THE MECHANISM OF THE SECRETION OF ACID BY THE GASTRIC MUCOSA

HORACE W. DAVENPORT AND R. B. FISHER

From the Department of Pathology, The University of Rochester School of Medicine and Dentistry, Rochester, New York, and the Department of Biochemistry, The University of Oxford, Oxford, England

Received for publication June 24, 1940

Hollander (1934) and Gilman and Cowgill (1931) and others have shown that the acid secretion of the gastric mucosa is pure hydrochloric acid of concentration such that it is isotonic with the blood. In forming the acid secretion the cells of the gastric mucosa of dogs raise the hydrogen ion concentration from $5 \times 10^{-8}$, the hydrogen ion concentration of blood, to 0.17 M, the hydrogen ion concentration of the acid secretion. The chloride ion concentration is raised from 0.11 M in plasma to 0.17 M in the secretion. Osmotic work is done in raising the concentration of the two ions. The minimal amount of energy needed to do the work is equal to the free energy increase obtained in raising the concentration of the ions. The free energy change can be calculated by means of the equation used by Borsook and Winegarden (1931) in their calculation of the work of the kidney. It has been found that the gastric mucosa must expend a minimum of 772 small calories per liter of secretion in concentrating the hydrogen ions and a minimum of 48 small calories per liter in concentrating the chloride ions. Since the osmotic pressures of blood and gastric juice are the same the mol fraction of water in each is the same. Consequently no reversible work is done when water passes from the blood to the secretion, and no reversible energy is expended. A very small amount of irreversible work is done on the water in overcoming viscosity when water moves at a finite rate. The energy necessary to perform this work is doubtless derived from the difference in hydrostatic pressure between the blood and the gastric juice.

Davenport (1939, 1940a, 1940b) has suggested that the mechanism of the secretion of acid is that expressed in figure 1. Some mechanism in the parietal cells whose rate of action is directly proportional to the rate of formation of carbonic acid in the cells secretes hydrogen ions and uses energy. The principle of electrical neutrality of solutions requires that exactly the same number of anions be present in the secretion as there are hydrogen ions. In order to satisfy the principle, chloride ions pass
from the plasma through the cells and into the secretion, being dragged along by the positive charge on the hydrogen ions. The chloride ions removed from the plasma are replaced by bicarbonate ions formed in the cells at the same time the hydrogen ions are formed (Bulger, Allen and Harrison, 1928). Water moves through the cells and into the secretion without osmotic work being done on it.

The movement of chloride ions from the plasma to the secretion is in effect the transport of ions under the influence of an electrical potential difference. The velocity of the movement, \( u_{Cl} \), is expressed by the equation

\[
u_{Cl} = U'_{Cl} \frac{dE}{dl}\]

where \( dE/dl \) is the potential gradient and \( U'_{Cl} \) is the mobility of the ion in the cells. If it were possible to replace part of the chloride by another anion \( A^- \) the velocity of the anion, \( u_A \), would be expressed by the equation

\[
u_A = U'_{A} \frac{dE}{dl}\]

Since the potential gradient is the same for each anion the relation between the concentrations of the anions in the plasma and gastric juice is expressed by the equation

\[
\frac{[A^-]_o}{[Cl^-]_o} = \frac{[A^-]_p}{[Cl^-]_p} \frac{U'_{A}}{U'_{Cl}}
\]
where the left hand term is the ratio of the concentrations in the gastric juice and the right hand term is the ratio of the concentrations in the plasma multiplied by the ratio of the mobilities of the anions.

The mobilities of the anions in the cells and through the several membranes involved are unknown and cannot be measured. However it is reasonable to assume that they are directly proportional to the mobilities in water. This assumption is expressed by the equations \( U'_A = k_A U_A \) and \( U'_\text{Cl} = k_{\text{Cl}} U_{\text{Cl}} \) where \( U_A \) and \( U_{\text{Cl}} \) are the mobilities in water and \( k_A \) and \( k_{\text{Cl}} \) are constants. The constants express the retarding action of the cell contents and membranes upon the free movement of the anions. No doubt the magnitude of the constants depends upon the pore size of the membranes, the viscosity of the cells, the size of the anions and other factors. Since these factors can only be guessed at it is inadvisable to attempt any theoretical derivation of their magnitudes.

