INFLUENCE OF CELLULAR AND PARACELLULAR CONDUCTANCE PATTERNS ON EPITHELIAL TRANSPORT AND METABOLISM

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ABSTRACT Theoretical analysis of transepithelial active Na transport is often based on equivalent electrical circuits comprising discrete parallel active and passive pathways. Recent findings show, however, that Na^+ pumps are distributed over the entire basal lateral surface of epithelial cells. This suggests that Na^+ that has been actively transported into paracellular channels may to some extent return to the apical (mucosal) bathing solution, depending on the relative conductances of the pathways via the tight junctions and the lateral intercellular spaces. Such circulation, as well as the relative conductance of cellular and paracellular pathways, may have an important influence on the relationships between parameters of transcellular and transepithelial active transport and metabolism. These relationships were examined by equivalent circuit analysis of active Na transport, Na conductance, the electromotive force of Na transport, the "stoichiometry" of transport, and the degree of coupling of transport to metabolism. Although the model is too crude to permit precise quantification, important qualitative differences are predicted between "loose" and "tight" epithelia in the absence and presence of circulation. In contrast, there is no effect on the free energy of metabolic reaction estimated from a linear thermodynamic formalism. Also of interest are implications concerning the experimental evaluation of passive paracellular conductance following abolition of active transport, and the use of the cellular voltage-divider ratio to estimate the relative conductances of apical and basal lateral plasma membranes.

INTRODUCTION

For an ionic active transport mechanism to promote transepithelial salt transport, a membrane must be traversed by pathways permitting passive co-ion transport in response to the electrochemical forces generated by the primary active process. Although this has long been evident (32, 33), only relatively recently have the nature and physiological significance of shunt pathways been investigated systematically (2, 6, 9–11, 14, 16–18, 28, 29, 31). On the basis of such investigation, it is now clear that the structure of paracellular channels varies greatly from tissue to tissue, giving rise to striking functional differences between "tight" and "loose" epithelia (18). Furthermore, in a given tissue the nature of paracellular channels may vary significantly, e.g., with muscular contraction (20), with changes in hydrostatic pressure gradients (2) or bathing fluid composition (6, 14, 28), or in the presence of drugs and hormones (10, 21, 31).

The importance of these considerations has led to histological studies using a variety of techniques, that aim at the distinction between effects on the limiting junction and the lateral intercellular space (LICS). It is noteworthy, however, that despite appreciation of the functional significance of such detail, most treatments of transepithelial ion transport consider only the gross physiological consequences of variation of paracellular permeability. Thus it is common to represent an epithelium by an equivalent electrical circuit that is made of discrete arrays of parallel pathways, where one or more permit transcellular active transport, and another is restricted to paracellular passive transport (Fig. 1) (see e.g. 23, 30, 32, 33, 36). With this type of model both the cellular transport mechanisms and the paracellular channels "see" only the concentrations and electrical potential differences measured in the external baths (excluding unstirred layer effects), and therefore they interact only indirectly.

Several lines of evidence suggest that for many tissues such a representation may be unrealistic. Thus, while it might have been expected that the Na^+ pump would be concentrated near the serosal surface of reabsorptive tissues and near the apical surface of secretory tissues, it has been demonstrated that in both types of tissue the Na^+ - K^+ ATPase is distributed over much of the basal-lateral surface of the epithelial cells believed responsible for transport (12, 27). Furthermore, although definitive information is lacking, it appears that there may not be free communication between the LICS and the serosal bathing solution: both theoretical and electron-microprobe analyses indicate that significant interstitial hypertonicity is possible (7, 8, 21). Wide variability in the relative resistance of the junction and the LICS has been reported in different tissues and under diverse conditions, suggesting physiological significance (2, 6, 10, 14, 17, 18, 28, 31).

The above considerations indicate the need for formal

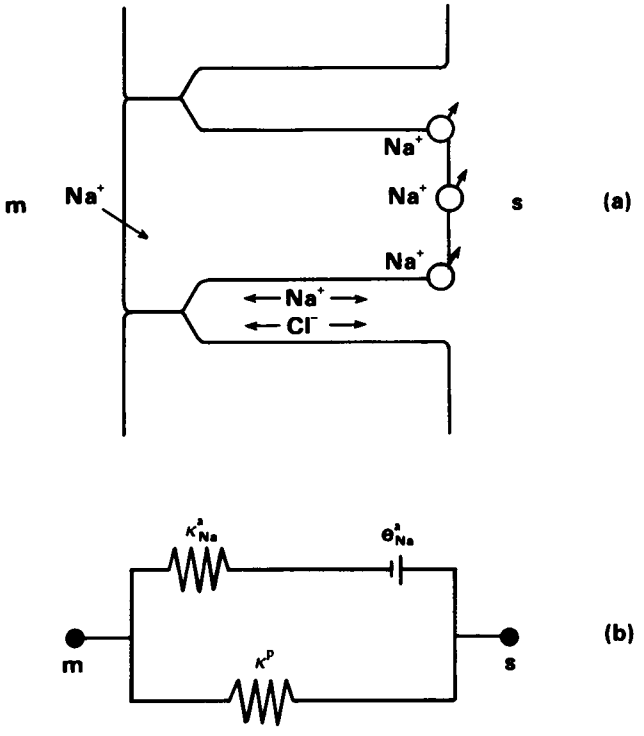

FIGURE 1 Standard representation of transepithelial Na^+ transport system. (*a*) Diagram: Na^+ moves passively out of the mucosal medium (m) down its electrochemical potential gradient into the cell at its apical surface. It is actively transported out of the cell near its basal surface, then moving freely into the serosal medium (s). Ions in the bathing solutions also cross the epithelium passively by way of a discrete paracellular pathway. (*b*) Equivalent circuit: Na^+ moves through an active transport pathway of conductance κ^a_{Na} from m to s, driven by the transepithelial electromotive force of active Na transport and negative chemical potential difference $[e^a_{Na} \equiv E^a_{Na} + (RT/F) \ln (c^m/c^s)]$, and the negative electrical potential difference $(-\Delta\psi)$. Ions from m and s also move passively through a parallel paracellular pathway of conductance κ^p.

