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

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The effects of changes in secretory concentrations of K^+, Cl^- and Na^+ on transmembrane potential difference (PD) and resistance were compared for secreting fundus and resting fundus of *Rana pipiens*. In the resting fundus experiments histamine was present, and SCN and omeprazole gave similar results. Increase of K^+ from 4 to 80 mM, decrease of Cl^- from 160 to 16 mM and decrease of Na^+ from 156 to 15.6 mM gave, respectively, 10 min after the change, in the secreting fundus $\Delta PD = 7.6$, 10.0 and -2.2 mV and in the resting fundus $\Delta PD = 4.3$, 14.4 and 0 mV. With cimetidine and no histamine, increase of K^+ from 4 to 80 mM gave a ΔPD which decreased to near zero after exposure to cimetidine for at least 30 min. For the same K^+ change, replacement of cimetidine with SCN or omeprazole and without histamine maintained ΔPD near zero and subsequent addition of histamine with inhibitor present gave a ΔPD of about 12 mV. The change in ΔPD was attributed to histamine increasing the secretory membrane area, which results in an increase in K^+ conductance. Increase in ΔPD in the resting fundus compared to the secreting fundus for a decrease from 160 to 16 mM Cl^- may be due to relatively little Cl^- entering the lumina from cells in the resting fundus, which would result in a greater change of the ratio intracellular Cl^-/luminal Cl^- in the resting fundus than in the secreting fundus for the decrease in Cl^- studied.

Introduction

The ion substitution method, in which we investigate the effect on transmembrane potential difference (PD) of the replacement of an ion by a relatively impermeant ion, has been used extensively to determine the characteristics of the ion pathways. Studies have been reported with K^+, Na^+, and Cl^- replacement in the nutrient solution of the secreting fundus and of the antrum of the stomach [1–6]. In such studies, 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 results in a decrease in the positivity of the nutrient was attributed to the existence of a simple conductance pathway [1]. Second, an anomalous PD response in which an increase in concentration of a cation such as K^+ or Na^+ results in an increase in the positivity of the nutrient was attributed to the existence of an electrogenic (Na^+K^+)-ATPase antiport [2–4] and an electrogenic NaCl symport [5,6]. As a consequence of these studies, simple K^+ and Cl^- conductance pathways [1], an electrogenic ($Na^+ + K^+$)-ATPase pump pathway [2–4] and an electrogenic NaCl symport pathway [5,6] have been postulated as present in the nutrient membrane. Similar studies in the resting (or in-

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hibited) fundus are underway but are not the basis for the present paper.

In the present paper, we focus our attention on the existence of K^+, Na^+ and Cl^+ conductance pathways in the secretory membrane of the secreting and resting (or inhibited) fundus since such studies by the ion substitution method have not been undertaken to any considerable extent thus far. Some sporadic results exist. For example, Flemstrom and Sachs [7] reported the existence of a Na^+ conductance pathway in the frog antral secretory membrane. In a study of the NaCl symport of the antral nutrient membrane, Carrasquer et al. [5] additionally reported that a Cl^- conductance pathway exists in the secretory membrane and confirmed the Na^+ conductance pathway found by Flemstrom and Sachs. Recently, some information on the PD response due to a change in K^+ concentration for relatively high secreting frogs, i.e. for H^+ rates greater than 4 μequiv. $\cdot h^{-1} \cdot cm^{-2}$, was reported for the secreting fundus [8]. The ΔPD for a change in secretory K^+ from 4 to 80 mM attained a maximum of about 8 mV and then declined towards control levels. As shown below, a similar maximum was obtained for slower secreting frogs, i.e. for H^+ rates below 4 μequiv. $\cdot h^{-1} \cdot cm^{-2}$, but generally the PD response did not decline to control levels.

In the studies discussed immediately above, histamine was present throughout each experiment. The question arose whether the PD response due to an ion such as K^+ might be different in the absence of histamine. Further, would the addition of histamine after its absence alter the PD response due to the same ion concentration change? The basis of these considerations is as follows.

