Electrical potential profile in rabbit ileum: role of rheogenic Na transport

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The electrical potential profile of rabbit ileum was investigated in vitro with the microelectrode technique. The transmural electrical potential difference (PD), designated $\psi_{ms}$, was immediately reduced by 60% upon cooling the tissue from 37 to 7°C; the PD across the mucosal membrane (transmucosal PD, $\psi_{mc}$) was simultaneously reduced by 37%. These electrical changes could not be attributed to alterations in either transmembrane ion concentration gradients or total tissue conductance. The $\psi_{mc}$ and $\psi_{ms}$ may have substantial values even after the concentration gradients of Na and K across the cell membrane are eliminated, provided that active transport mechanisms are still operative. Conversely, in the presence of approximately normal transmembrane ion concentration gradients, but when active transport mechanisms have been inhibited, $\psi_{mc}$ is reduced by 45% and $\psi_{ms}$ is zero. These observations are consistent with a model of electrolyte transport in which $\psi_{mc}$ and the normal transmembrane cation concentration gradients are established by rheogenic active transport of Na out of the cell. The $\psi_{mc}$ is generated both by rheogenic active Na transport and by cation concentration gradients which exist across the cell membrane. The Koefoed-Johnsen and Ussing model (Acta Physiol. Scand., 1958, vol. 42, p. 298) of electrolyte transport by epithelial cells does not adequately describe the electrical properties of ileum.

The Koefoed-Johnsen and Ussing model of the epithelial cell of frog skin suggests that the transepithelial potential is directly dependent on Na and K diffusion potentials across the outside and inside cell membranes. The active transport system consists of a forced Na-K exchange at the inside border which is electrically neutral. In the present study, the microelectrode technique was used to investigate rabbit ileum to determine if the electrical potential profile is consistent with the Koefoed-Johnsen and Ussing model of electrolyte transport or if a model featuring rheogenic ion transport is more appropriate, as indicated by the experiments of Rose and Schultz (24) and Frizzell and Schultz (10). Some of these data have been published in preliminary form (22).

1 Rheogenic transport is used to describe a current-generating process as suggested by Schwartz (28) and discussed in detail by Schultz et al. (25).
METHODS

White, male rabbits were killed by intravenous injection of pentobarbital. The terminal ileum was excised, opened along the mesenteric border, and rinsed in buffered electrolyte solution until free of intestinal content. The serosal musculature, submucoosa, and muscularis mucosa were stripped off using glass microscope slides.

Electrical measurements. For simultaneous measurements of $\psi_{ms}$ and $\psi_{mc}$, the tissue was held with the mucosal surface up between the halves of a Lucite chamber described in detail by Rose and Schultz (24). A continuous supply of bathing solution at 37°C was delivered from a reservoir to each half of the chamber. The $\psi_{ms}$ was monitored using Ringer-agar bridges connected through matched calomel half-cells to a Keithley model 602 electrometer and was recorded on one channel of a Texas Instruments dual-channel recorder. Tissue resistance was measured by passing current from an external source through silver-silver chloride electrodes which made contact through Ringer-agar bridges with the bathing solution.

Microelectrodes were prepared from borosilicate glass tubing with a vertical micropipette puller (David Kopf Instruments, model 700C). The pipettes were filled by boiling in methanol, allowed to exchange with distilled water, and equilibrated with 3 M KCl for at least 12 h. Electrodes were selected for a resistance of 5-20 MΩ and a tip potential of less than 5 mV.

A KCl-agar bridge connected the microelectrode to a calomel half-cell which, in turn, was connected to the high-impedance probe of a negative capacitance Medisensor A-35 amplifier. The Ringer-agar bridge in contact with the mucosal bathing solution was used as the reference electrode. The $\psi_{mc}$ was recorded on the second channel of the dual-channel recorder.

The microelectrode was held by a micromanipulator (Eric Sobotka Co. model MM-33) and driven by hand or by a stepping hydraulic drive unit (Kopf Instruments, model 607) with a minimum advance of 1 μm.