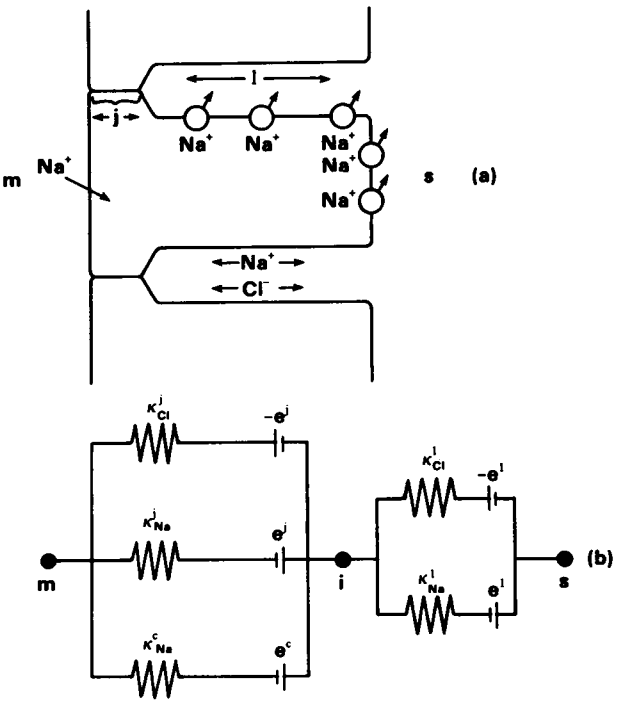

FIGURE 2 Detailed representation of transepithelial Na^+ transport system. (*a*) Diagram: Na^+ moves passively from the mucosal medium (m) down its electrochemical potential gradient into the cell at its apical surface. It is actively transported out of the cell along the entire basal-lateral surface into the interstitial region (i). It then moves either into the serosal medium (s) or back into the mucosal medium (m) in accord with the driving forces and conductances across the tight junction (j) and lateral intercellular spaces (l). Ions in the bathing solutions also cross the epithelium passively by this same paracellular pathway. (In reality, of course, Na^+ transport is highly distributed. Since the conductance of the intercellular region is presumably much lower than that of the extensive region bounding the basal surface, the point i, indicating a representative interstitial region, is placed between j and l. It is assumed that the serosal limiting membrane which separates the cell from the serosal bathing medium offers no significant barrier to ion movement.) (*b*) Equivalent circuit: Na^+ moves through the cellular active transport pathway of conductance κ^c_{Na} from m to i, driven by the transcellular electromotive force of active Na transport and negative chemical potential difference $[e^c_{Na} \equiv E^c_{Na} + (RT/F)\ln(c^m/c^i)]$, and the negative electrical potential difference $(-\Delta\psi^i)$. It may then move within the paracellular pathway, either across j into m or across l into s. Ions from m and s also move passively across the paracellular pathway.

treatments of transport systems incorporating the influence of significant paracellular permeability barriers. Ziegler (37) has discussed a model for Na transport in high-resistance epithelia in which Na is pumped across the lateral cell surface into the LICS. It is considered that under physiological conditions no significant Na transport occurs across the junction; Na^+ moves from the hypertonic LICS into the serosal compartment as a result of diffusion and/or bulk flow; the rate of Na movement is regulated by the width of the channel in the region of the desmosomes and basilar slit (37). Boulpaep and Sackin (2, 3), on the other hand, have considered the effect of distributed paracellular resistance on the evaluation of cell membrane resistance in epithelia. In their equivalent circuit analysis, they show that when the transepithelial potential is perturbed, the ratio of apical to basolateral voltage deflections differs from the corresponding ratio of membrane resistances to an extent that depends on the ratio of cellular-to-paracellular resistance and also on the ratio of junctional-to-LICS resistance.

In the present study, I have analyzed the influence of discrete cellular, junctional, and lateral interspace permeability barriers on various parameters of active transport and the associated metabolism (Fig. 2). For simplicity I have examined the case of Na^+ transport between identical NaCl solutions that is uncoupled to flows of other ions or water. In this first approach the influence of a highly distributed network is not considered. Although the resulting formulation is not quantitatively precise, it permits a systematic analysis, which can be modified for specific tissues or operating conditions.

GLOSSARY

A^c, A^a	Affinity.
c^i, c^m, c^s	NaCl concentration.
Δc	$c^s - c^m$.
e^β_α	Electromotive force.

E^c_{Na}, E^a_{Na} Electromotive force of Na-active transport system.
F Faraday constant.
I^β_α Electrical current.
I $I_{Na} + I_{Cl}$.
J^β_α Material flow.
J_r Rate of suprabasal metabolism.
L_{Na}, $L_{Na,r}$, L_r Phenomenological coefficients.
P^β_α Permeability.
q^c, q^a Degree of coupling.
R Gas constant.
R^{sp}, R^{bl}, R^c Electrical resistance.
T Absolute temperature.
z_α Ionic charge.
γ Stoichiometry J^c_{Na}/J_r of completely coupled cellular active transport mechanism.
ϵ $(J_{Na}/J_r)_{\Delta\bar{\mu}^j_{Na}=0}$
κ^β_α Partial conductance.
$\Delta\mu^\beta_{NaCl}$ Chemical potential difference.
$\Delta\bar{\mu}^\beta_\alpha$ Electrochemical potential difference.
ψ^i, ψ^m, ψ^s Electrical potential.
$\Delta\psi^\beta$ Electrical potential difference.

Superscripts i, m, and s refer to interstitial, mucosal, and serosal bathing solutions, respectively. Superscript β = j and l refer to junctional and lateral space permeability barriers, respectively; c, a, and p refer to cellular, transepithelial active (c + 1), and transepithelial passive (j + 1) pathways, respectively. Am refers to amiloride. Omission of superscript indicates net transepithelial measurement. Subscript α is Na, Cl.

The following polarity conventions are followed: potential differences are expressed with reference to the outermost of two bathing solutions; currents are considered positive in the direction from m to s (out to in).

FUNDAMENTAL RELATIONSHIPS

Forces

Because we ignore the contributions of ions other than Na^+ and Cl^-, for passive pathways $e^\beta_{Na} = e^\beta_{Cl} \equiv e^\beta$, and

$$e^j = (RT/F)\ln(c^m/c^j); \quad -\Delta\bar{\mu}^j_\alpha/F = e^j - z_\alpha\Delta\psi^j \tag{1a}$$

$$e^l = (RT/F)\ln(c^i/c^s); \quad -\Delta\bar{\mu}^l_\alpha/F = e^l - z_\alpha\Delta\psi^l \tag{1b}$$

$$e^p = (RT/F)\ln(c^m/c^s); \quad -\Delta\bar{\mu}_\alpha/F = e^p - z_\alpha\Delta\psi \tag{1c}$$

Here j, l, and p refer, respectively, to the junctional, lateral interspace, and total paracellular transepithelial permeability barrier. R, T, and F have their usual significance, and m, i, and s refer, respectively, to the mucosal, interstitial, and serosal bathing solutions. The symbols z and $\Delta\psi$ represent ionic charge and electrical potential difference and the subscript α refers to Na^+ or Cl^-.

For the transcellular and transepithelial active pathways

$$e^c_{Na} = E^c_{Na} + (RT/F)\ln(c^m/c^i) = E^c_{Na} + e^j \tag{2a}$$

and

$$e^a_{Na} = E^a_{Na} + (RT/F)\ln(c^m/c^s) = E^a_{Na} + e^p, \tag{2b}$$

where E^c_{Na} and E^a_{Na} are the electromotive force of the cellular and the transepithelial active Na^+ transport mechanism, respectively.