Substituting in equation (3) the equation

\[
\frac{k_A}{k_{\text{Cl}}} = \frac{[A^-]_P [\text{Cl}^-]_P}{[\text{Cl}^-]_P [A^-]_P} \frac{U_{\text{Cl}}}{U_A}
\]

(4)

is obtained.

If the proposed mechanism of secretion be correct the observed ratio of \( k_A \) to \( k_{\text{Cl}} \) should be constant when the concentrations of \( A^- \) and chloride in the plasma are varied. If the anions \( A^- \) and \( \text{Cl}^- \) are retarded in passing through the cells to exactly the same extent the ratio should be equal to unity. If the anion \( A^- \) is retarded to a greater extent the ratio should be less than unity, and the degree of deviation from unity is a measure of the degree of retardation.

Equation (4) can be tested experimentally by the substitution of bromide for part of the chloride in blood. Quastel and Yates (1934) and Troenhart (1935) have shown that when bromide is present in the blood it is secreted into the gastric juice, but they made no attempt to test the mechanism of secretion in the way outlined here. Hoppe (1906) and Lipschitz (1929) found the ratio of bromide to chloride in the gastric juice to be approximately the same as that in plasma, but their data are insufficient for accurate analysis.

In the experiments reported in this paper bromide was administered to dogs. The concentrations of bromide and chloride in the gastric juice and plasma were determined. The values of the mobilities of bromide and chloride in water at various concentrations are given in Landolt-Bornstein (1923). They were plotted in the graph shown as figure 2, and the mobilities at the observed plasma concentrations were read off. The several observed quantities were substituted in equation (4), and the ratio of the constants was calculated.

It is well known that when bromide is administered it displaces chloride
from the plasma in such a fashion that the total concentration of bromide and chloride remains constant. In the animals used in these experiments \([Br^-]_p + [Cl^-]_p = 0.112 \text{ M}\). Consequently for any given ratio \([Br^-]_p/\[Cl^-]_p\) there are unique values of \([Br^-]_p\) and \([Cl^-]_p\), and those values can easily be calculated. By reading off the values of \(U_{Br}\) and \(U_{Cl}\) corresponding to the values of \([Br^-]_p\) and \([Cl^-]_p\) the ratio \(U_{Br}/U_{Cl}\) can be calculated for any plasma bromide to chloride ratio. By this means it was found that as the ratio \([Br^-]_p/\[Cl^-]_p\) increases from 0.1 to 0.8 the ratio \(U_{Br}/U_{Cl}\) diminishes. Since it has been assumed that the actual mobilities in the secreting mechanism are directly proportional to the mobilities in water it should be found that as the ratio \([Br^-]_p/\[Cl^-]_p\) increases the ratio \(U'_{Br}/U'_{Cl}\) diminishes. By substituting the observed plasma and gastric juice bromide and chloride concentrations in equation (3) the experimentally determined values of \(U'_{Br}/U'_{Cl}\) can be calculated, and the ratio should be found to diminish as the plasma bromide to chloride ratio increases. The observation of such a diminution is as important a confirmation of the theory as is the constancy of the ratio \(k_{Br}/k_{Cl}\).

In the presentation and discussion of the results the ratio \(U'_{Br}/U'_{Cl}\) is denoted by the term secretion ratio, and the ratio \(k_{Br}/k_{Cl}\) is denoted by the term secretion constant.

