LETTER TO THE EDITOR

[Brief letters to the Editor that make specific scientific reference to papers published previously in THE JOURNAL OF GENERAL PHYSIOLOGY are invited. Receipt of such letters will be acknowledged, and those containing pertinent scientific comments and scientific criticisms will be published.]

Electrical Potential Differences and Electromotive Forces in Epithelial Tissues

Dear Sir:

Studies on intracellular electrical potentials in a variety of epithelial tissues which are involved in transmural Na transport have resulted in an apparent dichotomy. In tissues characterized by high transmural resistances such as isolated frog skin (1, 2), toad skin (3), and toad urinary bladder (4), the cell interior is electrically *positive* with respect to the outer or mucosal solution; the electrical potential profile across these tissues consists of two or more steps in the *same* direction that sum to give the total transmural potential difference (PD). In contrast, low resistance tissues such as rabbit ileum (5), bullfrog small intestine (6), rat colon (7), and renal tubular epithelium (8) are characterized by intracellular potentials that are electrically *negative* with respect to the mucosal solution; the electrical potential profile across these tissues consists of two steps in *opposite* directions that sum to give the transmural PD. These two types of profiles are illustrated in Fig. 1 using data obtained on frog skin (2) (Fig. 1 *a*) and rabbit ileum (5) (Fig. 1 *b*).

All of the tissues mentioned above are engaged in active Na transport from the mucosal (outer) to the serosal (inner) solution and share other similarities with respect to ion transport and intracellular ion composition. Thus, it is reasonable to inquire whether the differences in electrical potential profile *necessarily* reflect fundamentally different properties of the *transporting cells*. In particular, do these different profiles *necessarily* imply that the electromotive forces across the mucosal or outer membranes of high resistance epithelia are oriented in a direction opposite to those characteristic of low resistance epithelia? An analysis of the equivalent electrical circuit model illustrated in Fig. 2 provides an answer to this question.

In this circuit, E_m designates an electromotive force operating across the mucosal or outer membrane, R_1 is the internal resistance of this battery, and R_2 is a shunt resistance across this membrane. E_s, R_3, and R_4 are the respective parameters for the serosal or inner membrane. R_5 designates the resistance of a transepithelial, extracellular shunt; m, c, and s represent the mucosal, intracellular, and serosal electrodes. All electrical potential differences are given with reference to the potential of the mucosal solution which is taken as zero. The solutions of this circuit for the electrical PD across the mucosal membrane (Ψ_{mc}) and the transmural PD (Ψ_{ms}) are:

