J. Membrane Biol. 110, 139–146 (1989)

The Journal of
Membrane Biology

Effect of K^+ Channels in the Apical Plasma Membrane on Epithelial Secretion Based on Secondary Active Cl^- Transport

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Summary. Models of epithelial salt secretion, involving secondary active transport of Cl^- [9], locate the K^+ conductance of the plasma membrane exclusively in the basolateral membrane, although there is considerable experimental evidence to show that many secretory epithelia do have a significant apical K^+ conductance. We have used an equivalent circuit model to examine the effect of an apical K^+ conductance on the composition and flow rate of the fluid secreted by an epithelium in which secretion is driven by the secondary active transport of Cl^-. The parameters of the model were chosen to be similar to those measured in the dog tracheal mucosa when stimulated with adrenaline to secrete. We find that placing a K^+ conductance in the apical membrane can actually enhance secretion provided the proportion of the total cell K^+ conductance in the apical membrane is not greater than about 60%, the enabling effect on secretion being maximal when the proportion is around 10–20%. We also find that even when the entire cell K^+ conductance is located in the apical membrane, the secreted fluid remains relatively Na^+ rich. Analysis of the sensitivity of model behavior to the choice of values for the parameters shows that the effects of an apical K^+ conductance are enhanced by increasing the ratio of the paracellular resistance to the transcellular resistance.

Key Words epithelial secretion · potassium conductance · apical membranes · basolateral membranes · secondary active chloride secretion · equivalent circuits

Introduction

The model proposed by Silva et al. [9] to account for the secretion of electrolytes by the shark rectal gland has been successfully used to explain secretion by a wide range of epithelia (tracheal mucosa [14], salivary glands [6, 7], and lacrimal glands [11]). As shown in Fig. 1*a*, this model uses secondary active transport by a Na^+-K^+-$2Cl^-$ cotransporter to maintain the cytosolic Cl^- concentration above electrochemical equilibrium and thereby provides the driving force by which Cl^- can flow into the lumen through anion-selective channels in the apical membrane. This movement of negative charge into the lumen is balanced by the movement of Na^+ (and K^+) into the lumen from the interstitium through the tight junctions. The K^+ brought into the cell by the activity of the Na^+, K^+-ATPase and the Na^+-K^+-$2Cl^-$ cotransporter leaves the cell through K^+ channels in the basolateral membrane. In this model, secretion is thus due to an intraepithelial loop current that is carried by Cl^- ions across the apical membrane, by Na^+ (and K^+) ions across the tight junctions, and partly by K^+ ions (83%) and partly by the current of the Na^+, K^+-ATPase (17%) across the basolateral membrane. The equivalent circuit of this secretion model (Fig. 1*b*) makes clear that the driving force for the loop current, and hence the driving force for secretion, is equal to the difference between the Nernst potentials for Cl^- across the apical membrane and for K^+ across the basolateral membrane, provided that one may neglect the contribution of the Na^+, K^+-ATPase to the basolateral emf.

The model proposed by Silva et al. [9] does not allow for any component of secretion to be driven by movement of K^+ into the lumen across the apical membrane. Indeed, it is usually assumed that a significant apical K^+ conductance would actually impair the efficiency of the secretion mechanism by reducing the driving force for the intraepithelial loop current. This is by analogy with the thick ascending limb of the loop of Henle, an absorptive epithelium in which transport relies on an intraepithelial loop current, where the presence of basolateral K^+ channels has been ruled out because of the detrimental effect they would have on the intraepithelial loop current [3]. An additional objection that has been raised to the presence of apical membrane K^+ channels in secretory epithelia is that they would lead to formation of a K^+-rich primary fluid unless exchange of Na^+ for K^+ across the tight junctions is extremely effective.

