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Effect of amphotericin B and Cl^- removal on basolateral membrane K^+ conductance in frog corneal epithelium

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Increase in stromal K^+ concentration from 4 to 79 mM in an in vitro preparation of the frog cornea, in Cl^--free solutions, did not change the apical membrane fractional resistance, fR_0, or the transepithelial conductance, g_t; it depolarized the intracellular potential, V_0, by 38 mV and decreased the short-circuit current, I_{sc} by 2.9 $\mu A/cm^2$. These changes were similar to those observed for the same increase in stromal K^+ in control solutions except for the increase in g_t in the latter. When stromal K^+ was increased with 10^{-5} M amphotericin B, AmB, in the tear solution, fR_0 increased by 0.27 in control solutions and by 0.08 in Cl^--free solutions; respectively, g_t increased by 0.40 and by 0.17 mS/cm^2; I_{sc} decreased by 12 and by 11 mS/cm^2; V_0 depolarized by 9 and by 9.5 mV. These results support the concept that: (i) entrance of Cl^- into the cell is responsible in part for the bioelectrical changes observed when stromal K^+ is increased; and (ii) AmB decreases the partial K^+ conductance in the basolateral membrane of the frog cornea epithelium by a decrease in intracellular K^+.

Introduction

There are at least three conductive pathways in the corneal epithelium: A Cl^- conductance in the apical membrane, and a K^+ conductance and an electrogenic ($Na^+ + K^+$)-ATPase pump in the basolateral membrane [1–7]. In microelectrode experiments in which we increased the stromal K^+ from 4 to 79 mM in control solutions, we found an increase in transepithelial conductance, g_t, a decrease in short-circuit current, I_{sc}, and a depolarization of the intracellular potential, V_0 [6]. We did not see a change in the apical membrane fractional resistance, fR_0. These changes induced by an increase in stromal K^+ were compatible with a K^+ conductance in the basolateral membrane except for no change in fR_0. An increase in stromal K^+ should have resulted in an increase in the basolateral membrane conductance and an increase in fR_0. It could be possible that Cl^- may have entered the cell simultaneously with K^+ with a subsequent increase in the apical membrane Cl^- conductance. If this concept were correct, fR_0 might be expected to increase when stromal K^+ is increased in Cl^--free solutions. To test this possibility, experiments involving an increase in stromal K^+ in Cl^--free solutions are presented in this paper.

Amphotericin B (AmB) introduces Na^+ and K^+ conductances into the apical membrane of the corneal epithelium [8–10]; as a result, the intracellular Na^+ increases and the intracellular K^+ decreases to about 18% of control [9]. In experiments in which we measured the transepithelial potential without microelectrodes, we found different responses to changes in stromal K^+ with and without the antibiotic. We attributed the difference to a decrease in the basolateral membrane K^+ conductance with AmB as a result of a decrease in intracellular K^+. To test this hypothesis, data using microelectrodes in the presence of AmB are presented in this paper. In addition, experiments are reported herein in Cl^--free solutions in the presence of AmB.

Abbreviation: AmB, amphotericin B.