Control Ringer contained, in millimoles per liter: NaCl, 142; KHCO$_3$, 10; K$_2$HPO$_4$, 0.2; K$_2$HPO$_4$, 1.2; CaSO$_4$, 1.2; and MgSO$_4$, 1.2. HCO$_3$-free Ringer contained, in millimoles per liter: NaCl, 142; KH$_2$PO$_4$, 1.5; K$_2$HPO$_4$, 4.2; CaSO$_4$, 1.2; and MgSO$_4$, 1.2. K-free solution and Na-free solution were prepared from HCO$_3$-free Ringer by appropriate reciprocal replacement of K and Na. High-K solution was prepared from control Ringer by replacement of 128 meq/liter of Na with K. Na-free, K-free solution was prepared by replacement of NaCl, KH$_2$PO$_4$, and K$_2$HPO$_4$ with Tris buffer. The bathing solution was bubbled with a gas mixture of 95% O$_2$, 5% CO$_2$ when HCO$_3$ was present or 100% O$_2$ when HCO$_3$ was absent. The final pH of all bathing solutions was 7.0-7.2.

Determination of intracellular Na and K concentrations. The technique for determining intracellular solution concentrations of ileal mucosal strips has previously been described (9, 26). Briefly, mucosal strips weighing 100-200 mg were incubated as described for the individual experiment (see RESULTS) in media which contained [^1H]inulin. At the end of the incubation period, the tissues were removed, blotted on filter paper, weighed, and transferred to plastic tubes containing 2.0 ml of 0.1 N HNO$_3$. The tissues were extracted for at least 20 h by shaking at 4°C. Aliquots of the tissue extract and suitably diluted aliquots of the incubation media were assayed for $^3$H using scintillation spectrometry and for chemical Na and K content using flame photometry (Instrumentation Laboratory, Inc.). Total tissue water in individual mucosal strips was determined by drying each tissue sample to constant weight at 60°C. Correction for extracellular content of Na or K was based on the inulin space.

[^1H]inulin, $^2$Na, and $^4$K were obtained from New England Nuclear Corp. Radioisotopes were counted on a Packard Tri-Carb scintillation spectrometer.

The results are presented as mean values ± standard error; statistical comparisons were made with the paired-t test.

RESULTS

It was expected that the transmural PD across rabbit ileum results from electromotive forces operating across or within the cell membrane, since any diffusion potentials originating in the lateral intercellular spaces during electrolyte absorption would represent a serosa-negative emf capable of attenuating, but not causing, the serosa-positive PD (10). Because an emf across the cell membrane, even at only the serosal surface, could influence both $\psi_{mc}$ and $\psi_{ms}$, these PD's were measured simultaneously.

Temperature dependence of electrical properties. Cell concentrations of Na and K are expected to change slowly upon cooling ileal mucosa from 37 to 7°C; in the absence of permeability changes, any diffusion potentials originating in the lateral intercellular spaces would show only a delayed depolarization. If, however, rheogenic ion transport also contributes significantly to the development of the electrical potential profile, abrupt changes in electrical properties might be observed upon lowering the temperature as active transport processes are quickly slowed down.

Shown in Fig. 1 is an example of simultaneous recordings of the transmural PD of ileal mucosa and the transmucosal PD of a single cell in the tissue. The serosa-positive $\psi_{ms}$ of 3 mV is typical for rabbit ileum bathed in Ringer at 37°C. The $\psi_{mc}$ stabilized at -55 mV, cell interior negative with respect to the mucosal bathing solution. When cold Ringer was injected into the mucosal chamber for 10-20 s to bring the bathing solution to 4-7°C, an immediate depolarization of $\psi_{ms}$ and $\psi_{mc}$ was observed. If the tissue was kept cold for 1-2 min, $\psi_{ms}$ usually reached zero. In experiments on ileal mucosa from five rabbits, eight successful cell impalements were made in which $\psi_{mc}$ depolarized upon cooling and returned to approximately its original value.

[^1] The transmucosal recording infrequently increased slowly for a time before stabilizing. This is interpreted to represent gradual sealing of the cell membrane around the electrode and is considered a successful cell impalement if a stable PD is reached.
ELECTRICAL PROPERTIES IN ILEUM

FIG. 1. Simultaneous recordings of transmural PD across ileum and transmucosal PD of a single cell. Tissue bathed in control Ringer at 37°C. I, time of impalement of cell; R, time of microelectrode retraction. Tube that delivers bathing fluid to mucosal and serosal surfaces was clamped at time indicated. Control Ringer at 0°C was injected into mucosal chamber, and flow of warm Ringer was resumed. Figure redrawn from original recording.