Nevertheless, there is considerable experimental evidence to suggest that the apical membranes of

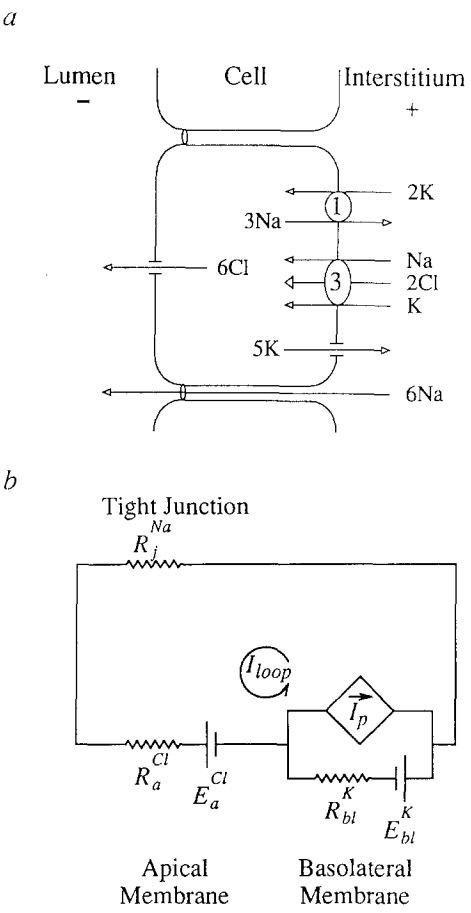


Fig. 1. (*a*) Standard model for secretion by secondary active Cl^- transport. (*b*) Equivalent circuit of the model (for definition of the symbols used, *see* text). In this model, there is no Na^+ battery in series with the Na^+ resistance of the tight junction because the interstitial and luminal Na^+ concentrations are identical. The current of the Na^+, K^+-ATPase, I_p, which is shown in parallel with the basolateral K^+ battery and resistance, is ignored by most authors because, as is discussed in the text, its contribution to the driving force for Cl^- secretion is only about 2%

many secretory epithelia do have a significant permeability to K^+.

(i) In canine tracheal mucosa, which has been shown to secrete K^+ at rest, and in which the rate of K^+ secretion can be enhanced by application of adrenaline [12] or barium [10] to the basolateral membrane, the apical membrane has been shown to have a measurable K^+ permeability [8].
(ii) The primary fluids of most exocrine glands so far studied in micropuncture experiments have been found to have K^+ concentrations somewhat higher than that in plasma [16].
(iii) In the dog mandibular gland there is substantial loss of intracellular K^+ into the saliva during the initial phase of secretion [1].
(iv) The luminal potentials of the secretory endpieces of the unstimulated cat sublingual gland are positive not negative [5], as would be expected if there were only Cl^- movement into the lumen from the cell.
(v) Since exocytotic vesicles in pancreatic acinar cells have been shown to contain K^+ channels [2] and these must be incorporated into the apical membrane during exocytosis, a K^+ conductance has to be present in the apical membrane during secretion unless the cell has some means of inactivating the K^+ channels after their incorporation into the plasma membrane.

Although these points provide only indirect evidence, when taken together they suggest rather strongly that a significant K^+ conductance is present in the apical membranes of many secretory epithelia.

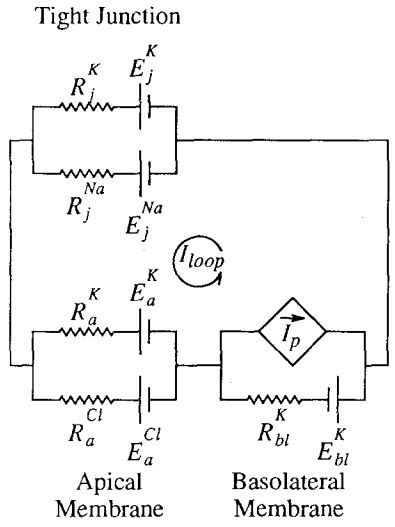
In this paper, a simple equivalent circuit model of a secretory epithelium has been used to investigate the effects of apical membrane K^+ channels on the rate and composition of the secretion produced by an epithelium, the transport mechanism of which is dependent on secondary active Cl^- transport. The major finding of this study is that the rate of secretion can actually be enhanced by placing K^+ channels in the apical membrane (which eliminates the resistance of the tight junctions from the path taken by part of the loop current driving secretion) and that even when the entire cell K^+ conductance is placed there, the secretion remains Na^+ rich.