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Materials and Methods

Bullfrog corneas (*Rana catesbeiana*) were mounted tear side up in a lucite chamber as previously described [5,6,11]. The tissue was supported by a copper grid with a slightly less radius of curvature than that of the in vivo cornea. An opening of 0.4 cm^2 communicated the upper (epithelial) chamber (0.2 ml) with the lower (stromal) chamber (0.3 ml). Both chambers were continuously perfused at a rate of about 5 ml/min to insure complete exchange in 5–10 s. A slight negative hydrostatic pressure was applied to the lower chamber to help secure the cornea to the copper grid. Control solutions contained (in mM): Na^+, 102; K^+, 4; Ca^{2+}, 1; Mg^{2+}, 0.8; Cl^-, 81; SO_4^{2-}, 0.8; HCO_3^-, 25; phosphate, 1; and glucose, 25. Cl^- was substituted with SO_4^{2-} in Cl^--free solutions and sucrose was added in equimolar amounts to maintain a constant osmolality. Increases in K^+ concentration were accomplished by substitution of K^+ for Na^+. Amphotericin B was added to the tear solution to a final concentration of 10^{-5} M. All solutions were continuously gassed with 95% O_2/5% CO_2. The pH of the solutions was 7.2–7.3. Two pairs of macroelectrodes and one microelectrode were used. One pair was used to measure the transepithelial potential difference (calomel electrodes connected via KCl bridges to within 0.5 mm of tissue surfaces); the other pair (AgCl-coated Ag wire loop electrodes, 4 mm from the tissue on either side) was used to send current. The intracellular potential, V_0, was recorded with 3 M KCl-filled microelectrodes which had an input resistance of 15–40 Mohm. Corneas were short-circuited using an automatic clamp device (Biomed. Inst., Germering, F.R.G.) except for brief perturbations that lasted about 200 ms, during which the transepithelial potential was clamped at +10 mV (stroma side positive). These perturbations, repeated every 1–2 s, were used to measure the conductance ($g_t = \Delta I_t/\Delta V_t$). The apical membrane fractional resistance was obtained as $fR_0 = R_0/(R_0 + R_i) = \Delta V_0/\Delta V_t$. V_t and I_t are the transepithelial voltage and current; and R_0 and R_i, the resistances across the apical and basolateral membranes, respectively. The values of I_{sc}, g_t, fR_0, and V_0 were recorded along with the microelectrode resistance on a multichannel recorder (Linseis, TYP 2065). I_{sc} is defined as positive when the current is from tear to stroma via the tissue. Hyperpolarization of V_0 (opposite of depolarization) is defined as an increase in the negative intracellular potential. Student's *t*-test with paired observations was performed to determine the level of significance.

Results

Effect of increasing stromal K^+ from 4 to 79 mM in Cl^--free (SO_4^{2-}) solutions

As stated in the Introduction, changes due to an increase in stromal K^+ were compatible with a K^+ conductance in the basolateral membrane [3,5–7] except for no change in fR_0. Results obtained with Cl^--free solutions are shown in Fig. 1A from a selected experiment and the compiled data, in Table I. Although Fig. 1A shows a small decrease in fR_0, the data in Table I show no significant change in this parameter. The g_t did not significantly change in Cl^--free solutions contrary to the increase observed in control solutions. The I_{sc} decreased in Cl^--free solutions, but not to the same extent as it did in control solutions [6] in which case it even became negative. To explain the results in Cl^--free solutions, we may infer that intracellular Cl^- is the only ion available to carry the negative current from cell to tear and there is no Cl^- in the tear solution to carry negative current from tear to cell so that I_{sc} could not be reversed as in the case

