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The Effect of Electric Current on HCl Secretion by Isolated Frog Gastric Mucosa

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Hoffmann (1889) was one of the first workers to maintain, on the basis of animal experiments, that stomach secretion was increased by direct current. Many confused and contradictory results have since been published. Claims have been made that direct current affects the motor but not the secretory activity of the human stomach (Schawerin, 1937), the motor and secretory activity (Kirstner, Gorinstein & Rudoy, 1931), and that it has no effect at all (Goldschmidt, 1895). All this early work can be criticized as insufficiently controlled. The secondary effects due to vagal stimulation, when the currents were large enough, were not separated from any direct action on the oxyntic cells.

Recently, Rehm (1945) has shown by controlled experiments on the stomach of a live dog that current passed through the wall of a secreting stomach from mucosa to serosa decreased the rate of secretion of hydrochloric acid, but that current passed from serosa to mucosa increased the rate of acid secretion. In a non-secreting stomach, acid production was not initiated by passing electric current through it in either direction.

These results became available to us during our investigation into the possibility that gastric mucosa could utilize electrical energy presented to it from external sources. Since acid secretion in frog gastric mucosa is accompanied by a change in the electrical potential difference across it, it seemed possible that the rate of secretion might be affected when this p.d. is changed by passing a current through the mucosa.

The experiments described in this paper show that currents enhancing the natural p.d. of isolated frog gastric mucosa increased the rate of acid secretion and sometimes even initiated it. Currents in the opposite direction decreased the rate of acid

secretion. The effect was specific to secretive gastric mucosa, i.e. mucosa which is capable of secreting hydrochloric acid (either spontaneously or by stimulation) whether or not it is actually secreting (Crane & Davies, 1947). The significance of the experimental results is discussed.

A part of the present work was communicated to the Biochemical Society (Crane, Davies & Longmuir, 1946).

EXPERIMENTAL

The materials, apparatus and methods used during these experiments were similar to those previously described by Crane, Davies & Longmuir (1948). Three species of frog (*Rana temporaria temporaria* L., *R. esculenta* L. and *R. esculenta ridibunda* Pallas) and toads (*Bufo bufo bufo* L.) were used.

Frog or toad gastric mucosa was mounted in a perspex holder held between two chambers at 25°. The Q_{HCl} of the mucosa (in μ l./mg. dry wt./hr.) was estimated from changes in pH of the secretory solution measured *in situ*. In most experiments it was also found by changing the secretory solution and estimating the acid content of the samples thus obtained either manometrically by the addition of a bicarbonate solution, or by electrometric titration using a glass electrode and 0.01N-NaOH delivered from a Conway burette.

Owing to the buffering capacity of the relatively large amount of mucus secreted by frog gastric mucosa, the HCl concentration determined from the pH of the secretory solution may be considerably less than the total concentration determined manometrically or by electrometric titration (cf. Davies & Longmuir, 1948). In cases where only a pH determination *in situ* was made the value of the acid concentration was corrected for this buffering effect.

The p.d. across the mucosa was measured with a battery-operated Marconi pH meter and potentiometer Type TF 511 C, using saturated calomel electrodes and saturated KCl bridges with internal ground-glass joints, which dipped

into the nutrient and secretory solutions. Current was passed through the mucosa by means of zinc-zinc acetate electrodes separated from the solutions bathing the mucosa by the agar layers previously described (Crane *et al.* 1948). The resistance was obtained from the slope of the p.d.-current graph, a correction being made for the resistance of the solution.

The order of procedure was as follows: after the p.d. across the mucosa had become steady, current was passed through the mucosa, usually for periods between 0.5 and 1 hr., alternating with 0.5 hr. rest periods when no current was passed. So that the natural rise and fall of the Q_{HCl} should not be misinterpreted as the result of applied currents, different directions and magnitudes of the currents were used in various orders in consecutive experiments. Errors in the determinations of the change in Q_{HCl} due to a current were in general less than ± 0.2 except at low rates of secretion, when accuracies up to $\pm 10^{-4}$ were obtainable. Currents used were usually those giving densities of 0.40 and 1.0 ma./cm.² of mucosa.