Flows (Currents)

$$I^\beta_\alpha \equiv z_\alpha F J^\beta_\alpha = \kappa^\beta_\alpha(e^\beta_\alpha/z_\alpha - \Delta\psi^\beta) \tag{3a}$$

where J represents material flow, and κ conductance. The superscript β refers to j, l, p, or c. For passive pathways, Eq. 3a is conveniently expressed also as

$$I^\beta_\alpha = -\kappa^\beta_\alpha\Delta\bar{\mu}^\beta_\alpha/z_\alpha F \text{ (passive)}. \tag{3b}$$

Since net Cl^- transport is assumed to be only passive and paracellular, transepithelial Cl^- current is given by

$$I_{Cl} \equiv I^p_{Cl} = I^j_{Cl} = I^l_{Cl}. \tag{4}$$

For Na^+, on the other hand, there are two components of conservative transepithelial flow I_{Na}, active and passive. Referring to these, respectively, as I^a_{Na} and I^p_{Na},

$$I_{Na} = I^a_{Na} + I^p_{Na} = I^c_{Na} + I^j_{Na} = I^l_{Na}. \tag{5}$$

(Implicit in the above relationships are the polarity conventions that I is positive in the direction from m to s; $\Delta\psi^j \equiv \Delta\psi^c - \psi^j - \psi^m$; $\Delta\psi^l = \psi^s - \psi^i$; and $\Delta\psi = \psi^s - \psi^m$.)

Conductances

Eqs. 1, 3, and 4 lead to the standard relationship for a series array for passive Cl^-, and by analogy, for passive Na^+ conductance:

$$\kappa_\alpha = \frac{\kappa^j_\alpha\kappa^l_\alpha}{\kappa^j_\alpha + \kappa^l_\alpha}. \tag{6}$$

RESULTS

Dependence of Flows and Elemental Forces on Forces Promoting Transport

It is useful first to compute net flows and elemental forces as a function of the forces $-\Delta\bar{\mu}_\alpha$ and E^c_{Na} that promote transport. Using Eqs. 1, 3–5 to relate Cl^- flows to forces, $I_{Cl} = \kappa^j_{Cl}\Delta\bar{\mu}^j_{Cl}/F = \kappa^l_{Cl}\Delta\bar{\mu}^l_{Cl}/F = \kappa^l_{Cl}(\Delta\bar{\mu}_{Cl} - \Delta\bar{\mu}^j_{Cl})/F$, so that

$$I_{Cl} = -FJ_{Cl} = \kappa_{Cl}\Delta\bar{\mu}_{Cl}/F = (\kappa^j_{Cl}\kappa^l_{Cl}\Delta\bar{\mu}_{Cl}/F)/(\kappa^j_{Cl} + \kappa^l_{Cl}) \tag{7}$$

and

$$\Delta\bar{\mu}^j_{Cl} = (\kappa^l_{Cl}\Delta\bar{\mu}_{Cl})/(\kappa^j_{Cl} + \kappa^l_{Cl}); \quad \Delta\bar{\mu}^l_{Cl} = (\kappa^j_{Cl}\Delta\bar{\mu}_{Cl})/(\kappa^j_{Cl} + \kappa^l_{Cl}). \tag{8}$$

For Na^+, from Eqs. 1, 2a, 3, and 5, $I_{Na} = \kappa^c_{Na}(E^c_{Na} - \Delta\bar{\mu}^j_{Na}/F) + \kappa^j_{Na}(-\Delta\bar{\mu}^j_{Na}/F) = \kappa^l_{Na}(-\Delta\bar{\mu}^l_{Na}/F) = \kappa^l_{Na}(-\Delta\bar{\mu}_{Na} + \Delta\bar{\mu}^j_{Na})/F$, giving

$$I_{Na} = \frac{\kappa^l_{Na}[-(\kappa^c_{Na} + \kappa^j_{Na})\Delta\bar{\mu}_{Na}/F + \kappa^c_{Na}E^c_{Na}]}{\kappa^c_{Na} + \kappa^j_{Na} + \kappa^l_{Na}} \tag{9}$$

and

$$\Delta\bar{\mu}^j_{Na} = \frac{\kappa^l_{Na}\Delta\bar{\mu}_{Na} + \kappa^c_{Na}FE^c_{Na}}{\kappa^c_{Na} + \kappa^j_{Na} + \kappa^l_{Na}}; \quad \Delta\bar{\mu}^l_{Na} = \frac{(\kappa^c_{Na} + \kappa^j_{Na})\Delta\bar{\mu}_{Na} - \kappa^c_{Na}FE^c_{Na}}{\kappa^c_{Na} + \kappa^j_{Na} + \kappa^l_{Na}}. \tag{10}$$

Adding Eqs. 8 and 10 gives the chemical potential difference of NaCl across the tight junction

$$\Delta\mu^{j}_{NaCl} = -2Fe^{j}_{\alpha} = \frac{\kappa^{l}_{Cl}\Delta\bar{\mu}_{Cl}}{\kappa^{j}_{Cl} + \kappa^{l}_{Cl}} + \frac{\kappa^{c}_{Na}FE^{c}_{Na} + \kappa^{l}_{Na}\Delta\bar{\mu}_{Na}}{\kappa^{c}_{Na} + \kappa^{j}_{Na} + \kappa^{l}_{Na}} \quad (11a)$$

and subtracting Eq. 8 from 10 gives the electrical potential difference

$$\Delta\psi^{j} = \frac{1}{2F}\left[-\frac{\kappa^{l}_{Cl}\Delta\bar{\mu}_{Cl}}{\kappa^{j}_{Cl} + \kappa^{l}_{Cl}} + \frac{\kappa^{c}_{Na}FE^{c}_{Na} + \kappa^{l}_{Na}\Delta\bar{\mu}_{Na}}{\kappa^{c}_{Na} + \kappa^{j}_{Na} + \kappa^{l}_{Na}}\right]. \quad (11b)$$

With identical bathing solutions at each surface in the absence of a transepithelial electrical potential difference (standard "short-circuit" conditions) Eqs. 11a, b reduce, respectively, to

$$\Delta\mu^{j}_{NaCl} = -2Fe^{j}_{\alpha} = \frac{\kappa^{c}_{Na}FE^{c}_{Na}}{\kappa^{c}_{Na} + \kappa^{j}_{Na} + \kappa^{l}_{Na}} > 0\ (\Delta c = 0, \Delta\psi = 0) \quad (12a)$$

and

$$\Delta\psi^{j} = 1/2\,\frac{\kappa^{c}_{Na}E^{c}_{Na}}{\kappa^{c}_{Na} + \kappa^{j}_{Na} + \kappa^{l}_{Na}} > 0\ (\Delta c = 0, \Delta\psi = 0) \quad (12b)$$

so that $-e^{j}_{\alpha} = \Delta\psi^{j}$. Referring to Eq. 1a, it is seen that under these conditions, $\Delta\bar{\mu}^{j}_{Cl} = 0$, $\Delta\bar{\mu}^{j}_{Na} > 0$, leading to backflux of actively transported Na^+ across the tight junction into the mucosal bathing solution. To determine the magnitude of such circulation it is necessary to evaluate the rates of active transepithelial and transcellular Na^+ transport.