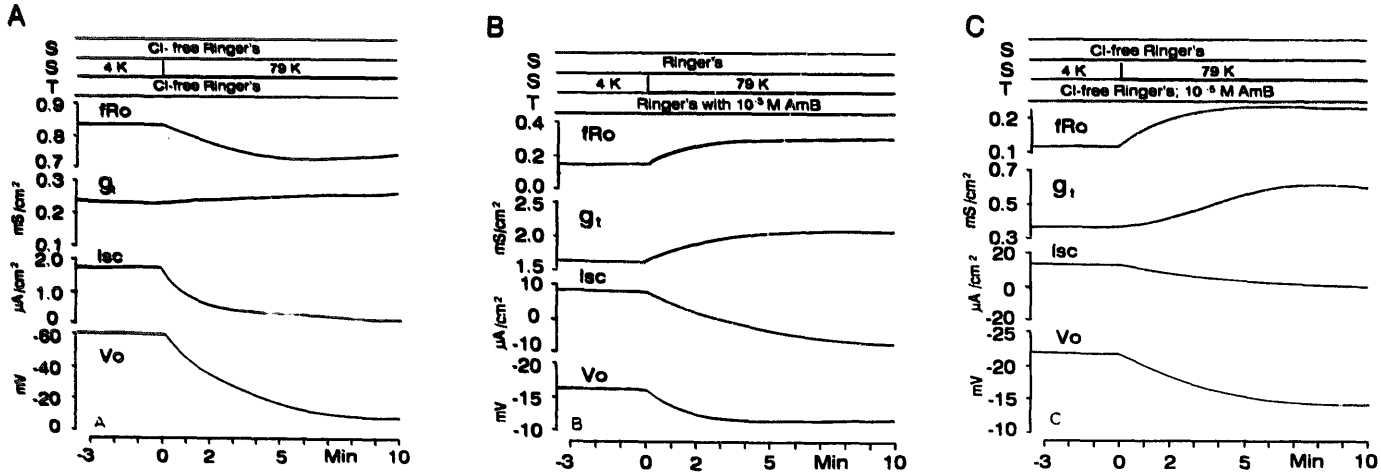

Fig. 1. Effect of increasing stromal K^+ from 4 to 79 mM in three selected experiments. (A) Cl^--free solns on both sides; (B) Control solns with 10^{-5} M amphotericin B in tear soln; (C) Cl^--free solns with 10^{-5} M amphotericin B in tear soln. Zero time when stromal K^+ was increased. Apical membrane fractional resistance, fR_0; transepithelial conductance in mS/cm^2, g_t;short-circuit current in μA/cm^2, I_{sc}; intracellular potential in mV, V_0.

TABLE I

Effect of changing stromal K^+ in the presence of Cl^--free (SO_4^{2-}) solutions

Values are mean ± S.E. Control values obtained before change in concentration. The other values are the changes obtained, respectively, 2, 5, and 10 min after change in concentration. Units are fR_0, unitless; g_t mS/cm^2; I_{sc}, μA/cm^2; and V_0, mV. a, $P < 0.01$; n.s., $P > 0.05$. The number of experiments = 9.

	Control	Changes in parameter		
		2 min	5 min	10 min
Increase stromal K^+ from 4 to 79 mM				
fR_0	0.74 ± 0.06	−0.01 ± 0.02 n.s.	−0.01 ± 0.02 n.s.	−0.02 ± 0.01 n.s.
g_t	0.23 ± 0.03	0.00 ± 0.00 n.s.	0.01 ± 0.01 n.s.	0.00 ± 0.01 n.s.
I_{sc}	3.3 ± 0.9	−1.5 ± 0.4 a	−2.7 ± 0.7 a	−2.9 ± 0.7 a
V_0	−53.6 ± 4.0	20.3 ± 2.2 a	34.6 ± 2.4 a	38.7 ± 3.5 a

of control solutions. The depolarization of V_0 was the same in Cl^--free as in control solutions, i.e., at 2, 5 and 10 min it depolarized by 23.1, 34.6 and 38.3 mV, respectively, in control solutions [6] and by 20.3, 34.6 and 38.1, respectively, in Cl^--free solutions.

Effect of increasing stromal K^+ from 4 to 79 mM with 10^{-5} M amphotericin B in the tear solution (in control solutions)

By measuring the transepithelial potential, we found a different response to changes in stromal K^+ with and without AmB [7]. Data from nine experiments are presented in Table II and graphically from one experiment in Fig. 1B. With AmB there was an increase in fR_0 of 0.27 when stromal K^+ was increased, contrary to no change without AmB; the g_t increased by 0.40 mS/cm^2 and the I_{sc} decreased by about 12 μA/cm^2, both by about the same magnitude as without AmB; and depolarization of V_0 was about 9 mV which is about one fourth that observed without AmB.

Effect of increasing stromal K^+ from 4 to 79 mM with 10^{-5} M amphotericin B in the tear solution (in Cl^--free (SO_4^{2-}) solutions)

Data are presented in Table III and graphically from one experiment in Fig. 1C. With an increase in

TABLE II

Effect of changing stromal K^+ in the presence of control solutions, and 10^{-5} M amphotericin B in tear solution

See Table I. The number of experiments = 12.

