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Potential difference responses to secretory K^+, Na^+ and HCO_3^- changes in secreting and resting states of frog stomach in Cl^--free media

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The effects of changes in secretory concentrations of K^+, Na^+ and HCO_3^- on transmucosal potential difference (PD) and resistance in Cl^--free (SO_4^{2-}) solutions were compared for secreting fundus and resting fundus of *Rana pipiens*. In the resting fundus experiments, histamine was not present in the nutrient solution and cimetidine was primarily used to obtain acid inhibition. Increase of K^+ from 4 to 80 mM, decrease of Na^+ from 156 to 15.6 mM and decrease of HCO_3^- from 25 to 5 mM gave, 10 min after the change, in the secreting fundus ΔPD values of 39.7, −11.9 and 3.2 mV, respectively. In the resting fundus, 1.5 to 2 h after the addition of cimetidine, the same changes in secretory ion concentration gave ΔPD values of 12.2, −5.6 and 1.5 mV, respectively. Replacement of cimetidine with SCN and without histamine yielded a ΔPD somewhat lower than that in cimetidine, namely 9 mV for a K^+ change from 4 to 80 mM. Subsequent addition of histamine with SCN present gave a ΔPD of about 21 mV. The change in PD was attributed to histamine increasing the secretory membrane area, leading to an increase in K^+ conductance. Another possibility is that histamine increases the K^+ conductance per se.

Introduction

The ion substitution method, in which we replace an ion by a relatively impermeant ion, has recently been used to determine the potential difference (PD) responses to secretory K^+, Cl^- and Na^+ changes in concentration in secreting and resting (inhibited) states of frog stomach in Cl^- media [1]. A natural extension of these studies is to investigate systematically such responses in Cl^--free media. This latter consideration constitutes the main purpose of the present paper.

In ion substitution studies on the nutrient side of the frog gastric mucosa, two types of PD responses were found. First, a normal PD response in which an increase in concentration of a cation, such as K^+ in the nutrient solution, resulted in a decrease in the positivity of the nutrient solution was attributed to the existence of a simple conductance pathway [2]. Second, an anomalous PD response in which an increase in concentration of a cation such as K^+ or Na^+ in the nutrient solution resulted in an increase in the positivity of the nutrient was attributed to the existence of an electrogenic ($Na^+ + K^+$)-ATPase antiport [3–5] and an electrogenic NaCl symport [6,7]. In such studies [1] with concentration changes of K^+, Cl^- and Na^+ on the secretory side, only normal PD

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responses occurred and hence the pathways for these ions in the secretory membrane may be considered to be simple conductance pathways. At present there is no evidence for ion-coupling mechanisms in the secretory membrane, i.e., no anomalous PD changes have been observed.

Furthermore, on the basis of previous studies [8–10], it became important to consider the PD changes due to changes in K^+ concentration in the absence and presence of histamine (Ref. 1). It was previously found [8,9] that, even though the H^+ rate with histamine was reduced or abolished by SCN, the area of the secretory membrane was maintained during inhibition of the H^+ rate to zero. It was also shown that, for the resting stomach [10], the addition of histamine in the presence of SCN produces a large increase in area of the secretory membrane without the establishment of acid secretion. Subsequent removal of SCN results in a substantial decrease in resistance [11,12]. Thus the establishment of H^+ secretion decreases the transmucosal resistance without changing the area of the secretory membrane. These findings led to the experiments described in the next paragraph.

In experiments with cimetidine (without histamine), SCN (with histamine) and omeprazole (with histamine), the PD response due to secretory changes in K^+ concentration was reduced compared to the response in the secreting state. Moreover, in the absence of histamine for all inhibitors, cimetidine, unlike the other two inhibitors, brought the ΔPD induced by changes in secretory K^+ concentration, usually in about 60 min, to near zero [1]. The subsequent replacement of cimetidine with SCN without histamine maintained the ΔPD near zero. The addition of histamine in the presence of SCN now produced a ΔPD of about 12 mV for a change from 4 to 80 mM K^+ in the secretory solution. We note that ΔPD is a measure of the conductance, i.e., the larger the ΔPD, the higher the partial conductance. A zero ΔPD implies that the K^+ conductance is essentially zero. Hence, histamine in the presence of SCN substantially increased the conductance. From the finding of Carlisle et al. [10] that histamine in the presence of SCN increases the surface area of the secretory membrane, we infer that the increase in conductance may well be associated with the increased area.