In previous studies [9,10], it was found that, even though the H^+ rate with histamine was reduced or abolished by SCN, the area of the secretory membrane was maintained until the rate was abolished. It has also been shown that, in a resting stomach, the addition of histamine in the presence of SCN produces the usual large increase in area of the secretory membrane without the establishment of acid secretion [11]. Recently, it was found that subsequent removal of SCN resulted in a substantial decrease in resistance [12]. In other words, the reestablishment of H^+ secretion results in a decrease in the transmucosal resistance without change in the area of the secretory membrane. In what follows it will be seen that the presence or absence of histamine influences the PD response of K^+ in the resting or inhibited fundus.

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 [13]. 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^- standard secretory (mucosal) solution which is hypertonic [12] contained: Na^+, 156; K^+, 4; and Cl^-, 160. For increases in K^+ concentration on the secretory side, K^+ replaced Na^+ and for decreases in Na^+ concentration, choline replaced Na^+. In the case of a decrease in Cl^- concentration, SO_4^{2-} replaced Cl^- and sucrose was added to make up any osmotic deficit.

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 [14]. The pH of the secretory solution was generally maintained between 4.7 and 5.0. In all experiments, both sides of the mucosa were gassed with 95% O_2/5% CO_2.

For inhibition, 20 mM SCN or 0.4 mM omeprazole in the nutrient solution decreased the H^+ secretory rate to zero. In the study of PD responses to ion changes in the inhibited fundus, histamine was always present except if specifically stated in the text that it was absent. Inspection of

the data indicated no difference between SCN-inhibited and omeprazole-inhibited fundi. Hence for presentation herein, the data are lumped. For studies with 1 mM cimetidine in the nutrient solution, the latter was first replaced with a histamine-free solution. Generally cimetidine takes at least 30 min to attain zero H^+ rate. In some experiments, no histamine was added at the beginning of the experiment and, under these circumstances, cimetidine gave zero H^+ rate in about 10 to 20 min.

In previous studies on the nutrient side, due to the existence of a diffusion barrier between the nutrient solution and the nutrient membrane, it took about 10 min (approx. five times constants) for the concentration of the ion at the cell membrane to attain the new concentration in the nutrient solution. In those studies, the PD and resistance were read at the 10 min mark following the change to the new solution. While there are no diffusion barriers in the form of connective tissue and muscle layers in the secretory membrane, there is a mucous coat for the surface cells and a mucous coat plus the dimensions of the tubular lumina for the tubular cells. From the results of studies of changing K^+ concentration in the secretory solution, it became evident that a 10 min period is also reasonable for the secretory side. If a PD maximum was present, it was also recorded. In other cases, the PD continued to increase slowly up to the 10 min mark so that in these cases the PD maximum was taken as the PD reading at 10 min. The latter usually occurs for poor and moderate H^+ secretory rates, i.e. for H^+ rates under 4 μequiv.$\cdot h^{-1} \cdot cm^{-2}$. In the experiments here, the H^+ rates were generally less that 4 μequiv.$\cdot h^{-1} \cdot cm^{-2}$.

Results

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

Experiments were performed in secreting and resting fundus in which the K^+ concentration in the secretory solution was changed either from 4 to 40 mM or from 4 to 80 mM and in each case back to 4 mM. Fig. 1 is a representative plot of resistance, PD and H^+ secretory rate versus time

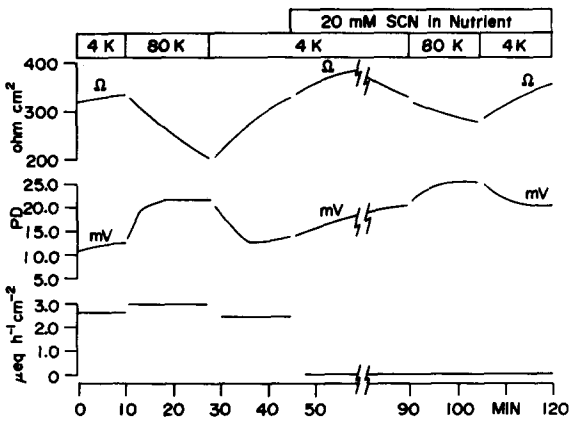

Fig. 1. Effect of changes in K^+ concentration on the secretory side from 4 to 80 mM K^+ and back to 4 mM K^+ without and with 20 mM SCN in nutrient. Resistance, PD and H^+ secretory rate are plotted vs. time. Concentrations are in mM.

from 4 to 80 mM K^+ and back to 4 mM in secreting and resting fundus. The increase in K^+ in secreting fundus gave an increase in PD and a marked decrease in resistance and the returning to 4 mM K^+ brought the PD and resistance back towards control levels. SCN (20 mM) in the nutrient solution initially increased the PD and resistance and later decreased the resistance. This effect has been previously reported [15,16]. In resting fundus, the increase in K^+ gave a smaller increase in PD and a smaller decrease in resistance compared to secreting fundus. The return to 4 mM K^+ brought the PD and resistance back toward control levels. The H^+ secretory rate showed a small increase in going from 4 to 80 mM K^+ and a decrease in returning to 4 mM K^+.