Methods. Bromide and chloride were determined by the potentiometric method of Hastings and van Dyke (1931). The method was carefully tested and found to be accurate to within 1 per cent. Thio-
cyranate was determined by the method of Lavietes, Bourdillon and Kling-
hoffer (1936). Since the solubility product of silver thiocyanate is almost identical with that of silver bromide thiocyanate is included in the titre of bromide in the potentiometric titration. When thiocyanate was present its independently determined concentration was subtracted from the apparent bromide concentration in order to obtain the true bromide concentration. The thiocyanate concentration was always small compared with that of bromide.

The gastric contents of dog 1 were sampled by means of a stomach tube. Dogs 2 and 3 were provided with Pavlov pouches. In the first group of experiments sodium bromide was added to the diets, and in the second group sodium thiocyanate was also added. At least 16 hours after feeding standard subcutaneous injections of histamine were given. During the second half-hour after injection samples of gastric juice were taken from dog 1, and samples were taken from dogs 2 and 3 as the juice was secreted. The rate of secretion by the pouch of dog 3 was measured and expressed as the number of milliliters of juice secreted during the second half-hour after injection. In that interval the rate of secretion was constant. Blood was obtained by venepuncture.

The secretion of bromide and chloride. The results obtained when bro-
mide alone was fed are presented in Table 1 and in the first half of Table 2 together with the calculated secretion ratios and constants. The relation of the secretion ratios and constants to the plasma bromide to chloride ratios are more clearly shown in Figures 3a and 3b where they are plotted as filled circles.

The theoretical secretion ratio is equal to the ratio of the mobilities of bromide and chloride in water multiplied by the ratio \( k_{Br}/k_{Cl} \), the secretion constant. The ratio of the mobilities in water for plasma bromide to chloride from 0.1 to 0.8 were calculated as explained above. These calculated ratios were then multiplied by the observed secretion ratio, 0.929. They were plotted as the curved line in Figure 3a. The observed secretion ratios plotted as filled circles are obviously distributed at random about the theoretical line, and as the plasma bromide to chloride ratio increases the secretion ratio diminishes exactly as predicted by the theory. On the other hand the values of the secretion constant plotted as filled circles in Figure 3b vary irregularly about their mean value, the deviations all lying within the narrow limits of 99.4 and 101 per cent of the mean.

<table>
<thead>
<tr>
<th>PLASMA</th>
<th>GASTRIC JUICE</th>
<th>SECRETION RATIO</th>
<th>ABSORPTION CONSTANT</th>
</tr>
</thead>
<tbody>
<tr>
<td>DOG NUMBER</td>
<td>CI⁻</td>
<td>Br⁻</td>
<td>( \frac{Br}{CI} )</td>
</tr>
<tr>
<td>1</td>
<td>0.102</td>
<td>0.011</td>
<td>0.108</td>
</tr>
<tr>
<td></td>
<td>0.089</td>
<td>0.026</td>
<td>0.097</td>
</tr>
<tr>
<td></td>
<td>0.087</td>
<td>0.030</td>
<td>0.104</td>
</tr>
<tr>
<td></td>
<td>0.082</td>
<td>0.029</td>
<td>0.108</td>
</tr>
<tr>
<td></td>
<td>0.079</td>
<td>0.035</td>
<td>0.113</td>
</tr>
<tr>
<td></td>
<td>0.072</td>
<td>0.042</td>
<td>0.118</td>
</tr>
<tr>
<td></td>
<td>0.071</td>
<td>0.045</td>
<td>0.122</td>
</tr>
<tr>
<td></td>
<td>0.068</td>
<td>0.046</td>
<td>0.127</td>
</tr>
</tbody>
</table>

All concentrations in mols per liter.
value of 0.929 ± 0.010. The data therefore establish without doubt that the secretion ratio diminishes as the plasma bromide to chloride ratio increases, and they demonstrate as well as can be expected that the secretion constant has a value constant within the limits of error and independent of the plasma bromide to chloride ratio. The figures further
illustrate the point that the data from all the dogs are entirely consistent, so that it may be concluded that the observed relation is a general one independent of individual variation or minor modifications in technique.