An important consideration in this paper was whether we could expect, for changes in the K^+ concentration, the reduction of ΔPD to near zero with cimetidine (without histamine) in Cl^--free solutions and, as in the case of Cl^- solutions [1], whether SCN would maintain the PD response at a low level in the absence of histamine and let the response rise towards control levels after the addition of histamine. In addition, the PD responses due to changes in secretory Na^+ and HCO_3^- in the secreting and resting states were considered.

Methods

Experiments were performed on fundi of stomachs of *Rana pipiens* by an in vitro method in which the stomachs were mounted between a pair of cylindrical chambers [11]. All experiments began with standard Cl^- solutions on both sides of the mucosa. The Cl^- nutrient (serosal) solution 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 10; and the new Cl^- secretory (mucosal) solution which is hypertonic [12] contained: Na^+, 156; K^+, 4; Cl^-, 160. After a steady state was obtained, these solutions were replaced with Cl^--free (SO_4^{2-}) solutions. The Cl^--free nutrient solution contained (in mM): Na^+, 102; K^+, 4; Ca^{2+}, 1; Mg^{2+}, 0.8; SO_4^{2-}, 41.3; HCO_3^-, 25; phosphate, 1; glucose 10; and sucrose 40. Two different Cl^--free secretory solutions were used for the K^+ experiments. The first contained (in mM): Na^+, 156; K^+, 4; SO_4^{2-}, 80; and sucrose, 80. The second contained (in mM): Na^+, 76; K^+, 4; Mg^{2+}, 40; SO_4^{2-}, 80; and sucrose, 120. In some experiments for increases in K^+ concentration on the secretory side, the first secretory solution was used and K^+ replaced Na^+. Later, when it was realized that there was a sizeable PD response to a change in Na^+ concentration, the second secretory solution was used. In the latter case for an increase in K^+ concentration, K^+ replaced Mg^{2+} and less sucrose was needed to maintain osmolarity. For a study of the PD response due to changes in Na^+ concentration, Mg^{2+} was substituted for Na^+ and an appropriate amount of sucrose was added. For a study of the PD response due to changes in HCO_3^- concentration, the Cl^--free (SO_4^{2-}) nutrient solution without phosphate was

used on the secretory side. In the case of a decrease in secretory HCO_3^-, SO_4^{2-} replaced HCO_3^- and sucrose was added to make up any osmotic deficit. The pH of the 25 mM HCO_3^- secretory solution was 7.3 and that of the 5 mM HCO_3^- secretory solution was 6.6.

In these experiments, the transmembrane resistance, the transmembrane potential difference (PD) and the H^+ secretory rate were measured. Two pairs of electrodes were used, one for sending current across the mucosa and the other for measuring the PD. The PD is considered positive when the nutrient side is positive relative to the secretory side of the stomach. The resistance was determined as the change in PD per unit of applied current. Current (20 μA per 1.3 cm^2 of tissue area) was applied for 1 or 2 s, first in one direction and 2 or 3 s later, in the other direction. The H^+ secretory rate was determined by the pH stat method of Durbin and Heinz [13]. The pH of the secretory solution was generally maintained between 4.7 and 5.0 except for HCO_3^- containing solutions. In all experiments, including the HCO_3^- experiments, both sides of the mucosa were gassed with 95% O_2/5% CO_2. For inhibition, cimetidine without histamine was placed in the nutrient solution in all experiments to a concentration of 1 or 2 mM. As stated in the Introduction, in some experiments, after cimetidine without histamine reduced the ΔPD due to K^+ changes in secretory concentration, the cimetidine was replaced with SCN without histamine present, the concentration of SCN being 20 mM in the secretory solution.