Relationship between Transepithelial and Transcellular Active Transport

Introducing Eqs. 1, 3b, and 6 into Eq. 5 shows that the rate of transepithelial active Na^+ transport is given by

$$FI^{a}_{Na} \equiv F^2J^{a}_{Na} = -\kappa^{l}_{Na}\Delta\bar{\mu}^{l}_{Na} + \kappa^{p}_{Na}\Delta\bar{\mu}_{Na} = -\kappa^{l}_{Na}(\Delta\bar{\mu}_{Na} - \Delta\bar{\mu}^{j}_{Na}) + \left(\frac{\kappa^{j}_{Na}\kappa^{l}_{Na}}{\kappa^{j}_{Na} + \kappa^{l}_{Na}}\right)\Delta\bar{\mu}_{Na},$$

which on the introduction of Eq. 10 leads to

$$J^{a}_{Na} = \left(\frac{\kappa^{c}_{Na}\kappa^{l}_{Na}}{\kappa^{j}_{Na} + \kappa^{l}_{Na}}\right) \cdot \left[\frac{-\kappa^{l}_{Na}\Delta\bar{\mu}_{Na}/F^2 + (\kappa^{j}_{Na} + \kappa^{l}_{Na})E^{c}_{Na}/F}{\kappa^{c}_{Na} + \kappa^{j}_{Na} + \kappa^{l}_{Na}}\right]. \quad (13a)$$

For transcellular active Na^+ transport, combining Eqs. 1–3 shows that

$$FI^{c}_{Na} \equiv F^2J^{c}_{Na} = \kappa^{c}_{Na}\,(FE^{c}_{Na} - \Delta\bar{\mu}^{j}_{Na}),$$

giving with Eq. 10,

$$J^{c}_{Na} = \kappa^{c}_{Na}\left[\frac{-\kappa^{l}_{Na}\Delta\bar{\mu}_{Na}/F^2 + (\kappa^{j}_{Na} + \kappa^{l}_{Na})E^{c}_{Na}/F}{\kappa^{c}_{Na} + \kappa^{j}_{Na} + \kappa^{l}_{Na}}\right]. \quad (13b)$$

Combining Eqs. 13a and b evaluates the extent of circulation, showing that irrespective of the magnitude of $\Delta\bar{\mu}_{Na}$, transcellular Na^+ transport exceeds transepithelial active Na^+ transport in the ratio

$$J^{c}_{Na}/J^{a}_{Na} = (\kappa^{j}_{Na} + \kappa^{l}_{Na})/\kappa^{l}_{Na} = 1 + \kappa^{j}_{Na}/\kappa^{l}_{Na} = \kappa^{j}_{Na}/\kappa^{p}_{Na}. \quad (14)$$

Equivalent Circuit Parameters

Manipulation of Eq. 13a allows the evaluation of parameters of the standard equivalent circuit formulation of Fig. 1 in terms of those of the more detailed representation of Fig. 2. First, setting $\Delta\bar{\mu}_{Na} = 0$ gives the short-circuit current:

$$I^{a}_{Na} = \frac{\kappa^{c}_{Na}\kappa^{l}_{Na}E^{c}_{Na}}{\kappa^{c}_{Na} + \kappa^{j}_{Na} + \kappa^{l}_{Na}} \quad (\Delta c = 0, \Delta\psi = 0). \quad (15)$$

Perturbing $\Delta\bar{\mu}_{Na}$ gives the apparent conductance of the active pathway:

$$\kappa^{a}_{Na} = \frac{\kappa^{c}_{Na}(\kappa^{l}_{Na})^2}{(\kappa^{j}_{Na} + \kappa^{l}_{Na})\,(\kappa^{c}_{Na} + \kappa^{j}_{Na} + \kappa^{l}_{Na})}. \quad (16)$$

Setting $I^{a}_{Na} = 0$ gives the apparent electromotive force of the active transport mechanism:

$$(\Delta\bar{\mu}_{Na}/F)_{I^{a}_{Na}=0} \equiv E^{a}_{Na} = (1 + \kappa^{j}_{Na}/\kappa^{l}_{Na})E^{c}_{Na}. \quad (17)$$

Thus it is seen that, in principle, E^{a}_{Na} will exceed the electromotive force of the cellular active transport mechanism. The significance of the discrepancy remains of course to be evaluated, and could vary greatly among various epithelia.[1]

Coupling of Transport and Metabolism: Stoichiometry

A fundamental question in the analysis of transport mechanisms is the extent to which active transport and the associated metabolic driving reaction are coupled. If the linear processes considered here are completely coupled,

[1] It is to be emphasized that the values of E^{a}_{Na} discussed here are measured under steady-state conditions, when it may be presumed that the applied forces are adequate to bring I^{a}_{Na} and I^{c}_{Na} to zero. As discussed elsewhere, values of E^{a}_{Na} based on conductances evaluated from perturbations of $\Delta\psi$ for seconds or less may be significantly in error (34).

the ratio of transport and suprabasal reaction flows J^a_{Na}/J_r will be constant on variation of $\Delta\bar{\mu}_{Na}$; with incomplete uncoupling J^a_{Na}/J_r will fall sharply as $\Delta\bar{\mu}_{Na}/F$ approaches E_{Na} (static head [13, 25]). Eq. 14 shows that since J^c_{Na}/J^a_{Na} is independent of $\Delta\bar{\mu}_{Na}$, if the cellular active transport mechanism is completely coupled, the observable transepithelial active transport system will be completely coupled as well. Nevertheless, the apparent stoichiometric ratio (e.g. Na^+/O_2) will be affected by circulation. Thus if the intrinsic stoichiometry of the cellular system is $J^c_{Na}/J_r \equiv \gamma$, that of the observable system will be

$$J^a_{Na}/J_r = \frac{\gamma}{1 + \kappa^i_{Na}/\kappa^l_{Na}} \quad \text{(complete coupling)}. \tag{18}$$

On the other hand, if the cellular transport system itself is incompletely coupled, circulation will influence the dependence of J^a_{Na}/J_r on $\Delta\bar{\mu}_{Na}$. The nature of this dependence may be shown clearly by the introduction of Kedem and Caplan's dimensionless parameter q(25), the "degree of coupling" between transport and metabolism, which for the observable system is given conveniently by

$$(q^a)^2 \equiv 1 - \frac{(J_r)_{J^a_{Na}=0}}{(J_r)_{\Delta\bar{\mu}_{Na}=0}}. \tag{19a}$$

It is seen that for a completely coupled system, in which the rate of suprabasal metabolism is zero when $J^a_{Na} = 0$, $(q^a)^2 = 1$; for a completely uncoupled system, in which J_r is constant on variation of $\Delta\bar{\mu}_{Na}$ and J^a_{Na}, $q^a = 0$; general thermodynamic considerations restrict q^2 to the range of $0 \le q^2 \le 1$ (25).