$$\Psi_{mc} = [(R_3R_s + R_5)E_mR_m - R_1R_mE_sR_s]/R_t \qquad (1)$$

and

$$\Psi_{ms} = R_5(E_sR_s + E_mR_m)/R_t \tag{2}$$

where

$$R_m = R_2/(R_1 + R_2),$$
$$R_s = R_4/(R_3 + R_4),$$

and

$$R_t = R_1R_m + R_3R_s + R_5 .$$

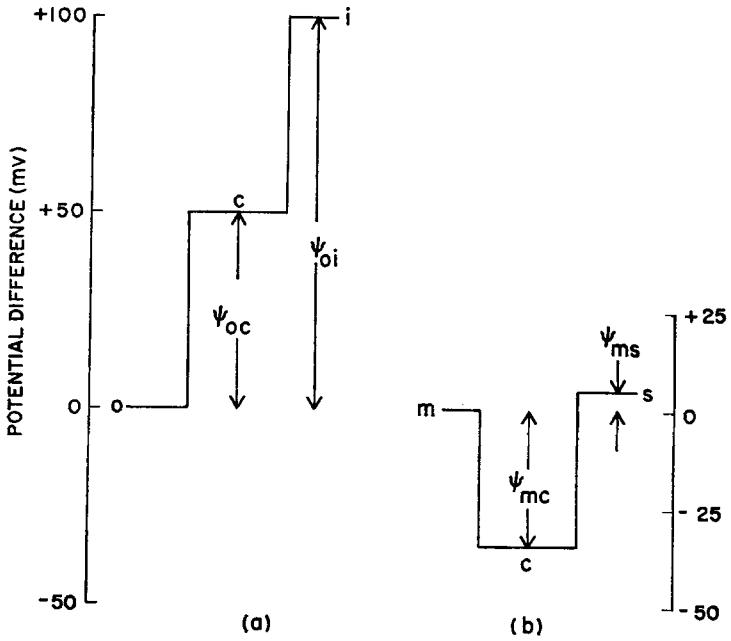

FIGURE 1. (*a*) Electrical potential profile across isolated frog skin; *o*, *c*, and *i* designate the outer solution, intracellular compartment, and inner solution, respectively. (*b*) Electrical potential profile across isolated rabbit ileum; *m*, *c*, and *s* designate the mucosal solution, intracellular compartment, and serosal solution, respectively.

These solutions take into account *the orientations of the electromotive forces as illustrated in Fig. 2.* Thus, a positive value for E_mR_m or E_sR_s indicates that the batteries are oriented as shown; a negative value indicates the reverse orientation. It should be noted that E_m is oriented in the same direction as E_s, and *opposite* to the direction previously suggested for several low resistance epithelia (5, 6, 8).

Clearly, only when the resistance of the extracellular pathway is much greater than that of the transcellular pathway [i.e. $R_5 \gg (R_1R_m + R_3R_s)$ or $R_5/R_t \cong 1$],

$$\Psi_{mc} \cong E_mR_m \tag{3}$$

and

$$\Psi_{ms} \cong E_sR_s + E_mR_m . \tag{4}$$

Ussing and Windhager (1) have shown that the shunt resistance across isolated frog skin, bathed by a sulfate-Ringer solution, is much greater than the total skin resistance, so that the relations given by equations 3 and 4 obtain.[1] Thus, using the illustrative data given in Fig. 1 *a*, for frog skin $E_mR_m = 50$ mv and $E_sR_s = 50$ mv.

We now inquire whether *these* electromotive forces could satisfy the electrical potential profile typical of low resistance tissues as exemplified by rabbit ileum (5) (Fig. 1 *b*) where $\Psi_{mc} = -35$ mv and $\Psi_{ms} = 5$ mv. Substituting these values into equations 1 and 2, we find that the electromotive forces derived from studies on frog skin will generate the electrical potential profile illustrated by Fig. 1 *b* when $R_5/R_t = 0.05$ and $R_3R_s = 0.20\ R_1R_m$. Stated in another way, under these conditions, the potential profile illustrated in Fig. 1 *b* is entirely consistent with an equivalent electrical circuit in which E_m is oriented in the same direction as E_s and opposite to the direction generally illustrated for low resistance epithelia (5, 6, 8). Studies on rabbit ileum have provided direct evidence for the presence of low resistance transmural shunts and a maximum value for R_5/R_t of 0.15 has been established (9); values as low as 0.1 or below have not been excluded. In addition, compelling evidence for low

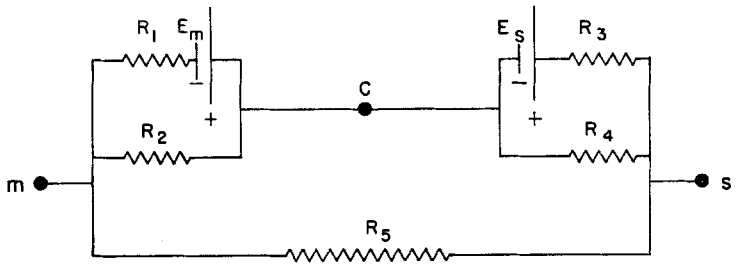

FIGURE 2. Equivalent electrical circuit model.

resistance shunt pathways, where values for R_5/R_t probably do not exceed 0.1, has been presented for proximal renal tubular epithelium (8, 10, 11).