In Table I, the maximum ΔPD and ΔPD at the 10 min mark after the change to both 40 and 80 mM K^+ in the secretory solution are shown. For secreting fundus, in going from 4 to 40 mM K^+, the maximum ΔPD was 3.7 mV and ΔPD at 10 min was 2.7 mV and for resting fundus, the corresponding changes were quite similar, namely 3.4 and 2.8 mV. Upon return to 4 mM K^+, the PD changes were in reverse order and of comparable magnitude. For secreting fundus, in going from 4 to 80 mM K^+, the maximum ΔPD was 8.2 mV and ΔPD at 10 min was 7.6 mV and, for resting fundus, the corresponding values were 4.7 and 4.3 mV. Unlike the change from 4 to 40 mM K^+ in

TABLE I

EFFECT ON PD 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 the transmembrane potential difference and corresponding resistance and columns labeled ΔPD and Δ*R* refer to changes in the two parameters following the change to the final concentration of the ion. Subscripts M and 10 refer, respectively, to the maximum (increasing K^+) or minimum (decreasing K^+) ΔPD and ΔPD at 10 min after the change in concentration and the corresponding values of resistance. Histamine was present throughout the experiments. SCN and omeprazole data are lumped.

No. of expts.	$[K^+]$ (mM) orig. soln.	final soln.	PD (mV)	ΔPD_M (mV)	ΔPD_{10} (mV)	R (ohm·cm^2)	ΔR_M (ohm·cm^2)	ΔR_{10} (ohm·cm^2)
Secreting state								
8	4	40	20.0 ± 5.3	3.7 ± 1.6 [a]	2.7 ± 2.7 [c]	246 ± 92	−53 ± 32 [a]	−82 ± 32 [a]
8	40	4	23.0 ± 3.6	−4.8 ± 0.9 [a]	−2.5 ± 2.4 [c]	162 ± 68	39 ± 36 [b]	78 ± 31 [a]
15	4	80	16.4 ± 5.0	8.2 ± 3.1 [a]	7.6 ± 3.7 [a]	284 ± 74	−143 ± 51 [a]	−129 ± 51 [a]
15	80	4	24.2 ± 4.6	−11.3 ± 2.6 [a]	−10.7 ± 3.1 [a]	155 ± 35	70 ± 47 [a]	99 ± 57 [a]
Resting state								
8	4	40	31.1 ± 7.4	3.4 ± 1.2 [a]	2.8 ± 1.7 [a]	260 ± 114	−54 ± 27 [a]	−60 ± 22 [a]
8	40	4	33.8 ± 6.1	−3.9 ± 1.5 [a]	−3.6 ± 1.8 [a]	200 ± 99	16 ± 45	31 ± 39
15	4	80	23.6 ± 8.4	4.7 ± 2.7 [a]	4.3 ± 3.2 [a]	306 ± 63	−74 ± 30 [a]	−74 ± 30 [a]
15	80	4	28.0 ± 6.2	-	−6.5 ± 2.5 [a]	230 ± 57	-	65 ± 44 [a]

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

resting fundus, the change from 4 to 80 mM K^+ produced PD changes which were markedly smaller than those in secreting fundus. Upon return to 4 mM K^+, there was no minimum in resting fundus, but ΔPD at 10 min was in reverse order and of somewhat greater magnitude than the PD change from 4 to 80 mM K^+.

The changes in resistance for secreting fundus were quite substantial for changes from 4 to 40 mM K^+ and from 4 to 80 mM K^+. The decreases in resistance at 10 min were, respectively, of the order of 80 and 130 ohm · cm^2. Upon return to 4 mM K^+, the resistance increased to near control levels. In resting fundus, the resistance decreases were less and, upon return to 4 mM K^+, the resistance showed a significant increase only for the change from 80 to 4 mM K^+.