It is of interest to relate the degree of coupling of the composite observable system to that of the cellular active transport mechanism:

$$(q^c)^2 \equiv 1 - \frac{(J_r)_{J^c_{Na}=0}}{(J_r)_{\Delta\bar{\mu}^i_{Na}=0}}. \tag{19b}$$

For linear systems, Eqs. 19a, b give

$$J_r = (J_r)_{\Delta\bar{\mu}_{Na}=0}\,[1 - (q^a)^2\,\Delta\bar{\mu}_{Na}/FE^a_{Na}] \tag{20a}$$

$$= (J_r)_{\Delta\bar{\mu}^i_{Na}=0}\,[1 - (q^c)^2\,\Delta\bar{\mu}^i_{Na}/FE^c_{Na}]. \tag{20b}$$

Introducing Eqs. 19b and 20b into Eq. 19a,

$$(q^a)^2 = 1 - \frac{[1 - (q^c)^2]}{1 - \dfrac{(q^c)^2(\Delta\bar{\mu}^i_{Na})_{\Delta\bar{\mu}_{Na}=0}}{FE^c_{Na}}}$$

and with Eq. 10,

$$(q^a)^2 = \frac{(q^c)^2}{1 + \left(\dfrac{\kappa^c_{Na}}{\kappa^i_{Na} + \kappa^l_{Na}}\right)[1 - (q^c)^2]}. \tag{21}$$

It is seen that for incompletely coupled systems the degree of coupling of the composite system is less than that of the cellular active transport mechanism [inasmuch as then $0 < (q^c)^2 < 1$, $(q^a)^2 < (q^c)^2$]. A possibly suprising finding is that for given q^c and κ^c_{Na}, $(q^a)^2$ is increased when κ^i_{Na} is increased. This is understandable on noting that increase of κ^i_{Na} results in decrease of $(\Delta\bar{\mu}^i_{Na})_{\Delta\bar{\mu}_{Na}=0}$ and therefore an increase of $(J_r)_{\Delta\bar{\mu}_{Na}=0}$, while not affecting $(J_r)_{J^a_{Na}=0}$ (see Eq. 19a).

In analyses of the relationship between rates of transport and metabolism it is often considered that the stoichiometry of a system is given by the ratio of flows at short circuit, $(J^a_{Na}/J_r)_{\Delta\bar{\mu}_{Na}=0}$. Eq. 21 shows, however, that in general this will not be the case. Thus, for a linear transport system,

$$J^a_{Na} = (J^a_{Na})_{\Delta\bar{\mu}_{Na}=0}\,(1 - \Delta\bar{\mu}_{Na}/FE^a_{Na}). \tag{22}$$

Introducing now Eq. 20a,

$$(J^a_{Na}/J_r) = \left(\frac{1 - \Delta\bar{\mu}_{Na}/FE^a_{Na}}{1 - (q^a)^2\,\Delta\bar{\mu}_{Na}/FE^a_{Na}}\right)(J^a_{Na}/J_r)_{\Delta\bar{\mu}_{Na}=0}, \tag{23}$$

so that in the "driving region" $(0 < \Delta\bar{\mu}_{Na} < FE^a_{Na})$, unless $(q^a)^2 = 1$, $(J^a_{Na}/J_r) < (J^a_{Na}/J_r)_{\Delta\bar{\mu}_{Na}=0}$.

Experimental Parameters at Open Circuit

It is interesting to know forces, flows, and flow ratios under physiological conditions, i.e. at open-circuit, $I = 0$. Forces may be considered under two circumstances: (*1*) with concentrations (and therefore $\Delta\mu_{NaCl}$) maintained constant, either by use of "infinite" baths or through-flow, as in the intestine or kidney; under these circumstances $J_{Na} = J_{Cl} \neq 0$, or (*2*) with the system allowed to reach static head, as in the gall bladder under nonsecretory conditions; in this case $\Delta\bar{\mu}_{Cl} = 0$ and $J_{Na} = J^a_{Na} + J^p_{Na} = J_{Cl} = 0$.

Case 1. Here the addition of Eqs. 3b and 9 gives

$$\Delta\bar{\mu}_{Na} = \frac{\kappa_{Cl}(\kappa^c_{Na} + \kappa^i_{Na} + \kappa^l_{Na})\,\Delta\mu_{NaCl} + \kappa^c_{Na}\,\kappa^l_{Na}\,FE^c_{Na}}{\kappa_{Cl}(\kappa^c_{Na} + \kappa^i_{Na} + \kappa^l_{Na}) + \kappa^l_{Na}\,(\kappa^c_{Na} + \kappa^i_{Na})} \quad (I = 0) \tag{24a}$$

and with identical bathing solutions at each surface

$$\Delta\bar{\mu}_{Na} = F\Delta\psi = \frac{\kappa^c_{Na}\,\kappa^l_{Na}\,FE^c_{Na}}{\kappa_{Cl}(\kappa^c_{Na} + \kappa^i_{Na} + \kappa^l_{Na}) + \kappa^l_{Na}\,(\kappa^c_{Na} + \kappa^i_{Na})} \quad (I = 0, \Delta c = 0). \tag{24b}$$

Case 2. In this case, from Eq. 9,

$$\Delta\bar{\mu}_{Na} = \frac{\kappa_{Na}FE^c_{Na}}{\kappa^c_{Na} + \kappa^i_{Na}} \quad (I = 0, \Delta\bar{\mu}_{Cl} = 0) \tag{25a}$$

and with Eqs. 1a–c, the chemical and electrical potentials are

$$\Delta\mu_{Na} \equiv -e = F\Delta\psi$$

$$= \frac{\kappa^c_{Na} F E^c_{Na}}{2(\kappa^c_{Na} + \kappa^j_{Na})} \quad (I = 0, \Delta\bar{\mu}_{Cl} = 0). \quad (25b)$$

For case *1*, the rate of salt transport is given by introducing Eq. 24a into Eq. 9:

$$J_{NaCl} = \kappa_{Cl}\kappa^l_{Na} \cdot \left[\frac{-(\kappa^c_{Na} + \kappa^j_{Na})\,\Delta\mu_{NaCl}/F^2 + \kappa^c_{Na}\,E^c_{Na}/F}{\kappa_{Cl}(\kappa^c_{Na} + \kappa^j_{Na} + \kappa^l_{Na}) + \kappa^l_{Na}\,(\kappa^c_{Na} + \kappa^j_{Na})}\right] \quad (I = 0) \quad (26a)$$

or with identical bathing solutions:

$$J_{NaCl} = \frac{\kappa_{Cl}\,\kappa^c_{Na}\,\kappa^l_{Na}\,E^c_{Na}/F}{\kappa_{Cl}(\kappa^c_{Na} + \kappa^j_{Na} + \kappa^l_{Na}) + \kappa^l_{Na}\,(\kappa^c_{Na} + \kappa^j_{Na})} \quad (I = 0, \Delta c = 0). \quad (26b)$$

Therefore salt reabsorption ($J_{NaCl} > 0$) will be increased by increase of κ_{Cl} or κ^l_{Na}, but (for $\Delta\mu_{NaCl} \geq 0$) decreased by increase of κ^j_{Na}. Increased passive permeability without change in permselectivity (i.e., proportionate increases in κ_{Cl}, κ^j_{Na}, and κ^l_{Na}) will increase reabsorption at $\Delta c = 0$; in the presence of a gradient, however, behavior will be more complex, depending on the magnitudes of the various conductances and forces.