Theory

List of Symbols Used

R_a, R_j, R_{bl}	Specific resistances of apical (*a*), junctional (*j*) and basolateral (*bl*) membranes (Eqs. (1a)–(1c)).
R_j^K, R_j^{Na}, R_j^{Cl}, R_a^K, R_a^{Cl}, R_{bl}^K	Partial specific resistances to K^+, Na^+ and Cl^- across membranes *j*, *a* and *bl* (Eqs. (1a)–(1c)).
p_j^K, p_j^{Na}	Partial specific resistances of junctional membrane when bathed symmetrically with isotonic KCl or NaCl (Eqs. (8a) and (8b)).
E_a, E_j, E_{bl}	Open-circuit potential differences across *a*, *j* and *bl* (Eqs. (2a)–(2c)).
E_j^K, E_j^{Na}, E_a^K, E_a^{Cl}, E_{bl}^K	Nernst potentials for K^+, Na^+ and Cl^- across membranes *j*, *a* and *bl* (Eqs. (2d)–(2h)).
I_{loop}	Intraepithelial loop current (Eq. (3)).
I_p	Current carried by the Na^+, K^+-ATPase (Eq. (2c)).
I_a^{Cl}, I_j^{Na}	Cl^- and Na^+ currents across membranes *a* and *j* (Eqs. (4) and (5)).

a



b

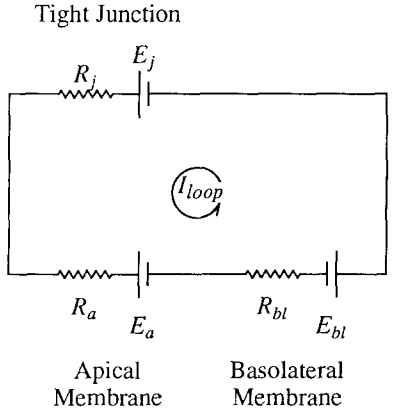


Fig. 2. (*a*) Equivalent circuit for an epithelium in which apical K^+ channels are present and Na^+-K^+ exchange across the tight junctions is permitted. The circuit is similar to that in Fig. 1*b* except that a K^+ battery is shown in series with a K^+ resistance in the apical membrane, and K^+ and Na^+ batteries, with K^+ and Na^+ resistances, are shown in parallel across the tight junction. (*b*) The same circuit, simplified by use of Thevenin equivalents (*see* Eqs. (1*a–c*) and (2*a–c*)). It can be described by Eq. (3). (*See* text for definition of symbols)

	The currents are defined as positive when the direction of ion flow is into the lumen (Eqs. (4) and (5)).
$[Na]_l$, $[Cl]_l$, $[K]_l$	Luminal ion concentrations (Eq. (6)).
$[Na]_i$, $[Cl]_i$, $[K]_i$	Interstitial ion concentrations.
$[Cl]_c$, $[K]_c$	Cytosol ion concentrations.

Figure 2*a* shows a more general equivalent circuit model for an epithelium than that shown in Fig. 1*b*, from which it differs in two respects: (i) it has a K^+ as well as a Cl^- conductance in the apical membrane and (ii) both K^+ and Na^+ currents across the tight junctions are permitted. By the use of Thevenin equivalents, we can simplify this circuit to that shown in Fig. 2*b*, where

$$R_j = \frac{R_j^K R_j^{Na}}{R_j^K + R_j^{Na}} \tag{1a}$$

$$R_a = \frac{R_a^K R_a^{Cl}}{R_a^K + R_a^{Cl}} \tag{1b}$$

$$R_{bl} = R_{bl}^K \tag{1c}$$

$$E_j = \left(\frac{E_j^K}{R_j^K} + \frac{E_j^{Na}}{R_j^{Na}}\right) R_j \tag{2a}$$