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

Fig. 2 is a representative plot of the resistance, PD and H^+ secretory rate versus time for concentration changes from 160 to 16 mM Cl^- and back to 160 mM Cl^- in the secretory solution for both secreting fundus and resting fundus. For secreting fundus, the decrease in Cl^- concentration from 160 to 16 mM in the secretory solution

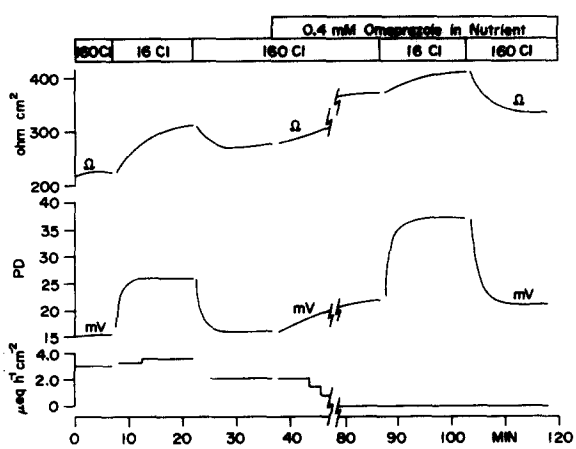

Fig. 2. Effect of changes in Cl^- concentration on the secretory side from 160 to 16 mM Cl^- and back to 160 mM Cl^- without and with 0.4 mM omeprazole in nutrient. Resistance, PD and H^+ secretory rate are plotted vs. time. Concentrations are in mM.

TABLE II

EFFECT ON PD AND RESISTANCE OF CHANGES IN Cl^- CONCENTRATIONS ON THE SECRETORY SIDE IN THE SECRETING AND RESTING FUNDUS

See Table I for details.

No. of expts.	$[Cl^-]$ (mM) orig. soln.	$[Cl^-]$ (mM) final soln.	PD (mV)	ΔPD_{10} (mV)	R (ohm·cm^2)	ΔR_{10} (ohm·cm^2)
Secreting state						
11	160	16	16.3±4.1	10.0±3.0 [a]	275±82	47±31 [a]
11	16	160	26.5±4.8	−8.8±4.2 [a]	342±95	−50±39 [a]
Resting state						
11	160	16	23.5±8.8	14.4±2.2 [a]	303±73	52±20 [a]
11	16	160	37.9±9.5	−14.6±2.8 [a]	354±69	−55±23 [a]

[a] $P < 0.01$.

caused an increase in PD, an increase in resistance and a small increase in H^+ rate. The return to 160 mM Cl^- brought the PD back to control levels, brought the resistance back partially to control levels, and resulted in a decreased H^+ secretory rate. As seen in Fig. 2, after omeprazole inhibited H^+ secretion, the same changes in Cl^- concentration produced qualitatively similar changes in PD and resistance. With the decrease in Cl^- concentration, the PD and resistance increased and upon return to 160 mM Cl^- the PD and resistance decreased, returning essentially to control levels. Quantitatively it should be noted that the magnitude of the change in PD is greater in resting fundus than in secreting fundus in going from 160 to 16 mM Cl^- and also in returning to 160 mM Cl^-.

For Cl^-, there was at no time a distinctive maximum or minimum. Hence in Table II only ΔPD at the 10 min mark and the corresponding change in resistance are shown. In secreting fundus, ΔPD was on the average 10.0 mV and, in resting fundus (lumped omeprazole and SCN data (see Methods)), ΔPD was on the average 14.4 mV. The difference is significant ($P < 0.01$). An explanation of the difference is given in the Discussion below. The resistance increased with a decrease in Cl^- and vice versa. The changes in resistance were in all cases about 50 ohm · cm^2 in magnitude.

TABLE III

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

See Table I for details.