Even with complete coupling, the ratio of flows J_{NaCl}/J_r at open circuit is in general a complex function of the conductances and forces, as can be seen by combining Eqs. 13b, 24a, and 26a. It is useful, however, to consider the situation with identical bathing solutions. Then $(J_{NaCl}/J_r)_{I=0,\Delta c=0}$ is given by $[(J_{NaCl})_{I=0,\Delta c=0}/(J_{Na})_{\Delta\bar{\mu}^j_{Na}=0}][(J_{Na}/J_r)_{\Delta\bar{\mu}^j_{Na}=0}][(J_r)_{\Delta\bar{\mu}^j_{Na}=0}/(J_r)_{I=0,\Delta c=0}]$. Evaluating the first ratio from Eqs. 9, 10, and 26b, denoting the second ratio by ϵ, and evaluating the third ratio from Eqs. 10, 20b, and 24b, then gives

$$J_{NaCl}/J_r = \frac{\kappa_{Cl}\,\kappa^l_{Na}\,\epsilon}{\kappa_{Cl}[\kappa^c_{Na}[1 - (q^c)^2] + \kappa^j_{Na} + \kappa^l_{Na}] + \kappa^l_{Na}[\kappa^c_{Na}[1 - (q^c)^2] + \kappa^j_{Na}]} \quad (I = 0, \Delta c = 0). \quad (27)$$

Since $[1 - (q^c)^2] \geq 0$, it is seen that the rate of net salt reabsorption per unit rate of suprabasal metabolism will be increased by increase of κ_{Cl} or κ^l_{Na}, and decreased by increase of κ^j_{Na}, as would be anticipated. Also noteworthy is the fact that increasing κ^j_{Na} or κ^l_{Na}, each of which has the same effect on q^a (see Eq. 21), has opposing influences on open circuit J_{NaCl} and J_{NaCl}/J_r. Therefore, whereas for maximal effectiveness of salt reabsorption it is desirable that $(q^c)^2$ be as large as possible, the same is not true for $(q^a)^2$, the corresponding parameter of the transepithelial active transport system.

Free Energy of the Metabolic Driving Reaction

A complete formal characterization of transport and metabolism requires, in addition to the above formulation, the specification of the dependence of flows on the free energy of the metabolic reaction driving transport. Assuming, as above, linear dependencies of flows on forces gives the general linear nonequilibrium thermodynamic representation:

$$J^a_{Na} = L_{Na}(-\Delta\bar{\mu}_{Na}) + L_{Na,r}A^a \quad (28)$$

$$J_r = L_{Na,r}(-\Delta\bar{\mu}_{Na}) + L_r A^a. \quad (29)$$

Here A^a is the affinity (or under usual experimental conditions the negative Gibbs free-energy change) of the metabolic driving reaction, and the L are phenomenological (kinetic) coefficients; incorporating the Onsager reciprocal relation, the cross-coefficients are considered equal (5, 13).

Assuming the validity of Eqs. 28 and 29, attempts have been made to determine A^a by nondestructive means by measurements of transport and metabolism (5). Thus, for the composite epithelial system, assuming constancy of A^a on brief perturbation of $\Delta\psi$,

$$A^a = -(J^a_{Na})_{\Delta\bar{\mu}_{Na}=0}/[dJ_r/d(F\Delta\psi)] \; (\Delta c = 0). \quad (30)$$

Interest in A^a derives from the fact that in principle it appears to represent a pure energetic factor, in contrast to E^a_{Na}, which includes kinetic components as well (5). Accordingly, it is pertinent to question the accuracy with which the application of Eq. 30 to the present model will evaluate A^c, the affinity of the cellular active transport mechanism:

$$A^c = -(J^c_{Na})_{\Delta\bar{\mu}^j_{Na}=0}/[dJ_r/d(\Delta\bar{\mu}^j_{Na})]. \quad (31)$$

Dividing Eq. 30 by 31,

$$A^a/A^c = \left[\frac{(J^a_{Na})_{\Delta\bar{\mu}_{Na}=0}}{(J^c_{Na})_{\Delta\bar{\mu}^j_{Na}=0}}\right] \Big/ \left[\frac{d(\Delta\bar{\mu}^j_{Na})}{d(F\Delta\psi)}\right].$$

Evaluating the numerator of this expression from Eqs. 2, 3a, and 15, and the denominator by differentiation of Eq. 10 shows that $A^a/A^c = 1$. Therefore, in contrast to the case for evaluation of E^c_{Na}, the evaluation of the affinity of the cellular active transport mechanism is given directly by manipulations of the intact composite system, being unaffected by the histological features of the epithelial transport system under consideration.

Dependence of Passive Conductance on Parameters of Active Transport

The analysis of active transport by means of either a thermodynamic or voltage-source equivalent circuit formulation requires evaluation of the rate of transepithelial active transport and the conductance of the active pathway. Usually this necessitates calculation of the contribution of passive current to total current flow. Often this is done by measuring I both in the absence and presence of amiloride, under the assumption that when active transport is abolished the residual conductance κ^p represents that normally referable to the paracellular pathway (23, 24, 26). Gordon (20) has recently suggested, however, that in association with its depression of the rate of active transport amiloride depresses the concentration of salt in the paracellular pathway, so that the passive conductance measured in the presence of amiloride must be less than that obtaining in its absence. It is of interest to examine the implications of this possibility quantitatively in terms of the present formulation.

For this purpose it is convenient to begin with the Goldman relationship, assuming a constant electrical field in both the junctional and lateral space permeability barriers (19, 22). (It is not assumed that the fields in regions j and l are equal.) For solutions of NaCl Hodgkin and Katz's Eq. 3.0 (22) becomes

$$I^\beta = \frac{-F^2\,\Delta\psi^\beta}{RT} \cdot \left[\frac{P^\beta_{Na}\,c' + P^\beta_{Cl}\,c'' - (P_{Na}\,c'' + P_{Cl}\,c')\exp(F\Delta\psi^\beta/RT)}{1 - \exp(F\Delta\psi^\beta/RT)}\right], \tag{32}$$

where $'$ and $''$ refer to outer and inner baths, respectively. Thus, in general, I^p shows a complex dependence on $\Delta\psi$. However, in a study of the kinetics of isotope flows of passive pathways of the toad urinary bladder it was found that $P_{Cl}/P_{Na} = 1.02$ (29). We shall consider therefore that $P_{Na} \simeq P_{Cl} \equiv P$, $P^j_{Na} = P^j_{Cl} \equiv P^j$ and $P^l_{Na} = P^l_{Cl} \equiv P^l$. In this case Eq. 32 reduces to

$$I^\beta = -\frac{F^2\Delta\psi^\beta P^\beta}{RT}(c' + c'') \tag{33}$$

so that

$$\kappa^j = \frac{F^2P^j}{RT}(c^m + c^i) \tag{34a}$$

and

$$\kappa^l = \frac{F^2P^l}{RT}(c^i + c^s). \tag{34b}$$

Restricting our consideration to the case where $c^m = c^s = c$, we have then with Eqs. 1a and 6, writing P for $P^jP^l/(P^j + P^l)$,

$$\kappa^p = \frac{F^2}{RT}\left(\frac{P^jP^l}{P^j + P^l}\right)(c + c^i) = \frac{F^2Pc}{2\,RT}\left[1 + \exp\left(\frac{-Fe^j}{RT}\right)\right] \tag{35}$$

and with Eq. 11a

$$\kappa^p = \frac{F^2Pc}{2RT}\left\{1 + \exp\left[\frac{F}{2RT}\left(\frac{\kappa^c_{Na}}{\kappa^c_{Na} + \kappa^j_{Na} + \kappa^l_{Na}}\right) \cdot \left(E^c_{Na} - \frac{\Delta\psi}{1 + \kappa^j_{Na}/\kappa^l_{Na}}\right)\right]\right\} \qquad (\Delta c = 0). \tag{36}$$