It should be stressed that the ability of E_sR_s to affect Ψ_{mc} and, under some circumstances, to result in a polarity opposite to that of E_mR_m, is absolutely dependent on the presence of a finite shunt pathway (i.e., $R_5 < \infty$); in the absence of electrical coupling between E_m and E_s, the transmembrane electrical potential difference will *always* reflect the orientation of the electromotive force across the membrane. In the presence of a low resistance shunt ($R_5/R_t \cong 0$), the relation between R_1R_m and R_3R_s simply defines the *minimal* magnitude of E_sR_s needed to reverse the influence of E_mR_m on Ψ_{mc}. Thus, in general, when the electromotive forces are oriented as shown in Fig. 2,

$$\Psi_{mc} < 0 \text{ when } E_sR_s > [(R_3R_s + R_5)/R_1R_m]E_mR_m \tag{5}$$

and

$$\Psi_{mc} > 0 \text{ when } E_sR_s < [(R_3R_s + R_5)/R_1R_m]E_mR_m\,. \tag{6}$$

[1] According to Ussing and Windhager (1), $R_5 = 24{,}000$ ohm cm^2 when the total transepithelial resistance was 3300 ohm cm^2. Thus, $(R_1R_m + R_3R_s) = 3800$ ohm cm^2 and $R_5/R_t = 0.86$.

Clearly, when $R_5 = \infty$, $\Psi_{mc} \geq 0$. Further, the transition from $\Psi_{mc} > 0$ (Fig. 1 *a*) to $\Psi_{mc} < 0$ (Fig. 1 *b*) can result entirely from a decrease in R_5, all other parameters remaining constant.

This analysis derives qualitative support from the results of studies of the electrical potential profile across high resistance epithelial tissues under short-circuit conditions. When isolated frog skin (2), toad skin (3), or toad urinary bladder (4) is short-circuited by the application of an external transepithelial current, the intracellular potential becomes negative with respect to the outer (or mucosal) solution, a polarity opposite to that observed under open-circuit conditions. Further, this reversal in polarity is observed immediately following the application of the short-circuit current (2, 4), so that it cannot reasonably be attributed to significant alterations in intracellular ionic concentrations. Clearly, the short-circuit condition is electrically analogous to the condition in which $R_5 = 0$. Thus, the simple expedient of "inserting" a high conductance pathway across a high resistance tissue transforms the electrical potential profile from that illustrated by Fig. 1 *a* to one that resembles that illustrated by Fig. 1 *b*; a reorientation of the electromotive force across the outer or mucosal membrane need not be invoked.[2] It follows that the finding that the intracellular electrical potential in low resistance tissues is negative with respect to the mucosal solution *may be* a consequence of the fact that these tissues are, to a large extent, "self short-circuited" by the presence of high-conductance extracellular transepithelial shunt pathways.

In summary: (*a*) in the presence of transmural low resistance shunts, transmembrane electrical potential differences need not reflect the *magnitude* or the *direction* of the electromotive force operating across the membrane. Current flow through the shunt permits electrical coupling between electromotive forces across opposing boundaries (11). Thus, the magnitude and orientation of Ψ_{mc} in low resistance tissues do not provide grounds for deductions regarding the relative ionic permeabilities, etc., across the mucosal membrane. (*b*) The markedly different electrical potential profiles illustrated in Fig. 1 *need* not reflect fundamental differences with respect to the conductive properties of the outer or mucosal membranes of the epithelial cells but may be, in part or entirely, attributable to differences in the conductive properties of extracellular pathways; the electromotive force across the mucosal or luminal membrane of low resistance tissues *may be* oriented in the same direction that appears to obtain in the high resistance tissues cited above.

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[2] Cereijido and Curran (2) found that under open-circuit conditions, Ψ_{mc} was much greater in skins bathed by sulfate Ringer (+66 mv) than in skins bathed by chloride Ringer (+36 mv); however, under short-dircuit conditions, Ψ_{mc} was independent of the nature of the anion (−18 mv). Further, Ussing and Windhager (1) found that the five- to eightfold decrease in the shunt resistance across frog skin brought about by the presence of hypertonic urea-sulfate-Ringer in the outer solution resulted in a reversal of the electrical polarity of Ψ_{mc} under open-circuit conditions; the addition of urea to the outer solution resulted in a marked reduction in R_5 and concomitantly transformed the electrical potential profile from that illustrated in Fig. 1 *a* to that illustrated in Fig. 1 *b*. These observations are consistent with the predictions of equations 5 and 6.

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