No. of expts.	$[Na^+]$ (mM) orig. soln.	$[Na^+]$ (mM) final soln.	PD (mV)	ΔPD_{10} (mV)	R (ohm·cm^2)	ΔR_{10} (ohm·cm^2)
Secreting state						
7	156	15.6	20.2±3.9	−2.2±1.0 [a]	327±120	17±8 [a]
7	15.6	156	18.0±4.0	1.2±1.2 [b]	344±158	−22±21 [b]
Resting state						
7	156	15.6	34.7±6.1	−0.6±1.6	267±128	28±18 [a]
7	15.6	156	34.1±5.8	−1.2±1.4	297±135	−34±20 [a]

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

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

Table III shows the changes in ΔPD at the 10 min mark and the corresponding changes in resistance for Na^+ changes from 156 to 15.6 mM Na^+ and back to 156 mM Na^+. In secreting fundus, ΔPD was −2.2 mV for the decrease in Na^+ concentration and the change in resistance was 17 ohm · cm^2. Upon return to 156 Na^+, ΔPD was 1.2 mV and the resistance returned to control values. All these changes although small were significant. In resting fundus, the PD changes were not significant but the resistance changes although small (of the order of 30 ohm · cm^2) were significant.

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

In some experiments after a steady H^+ secretory rate was established, the solutions on both sides of the gastric mucosa were replaced with fresh solutions and no histamine was added to the new nutrient solution. The addition of cimetidine (1 mM) to the nutrient solution brought the H^+ rate to zero. Then, the K^+ concentration was changed from 4 to 80 mM and back to 4 mM in the secretory solution. The initial changes from 4 to 80 mM might give a ΔPD of several mV. In about 30 min or more, ΔPD resulting from the changes from 4 to 80 mM K^+ and back to 4 mM became increasingly smaller. In nine experiments in which the K^+ concentration was changed at least 30 min after cimetidine, an increase from 4 to 80 mM K^+ gave an insignificant ΔPD, namely ΔPD = -0.6 ± 1.5 (S.D.) mV and, in seven experiments, the reverse change gave a small ΔPD, namely ΔPD = -1.2 ± 1.1 (S.D.) mV. The insignificant or small PD response can be attributed to the decrease in secretory area by cimetidine in the absence of histamine (see Introduction).

The next series of experiments involved the eventual introduction of histamine to the nutrient solution. In these experiments, no histamine was added to the nutrient solution in the initial stages and cimetidine at a concentration of 1 mM in the nutrient solution was used as above to bring the H^+ rate to zero. Then, as above, the changes from 4 to 80 mM K^+ and back to 4 mM gave in about

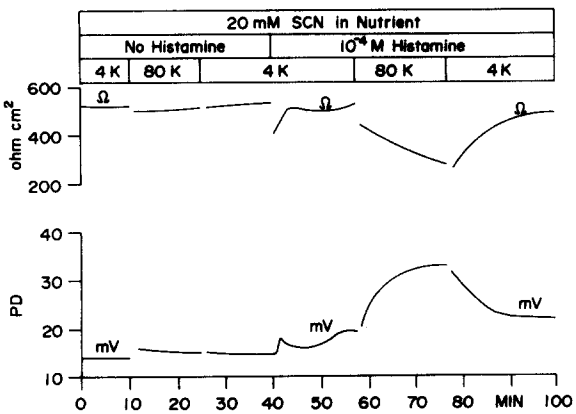

Fig. 3. Effect of changes in K^+ concentration on the secretory side from 4 to 80 mM K^+ and back to 4 mM K^+ in the presence of SCN without and with 10^{-4} M histamine. Concentrations are in mM.

30 min or more after cimetidine ΔPD close to zero. At this point the nutrient solution was replaced with a fresh solution without cimetidine and SCN was added to the nutrient solution to a concentration of 20 mM. Fig. 3 shows the remaining steps of the experiment. The changes from 4 to 80 mM K^+ and back to 4 mM K^+ maintained ΔPD close to zero. Then histamine was added to the nutrient solution to a concentration of 10^{-4} M. As stated in the Introduction, the addition of histamine causes the surface area of the secretory membrane to increase [11] and, as Fig. 3 shows, the change from 4 to 80 mM K^+ in the secretory solution caused an increase in PD of about 13 mV and the return to 4 mM K^+ brought the PD back to control levels.

We note that omeprazole gave the same results as SCN. In three experiments with 20 mM SCN and two experiments with 0.4 mM omeprazole in the nutrient solution, the addition of histamine caused in each case the marked increase in PD, due to the changes in K^+ concentration from 4 to 80 mM. The average value of ΔPD for these five experiments was 12.4 ± 4.7 (S.D.) mV ($P < 0.01$).