RESULTS

It has previously been shown (Crane *et al.* 1948) that the secretory side of isolated frog gastric mucosa is negative with respect to the nutrient (submucosal) side, the mean p.d. across the mucosa being -30 mV. Currents passed through the membrane from nutrient to secretory side increased the magnitude of the p.d. across it and are called enhancing currents. Currents passed in the opposite direction are called opposing currents. A small opposing current decreased the p.d. across the mucosa; on increasing the opposing current the net p.d. became zero and finally increased in the opposite direction. This is shown in Fig. 1, in which the p.d. across the mucosa is plotted

Fig. 1. Relationship between p.d. across an isolated frog gastric mucosa and current density in it. (Slope of curve at any point = resistance of 1 cm.² of mucosa.)

against the applied current density for a typical frog gastric mucosa. The characteristics of this curve will be discussed elsewhere. It is shown here because it formed the basis for the choice of current densities used; 0.4 ma./cm.² was usually below, and 1.0 ma./cm.² usually above, the value at which the

change in slope occurred (breakdown current density). Current densities below this breakdown value produced no detectable irreversible change in the mucosa. Current densities just above the breakdown value seemed to be the maximum compatible with subsequent normal functioning of the mucosa.

Gastric mucosae from 28 frogs and 2 toads were used in these experiments, during which current was passed for eighty-four separate periods. Comparable quantitative data were obtained for sixty-one of these periods. Control experiments, which have been described elsewhere (Crane *et al.* 1948), were carried out with 150 other frog gastric mucosae through which no current was passed. Results are described for secretive mucosae when they were initially (a) secreting and (b) not secreting, for non-secretive gastric mucosae and for six non-gastric membranes.

Secretive mucosae initially secreting acid. In sixteen out of seventeen cases an enhancing current increased the rate of acid secretion from a Q_{HCl} between 0.2 and 2 during control periods to a Q_{HCl} between 1 and 4 while the current was passing. In one experiment the Q_{HCl} was reduced by 0.1 during the passage of an enhancing current of density 0.4 ma./cm.². Histamine had been added to the nutrient solution in six of these seventeen cases. Fig. 2 shows the frequency distribution of the increase in Q_{HCl} , and Fig. 3 the increase plotted against the initial Q_{HCl} . There was no significant difference between the Q_{HCl} increases for the current densities of 0.4 and 1.0 ma./cm.²; the mean increases were 1.0 ± 0.3 and 1.2 ± 0.2 respectively. Figs. 2 and 3 also show the results for opposing currents. In six out of nine experiments the Q_{HCl} was abolished by an opposing current density of 0.4 or 1.0 ma./cm.². In two out of nine experiments 1.0 ma./cm.² reduced the Q_{HCl} almost but not quite to zero; in one case 0.4 ma./cm.² had no apparent effect on a Q_{HCl} of 0.3. Figs. 2 and 3 show further that the absolute change in Q_{HCl} was of the same order of magnitude for both enhancing and opposing currents. The fractional change in Q_{HCl} was greater for enhancing currents; the rate of acid secretion in most cases (twelve out of seventeen) was more than doubled by an enhancing current, whereas in not one case out of nine was it reduced by more than its own value. Such a reduction would correspond to an absorption of acid or secretion of alkali. The mean fractional increase in Q_{HCl} ($\Delta Q_{HCl}/Q_{HCl}$) for the twelve experiments with an enhancing current density of 1.0 ma./cm.² was 2.1 ± 0.4 and for the five experiments with 0.4 ma./cm.² 1.4 ± 0.7 . Thus there is no significant difference between the two current densities. The mean fractional decrease of Q_{HCl} for the nine experiments with opposing currents was 0.8 ± 0.1 . For all seventeen experiments with enhancing currents the mean fractional increase in

Fig. 2. Frequency distribution of changes in Q_{HCl} due to currents enhancing or opposing the natural p.d. across isolated frog gastric mucosa.

Table 1. *Initiation of hydrochloric acid secretion by enhancing current*

Reference number of mucosa	P.d. level (mV.)	Experimental time				Current density (ma./cm. ²)	Q_{HCl}		
		At addition of histamine (hr.) (min.)	At commencement of current (hr.) (min.)	At end of current (hr.) (min.)			Before current	During current	After current
145	36	—	1 4	2 29	1.0		0.0	0.4	0.0
182	37	—	1 51	2 17	0.4		0.0	1.9	0.6
141	24	1 13	2 35	3 42	1.0		0.0	2.0	2.0
229	28	1 18	3 13	4 29	0.65		0.0	0.4	0.3
229	29	1 18	7 57	9 31	1.0		0.0	0.5	0.3

Q_{HCl} was 1.9 ± 1.0 ; this is barely significantly different from the value for the fractional decrease with an opposing current.

Secretive mucosae not initially secreting acid. Besides the experiments already discussed, Fig. 3 shows five cases (four mucosae) in which the Q_{HCl} rose from zero during the passage of an enhancing current. More detailed results for these cases of apparent initiation of acid secretion by an electric current are given in Table 1. The pH changes of the secretory solution were followed continuously by means of a glass electrode and in all five cases the pH began to decrease immediately after the current was switched on. In one case (no. 141) the Q_{HCl} remained unaltered when the current stopped; in three other cases the Q_{HCl} became smaller and in the remaining case acid secretion ceased when the current was switched off.

