARZENIE TRANSPORTU SODU I METABOLITÓW W PEČHERZYKACH BŁON RĄBKA SZCZOTECZKOWEGO NEREK SZCZURÓW ZATRUTYCH MALEINIANEM**

**Streszczenie**

Zbadano wpływ maleinianu na transport glukozy, feniloalaniny i fosforanów, zależny od Na⁺, do pęcherzyków błon rąbka szczoteczkowego otrzymanych z kory nerek szczurów. Stwierdzono, że sam maleinian nie miał wpływu na te pęcherzyki. Związek ten wyraźnie hamował transport glukozy i feniloalaniny do pęcherzyków, gdy otrzymywano je ze skrawków kory nerek inkubowanych w obecności maleinianu, podczas gdy transport fosforanów w tych warunkach był znacznie stymulowany. Preinkubacja skrawków kory nerek z acetooctanem zapobiegała toksycznemu działaniu maleinianu. Pęcherzyki otrzymane z nerek szczurów zatruty maleinianem były bardziej przepuszczalne dla Na⁺. Stężenie cAMP w nerkach tych szczurów było obniżone o 50% w porównaniu do grupy kontrolnej. Wyniki te wskazują, że powstający z maleinianu maleilo CoA, którego powstawaniu zapobiega acetooctan, jest czynnikiem toksycznym uszkadzającym błonę luminalną kanalików. Dane te sugerują, że zahamowanie transportu glukozy i feniloalaniny, zależne od Na⁺, jest wyrazem rozkojarzenia transportu Na⁺ i badanych substratów, które jest spowodowane zwiększoną przepuszczalnością pęcherzyków dla Na⁺. Stymulacja transportu fosforanów może być uwarunkowana spadkiem stężenia cAMP w nercie. Występujące po maleinianie rozkojarzenie między transportem Na⁺ i metabolitów przez błonę luminalną kanalików nerkowych może być wyrazem uszkodzenia uogólnionego reabsorpcji substratów w kanalikach proksymalnych nerek.

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