Since, in the presence of a sufficiently high concentration of amiloride $\kappa^c_{Na} \simeq 0$,

$$\kappa^{p,Am} = F^2Pc/RT \qquad (\Delta c = 0). \tag{37}$$

Therefore, assuming no effect of amiloride on tissue structure (and therefore P) the ratio of the passive conductance in the absence and presence of amiloride (in Gordon's terms, G_p/G^a_p) is given by

$$\kappa^p/\kappa^{p,Am} = 1/2\,[1 + \exp(-Fe^j/RT)] = 1/2\left\{1 + \exp\left[\frac{F}{2RT}\left(\frac{\kappa^c_{Na}}{\kappa^c_{Na} + \kappa^j_{Na} + \kappa^l_{Na}}\right) \cdot \left(E^c_{Na} - \frac{\Delta\psi}{1 + \kappa^j_{Na}/\kappa^l_{Na}}\right)\right]\right\} \qquad (\Delta c = 0). \tag{38}$$

so that in general κ^p will differ from $\kappa^{p,Am}$, to an extent influenced by $\Delta\psi$. However, if either κ^j_{Na} or κ^l is large relative to κ^c_{Na}, the discrepancy between κ^p and $\kappa^{p,Am}$ will be small (i.e., $\kappa^p/\kappa^{p,Am} \simeq 1$) and if κ^j_{Na} is large relative to κ^l_{Na}, the influence of $\Delta\psi$ will be slight.

Plasma Membrane Resistance Ratio

A quantity of fundamental interest in the analysis of cellular transport is the fraction of cellular resistance attributable to each of the two limiting plasma membranes. This is usually evaluated from the voltage divider ratio, measured with an intracellular microelectrode on brief perturbation of the transepithelial potential difference $\Delta\psi$. Thus for a cellular resistance $R^c \equiv R^{ap} + R^{bl}$, where R^{ap} and R^{bl} refer to the apical and basolateral plasma membrane resistances, respectively, if the resistance of the LICS is insignificant (so that $\Delta\psi^j = \Delta\psi$),

$$\frac{R^{ap}}{R^{bl}} \equiv \frac{\kappa^{bl}}{\kappa^{ap}} = \frac{\delta\Delta\psi^{ap}/\delta\Delta\psi}{1 - \delta\Delta\psi^{ap}/\delta\Delta\psi} \tag{39}$$

and the fractional resistance of the outer membrane is given by

$$\frac{R^{ap}}{R^{c}} = \frac{\delta\Delta\psi^{ap}}{\delta\Delta\psi}. \tag{40}$$

As pointed out by Boulpaep and Sackin (3,4), however, if the lateral interspace contributes significantly to the paracellular resistance (in which case $\Delta\psi^{j} \neq \Delta\psi$) the ratio of apical to basolateral resistance is not given by the apparent ratio of apical to basolateral voltage deflections (3, 4).

For the present model, for the case of identical solutions at each surface the relationships between the resistance ratios and $\delta\Delta\psi^{ap}/\delta\Delta\psi$ are readily obtained. Since $\Delta\psi^{j} \equiv \Delta\psi^{ap} + \Delta\psi^{bl}$,

$$\frac{\delta\Delta\psi^{bl}}{\delta\Delta\psi^{j}} = 1 - \frac{\delta\Delta\psi^{ap}}{\delta\Delta\psi^{j}},$$

so that

$$\frac{R^{ap}}{R^{bl}} = \frac{\delta\Delta\psi^{ap}}{\delta\Delta\psi^{bl}} = \frac{\delta\Delta\psi^{ap}/\delta\Delta\psi^{j}}{1 - \delta\Delta\psi^{ap}/\delta\Delta\psi^{j}}. \tag{41}$$

Introducing now the identity $\delta\Delta\psi^{ap}/\delta\Delta\psi^{j} \equiv (\delta\Delta\psi^{ap}/\delta\Delta\psi)/(\delta\Delta\psi^{j}/\delta\Delta\psi)$, and evaluating the denominator of this expression by differentiation of Eq. 11b,

$$\frac{R^{ap}}{R^{bl}} \equiv \frac{\kappa^{bl}}{\kappa^{ap}} = \frac{\delta\Delta\psi^{ap}/\delta\Delta\psi}{\left[\frac{1}{2}\left(\frac{1}{1 + \kappa^{j}/\kappa^{l}} + \frac{1}{1 + \kappa^{c}/\kappa^{l} + \kappa^{j}/\kappa^{l}}\right) - \delta\Delta\psi^{ap}/\delta\Delta\psi\right]} \tag{42}$$

and

$$\frac{R^{ap}}{R^{c}} = \frac{2\delta\Delta\psi^{ap}/\delta\Delta\psi}{\frac{1}{1 + \kappa^{j}/\kappa^{l}} + \frac{1}{1 + \kappa^{c}/\kappa^{l} + \kappa^{j}/\kappa^{l}}}. \tag{43}$$

It will be noted that if both κ^{c} and κ^{j} are small relative to κ^{l}, Eq. 42 becomes equivalent to Eq. 39 and Eq. 43 becomes equivalent to Eq. 40. Otherwise, however, the plasma membrane resistance ratio cannot be derived accurately from the voltage-divider ratio without knowledge of the relative magnitudes of both cellular and paracellular conductances.