	Control	Changes in parameter		
		2 min	5 min	10 min
Increase stromal K^+ from 4 to 79 mM				
fR_0	0.14 ± 0.01	0.11 ± 0.02 a	0.17 ± 0.04 a	0.27 ± 0.06 a
g_t	0.94 ± 0.16	0.17 ± 0.02 a	0.28 ± 0.04 a	0.40 ± 0.07 a
I_{sc}	8.8 ± 0.8	−5.6 ± 08 a	−10.5 ± 1.3 a	−12.4 ± 1.2 a
V_0	−21.8 ± 0.9	4.2 ± 0.4 a	6.4 ± 0.7 a	9.0 ± 1.1 a

TABLE III

Effect of changing stromal K^+ in the presence of Cl^--free (SO_4^{2-}) solutions, and 10^{-5} M amphotericin B in tear solution

See Table I. The number of experiments = 10.

	Control	Changes in parameter		
		2 min	5 min	10 min
Increase stromal K^+ from 4 to 79 mM ($N = 10$)				
fR_0	0.10 ± 0.02	0.05 ± 0.01 a	0.07 ± 0.01 a	0.08 ± 0.01 a
g_t	0.37 ± 0.02	0.09 ± 0.01 a	0.16 ± 0.02 a	0.17 ± 0.02 a
I_{sc}	11.0 ± 1.3	−5.1 ± 0.7 a	−9.0 ± 1.4 a	+10.8 ± 1.8 a
V_0	−20.0 ± 1.4	4.6 ± 0.8 a	7.8 ± 1.4 a	9.5 ± 1.8 a

stromal K^+, fR_0 increased by 0.08 and g_t increased by 0.17 mS/cm^2. These changes are smaller than the changes observed in Cl^- solutions, as described in the preceding paragraph. The decrease in the I_{sc} of about 12 μA/cm^2 and the depolarization of V_0 of 9.5 mV were of about the same magnitude as those observed with Cl^- solutions.

Discussion

Let us first discuss the results obtained in the absence of AmB. With an increase in stromal K^+ from 4 to 79 mM, the apical membrane fractional resistance, fR_0, did not change in Cl^--free solutions as previously observed in control solutions [6]. At first glance from the result in Cl^--free solutions, it appears that the lack of change in fR_0 with an increase in stromal K^+ in control solutions is not due to the entrance of Cl^- into the cell, as conjectured in the Introduction. Analysis of all parameters studied will support the original conjecture. For example, the lack of change in fR_0 could be explained if the increase in K^+ conductance in the basolateral membrane were smaller with an increase in stromal K^+ in Cl^--free solutions than in Cl^- solutions. This supposition is supported by the lack of change in g_t when stromal K^+ is increased in Cl^--free solutions (see below). Let us consider the other findings when stromal K^+ was increased: (i) the transepithelial conductance, g_t did not change in Cl^--free solutions while it increased in control solutions [6]; (ii) the short-circuit current, I_{sc}, decreased from 3.3 to 0.4 μA/cm^2 in Cl^--free solutions as mentioned above, while the decrease was larger and even reversed from 5.2 to −4.9 μA/cm^2 with Cl^- present; and (iii) the intracellular potential, V_0, depolarized to the same extent in Cl^--free solutions as in control solutions.

The increase in g_t in Cl^- solutions may be explained as follows: (i) increase in the basolateral membrane K^+ conductance as a result of an increase in both stromal and intracellular K^+ concentrations; (ii) increase in the apical membrane Cl^- conductance as a result of the entrance of Cl^- across the apical mem-

brane concomitant with the entrance of K^+ across the basolateral membrane to maintain electroneutrality; and (iii) cell swelling as a result of the entrance of both ions with a further increase in permeability across the plasma membranes [12]. It should be noted that the increase in intracellular concentration and swelling may be unmeasurable since it takes about 20 mm Hg (about 1 mOsm) to induce the stretch effect [13]. In Cl^--free solutions, since there is no Cl^- entering the cell from the apical solution, entrance of K^+ will be limited and there will be essentially no cell swelling. At best, with an increase in stromal K^+, there will be a smaller increase in basolateral membrane conductance in the absence than in the presence of Cl^-. Furthermore, there will not be a noticeable increase in g_t. It should also be noted that in Cl^--free solutions, most of the resistance across the cell is across the apical membrane (high fR_0); therefore, changes in the basolateral membrane conductance will have minimal influence on the total conductance.