$$E_a = \left(\frac{E_a^K}{R_a^K} + \frac{E_a^{Cl}}{R_a^{Cl}}\right) R_a \tag{2b}$$

$$E_{bl} = \left(\frac{E_{bl}^K}{R_{bl}^K} + I_p\right) R_{bl} \tag{2c}$$

$$E_j^K = \frac{RT}{F} \log\left[\frac{[K]_i}{[K]_l}\right] \tag{2d}$$

$$E_j^{Na} = \frac{RT}{F} \log\left[\frac{[Na]_i}{[Na]_l}\right] \tag{2e}$$

$$E_a^K = \frac{RT}{F} \log\left[\frac{[K]_c}{[K]_l}\right] \tag{2f}$$

$$E_a^{Cl} = \frac{-RT}{F} \log\left[\frac{[Cl]_c}{[Cl]_l}\right] \tag{2g}$$

$$E_{bl}^K = \frac{RT}{F} \log\left[\frac{[K]_c}{[K]_i}\right]. \tag{2h}$$

The intraepithelial loop current (I_{loop}) for the model epithelium specified in Fig. 2*b* is given by

$$I_{loop} = \frac{E_j - E_a + E_{bl}}{R_j + R_a + R_{bl}}. \tag{3}$$

The rate of secretion of Cl^- is given by the Cl^- current (I_a^{Cl}) across the apical membrane

$$I_a^{Cl} = \frac{E_a^K - E_a^{Cl} + I_{loop} R_a^K}{R_a^K + R_a^{Cl}}. \tag{4}$$

As we would expect, the rate of Cl^- secretion is no longer identical to the size of the intraepithelial loop current, but now is also influenced by the extent of electrically coupled KCl movement across the apical membrane.

The rate of secretion of Na^+ is given by the Na^+ current across the tight junctions

$$I_j^{Na} = \frac{E_j^{Na} - E_j^K + I_{loop} R_j^K}{R_j^{Na} + R_j^K}. \tag{5}$$

We now wish to solve this equivalent circuit model so as determine the secretory rate and the

composition of the secreted fluid. To do so we make the following assumptions:

1. The secreted fluid is isotonic. This implies that

$$[Cl]_l = [Na]_l + [K]_l = [Na]_i + [K]_i = [Cl]_i \quad (6)$$

which is equivalent to stating that the water permeability of the epithelium is so high that it cannot maintain an osmotic gradient. This assumption, although not essential, considerably simplifies the calculations involved in solving the model. (In fact, we have tried reducing the epithelial water permeability so that osmotic gradients can be maintained, and we find that it does not alter the ionic proportions in the secreted fluid.)

2. The cytosol composition does not vary with secretory rate. The assumption that the cytosol composition remains constant irrespective of the secretory rate is a considerable simplification. It is, however, very conservative because changes in cell composition would actually reduce the effects of changes in cell membrane parameters on the rate and composition of secretion.

3. Ion transport across the epithelium is at steady state.

4. The net ion fluxes into the luminal compartment determine the composition of the luminal fluid, that is

$$[Na]_l = \frac{I_j^{Na}}{I_a^{Cl}} [Cl]_l. \quad (7)$$

5. The pump current (I_p) is one sixth of the apical Cl^- current. This assumption is a necessary consequence of the stoichiometry of the transport model depicted in Fig. 1*a*. In this model, for every six Cl^- ions leaving the cell across the apical membrane, there must be three cycles of the Na^+-K^+-$2Cl^-$ cotransporter in order to maintain a steady content of Cl^- in the cytosol. The three Na^+ ions thereby brought into the cytosol by the cotransporter are then exchanged for two K^+ ions by the Na^+, K^+-ATPase. Thus, for every six Cl^- ions leaving the cell, the Na^+, K^+-ATPase will pump out one positive charge.