In Cl^- solutions it was found that cimetidine caused ΔPD, due to changes from 4 to 80 mM K^+ and back to 4 mM K^+, to decrease in magnitude in the course of time. The change in magnitude of ΔPD decreased to about zero. In Cl^--free (SO_4^{2-}) solutions, since the ΔPD without cimetidine present was about 40 mV on the average compared to about 8 mV in Cl^- media [1] for the change from 4 to 80 mM K^+, it was necessary to use longer times to bring the ΔPD down with cimetidine (without histamine). The data presented are for periods generally of 1.5 to 2 h after the addition of cimetidine in a histamine-free nutrient solution. While longer periods continued to bring the ΔPD down further to varying extents in different experiments, the interval of 1.5 to 2 h was reasonable to show that cimetidine (without histamine) causes ΔPD to decrease with time. For concentration changes of secretory Na^+ after cimetidine, ΔPD was essentially the same for prolonged periods of time.

Also as previously considered [1], the PD and resistance were read at the 10-min mark following the change to the new secretory solution. The secretory membrane has a mucous coat for the surface cells and a mucous coat plus the dimensions of the tubular lumina for the tubular cells. Hence the PD response is not immediate upon changing the solution and, from previous experience [1], it became evident that a 10 min period is reasonable for the secretory side.

Results

PD responses and resistance changes of the secreting fundus and resting fundus due to changes in K^+ concentration in Cl^--free solutions

Experiments were performed in secreting and resting (or inhibited) fundus in which the K^+ concentration in the secretory solution was changed from 4 to 80 mM and back to 4 mM. Fig. 1 is a representative plot of resistance, PD and H^+ secretory rate versus time for the changes in K^+ concentration in the secretory solution in secreting and resting fundus. The increase in K^+ concentration in secreting fundus gave a marked increase in PD and a decrease in resistance and the return to 4 mM K^+ brought the PD and resistance back towards control levels. The H^+ secretory rate showed an increase in going from 4 to 80 mM K^+ and a decrease on returning to 4 mM K^+ which confirms previous work [14]. Cimetidine (1 mM) in a histamine-free nutrient solution caused substantial increases in PD and resistance. This effect has been previously reported [15]. In resting fundus, the increase in K^+ gave in about 1.5 h a much smaller increase in PD compared to secreting fundus while the decrease in resistance was essentially the same in both situations.

In Table I, the ΔPD values at the 10-min mark after the increase in K^+ from 4 to 80 mM in the secretory solution are shown for substitution of K^+ for both Mg^{2+} and Na^+. The corresponding changes in PD, whether Na^+ or Mg^{2+} were used, were practically the same for both secreting and

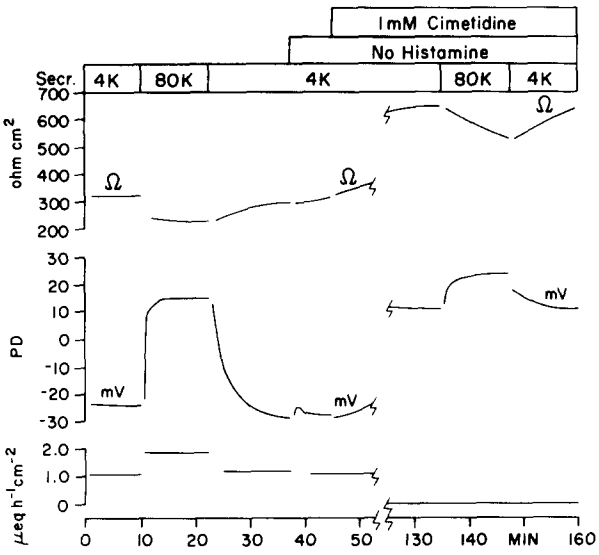

Fig. 1. Effect of changes in K^+ concentration on the secretory side from 4 to 80 mM K^+ and back to 4 mM K^+ without and with 1 mM cimetidine in nutrient. In going from 4 to 80 mM K^+, K^+ replaced Mg^{2+}. No histamine was present during cimetidine inhibition. Resistance, PD and H^+ secretory rate are plotted vs. time. Concentrations are in mM.

resting fundus. The change of K^+ from 4 to 80 mM was associated with a change of Na^+ from 156 to 80 mM. Such a Na^+ change should produce a decrease in ΔPD of about 3.5 mV magnitude (see Table II for Na^+ data). This change was not observed since, being quite small, it is obscured by biological variations and, for this reason, the data of Na^+ and Mg^{2+} are almost identical. The results are as follows.