On five occasions four other secretive mucosae failed to secrete hydrochloric acid when enhancing

Fig. 3. Relationship between Q_{HCl} and ΔQ_{HCl} due to currents enhancing or opposing the natural p.d. across isolated frog gastric mucosa.

current was passed through them, although they secreted acid at some other time during the experiment. Results for one of these mucosae are shown in Fig. 6; in two others the current was passed before secretion commenced. One of these secreted spontaneously and the other after addition of histamine. The fourth mucosa had finished secreting before the current was passed.

Non-secretive mucosae. Seven mucosae failed to secrete acid at any time during the experiments. Enhancing currents were passed through all these mucosae on sixteen occasions in all, twelve after the addition of histamine. Opposing currents were passed through these mucosae on nine other occasions, six after the addition of histamine. Since the pH of the secretory solution of a non-secreting mucosa was between 6 and 7, its measurement gave a very sensitive method for detecting small hydrochloric acid concentrations. The Q_{HCl} of the above mucosae was less than 10^{-4} ; the current densities were usually 0.4 or 1.0 ma./cm.², but current densities up to even 50 ma./cm.² failed to produce acid.

Other membranes. Similar negative results with currents passed in either direction were obtained with all other membranes examined: oesophageal, pyloric, duodenal and rectal mucosa, frog skin, cellophan and dead gastric mucosa. None of these membranes (twenty-three experiments) produced acid (Q_{HCl} less than 10^{-4}) and the alteration of the rate of acid secretion by an electric current thus appears to be specific to secretive gastric mucosa. It is interesting that a mucosa which secreted acid spontaneously and which responded to enhancing and opposing currents failed to secrete acid, even with an enhancing current density of 2 ma./cm.², when its respiration was maximally inhibited by cyanide.

Results for individual mucosae. Figs. 4–8 give examples of the results for typical mucosae. Results of control experiments are shown in Figs. 6–8 of another paper (Crane *et al.* 1948). Fig. 4 shows results for a mucosa in which secretion began after the addition of histamine (5×10^{-5} M) to the nutrient solution. Subsequently an opposing current density of 0.4 ma./cm.², passed through the tissue from secretory to nutrient side, reduced the Q_{HCl} by 2.2. It produced a p.d. of 93 mV. across the mucosa, opposite in sign to its natural p.d. of -26 mV. After a control period when acid secretion recovered slightly, an equal current passed through the mucosa in the opposite direction, enhanced the p.d. across it to -148 mV. The Q_{HCl} increased by 1.9 and returned afterwards to a lower value. The resistance of this mucosa was reduced by about half during the passage of the current; the breakdown current density was unusually low and with 0.4 ma./cm.² the resistance was already below its low current value.

Fig. 5 shows the effect of an enhancing current (1 ma./cm.²) on a spontaneously secreting mucosa. The current was passed for three separate periods. During the first two of these the Q_{HCl} was higher than during the preceding and following control

Fig. 4. Effect of enhancing and opposing currents on p.d., Q_{HCl} and resistance of isolated frog gastric mucosa.

Fig. 5. Effect of enhancing currents (1.0 ma./cm.²) on p.d., Q_{HCl} and resistance of isolated frog gastric mucosa.

periods, and the resistance only one eighth of its normal value. It is interesting that in this case a similar enhancing current after 9 hr. experimental time (E.T.) had no appreciable effect, although the mucosa had responded to histamine at 6 hr. 30 min. E.T. Such anomalous results were observed on some other occasions many hours after mounting.

Fig. 6 shows the behaviour of a mucosa which secreted for two separate periods, once spontaneously

from 2 hr. 30 min. to 3 hr. 30 min. E.T., and again between 5 hr. 30 min. and 9 hr. E.T., after the addition of histamine. On three occasions during secretion an enhancing current increased the Q_{HCl} ; but on two other occasions when the mucosa was not already secreting an enhancing current produced no acid whatever.

Fig. 6. Effect of enhancing currents (0.4 and 1.0 ma./cm.²) on p.d., and Q_{HCl} of isolated frog gastric mucosa.

Fig. 7. Effect of large enhancing currents (up to 52 ma./cm.²) on p.d. across non-secretive isolated frog gastric mucosa and on H^+ ion concentration of the secretory solution.