6. All resistances are constant apart from those in the tight junctions, which are taken to be inversely proportional to the mean of the concentrations of Na^+ (or K^+) in the luminal and interstitial solutions. Thus

$$R_j^K = \frac{(2 \times 155)p_j^K}{([K]_i + [K]_l)} \quad (8a)$$

$$R_j^{Na} = \frac{(2 \times 155)p_j^{Na}}{([Na]_i + [Na]_l)} \quad (8b)$$

where p_j^K and p_j^{Na} represent the specific resistance of the junctional membrane, j, when it is bathed, respectively, with symmetrical, "isotonic" (155 mmol/liter) solutions of KCl or NaCl. Strictly speaking, the resistances of all three membranes are dependent on the ionic composition of the bathing fluids, but it is only across the tight junctions that changes in the ion gradients could lead to substantial changes in the partial specific resistances of the membrane, so that the resistances of the apical and basolateral membranes can be assumed to be constant. Our use of a simple formula, in which resistance is considered to be inversely proportional to the mean ionic concentration across the tight junctions, rather than the Goldman equation [4] requires justification. The Goldman equation for the current, I, carried into the lumen by an ion flux across the tight junction, j, is given by

$$I = \frac{-z^2PEF^2}{RT} \frac{[C]_l \exp(zEF/RT) - [C]_i}{\exp(zEF/RT) - 1} \quad (9)$$

where P is the permeability of the membrane, j, separating compartments l and i containing the ion in concentrations $[C]_l$ and $[C]_i$, E is the potential of the lumen, l, (with respect to the interstitium, i), and z, R, T and F have their usual meanings. The equation can be expanded as a power series using the Bernoulli numbers, B_n, taking account of the fact that B_n is equal to zero when n is an odd number greater than 1

$$I = -PF \sum_{n=0}^{n=\infty} \left[B_n \frac{([C]_l(-1)^n - [C]_i)}{n!} \left(\frac{zEF}{RT}\right)^n \right] \quad (10a)$$

$$I = PF([C]_i - [C]_l) + PF \frac{([C]_i + [C]_l)}{2} \left(\frac{zEF}{RT}\right) + PF \frac{([C]_i - [C]_l)}{12} \left(\frac{zEF}{RT}\right)^2 + PF \frac{([C]_i - [C]_l)}{720} \left(\frac{zEF}{RT}\right)^4 + \cdots \quad (10b)$$

The first two terms of this expansion are sufficient to provide a good approximation to the Goldman equation in the range of interest in the model circuit (when the ion current is flowing from high to low concentration and the voltage is less than 50 mV). In other words, to a first approximation, the resistance is inversely proportional to the mean of the concentrations of the ions bathing the membrane. (In fact, we have also studied a version of the model in which all ion currents were calculated with the Goldman equation, but its use did not alter the results appreciably.)

Table 1. Initial values of the parameters used in the secretion model[a]

p_j^{Na}	600 Ω cm²
p_j^{K}	600 Ω cm²
R_a^{Cl}	274 Ω cm²
R_{bl}^{K}	154 Ω cm²
$[Cl]_i$	160 mmol/liter
$[Na]_i$	155 mmol/liter
$[K]_i$	5 mmol/liter
$[Cl]_c$	54 mmol/liter
$[K]_c$	155 mmol/liter

[a] With the exception of the Cl^- resistance of the tight junctions, which was assumed to be infinite, the values we used are those measured for dog tracheal mucosa [13, 15]. For explanation of symbols used, see text.

We can solve the model circuit in the following way: Substituting Eqs. (4) and (5) into Eq. (7) we obtain

$$\frac{[Na]_l}{[Cl]_l} = \left(\frac{E_j^{Na} - E_j^{K} + I_{loop} R_j^{K}}{E_a^{K} - E_a^{Cl} + I_{loop} R_a^{K}}\right)\left(\frac{R_a^{K} + R_a^{Cl}}{R_j^{Na} + R_j^{K}}\right). \quad (11)$$

This is a nonlinear equation with a single independent variable, $[Na]_l$. This is so because once $[Na]_l$ is specified, all the other unknowns in the equation are set. Thus, in Eq. (11), $[Cl]_l$, R_a^{K}, R_a^{Cl} and E_a^{Cl} are constants independent of $[Na]_l$. $[K]_l$ can be calculated from $[Na]_l$ using Eq. (6), and can then be used to calculate E_j^{K}, E_j^{Na}, E_a^{K}, R_j^{K} and R_j^{Na}. The only remaining unknown in Eq. (11) is I_{loop} which can be calculated from Eq. (3) alone (if we set the pump current, I_p, to zero) or by solving Eqs. (3) and (4) simultaneously (if we set $I_p = I_{Cl}^a/6$). For this study we have used the secant method to find the value of $[Na]_l$ for which the left-hand side of Eq. (11) equals the right-hand side.