DISCUSSION

The above analysis demonstrates that paracellular parameters may have an important influence on several aspects of transepithelial transport and metabolism. An intuitive understanding of the basis of this influence is afforded by examination of Eqs. 11a and b, noting first how the cellular and paracellular conductances affect the environment of the pump. With the κ^{l}_{α} large relative to the κ^{j}_{α} and κ^{c}_{Na}, $\Delta\mu^{j}_{NaCl} \simeq \Delta\mu_{NaCl}$ and $\Delta\psi^{j} \simeq \Delta\psi$, so that conditions at the basal lateral surface are the same as in the serosal bathing solution, as is commonly assumed, and transepithelial and transcellular transport and equivalent circuit parameters are identical (see e.g. Eqs. 14, 16, and 17). Otherwise, however, conditions in the LICS and serosal bath will differ and salt will leak across the junction. Transcellular J^{c}_{Na} then exceeds transepithelial J^{a}_{Na} in accord with the magnitude of $\kappa^{j}_{Na}/\kappa^{l}_{Na}$ (Eq. 14), and the cellular and epithelial equivalent circuit parameters differ, with $\kappa^{c}_{Na} > \kappa^{a}_{Na}$ (Eq. 16) and $E^{c}_{Na} < E^{a}_{Na}$ (Eq. 17). Similarly with respect to quantities more explicitly dependent on metabolism, the intrinsic stoichiometry of transport and metabolism γ will exceed the apparent stoichiometry J^{a}_{Na}/J_{r} to an extent proportional to $\kappa^{j}_{Na}/\kappa^{l}_{Na}$ (Eq. 18), and if coupling is incomplete, $|q^{c}|$ will exceed $|q^{a}|$ (Eq. 21).

The magnitude of transepithelial forces and flows at open circuit, the physiological condition, is influenced by similar considerations. Thus both the rate J_{NaCl} and the efficacy J_{NaCl}/J_{r} of salt transport (13) are enhanced by increase of κ_{Cl} or κ^{l}_{Na}, but depressed by increase of κ^{j}_{Na} (Eqs. 26b and 27). With identical bathing solutions, an increase of paracellular conductance, as might result from a generalized dilatation without change of permselectivity, would increase both transport and efficacy; with transepithelial concentration gradients function becomes more complex.

Of special interest is the observation that even under circumstances in which standard equivalent circuit analysis will significantly overestimate E^{c}_{Na} (Eq. 17), the affinity A^{a} evaluated by thermodynamic analysis of the intact composite system equals the affinity of the cellular active transport mechanism, A^{c}. This is consistent with the consideration that whereas the affinity is an energetic parameter, the electromotive force of Na^{+} transport incorporates kinetic factors as well (5).

Although our model greatly oversimplifies the biological system, it facilitates intuitive understanding of the influence of the cellular and paracellular conductances on the several functions under consideration. This may be appreciated by comparing functions of the transepithelial active pathways and the cellular pathways under certain limiting conditions. This is done in Table I for a loose epithelium (κ^{j}_{Na} and $\kappa^{l}_{Na} \gg \kappa^{c}_{Na}$) in the absence ($\kappa^{j}_{Na} \ll \kappa^{l}_{Na}$) and presence ($\kappa^{l}_{Na} < \kappa^{j}_{Na}$) of circulation, and for a tight epithelium (κ^{j}_{Na} or $\kappa^{l}_{Na} \ll \kappa^{c}_{Na}$), again in the absence ($\kappa^{j}_{Na} \ll \kappa^{l}_{Na} \sim \kappa^{c}_{Na}$) and presence ($\kappa^{l}_{Na} \ll \kappa^{j}_{Na} \sim \kappa^{c}_{Na}$) of circulation. As is seen, the relationships vary greatly. While it is not possible to make detailed predictions a priori, it is evident that physiological and pathological changes in cellular and paracellular configuration (e.g. narrowing or widening of the junction, changes of paracellular tortuosity, or basolateral amplification) could influence function by effects on either tissue tightness or circulation. To the extent that change in basolateral membrane surface area is associated

TABLE I
EFFECTS OF CONDUCTANCE PATTERNS ON TISSUE FUNCTIONS

Equation	Function	Loose epithelium		Tight epithelium	
		$\kappa^{j}_{Na} \ll \kappa^{l}_{Na}$	$\kappa^{l}_{Na} \ll \kappa^{j}_{Na}$	$\kappa^{j}_{Na} \ll \kappa^{l}_{Na} \sim \kappa^{c}_{Na}$	$\kappa^{l}_{Na} \ll \kappa^{j}_{Na} \sim \kappa^{c}_{Na}$
11a	$\Delta\mu^{j}_{NaCl}$	~0	~0	$\sim F(E^{c}_{Na} - \Delta\psi)/2$	$\sim FE^{c}_{Na}/2$
14	J^{a}_{Na}/J^{c}_{Na}	~1	<1/2	~1	~0
16	$\kappa^{a}_{Na}/\kappa^{c}_{Na}$	~1	<1/4	~1/2	~0
17	E^{a}_{Na}/E^{c}_{Na}	~1	>2	~1	$\sim\kappa^{l}_{Na}/\kappa^{j}_{Na}$
18	$(J^{a}_{Na}/J_{r})/\gamma$	~1	<1/2	~1	0
21	$(q^{a})^2/(q^{c})^2$	~1	~1	1/2 – 1	1/2 – 1
43	$(\delta\Delta\psi^{ap}/\delta\Delta\psi)/(R^{ap}/R^{c})$	~1	$<\kappa^{l}_{Na}/\kappa^{j}_{Na}$	~3/4	$\sim(3/4)(\kappa^{l}_{Na}/\kappa^{j}_{Na})$

Tissues are exposed to identical NaCl solutions at the two surfaces. In loose epithelia, κ^{j}_{Na} and $\kappa^{l}_{Na} \gg \kappa^{c}_{Na}$, whereas in tight epithelia, κ^{j}_{Na} or $\kappa^{l}_{Na} \ll \kappa^{c}_{Na}$. Circulation will be relatively limited if $\kappa^{j}_{Na} \ll \kappa^{l}_{Na}$, but significant if $\kappa^{l}_{Na} < \kappa^{j}_{Na}$.

with change in the number of pump sites, it would influence not only LICS tortuosity, and thus κ^{l}_{Na}, but κ^{c}_{Na} as well.

Because the present treatment predicts large functional differences under varied circumstances it is necessary to ask to what extent the model is realistic. Clearly the formulation is inapplicable to systems in which electroneutral NaCl transport or other coupled flows are important (15). The situation is less clear when, in the absence of coupled flows, ionic active transport is attributable predominantly but not solely to Na^+: to the extent that other ionic flows contribute to transcellular current the treatment will of course be inexact. A well documented example is the recent study of Biber et al. (1) in frog skins (*Rana pipiens*). In these tissues, although unidirectional Cl^- fluxes with identical (115 mM) external and internal Cl^- concentrations were large, net Cl^- flux averaged only some 0.10 μeq/cm^2 h (Table I), as compared with a mean short circuit current of 1.36 μeq/cm^2 h. Thus in this case the error does not seem inordinate. However, analysis of ionic transport patterns and paracellular conductance profiles in different tissues under varied conditions will be required for full evaluation of the relevance of the present model.

Clearly the calculations of Table I are crude and cannot be considered to have quantitative significance. More precise analysis must await much more detailed knowledge of tissue structure, composition, and transport parameters than is presently at hand. Of particular importance is the distribution and strength of the Na^+ pumps, and the nature of the interaction between salt and water flow. If and when such information becomes available it should be possible to formulate appropriate highly distributed equivalent circuits permitting the prediction and correlation of tissue functions under diverse circumstances. While the mathematical analysis of such systems will necessarily be complex, it should be practical, given the availability of powerful computer simulation techniques for the treatment of multicompartment systems (see e.g. 35).

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