Upon rewarming, the $\psi_{ms}$ and $\psi_{mc}$ at 37°C were $2.4 \pm 0.7$ and $-39.5 \pm 13.3$ mV, respectively, and at 4–7°C the values were $1.0 \pm 0.4$ and $-24.8 \pm 8.8$ mV, respectively. Thus, low temperatures brought about a statistically significant depolarization in $\psi_{ms}$ of $1.4 \pm 0.2$ mV ($P < 0.01$) and a depolarization in $\psi_{mc}$ of $14.7 \pm 1.4$ mV ($P < 0.01$). A slight temporary hyperpolarization (mean, $0.2 \pm 0.1$ mV) of $\psi_{ms}$ was usually evident upon warming. When the tip of the microelectrode was suspended in the bathing solution several millimeters above the tissue rather than in the cell interior, injections of cold Ringer had no effect on the potential of the microelectrode with respect to the reference electrode. This demonstrates that the effect of cold was not simply to alter electrode potentials.

A decrease in transmural tissue resistance alone could account for a smaller transmural PD across an epithelial tissue. Upon brief cooling, however, tissue resistance did not change detectably; thus, the changes in $\psi_{ms}$ in Fig. 1 cannot be attributed to the effect of cold on total tissue resistance.

Intracellular ionic composition. The possibility that intracellular concentrations of Na and K ([Na], [K]) change rapidly enough to account for the electrical changes shown in Fig. 1 was investigated using several individual samples of intestinal muscosa from each of five rabbits. The tissue segments were incubated for 2 h at either 37 or 4°C in control Ringer. Tissue incubated at 37°C maintained [K], at $127 \pm 7$ meq/liter and [Na], at $81 \pm 8$ meq/liter (Fig. 2A). When bathed at 4°C, [K], decreased and [Na], increased, but the changes occurred too slowly to account for the immediate electrical effects seen in Fig. 1. The results of these experiments, as those obtained from any technique which considers the intestinal muscosa to be composed of a homogeneous group of cells, are subject to reinterpretation upon the application of a more specific methodology. Thus, the following discussion assumes that the overall intracellular Na and K concentrations observed under both control and experimental conditions apply to the polar transporting cells.

In another series of experiments, several samples of muscosa from each of six rabbits were preincubated at 4°C in K-free solution (with Ca and Mg = 0, EDTA = 1 mM) to lower [K], and raise [Na]. These tissues were then incubated in control Ringer at 37°C to determine how rapidly the cells could reaccumulate K and extrude Na to return to normal conditions. At least 30 min were required in tissue from each animal tested (Fig. 2B).

Several tissue samples from these experiments were investigated at the end of 90 min of incubation at 4°C to determine their electrical properties in the cold and then to find how rapidly these properties returned to normal upon warming the tissue to 37°C. Shown in Fig. 3 are the results obtained on a representative tissue sample in control Ringer. At 7°C these tissues had a $\psi_{ms}$ of essentially zero and an average $\psi_{mc}$ of $13 \pm 4$ (n=40). Upon rapid warming to 37°C, the tissues developed a $\psi_{ms}$ of 3–4 mV within 90 s. $\psi_{mc}$ also increased rapidly and attained a mean value of $31 \pm 4$ mV (n=15) during the period 3–10 min after warming. Glucose was

$^3$ EDTA, ethylenediamine tetracetic acid.
added to the bathing solution (5 mM, final concn) to demonstrate that the transmural electrical response associated with active sugar transport is still obtained, although reduced in magnitude from the normal response in vitro (2.5 mV; ref. 24, Fig. 7) possibly because the present tissue had been under conditions in vitro for 140 min.

Tissue samples pretreated in the same way were also investigated by briefly warming the mucosal solution while the microelectrode tip was in a cell. In Fig. 4, $\psi_{ms}$ and $\psi_{mc}$ at 7°C were 1.2 and $-10$ mV, respectively. The peak responses 20 s after warming to 37°C were 3.4 and $-20$ mV, respectively. This demonstrates the occurrence of simultaneous changes in $\psi_{ms}$ and $\psi_{mc}$ when conditions are suddenly made favorable for active transport processes.