Fig. 7 shows results for a typical non-secretive mucosa: an enhancing current density of 1.0 ma./cm.² for over an hour produced no observable effect except that the p.d. was reduced slightly. Subsequent current densities of 2.6, 10 and 52 ma./cm.² also failed to produce any acid (Q_{HCl} less than 10^{-4}), but these high-current densities polarized the mucosa, even reversing the sign of the subsequent p.d. in the case of 50 ma./cm.² Such high currents in either direction could damage secreting mucosa so much that they became permeable to the ions present and the pH of the secretory solution rose.

Fig. 8 shows the results of an experiment designed to discover whether mucosa could secrete acid when a p.d. across it was maintained opposite in sign to its natural p.d. An opposing current was switched on at 1 hr. 20 min. E.T. and was adjusted so that the p.d. across the mucosa was 5 mV. in the opposite direction to its natural p.d. of about 30 mV. The reduction of this balancing current during the next 4 hr. suggests that the natural p.d. of the mucosa was

Fig. 8. Secretion with p.d. across isolated frog gastric mucosa maintained at +5 mV. by the application of a current. Effect of 0.01 M-NaCNS on Q_{HCl} and p.d.

decreasing during this time, as has previously been found (Crane *et al.* 1948). The secretion curve shows that the spontaneous secretion was increased by the addition of histamine at 2 hr. 30 min. and the Q_{HCl} continued to increase, rising slightly to 2.8 after the current was switched off. The p.d. was now -11 mV. but rose to -20 mV. on the addition of sodium thiocyanate (final concentration 0.01 M) to the nutrient solution, which reduced the Q_{HCl} to 0.4. This substantiates the previous assumption that the p.d. was reduced at the onset of secretion (cf. Crane *et al.* 1948).

DISCUSSION

Polarity of the effect. In the experiments on human patients (e.g. Goldschmidt, 1895; Kirstner *et al.* 1931; Schawerin, 1937) low-current densities were used, less than about 0.5 ma./cm.² of electrode area. The current was passed between parallel electrodes on the dorsal and ventral surfaces of the body at the level of the stomach, so that it was impossible to investigate the effects of currents in different directions through the stomach wall. Moreover, vagal stimulation was not separated from any direct effect on the mucosa.

The experiments of Rehm (1945) on dogs, together with those on isolated frog gastric mucosae presented in this paper, establish the remarkable fact that the rate of secretion of acid by the stomach of a living animal and by isolated gastric mucosa can be altered by the passage of direct current. Since currents from the nutrient to the secretory side of the membrane enhanced the natural p.d. and increased the rate of acid secretion, whilst currents in the opposite direction opposed the natural p.d. and decreased the rate of secretion, the effects cannot be due to stimulation of nerve endings.

These two independent series of results also show that the applied currents do not alter the Q_{HCl} by emptying reservoirs of acid in the mucosa or damming back the acid. If this were the case the raised Q_{HCl} during enhancing current flow would be counterbalanced immediately afterwards by a Q_{HCl} depressed below normal. Similarly, after opposing currents, a Q_{HCl} above normal would be expected. These effects did not occur. An electroendosmotic effect on the secretion of water cannot be the sole cause, since this would merely produce a more dilute secretion containing the same total amount of acid.

In general, frog gastric mucosa appeared to be little, if at all, damaged by the current densities used. Current densities of 0.4 ma./cm.² had no effect on the subsequent p.d. of the mucosa (Fig. 4), but the p.d. was sometimes temporarily reduced for 10–30 min. after current densities of 1.0 ma./cm.² (Fig. 5). A few poor mucosae, however, never recovered their original p.d. after 1.0 ma./cm.². Higher current densities were more injurious; the effect of progressively increasing enhancing currents on the p.d. may be seen in Fig. 7. In general, we confirmed Rehm's results (Rehm, 1945) that high opposing currents caused more damage than similar enhancing currents. A comparison of the relative change in Q_{HCl} in Rehm's and our own experiments is interesting. The examples given by Rehm (1945) (e.g. his Figs. 2, 3A, 3B, 4A) suggest that for 1 ma./cm.² an enhancing current increased the Q_{HCl} by c. 20% and the same opposing current decreased it by c. 60%; whereas in the present experiments the

average increase was 210% and the average decrease 80% with the same current densities. The gastric mucosa of the dogs used by Rehm (1945) had Q_{HCl} values up to about 50, whilst the isolated frog mucosa used in these experiments had Q_{HCl} values up to about 4.