The difference in response of I_{sc} to the increase in stromal K^+ between control and Cl^--free solutions may be explained as follows: In control solutions, I_{sc} is carried by the movement of K^+ across the basolateral membrane into the stroma and by the movement of Cl^- across the apical membrane into the tear. With the increase in stromal K^+, there is a reversal of the movement of K^+ and Cl^- across the respective membranes, with the result of a decrease and even a reversal of I_{sc}. In Cl^--free solutions, with 4 mM K^+, the I_{sc} may be carried across the apical membrane by the residual intracellular Cl^-. When K^+ was increased to 79 mM, the I_{sc} was reduced towards zero but it could not be reversed because of the absence of Cl^- in the tear solution. The lack of reversal of the I_{sc} in Cl^--free solutions suggests that the contribution of the paracellular pathway to the I_{sc} when stromal K^+ is increased is nil or minimal despite the presence of asymmetrical solutions.

Before we discuss the changes observed in V_0, we will refer to Fig. 2 which shows schematically the electrogenic pathways in the corneal epithelium, which in the absence of AmB are: the simple K^+ conductive $(R_K - E_K)$ pathway and the $(Na^+ + K^+)$-ATPase pump $(R_P - E_P)$ in the basolateral membrane, and the Cl^- conductive $(R_{Cl} - E_{Cl})$ pathway in the apical membrane [1–7]. From Fig. 2, in the absence of AmB, it follows that

$$V_0 = E_{Cl} + I_c R_{Cl} \tag{1}$$

$$V_i = E_P R_K/(R_K + R_P) + E_K R_P/(R_K + R_P) - I_c R_P R_K/(R_K + R_P) \tag{2}$$

where V_0 and V_i are the potentials of the tear and

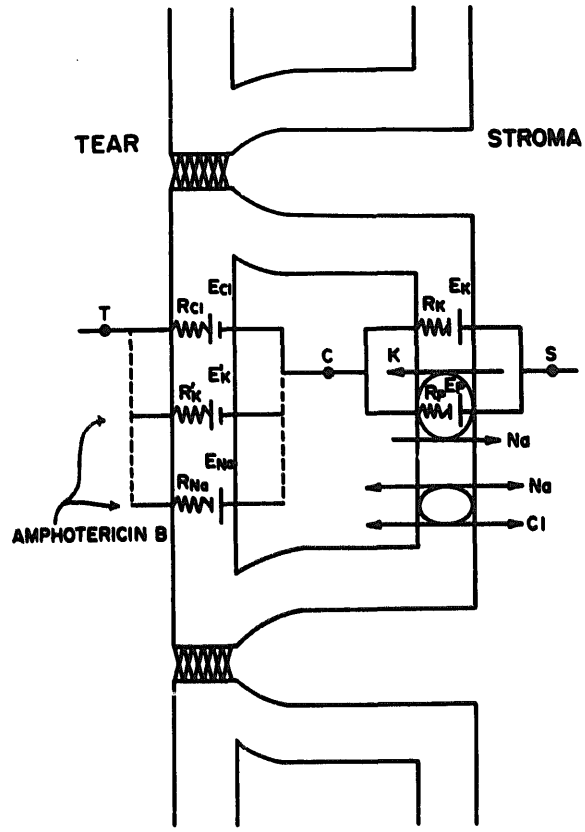

Fig. 2. Schematic representation of some of the ion pathways in the cornea epithelial cells. Es and Rs are the respective emfs and resistances. In the basolateral membrane there are a simple K^+ conductive pathway and an electrogenic $(Na^+ + K^+)$-ATPase pump. In the apical membrane there is a simple Cl^- conductive pathway and in the presence of amphotericin B there are also simple Na^+ and K^+ conductive pathways.

stromal solutions, respectively, with reference to the cell, i.e., when V_0 and V_i are positive the tear and stromal solutions are positive to the cell. E and R are the respective emfs and resistances of the simple Cl^- conductive (Cl), the simple K^+ conductive (K) and the $(Na^+ + K^+)$-ATPase (P) pathways. I_c is the transcellular current, considered positive from tear to stroma; I_c is equal to the sum of the applied current and the current through the intercellular spaces. Under short-circuit conditions the magnitude of the transintercellular current is zero and I_c equals I_{sc}; and under open circuit conditions the magnitude of the transintercellular current equals I_c.