Electrical properties and ion concentrations in poisoned tissue. Experiments were performed at 37°C to determine the transmural and transmucosal PD's in tissue that had approximately the normal high intracellular K concentration and low Na concentration and that had active transport mechanisms for ions inhibited. Tissue was brought to this state by bathing it for 90 min at 4°C in high K solution which was bubbled with 95% N$_2$ - 5% CO$_2$ and which contained NaCN and ouabain (1 mM). The tissue was then mounted in chambers for measuring the electrical properties with control Ringer at 37°C as the bathing solution. The transmural PD was initially very low and decreased to zero within 2-6 min in experiments on one sample of tissue from each of seven rabbits (Fig. 5). During the first 10 min of intracellular potential measurements, $\psi_{mc}$ averaged $-22 \pm 5$ mV. Assuming that the preincubation procedure has not permanently altered membrane permeability properties, these studies suggest that $-22$ mV of

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1 The smaller changes in $\psi_{ms}$ and $\psi_{mc}$ in Fig. 4 than in Fig. 3 may be due to a failure of the tissue to reach 37°C because the mucosal solution was warmed only briefly. In addition, the gradual initial decline of $\psi_{mc}$ might indicate poor sealing of the cell membrane around the microelectrode which would be likely to reduce the $\psi_{mc}$ response to warming (see relevant discussion in ref. 24).
the normal intracellular potential (36 mV) might be attributed to normal transmembrane ion concentration gradients in the absence of rheogenic active transport of ions.

Experiments were performed to determine whether Na and K movements across the cell membrane were rapid enough to change significantly the transmembrane concentration gradients during the early phase of the experiment seen in Fig. 5. Ileal mucosa from four rabbits was bathed for 90 min at 4°C in high K solution which contained NaCN and ouabain. The tissue was then incubated at 37°C in control Ringer for 25 min. As seen in Table 1, a significant fraction of intracellular K and water left the cell during the first 5 min of incubation. The net efflux of electrolyte from the cells appears to have been an approximately isotonic solution of KCl, and thus the intracellular concentrations of Na and K did not change markedly. Because the transmural PD remained at zero while substantial Na and K concentration gradients existed across the cell membrane, we may conclude that the normal low value of [Na+] and the high value of [K+] are not responsible for generation of the PD.

Tissue that had approximately normal intracellular Na and K concentrations and that had active transport of ions inhibited by ouabain and cyanide (prepared as above) was also investigated to examine the immediate effect of cold on the transmural and transmucosal PD’s as previously determined (Fig. 1) on control tissue. Electrical measurements were made within 5–10 min after the tissue had been mounted in the chambers and bathed in control Ringer. In 15 successful cell impalations on tissue from five rabbits, ϕmc and ϕms at 37°C were +0.2 ± 0.1 and −24 ± 2 mV, respectively. The values at 4–7°C were +0.1 ± 0.1 and −22 ± 2 mV, respectively. Thus, no significant depolarization of ϕms was brought about by low temperatures under these conditions.

The effect of rapid inhibition of active transport by addition of ouabain and cyanide to tissue from four rabbits under control conditions was also investigated. As seen in a representative experiment (Fig. 6) exposure to poisons at 37°C eliminated ϕms within 10–15 min. During this time, ϕmc decreased from a control value of +40 mV (n = 26) to −20 to −25 mV. Further depolarization of ϕmc was gradual and occurred at approximately the same rate as dissipation of Na and K concentration gradients across the cell membrane.

**DISCUSSION**

Although the transmural electrical potential difference across mammalian small intestine has been measured in many previous studies, a clear understanding of the nature and site of the underlying electromotive forces responsible for generation of the PD has not been achieved. It has been apparent that the transmural PD is associated, either directly or indirectly, with the normal process of electrolyte absorption. Thus, active transport of Na and possibly other ions has been implicated in its generation (25). Because the transmural PD is the net result of an electrical potential difference across the individual mucosal and serosal cell membranes, additional information about the intracellular potential was necessary to better understand the electrical properties of ileum.

In the current concept of active transport, a membrane-contained carrier is considered to be a primary participant; operation of the carrier is thought to be a highly temperature-sensitive process. Since the temperature of the tissue was a condition which could quite easily and quickly be adjusted, the electrical potential profile of rabbit ileum was studied at 37 and at 7°C, both when the cells had their normal intracellular ionic composition and when [K+] and [Na+] were artificially adjusted.

Na and K concentration gradients existing across the cell membrane under control conditions could result in diffusion potentials and thereby account for part or all of the measured transmucosal PD. If these ion gradients.