In secreting fundus, with Mg^{2+} replacement $\Delta PD = 38.9$ mV and with Na^+ replacement $\Delta PD = 40.4$ mV. Upon return to 4 mM K^+, the corresponding values of ΔPD were -39.3 and -37.9 mV, respectively, showing excellent reversibility in both cases. In resting fundus for a K^+ increase, the corresponding values of ΔPD were again close, namely 12.7 and 11.8 mV and upon return to 4 mM K^+, there was again excellent reversibility in both cases.

The changes in resistance for secreting fundus were quite substantial for increases from 4 to 80 mM K^+, namely a decrease of the order of about 150 ohm · cm^2 in both cases. Upon return, the resistance increased to near control levels. In rest-

TABLE I

EFFECT ON POTENTIAL DIFFERENCE AND RESISTANCE OF CHANGES IN K^+ CONCENTRATIONS ON THE SECRETORY SIDE IN THE SECRETING AND RESTING FUNDUS

Values are means ± S.D. Student's *t*-test using paired observations was used to determine the level of significance. Columns labeled PD and *R* refer to the control values of transmembrane potential difference and corresponding resistance and columns labeled ΔPD and ΔR refer to changes in the two parameters 10 min after the change to the final concentration of the ion. Histamine was absent during cimetidine inhibition.

Number of expts.	$[K^+]$ (mM) orig. soln.	$[K^+]$ (mM) final soln.	PD (mV)	ΔPD (mV)	*R* (ohm · cm^2)	ΔR (ohm · cm^2)
Secreting state: Mg^{2+} replacement by K^+ and return to control						
6	4	80	−21.2 ± 5.3	38.9 ± 5.9 [a]	341 ± 38	−137 ± 44 [a]
6	80	4	16.7 ± 4.2	−39.3 ± 5.2 [a]	190 ± 40	106 ± 43 [a]
Secreting state: Na^+ replacement by K^+ and return to control						
6	4	80	−17.1 ± 5.3	40.4 ± 7.5 [a]	381 ± 74	−160 ± 69 [a]
6	80	4	23.0 ± 6.2	−37.9 ± 8.0 [a]	216 ± 44	146 ± 68 [a]
Resting state: Mg^{2+} replacement by K^+ and return to control						
6	4	80	13.1 ± 6.8	12.7 ± 4.2 [a]	551 ± 223	−141 ± 60 [a]
6	80	4	24.2 ± 6.1	−12.8 ± 3.6 [a]	418 ± 192	140 ± 61 [a]
Resting state: Na^+ replacement by K^+ and return to control						
6	4	80	9.1 ± 2.1	11.8 ± 7.7 [b]	679 ± 140	−154 ± 92 [a]
6	80	4	21.1 ± 8.5	−12.2 ± 7.9 [b]	532 ± 146	75 ± 56 [c]

[a] $P < 0.01$; [b] $P < 0.02$; [c] $P < 0.05$.

ing fundus, the resistance decreases were also of the order of 150 ohm · cm^2 in both cases but percentagewise they were smaller. Upon return, the resistance increased in both cases but attained the control level for K^+ replacement with Mg^{2+} only.