From the definition of apical membrane fractional resistance,

$$fR_0 = R_{Cl}[R_{Cl} + R_K R_P/(R_K + R_P)]^{-1} \tag{3}$$

Under short circuit conditions, we obtain from Eqns. 1–3

$$V_0 = V_i = (1 - fR_0)E_{Cl} + fR_0[E_P R_K/(R_K + R_P) + E_K R_P/(R_K + R_P)] \tag{4}$$

If we assume that with K^+ in the bathing solutions $R_P \gg R_K$ [6], Eqn. 4 may be simplified to

$$V_0 = (1 - fR_0)E_{Cl} + fR_0E_K \quad (5)$$

Since our results showed that fR_0 did not change, changes in V_0 with a change of stromal K^+ should, according to Eqn. 5, depend mainly on changes in E_K. This is probably the reason why changes in V_0 as a result of increasing stromal K^+ were about the same in control as in Cl^--free solutions despite the difference in the response of g_t between the two conditions.

We shall now consider the results in the presence of AmB. When stromal K^+ was increased in Cl^- solutions, fR_0 increased, contrary to the lack of change without the antibiotic. At least two factors may contribute to this difference. First, with AmB and with 4 mM K^+ in the solutions, fR_0 is very low (about 0.1) so that the major resistance across the cell is across the basolateral membrane; therefore, a decrease in the basolateral membrane resistance when stromal K^+ is increased should noticeably affect fR_0. Second, the K^+ conductance in the basolateral membrane is probably lower with than without AmB in the tear solution (see below); hence, with AmB present, the relative increase in the basolateral membrane K^+ conductance (and fR_0) with an increase in stromal K^+ must be higher than in the absence of AmB.

With AmB, removal of Cl^- from the solutions decreased the fR_0 response due to an increase in stromal K^+ compared to control solutions, i.e., it increased by about 0.1 in Cl^--free solutions compared to 0.27 in control solutions. This result supports the sequence of events discussed in the absence of AmB: increase in stromal K^+ results in an increase in basolateral membrane conductance; in the presence of Cl^- in the tear solution, both K^+ and Cl^- enter the cell, with a further increase in the K^+ conductance and an increase in the apical membrane conductance; with Cl^- present, cell swelling may contribute also to the total conductance.

Cell swelling may also increase a Ca^{2+}-dependent K^+ conductance [14]. The question arises whether a deficiency in soluble Ca^{2+} may be the reason for a small response of the K^+ conductance in the basolateral membrane when stromal K^+ is increased in Cl^--free solutions [15,16]. This is unlikely since: (i) we do our experiments at a pH of 7.2–7.3, lower than those reported by Jensen et al. [16] (> 7.6) who used gluconate as the substitute ion; (ii) the solubility product of $CaSO_4$ is $3.7 \cdot 10^{-5}$ which is very close to the product of our solutions of $3.75 \cdot 10^{-5}$; (iii) we measured the Ca^{2+} concentration with a Ca^{2+} electrode (Orion Research, Inc.) and obtained the close values of 0.6 and 0.5 mM, respectively, for our Cl^- and SO_4^{2-} solutions; (iv) Wolosin and Candia [17] showed an increase in the basolateral membrane K^+ conductance by epinephrine, by forskolin and by the Ca^{2+} ionophore A23187 in SO_4^{2-} as in Cl^- solutions; and (v) the depolarization observed by us with the stromal K^+ increase was the same with and without Cl^-, whether AmB was present or not (Ref. 6 and present experiments). Hence, we do not believe that Ca^{2+} in our experiments plays a major role on the effects obtained as a result of Cl^- removal.