The observed constancy of the secretion constant over a wide range of concentrations clearly demonstrates that equation (4) is a correct statement of the mechanism of the secretion of bromide and chloride. Consequently it can be concluded that in all probability bromide and chloride are secreted by the same mechanism and that the mechanism acts on the ions through their negative charges in the manner postulated.

It may also be concluded that the assumption that the mobilities of the ions in the cells are directly proportional to their mobilities in water is correct. The secretion constant is a measure of the retardation of transport across the cells of the mucosa of bromide relative to chloride due to causes other than the differences in mobility of the ions in the cells. Since it is clear that such retardation might be expected to occur as a result of differences in the ease of passage across cell membranes it is reasonable to expect that it might bear a relation to the relative sizes of the ions. In this connection it is of interest to note that the ratio of the ionic radii of chloride and bromide derived from the data given by Pauling (1939) is...
0.926 whilst the mean value of the secretion constant is 0.929. The correspondence between these values may be pure coincidence, and in any event there is no secure theoretical basis on which to found any expectation concerning the relation between ionic dimensions and transport across a cell membrane.

The data in table 1 and in the first half of table 2 also show that the acidity of the gastric secretion, the total halide concentration of the gastric secretion and the rate of secretion are entirely independent of the plasma bromide to chloride ratio. These facts strongly support the conclusion that the mechanism secreting acid is completely unaffected by the substitution of bromide for chloride. The acid secreting mechanism is indifferent to the chemical nature of the anion, and provided that an ion with a negative charge is present the mechanism is capable of secreting hydrogen ions at the same rate and at the same concentration as when chloride alone is present.

**Inhibition by thiocyanate.** Davenport (1940b) has shown that the carbonic anhydrase in the parietal cells and the secretion of acid are inhibited by thiocyanate ions. He postulated that the parietal cell carbonic anhydrase catalyses the hydration of carbon dioxide to carbonic acid and that the ionization of the carbonic acid provides the hydrogen ions for the acid secretion. When the rate of hydration of carbon dioxide is reduced by inhibition of the enzyme the rate of secretion of hydrogen ions is proportionately reduced.

The secretion of chloride ions is also reduced. According to the theory outlined in this paper the reason for the reduction of chloride secretion is that the diminution of the production of hydrogen ions reduces the number of positive charges in the secretion. The fewer hydrogen ions secreted the fewer anions are needed to maintain electrical neutrality of the secretion. Since the inhibition has no direct effect upon the secretion of the anions there should be no difference between the relation of bromide to chloride during normal and during inhibited secretion. Consequently it would be predicted that during inhibition the secretion ratio would bear the same relation to the plasma bromide to chloride ratio and that the secretion constant would be identical with that found during uninhibited secretion. However the total halide concentration of the secretion should be reduced. If on the other hand this theory be wrong in that the secretion of chloride is effected by some active mechanism acting directly on the chloride it would be expected that the inhibition of secretion would greatly upset the relation of bromide to chloride. Therefore the secretion ratio and secretion constant should differ from those found during uninhibited secretion.

These predictions were tested by the administration of bromide and chloride together with thiocyanate to dog 3. Bromide and thiocyanate together are more toxic than either alone, and only the lower bromide to
chloride ratios could be attained. The results are presented in table 2, and they can be compared with control observations on the same dog.

The results clearly show that when thiocyanate is present the acidity and the total halide concentration of the secreted juice and the rate of secretion are reduced. These results agree with the theory developed by Davenport (1940b) upon the postulate that as a first approximation the rate of secretion of acid is directly proportional to the rate of formation of carbonic acid in the parietal cells. However the secretion ratio varies with the plasma bromide to chloride ratio in exactly the same manner as when the secretion is not inhibited. The mean value of the secretion constant, $0.920 \pm 0.011$, is identical with the value $0.920 \pm 0.010$ obtained in the control experiments.