PD responses and resistance changes of the secreting fundus and resting fundus due to changes in Na^+ concentration in Cl^--free solutions

Fig. 2 is a representative plot of the resistance, PD and H^+ secretory rate versus time for concentration changes from 156 to 15.6 mM Na^+ and back to 156 mM Na^+ in the secretory solution in both secreting fundus and resting fundus. For secreting fundus, the decrease in concentration from 156 to 15.6 mM in the secretory solution caused a decrease in PD, an increase in resistance and a decrease in H^+ rate. The return to 156 mM Na^+ brought the PD back to control levels, the resistance partially back to control levels and resulted in an increased H^+ rate. After inhibition with cimetidine, the decrease in Na^+ concentration produced a smaller change in PD and a greater change in resistance. Upon return to 156 mM Na^+, the PD and resistance returned to near control levels.

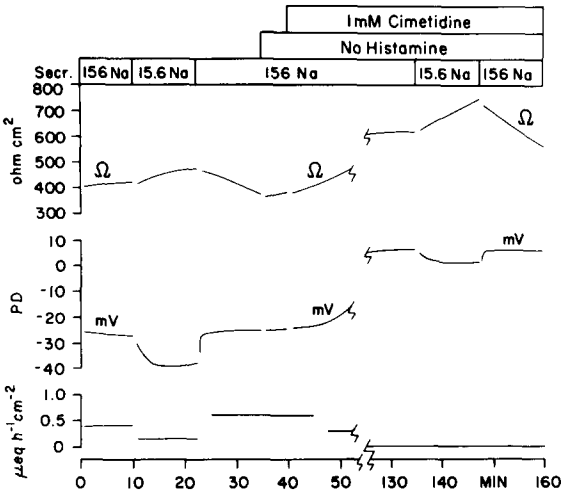

Fig. 2. Effect of changes in Na^+ concentration on the secretory side from 156 to 15.6 mM Na^+ and back to 156 mM Na^+ without and with 1 mM cimetidine in nutrient. No histamine was present during cimetidine inhibition. Resistance, PD and H^+ secretory rate are plotted vs. time. Concentrations are in mM.

In Table II, the ΔPD values at the 10-min mark and the corresponding change in resistance are shown. In secreting fundus, ΔPD was on the average -11.9 mV and, in resting fundus, ΔPD was on the average -5.6 mV for the decrease in Na^+ concentration. The difference in response between secreting and resting fundus is significant ($P < 0.01$). The resistance in going from 156 to 15.6 mM Na^+ increased by about 100 ohm · cm^2 for resting fundus and did not increase significantly for secreting fundus. Upon return to 156 mM Na^+, the resistance decrease was of the order of 150 ohm · cm^2 for resting fundus and 100 ohm · cm^2 for secreting fundus.

PD responses and resistance changes of the secreting fundus and resting fundus due to changes in HCO_3^- concentration in Cl^--free solutions

Table III shows the changes in PD and the corresponding changes in resistance for HCO_3^- changes from 25 to 5 mM and back to 25 mM. In secreting fundus, ΔPD was 3.2 mV for the decrease in HCO_3^- concentration. This change is equivalent to 4.6 mV for a 10-fold change in HCO_3^- concentration. For the resting state, the same decrease in HCO_3^- concentration gave a ΔPD of 1.5 mV which is equivalent to 2.1 mV per 10-fold change in HCO_3^- concentration. No other PD changes and no resistance changes were significant.

Effect of the absence and later presence of histamine on the PD response of K^+ in the resting fundus

As already mentioned, cimetidine (without histamine) in the nutrient solution caused ΔPD to decrease substantially in the course of time for changes in secretory K^+ from 4 to 80 mM and back to 4 mM. In some experiments after cimetidine brought the PD changes down substantially, the nutrient solution was replaced with a fresh solution without cimetidine and without histamine and SCN was added to the secretory solution to a concentration of 20 mM. Fig. 3 shows the remaining steps of the experiment. Changes in secretory concentration were made from 4 to 80 mM K^+ and back to 4 mM K^+ and at each change SCN was added immediately to the secretory solution

TABLE II

EFFECT ON POTENTIAL DIFFERENCE AND RESISTANCE OF CHANGES IN Na^+ CONCENTRATIONS ON THE SECRETORY SIDE IN THE SECRETING AND RESTING FUNDUS

See Table I for details.