**TABLE 1. Intracellular electrolyte composition of tissue bathed in control Ringer after preincubation in high-K solution with ouabain and cyanide**

<table>
<thead>
<tr>
<th>Time, min</th>
<th>Na</th>
<th>K</th>
<th>Na (mg/liter)</th>
<th>K (mg/liter)</th>
<th>Na (mg/dry wt)</th>
<th>K (mg/dry wt)</th>
<th>HCO3 (mEq/liter)</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>1</td>
<td>1</td>
<td>25.9 ± 6</td>
<td>149 ± 4</td>
<td>224 ± 62</td>
<td>1244 ± 59</td>
<td>8.31 ± 0.31</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>0</td>
<td>34.9 ± 12</td>
<td>133 ± 8</td>
<td>200 ± 77</td>
<td>745 ± 36</td>
<td>5.80 ± 0.67</td>
</tr>
<tr>
<td>5</td>
<td>0</td>
<td>0</td>
<td>53.8 ± 10</td>
<td>134 ± 7</td>
<td>233 ± 72</td>
<td>711 ± 62</td>
<td>5.34 ± 0.42</td>
</tr>
<tr>
<td>10</td>
<td>b</td>
<td>b</td>
<td>60.0 ± 10</td>
<td>132 ± 5</td>
<td>269 ± 78</td>
<td>562 ± 27</td>
<td>4.28 ± 0.24</td>
</tr>
<tr>
<td>15</td>
<td>e</td>
<td>e</td>
<td>50.0 ± 11</td>
<td>120 ± 6</td>
<td>196 ± 46</td>
<td>484 ± 19</td>
<td>3.93 ± 0.29</td>
</tr>
<tr>
<td>20</td>
<td>e</td>
<td>e</td>
<td>53.8 ± 10</td>
<td>137 ± 8</td>
<td>208 ± 60</td>
<td>466 ± 17</td>
<td>3.74 ± 0.22</td>
</tr>
<tr>
<td>25</td>
<td>e</td>
<td>e</td>
<td>53.0 ± 14</td>
<td>118 ± 6</td>
<td>210 ± 52</td>
<td>479 ± 30</td>
<td>4.09 ± 0.33</td>
</tr>
</tbody>
</table>

Values are means ± SE. Tissue samples were preincubated 90 min at 4°C and then incubated at 37°C in control Ringer for the time indicated.
resulting change in $\psi_{mc}$ due to an alteration in membrane permeability to a given ion would be about 10% of the control value ($\approx -36\,\text{mV}$) or 4 mV; since the observed change was 15 mV, we must conclude that temperature-induced changes in $\psi_{mc}$ are too great to be the sole result of changes in the diffusion potential of a single ion.

The possibility should also be considered that temperature changes result in alterations of cell membrane selectivity to a pair of ions present in high concentrations. For instance, the $\psi_{mc}$ of $-36\,\text{mV}$ under control conditions could result from diffusion potentials established by the high [K]$_i$ and low [Na]$_i$ relative to the bathing solution and a cell membrane $P_{Na}/P_K$ selectivity of approximately 0.2. If $P_{Na}/P_K$ increases upon cooling, the depolarization of $\psi_{mc}$ would be explained. However, other observations, such as the development of a large $\psi_{mc}$ in the absence of normal transmembrane ion gradients, are inconsistent with the diffusion potential hypothesis. In addition, it seems unlikely that other procedures which quickly depolarize $\psi_{mc}$ or $\psi_{ms}$, such as exposure of the tissue to poisons or to anaerobic conditions (1), would induce the same change in passive permeability properties as low temperatures.

The transmural PD and part of the transmucosal PD appear to result from some process directly dependent on cellular metabolism. There is good evidence that Na (7, 27) and Cl (7) are actively absorbed and HCO$_3^-$ is actively secreted by rabbit ileum in vitro (5). Absorption of Cl would not account for the observed serosa-positive $\psi_{ms}$ under control conditions. Although absorption of Cl across the mucosal border into the cell could contribute to the intracellular electrical negativity, previous experiments (24) have indicated that abrupt replacement of Cl in the mucosal solution with SO$_4$ results in no significant change in $\psi_{mc}$. It was also previously found that the electrical potential profile does not change appreciably when HCO$_3^-$ is reduced from 10 to 0 meq/liter (24). Addition of the carbonic anhydrase inhibitor acetazolamide had no effect on $\psi_{mc}$ or $\psi_{ms}$ of ileal mucosa bathed either in HCO$_3^-$-free Ringer or in Ringer having [HCO$_3^-$] = 10 meq/liter. Thus, active transport of anions does not appear to be a primary event in establishing the electrical potential profile of rabbit ileum. Because a significant transmural PD is developed only when Na is present in the bathing solution (27) and the PD is immediately increased when actively transported sugars or amino acids make more Na available to the transport mechanism, it seems likely that $\psi_{ms}$ is a result of rheogenic active Na transport at the basolateral membranes.