Of interest also is ΔPD due to changes in Cl^- concentration from 160 to 16 mM and back to 160 mM for a control period (histamine present) with H^+ secretion and for the period after cimetidine (without histamine) reduced ΔPD for K^+ changes to near zero values. In five experiments the change

from 160 to 16 mM Cl^- gave $\Delta PD = 8.8 \pm 3.0$ (S.D.) mV for the control period and 12.6 ± 6.4 (S.D.) mV after cimetidine reduced ΔPD for K^+ to near zero values. Upon return to 160 mM Cl^-, the corresponding ΔPD values were -8.7 ± 3.8 (S.D.) mV and -13.8 ± 5.4 (S.D.) mV. Thus even though ΔPD goes to zero for K^+, ΔPD for Cl^- is greater with cimetidine than without cimetidine. A plausible reason will be considered in the Discussion.

We examined whether SCN in the absence of histamine would reduce the magnitude of ΔPD to 1 or 2 mV for changes of secretory K^+ from 4 to 80 mM and back to 4 mM. In 2.5 h, ΔPD was reduced from 11 mV to about 6.5 mV. SCN was washed out and a fresh nutrient solution with 1 mM cimetidine was used. In about 50 min, ΔPD was reduced for the same changes in K^+ concentration to less than 2 mV. Addition of histamine (10^{-4} M) gave $\Delta PD = 9.7$ mV for the increase from 4 to 80 mM K^+ and $\Delta PD = -12.2$ mV for the decrease from 80 to 4 mM K^+.

Discussion

From the definition of normal and anomalous PD responses in the Introduction, it appears that K^+, Na^+ and Cl^- give normal PD responses and hence the pathways for these ions may be considered to be simple conductance pathways in the secretory membrane. At present there is no evidence for ion-coupling mechanisms which could give anomalous PD changes.

We find that for the secreting fundus K^+, Na^+ and Cl^- contribute to ΔPD such that the sum of the ΔPD values, per 10-fold changes in concentration, is about 16 mV; and for the resting fundus K^+, Cl^- and HCO_3^- contribute to ΔPD such that the sum of the ΔPD values is about 20 mV. The contribution of HCO_3^- to the sum is about 2 mV [17]. The explanation of a sum of ΔPD values per 10-fold change in ionic concentrations less than 58 mV lies partly in the inability of the ions to attain the same concentration at the border of the plasma membranes of the lumina that exists in the secretory solution. Another factor which needs consideration is the partial proton conductance.

Furthermore, for Cl^- there is an additional complication. Let us examine the change in PD when Cl^- is changed from 160 to 16 mM in the secretory solution. In resting fundus, for 16 mM Cl^- in the secretory solution, the concentration of Cl^- near the plasma membranes of the lumina would be lower than in secreting fundus because for resting fundus it is reasonable to assume that relatively little Cl^- enters the lumina from the cells. On the assumption that the intracellular Cl^- concentration remains about the same shortly after the change in secretory Cl^- concentration, the change of the ratio of the intracellular to luminal Cl^- concentration when secretory Cl^- is decreased from 160 to 16 mM will be greater in resting than in secreting fundus. Therefore, ΔPD when secretory Cl^- is decreased from 160 to 16 mM should be greater in resting than in secreting fundus.

An important finding in the present studies is the dependence of ΔPD for K^+ on the surface area, i.e., an increase in K^+ resistance with a decrease in surface area. This was borne out particularly by the fact that addition of histamine in the presence of SCN increased the surface area [11] and the experimental finding that, under these circumstances, ΔPD for an increase of K^+ from 4 to 80 mM in the secretory solution increased from practically zero to about 12 mV. The latter resulted from a decrease in K^+ resistance with the increase in surface area following the addition of histamine.

It is also to be noted that the increase in ΔPD after histamine occurred irrespective of whether the inhibitor was SCN, omeprazole or cimetidine.

The effects of cimetidine on the ΔPD of K^+ and Cl^- concentration changes in the secretory solution are of interest in light of a postulate made by Clausen et al. [18]. Their postulate is that the characteristics of the secretory membrane do not change when the secretory membrane area is markedly changed, e.g., the partial conductances of K^+ and Cl^- remain the same. This postulate is not supported by our finding that cimetidine reduces ΔPD for K^+ changes but does not reduce ΔPD for Cl^- changes. Our results confirm our previous finding [12] that the characteristics of the membrane are changed despite the fact that there may be no change in secretory membrane area.

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