For the initial parameters of the model (Table 1), we have taken values from the literature [13, 15] that are appropriate for dog tracheal mucosa except that we began with the assumption that the tight junctions were completely cation selective. The tracheal mucosa was chosen because it is the only mammalian secretory epithelium for which good experimental estimates of all the required membrane parameters are available. As will be shown, however, the conclusions to be drawn from this analysis are not markedly dependent on the values chosen.

Results and Discussion

We used the model of epithelial secretion with the parameters given in Table 1 to investigate the effects of luminal K^+ channels on the rate and composition of the secretion. We did this by holding the total cell K^+ conductance fixed, while varying its partition between the apical and basolateral membranes. In the control state (*see* Table 2), with the K^+ conductance confined entirely to the basolateral membrane, the model epithelium secreted Cl^- at a rate of 62.5 μA cm^{-2}. Since, under these conditions, there was no transport of K^+ ions across the apical membrane, the secretory rate was equal to the intraepithelial loop current. The luminal K^+ concentration was 5 mmol/liter as a result of the movement of K^+ through the tight junctions, and the luminal potential was −37.4 mV with respect to the interstitium. The secretory rate predicted by the model was well within the range of values measured experimentally in the dog tracheal mucosa when it had been stimulated with adrenaline to secrete [14].

Figure 3 shows the effects of progressively transferring more and more of the K^+ conductance to the apical membrane on (i) the secretion rate as estimated by the Cl^- current across the apical membrane, (ii) the intraepithelial loop current, (iii) the luminal K^+ concentration, and (iv) the luminal potential difference with respect to the interstitium. As more and more of the K^+ conductance was transferred to the apical membrane from the basolateral membrane, the rate of Cl^- secretion increased initially to a maximum of 67.2 μA cm^{-2} (when 17% of the total cell K^+ conductance was located in the apical membrane and the luminal K^+ concentration was 19.6 mmol/liter). Further increases in the relative contribution of apical K^+ channels to the total cell membrane K^+ conductance caused the secretion rate to decline once more, although it was not until about 60% of the total K^+ conductance was in the apical membrane that the Cl^- secretory rate fell below the control value. When the cell K^+ conductance was confined entirely to the apical membrane, the rate of Cl^- secretion was reduced to 20.3 μA cm^{-2} (32% of the control), the luminal potential difference fell to −3.9 mV and the luminal K^+ concentration increased to 38.5 mmol/liter.

The enhancement in secretion rate brought about by placing K^+ channels in the apical membrane arises because part of the loop current driving secretion needs only to pass via the apical Cl^- and K^+ channels, whereas the entire loop current in the usual model must pass across the tight junctional resistance as well as the apical Cl^- and the basolateral K^+ channels. The Cl^- current flowing across the apical membrane can thus be higher when some K^+ channels are present in the apical membrane although the extent of this enhancement is limited by the accumulation of K^+ in the lumen, which leads to a reduction in the Nernst potential for K^+