Summarized in Table 2 are estimates of the contribution of rheogenic Na transport to $\psi_{mc}$ from each of the four research techniques discussed above. Na transport appears to develop a transmucosal PD of approximately $-15\,\text{mV}$. The contributions of transmembrane ion concentration gradients and rheogenic ion transport to the electrical potential profile are shown schematically in Fig. 8.

The equivalent electrical circuit model previously...
TABLE 2. Contribution of rheogenic ion transport to transmucosal PD

<table>
<thead>
<tr>
<th>Expt</th>
<th>Cooling Control Tissue From 37 to 7°C</th>
<th>Warming K-Depleted Tissue from 7 to 37°C</th>
<th>Tissue Preincubated in High-K Solution with Cyanide and Ouabain</th>
<th>Tissue Poised with Cytoside and Ouabain under Control Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Δψmc</td>
<td>15 mV</td>
<td>18 mV</td>
<td>14 mV</td>
<td>16 mV</td>
</tr>
</tbody>
</table>

Presented to describe the electrical properties of ileum (24) can now be discussed in terms of the likely contribution to the emf's at the mucosal and serosal borders (Ems and Ecs, respectively) due to transmembrane diffusion potentials and rheogenic Na transport. The observation that ψms is immediately eliminated by experimental conditions which inhibit electrolyte transport and the conclusion that rheogenic Na transport is directly responsible for establishment of the serosa-positive PD under control conditions allow us to suggest that the Na pump contributes directly to the emf at the cell membrane, perhaps representing part of E, under control conditions. An increase in the magnitude of E, (by increasing pump activity) would result in the serosal solution becoming more positive with respect to the mucosal solution, provided that the shunt resistance is not zero. The cell interior becomes more negative with respect to the mucosal solution in response to an increase in the emf at the serosal border (Ecs) (e.g., the experimental conditions in Fig. 3) because the shunt resistance is not infinite. It has previously been concluded from ion flux determinations (10) and electrical measurements (24) that the extracellular shunt path is the site of most transmural NaCl diffusion. Therefore, the low resistance extracellular shunt path in ileum prevents development of a large ψms and much of the change in E, when the rate of Na transport is suddenly altered appears as a change in ψmc. In the absence of pump activity, ψms is zero; ψmc and ψcs are equal but do not approach zero until more than 1 h after active transport has ceased, at which time the Na and K gradients are also greatly dissipated.

The Koefoed-Johnsen and Ussing model of an epithelial cell (15) based on experiments performed on frog skin includes coupled active transport of Na and K in opposite directions at the inward-facing membrane. Such a forced exchange of cations would not be rheogenic and, therefore, pump activity would not directly contribute to a transepithelial PD. The PD would originate, instead, from the normal intracellular ion concentrations which are maintained different from the bathing media by active transport and from asymmetric permeability properties at the two cell surfaces. It is informative to compare certain observations from the present study with those made on other epithelial tissues. Under conditions when the potassium concentration gradient across the serosal cell surface is reduced or reversed from control conditions, the PD across the serosal membrane of ileum, bladder (8), and skin (3) does not change as predicted by the Koefoed-Johnsen and Ussing model. Also, the short-circuit current and transepithelial PD of ileum, amphibian bladder (13), and skin are reduced by application of metabolic inhibitors, ouabain, or anaerobic conditions too quickly to be accounted for by alterations in tissue Na and K content. Thus, the transepithelial PD in skin and bladder may be the direct result of some process closely associated with cellular metabolism, such as rheogenic ion transport.

Rheogenic transport mechanisms have also recently been discussed as possible origins of the spontaneous 2- to 7-mV transmural PD's across goose, monkey, and human gallbladders (11, 21) and the amphotericin B-induced PD across rabbit gallbladder (23). It therefore appears that the Koefoed-Johnsen and Ussing model of electrolyte transport inadequately describes the electrophysiologic properties of a variety of epithelial tissues. The information currently available on mammalian ileum supports a model in which the transmural PD originates directly from active Na transport at the serosal membrane; the negative intracellular potential appears to derive from at least two independent electromotive forces: symmetric K and Na diffusion potentials at the mucosal and serosal cell surfaces and a superimposed rheogenic active Na transport mechanism at the serosal membrane.

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