With AmB present, an increase in stromal K^+ increased g_t. This increase in g_t was greater with Cl^- (0.40 mS/cm^2) than without Cl^-(0.17 mS/cm^2). Again this finding may be explained as in the discussion on fR_0 in the preceding paragraph, with the entrance of Cl^- and K^+ into the cell and cell swelling.

While, without AmB, I_{sc} is conducted across the apical membrane by Cl^- only, with the antibiotic I_{sc} is also conducted by Na^+ and K^+; that is, with AmB present, I_{sc} is conducted across the apical membrane by the movement of K^+ and Cl^- from cell to tear and by the movement of Na^+ from tear to cell [9]. With AmB, contrary to the observation without AmB, I_{sc} was about the same whether Cl^- was present (9 μA/cm^2) or not (11 μA/cm^2) under baseline conditions (4 mM K^+). Also the response of the I_{sc} to the increase in stromal K^+ was about the same in the presence (-12 μA/cm^2) or absence (-11 μA/cm^2) of Cl^- from the solutions. The similarity of these changes in I_{sc} suggests that, in the presence of AmB, K^+ and Na^+ are mainly responsible for I_{sc}.

When evaluating the changes in V_0 in the presence of AmB, Eqn. 4 may not be simplified since fR_0 is affected by the increase in stromal K^+. Also, Na^+ and K^+ conductances in the apical membrane must be taken into consideration [8–10]. Eqn. 4 may be written as

$$V_0 = V_i = (1 - fR_0)E_A + fR_0[E_PR_K/(R_K + R_P) + E_KR_P(R_K + R_P)] \quad (6)$$

where E_A is the Thevenin emf across the apical membrane, including the Na^+, K^+ and Cl^- pathways. Changes in V_0 were smaller with than without AmB, i.e., V_0 depolarized by 38 mV in the absence of AmB whether in control solutions [6] or in Cl^--free solutions (Fig. 1A, Table I), while it depolarized by only about 9 mV in the presence of AmB (Figs. 1B and 1C; Tables II, III). The results may be explained according to Eqn. 6 by (i) an increase in E_P simultaneous with a decrease in E_K when stromal K^+ was increased with AmB in the tear solution (see Refs. 2, 18 and 19 for details); and (ii) a decrease in the contribution of the E_K term of Eqn. 6 if the fraction $[R_P/(R_K + R_P]$ is much smaller than 1 at the time stromal K^+ was increased with AmB in the tear solution. In either case, (i) or (ii), the partial

K^+ conductance in the basolateral membrane must have decreased with AmB. This decrease in the basolateral membrane K^+ conductance must be due to a decrease in cellular K^+ observed following addition of AmB [9].

An increase in E_P was suggested as the reason for the anomalous PD response when the stromal K^+ was increased from 0 to 4 mM [5,6]. In experiments with transepithelial PD measurements [5], the PD increased and, in the micropuncture experiments [6], V_0 initially hyperpolarized contrary to the expected increase in PD and contrary to the expected depolarization of V_0 when stromal K^+ was increased from 0 to 4 mM. In those experiments, exposure to 0 mM K^+ must have increased R_K, with a decrease in the contribution of the term with E_K and an increase in the contribution of the term with E_P. An anomalous response was not observed in present experiments with AmB because the increase in the K^+ concentration to 79 mM must have increased the K^+ conductance sufficiently for a normal response (depolarization), but the response was not as high as that observed in the absence of AmB. Similar arguments explained the normal and anomalous PD responses in frog stomach [18,19].

In conclusion, the presence of Cl^- in the bathing media affects the bioelectrical responses, with and without AmB in the tear solution, to an increase in stromal K^+, probably by entering the cell across the apical membrane as K^+ enters across the basolateral membrane and probably by inducing some cell swelling. Addition of AmB to the tear solution appears to decrease the partial K^+ conductance of the basolateral membrane, as shown by a decrease in the depolarization observed with an increase in stromal K^+. This is probably due to the decrease in intracellular K^+ as it diffuses into the tear solution.

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