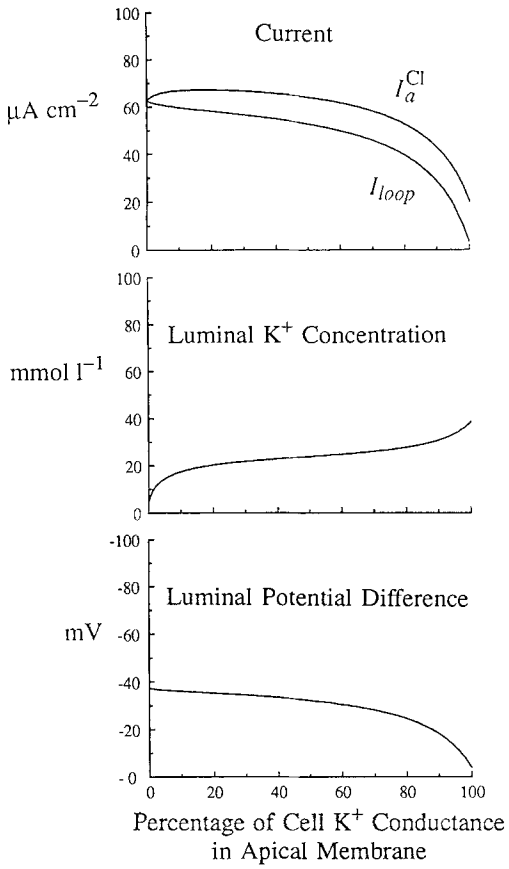


Fig. 3. Effect of changing the proportions of the cell K^+ conductance located in the basolateral and apical membranes on the secretion properties of the model specified in Fig. 2. (*See* text for definition of symbols)

across the apical membrane and so to a reduction in the driving force for Cl^- exit. The inhibition of the Cl^- current by an increase in luminal K^+ concentration also explains our finding that the secreted fluid is always Na^+ rich. Since the Nernst potential for K^+ and, hence, the rate of secretion declines as luminal K^+ concentration increases, the rate of secretion will be limited by the ability of the tight junctions to exchange Na^+ for K^+ so as to maintain a low luminal K^+ concentration and a Na^+-rich secretion.

We estimated how sensitive the behavior of the model was to changes in the transport parameters.

Influence of the Electrogenic Na^+ Pump

Setting the current carried by the Na^+, K^+-ATPase to zero (equivalent to making the pump stoichiometry for transport of Na^+ and K^+ equal to unity), reduced the Cl^- secretion rate only slightly and caused only small changes in luminal K^+ concentration and potential regardless of the size of the apical K^+ conductance. As can be seen from Eq. (2c), this was to be expected because although the Na^+, K^+-ATPase carried 17% of the intraepithelial loop current, it accounted for only about 2% of the basolateral emf and, hence, contributed only a correspondingly small fraction to the total driving force for Cl^- secretion.

Influence of the Tight Junctional Resistance

Increasing the resistance of the tight junctions to cations, while leaving the relative resistances to K^+ and Na^+ unchanged, had the expected effect of reducing the rate of Cl^- secretion and increasing the luminal potential, but it made the effect on secretion of placing a K^+ conductance in the apical membrane even more favorable. For example (*see* Table 2, panel *a*), when we increased the tight junctional resistance to K^+ and Na^+ by a factor of 2, we found that the Cl^- secretion rate when all the K^+ conductance was in the basolateral membrane was only 39.1 μA cm^{-2} but that it rose to 44.4 μA cm^{-2} when 25% of the total K^+ conductance was relocated in the apical membrane.

Influence of the Tight Junctional Cation Selectivity

Increasing the relative permeability of the tight junctions to K^+ over Na^+ had little effect on the stimulatory effects of apical K^+ channels. For example (Table 2, panel *b*), decreasing the K^+ resistance of the tight junctions by 50% did not alter the maximal rate of secretion. Nevertheless, it did influence the size of the K^+ concentration in the luminal fluid: when the K^+ conductance was confined to the basolateral membrane, the luminal K^+ concentration increased to 8.3 mmol liter^{-1}, and when the K^+ conductance was located exclusively in the apical membrane, it was reduced to 34 mmol liter^{-1}. Furthermore, the rate of secretion when all the K^+ channels are located in the apical membrane is higher when the tight junctional resistance is reduced (*cf.* Table 2 panel *c* with Table 2 panel *a*) as would be expected if the rate of junctional exchange of Na^+ for K^+ limits the rate of secretion.