Number of expts.	$[Na^+]$ (mM)		PD (mV)	ΔPD (mV)	R (ohm·cm^2)	ΔR (ohm·cm^2)
	orig. soln.	final soln.				
Secreting state						
6	156	15.6	-20.9 ± 10.5	-11.9 ± 2.1 [a]	391 ± 130	49 ± 65
6	15.6	156	-30.0 ± 8.9	11.6 ± 2.9 [a]	440 ± 98	-107 ± 31 [a]
Resting state						
6	156	15.6	4.2 ± 4.7	-5.6 ± 1.1 [a]	462 ± 130	109 ± 24 [a]
6	15.6	156	-1.5 ± 3.8	5.3 ± 0.8 [a]	560 ± 157	-147 ± 57 [a]

[a] $P < 0.01$.

to a concentration of 20 mM. The changes from 4 to 80 mM K^+ gave a ΔPD of 9.0 mV and the return to 4 mM K^+, a ΔPD of -10.7 mV. Then histamine was added to the nutrient solution to a concentration of 10^{-4} M. As a consequence of this addition, the resistance in Cl^--free (SO_4^{2-}) solutions decreased. This result is in accord with the statement in the Introduction that histamine causes the surface area of the secretory membrane to increase [10] and, furthermore, as Fig. 3 shows, the change from 4 to 80 mM K^+ in the secretory solution caused an increase in PD of 24.6 mV and the return to 4 mM K^+, a decrease of 24.3 mV.

In four experiments, with SCN inhibition and in the absence of histamine, the increase from 4 to 80 mM K^+ gave an average ΔPD of 9.0 ± 2.3 (S.D.) mV and the decrease to 4 mM K^+ gave an average ΔPD of -10.4 ± 3.7 (S.D.) mV. After the introduction of histamine to the nutrient solution to a concentration of 10^{-4} M, the corresponding average ΔPD values were 21.4 ± 4.4 (S.D.) mV and -21.1 ± 5.6 (S.D.) mV. Moreover, in five experiments, the introduction of histamine in the nutrient solution to a concentration of 10^{-4} M gave about 10 min later a decrease in resistance of 115 ± 51 (S.D.) ohm · cm^2 (from 381 ± 207 (S.D.) ohm · cm^2 to 266 ± 172 (S.D.) ohm · cm^2).

We also note that a similar experiment with SCN inhibition for 10-fold changes in secretory Na^+ concentration gave changes in PD which were not essentially different in the absence and in the presence of histamine.

TABLE III

EFFECT ON POTENTIAL DIFFERENCE AND RESISTANCE OF CHANGES IN HCO_3^- CONCENTRATIONS ON THE SECRETORY SIDE IN THE SECRETING AND RESTING FUNDUS

See Table I for details.

Number of expts.	$[HCO_3^-]$ (mM)		PD (mV)	ΔPD (mV)	R (ohm·cm^2)	ΔR (ohm·cm^2)
	orig. soln.	final soln.				
Secreting state						
5	25	5	-10.1 ± 7.2	3.2 ± 1.1 [a]	369 ± 164	-34 ± 34
5	5	25	-7.1 ± 7.1	-0.4 ± 2.1	345 ± 144	8 ± 11
Resting state						
5	25	5	3.5 ± 3.5	1.5 ± 0.5 [a]	444 ± 165	3 ± 11
5	5	25	5.4 ± 3.7	0.1 ± 0.7	428 ± 131	22 ± 28

[a] $P < 0.01$.

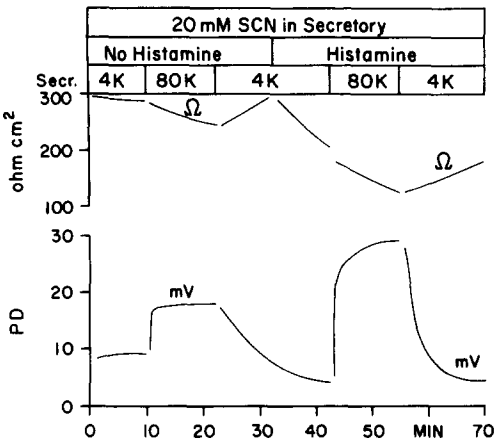

Fig. 3. Effect of changes in K^+ concentration on the secretory side from 4 to 80 mM K^+ and back to 4 mM K^+ in the presence of SCN in the secretory solution without and with 10^{-4} M histamine. Concentrations are in mM.