In Rehm's (1945) experiments the change in Q_{HCl} was found to be roughly proportional to the current used (0–4 ma./cm.²) for both enhancing and opposing currents, the latter being about three times as effective as the former. The present experiments give information only for current densities of 0.4 and 1.0 ma./cm.², but for these the absolute change in Q_{HCl} was not very different, and while the fractional change in Q_{HCl} was 1.5 times as great for the higher as for the lower current density, the difference was not significant. However, the power consumed at these two current densities may be similar. It seems possible that there is a real difference in the ΔQ_{HCl} : current relationships of dog and frog gastric mucosa, but more results are needed.

Specificity. The increased production of acid when enhancing current is passed through secretive gastric mucosa is extremely specific. In twenty-one out of twenty-two cases enhancing current increased the Q_{HCl} of gastric mucosae already secreting acid. In the remaining case ΔQ_{HCl} was -0.1 ± 0.2 , but this is not significantly negative.

It is interesting that while in five out of ten cases enhancing current produced no acid in secretive mucosae not already secreting, in the other five it initiated acid secretion. It is extremely unlikely that spontaneous acid secretion should have chanced to begin in all cases just as the current was switched on (see Table 1). Rehm (1945) found no initiation of acid secretion by enhancing current (density up to 7 ma./cm.²) in any of sixteen cases with live dogs. However, since 'spontaneous' secretion of acid can occur in isolated frog gastric mucosa, but does not occur in the stomachs of live dogs, this difference of behaviour is perhaps not surprising.

The absence of any acid production when current was passed on twenty-five occasions through non-secretive gastric mucosae and on twenty-three occasions through oesophageal, pyloric, duodenal, rectal mucosae, frog skin, cellophan and dead gastric mucosa, strongly suggests that the effect is specific to secretive gastric mucosae, and shows that it is not due to a simple electrolysis. This is confirmed by the absence of any evidence of alkali secretion due to the passage of a current through gastric mucosae or any of the other membranes used.

Significance of the results. Nearly 90 years ago Brücke (1859) suggested that the electromotive forces in gastric mucosa may enable it to send an acid fluid towards the secretory surface and a basic fluid in the opposite direction. Since then many workers (e.g. Engelmann, 1872; Boenheim, 1930;

Keller, 1932) have suggested that glands produce their secretions by electroendosmosis. An attempt was made by Mudd (1926) to prove this hypothesis by applying an electric field, and he believed his data on mammalian serous membranes 'to indicate a probability approaching certainty that electroendosmotic effects are a factor in glandular secretion'.

The first controlled experiments were carried out by Rehm (1945) on the stomachs of live dogs; he has produced much other evidence with this tissue in support of the hypothesis that 'electrical energy provides the energy for the production of osmotic work by living cells' (Rehm, 1943, 1944, 1946; Rehm & Enelow, 1945; Rehm & Hokin, 1947). This work has been confirmed and extended by experiments on isolated frog gastric mucosa (Crane *et al.* 1946, 1948; Crane & Davies, 1947; Davies, Longmuir & Crane, 1947).

It has been shown (Davies, 1948) that, however complex the intermediary processes, the H^+ ions which are elaborated by oxyntic cells come initially from the H atoms in water. In this process electrical work must be done to separate the charges. The experiments of Rehm *et al.* and the present writers, referred to above, together with those recorded in this paper, make it difficult to avoid the conclusion that secreting gastric mucosa can use electric energy from an external source in the production of acid.

Interpretation of the effect. An electron-cycle mechanism of acid secretion has been proposed (Crane *et al.* 1948), in which H atom and electron transport systems are coupled to produce a net

separation of H^+ and OH^- ions in the pericanalicular zone of the oxyntic cells. On the basis of the electron-cycle mechanism, the electrical power available from the applied currents and from metabolism will be compared, in a forthcoming paper, with the power needed to produce the observed values of the Q_{HCl} .

SUMMARY

1. Currents up to 50 ma./cm.² were passed through isolated frog gastric mucosa, in directions both enhancing and opposing the natural p.d.

2. In gastric mucosae secreting acid, enhancing currents (from nutrient to secretory side) increased the Q_{HCl} : for 0.4 ma./cm.², mean $\Delta Q_{HCl} = 1.0 \pm 0.3$; for 1.0 ma./cm.², mean $\Delta Q_{HCl} = 1.2 \pm 0.2$. Similar opposing currents decreased the Q_{HCl} by the same order of magnitude; in many cases secretion was stopped.

3. Four secretive gastric mucosae, not initially secreting acid, commenced to do so when an enhancing current was passed through them; in four other secretive gastric mucosae acid secretion was not initiated by enhancing currents.

4. In all cases currents passed through non-secretive gastric mucosa failed to initiate acid secretion.

5. No other membranes examined (oesophageal, pyloric, duodenal and rectal mucosae, frog skin, cellophan and dead gastric mucosa) produced hydrochloric acid with any currents applied.

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