Influence of the Transcellular Resistance

Increasing the rate of secretion by reducing the apical membrane Cl^- resistance or basolateral membrane K^+ resistance also enhanced the effects of

Table 2. Solutions of the model specified in Fig. 2 for various values of the model parameters[a]

		Percent of K^+ conductance in apical membrane	Net Cl^- secretion ($\mu A\ cm^{-2}$)	$[K]_l$ (mmol/liter)
Control	$p_j^K = p_j^{Na} = 600\ \Omega\ cm^2$	0	62.5	5.0
(Table 1)	$R_a^{Cl} = 274\ \Omega\ cm^2$	17	67.2	19.6
		100	20.3	38.5
a	$p_j^K = p_j^{Na} = 1200\ \Omega\ cm^2$	0	39.1	5.0
	$R_a^{Cl} = 274\ \Omega\ cm^2$	25	44.4	27.6
		100	12.4	43.3
b	$p_j^K = 300\ \Omega\ cm^2$	0	63.5	8.3
	$p_j^{Na} = 600\ \Omega\ cm^2$	17	67.2	19.5
	$R_a^{Cl} = 274\ \Omega\ cm^2$	100	28.5	34.0
c	$p_j^K = p_j^{Na} = 600\ \Omega\ cm^2$	0	72.4	5.0
	$R_a^{Cl} = 137\ \Omega\ cm^2$	22	80.3	24.6
		100	23.1	41.6
d	$p_j^K = p_j^{Na} = 600\ \Omega\ cm^2$	0	44.4	5.0
	$R_a^{Cl} = 274\ \Omega\ cm^2$	11	47.7	15.9
	$R_j^{Cl} = 600\ \Omega\ cm^2$	100	16.5	39.5

[a] The net Cl^- current into the lumen and the luminal K^+ concentration, $[K]_l$, are shown for five sets of model parameters, for each of which, three different values have been assigned to the proportion of the total cell K^+ conductance in the apical membrane: (i) no K^+ conductance in the apical membrane, (ii) that proportion of the K^+ conductance in the apical membrane that gave rise to the maximum rate of Cl^- secretion, and (iii) all the K^+ conductance in the apical membrane. It should be noted that it is only in the last set of model parameters (panel *d*), where the junctional Cl^- conductance was finite, that there was a Cl^- current across the tight junction.

placing part of the K^+ conductance in the apical membrane. For example (Table 2, panel *c*), when the apical membrane resistance for Cl^- was reduced by 50%, the location of 22% of the total K^+ conductance in the apical membrane increased the rate of Cl^- secretion by up to 11% and the luminal K^+ concentration rose to 24.6 mmol/liter.

Effect of Permitting Anion Flow through the Tight Junctions

An unexpected finding was that making the tight junctions permeable to Cl^- did not enhance the effectiveness of placing K^+ channels in the apical membranes. We had expected that apical K^+ channels would ameliorate the adverse effects of reducing the cation selectivity of the tight junctions, but, in fact, when we eliminated the selectivity of the tight junctions between cations and anions ($R_j^{Na} = R_j^K = R_j^{Cl} = 600\ \Omega\ cm^2$), and used a multidimensional, nonlinear equation-solving routine to find the roots of the resulting simultaneous nonlinear equations in three unknowns, we found that, although the secretory rate was reduced by 19%, as we had expected, the introduction of an apical K^+ conductance did not enhance secretion more than when the junctions were cation selective (Table 2, panel *d*).

This analysis has three major conclusions. First, that apical K^+ channels need not inhibit epithelial Cl^- secretion; rather, they may actually increase it. Second, apical K^+ channels do not result in the production of an especially K^+-rich primary fluid; on the contrary, even when the entire cell K^+ conductance is in the apical membrane, the luminal K^+ concentration is never much more than 40 mmol/liter. Third, the primary fluid K^+ concentrations that have been measured in micropuncture experiments on various exocrine glands [16] are all in a range that would arise if apical K^+ channels were present and were acting to enhance the rate of secretion.

This study was supported by the National Health and Medical Research Council of Australia.

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Received 20 October 1988; revised 31 March 1989