Discussion

From the definitions of normal and anomalous response in the Introduction, it appears that K^+, Na^+ and HCO_3^- gave normal PD responses and hence the pathways for these ions may be considered to be simple conductance pathways in the secretory membrane. In Cl^--free as in Cl^- solutions, there is no evidence for ion-coupling mechanisms which could produce an anomalous PD response.

Since K^+ substitution for Mg^{2+} and for Na^+ gave similar changes in PD as mentioned earlier, we can average these results. We obtain an average ΔPD of 30.3 mV per 10-fold increase in K^+ concentration which is in accord with the value of 31 mV previously obtained [16]. For the decrease in K^+ concentration, we obtained 29.7 mV per 10-fold change in K^+ concentration which is a bit higher than that previously obtained, namely 27.4 mV [16].

In Cl^--free media, ΔPD as stated above was 30.3 mV for a 10-fold increase of secretory K^+ concentration whereas, in Cl^- media, ΔPD was less than 8 mV [1] for the same increase in K^- concentration. A reasonable explanation of the difference may be due to the shunting effect of the high Cl^- conductance of the secretory membrane (for other factors, see Ref. 1). In the absence of Cl^-, it would then be expected that ΔPD for K^+ changes in concentration would be substantially higher. If the K^+ conductance were the only Nernstian pathway of any importance, we would then expect a change of 58 mV instead of 30.3 mV. In this study, we find that for the secreting fundus Na^+ and HCO_3^- also contribute to ΔPD such that the sum of all three $|\Delta PD|$ values, per 10-fold changes in concentration, was about 47 mV which is close to 58 mV. This difference may be due to the conductance of the proton pump pathway. The use of an HCO_3^- solution on the secretory side undoubtedly changes the H^+ concentration profile along the lumen of the tubule and therefore ΔPD may simply be the consequence of a change in H^+ concentration.

Cimetidine without histamine in 1.5 to 2 h caused a marked decrease in $|\Delta PD|$ for changes in concentration of K^+, Na^+ and HCO_3^- compared to $|\Delta PD|$ for secreting fundus. The replacement of cimetidine with SCN in the absence of histamine produced a further decrease in the PD response due to changes in secretory K^+ concentration. The addition of histamine in the presence of SCN increased the PD response. In such studies in Cl^- media [1], the increase in $|\Delta PD|$ was attributed to histamine increasing secretory membrane area which, in turn, resulted in an increase in K^+ conductance. This hypothesis can also account for the enhancement of the PD response after the introduction of histamine in the presence of SCN in Cl^--free media. In a similar experiment involving Na^+ in the presence of SCN, there was no significant difference in the PD response in the presence and absence of histamine. Why histamine should affect the PD response due to concentration changes of K^+ and Na^+ differently has not as yet been established.

Of interest in this study is the fact that the addition of histamine in the presence of SCN in Cl^--free media decreased the resistance significantly while, in Cl^- media under the same circumstances, the decrease in resistance was not significant [12]. Tentatively one might argue that the decrease in resistance due to histamine is obscured by the shunting effect of Cl^- in Cl^- media while it is unmasked in the absence of Cl^-. There remains, however, the need to study the effects of histamine in greater detail in both media

While we have associated the decrease in K^+ resistance with an increase in surface area, we cannot exclude the possibility that histamine may act directly to increase K^+ conductance per se by opening K^+ channels. This possibility arises from the fact that histamine addition had no effect on the PD responses due to Na^+. At this stage, we can only conclude that histamine increases secretory membrane area leading to a decrease in K^+ resistance and/or decreases K^+ resistance directly.

Acknowledgments

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