These results prove that the relation of bromide to chloride in the gastric juice is a function only of the relation of bromide to chloride in the plasma and of the physico-chemical properties of the anions. That relationship is not disturbed by very considerable diminution of the rate of secretion of hydrogen ions. Thiocyanate does not interfere directly with the secretion of the anions, and the total halide concentration of the gastric juice is reduced only because the secretion of hydrogen ions is reduced. These facts very strongly support the theory of acid secretion outlined in this paper, and it can be concluded that the passive character of the secretion of the anions is fully established. Further work on the mechanism of acid secretion must endeavor to explain fully the means by which the hydrogen ions are concentrated and secreted.

**Conclusion.** The results show that the concentration of bromide in the gastric secretion is always greater than the concentration in the plasma. In the observations on dogs 1 and 2 and in the uninhibited observations on dog 3 the ratios of bromide in the gastric juice to bromide in the plasma are on the average 1.38, 1.55 and 1.60 respectively. This means that in secreting a mol of bromide the gastric mucosa of dog 1 expended a minimum of 199 small calories, dog 2 expended a minimum of 270 small calories, and dog 3 expended a minimum of 289 small calories. Only two explanations of this fact are possible. Either the gastric mucosa contains a mechanism specifically fitted for doing work in the secretion of bromide which is called upon only when concentrations of bromide enormously in excess of the normal are experimentally produced, or the mechanism secreting chloride is capable of switching over to the secretion of bromide at any concentration with only a small loss in efficiency. The second possibility is more probably the true one. Since the chemical properties of bromide and chloride, aside from the similarity of their negative charges, are so different it is again more likely that the mechanism acting on chloride acts on the ion through the negative charge in the manner postulated and is hence also capable of acting on bromide through its negative charge.

The energy used in concentrating bromide and chloride can easily be...
supplied by the mechanism secreting hydrogen ions. A minimum of 772 calories is required to secrete the hydrogen ions in a liter of acid secretion. If the hydrogen ions must pull an equal number of anions along with them the energy used in attaining the high hydrogen ion concentration is in part also used to raise the concentration of the anions. Consequently the expenditure of 820 calories on the hydrogen ions in forming one liter of secretion would result in raising the potential energy of the hydrogen ions by 772 calories and of the anions by 48 calories.

In conclusion we particularly wish to emphasize that we demonstrate in this paper the passive character of the transport of bromide and chloride from plasma to gastric juice, and that we demonstrate this passivity by showing that the two anions behave differently, the differences in behavior being explicable in terms of those physico-chemical properties of the ions which would be expected to be involved in their passive translocation. These experiments can be taken to support the view that the active process in the secretion of hydrochloric acid by the gastric mucosa is the secretion of hydrogen ions.

We are indebted to Drs. E. S. Nasset, W. B. Hawkins and S. C. Madden for preparing the Pavlov pouches.

SUMMARY

Bromide is secreted by the gastric mucosa. Over a wide range of concentrations of bromide in the plasma the rate of secretion of bromide is of the same order as the rate of secretion of chloride.

The concentration of bromide and chloride in the gastric juice is always greater than that in the plasma. Osmotic work is done in concentrating chloride, and it is concluded that the work is performed on the two anions by the same mechanism.

The rate of secretion of the gastric juice and the acidity and total halide concentration of the secretion are completely independent of the plasma bromide to chloride ratio.

The apparent mobilities of bromide and chloride in the cells of the gastric mucosa are directly proportional to their mobilities in water.

When the rate of secretion of the gastric juice and the acidity and total halide concentration are reduced by inhibition by thiocyanate the relation of bromide to chloride in the gastric juice remains exactly the same function of the plasma bromide to chloride ratio as it is during uninhibited secretion.

It is concluded that the mechanism concentrating and secreting bromide and chloride acts only through the negative charges on the ions.

An incomplete theory of the mechanism of the secretion of hydrochloric acid by the gastric mucosa is proposed.
REFERENCES


This Journal 128: 725, 1940.

This Journal 129: 505, 1940.

GILMAN, A. AND G. R. COWGILL. This Journal 99: 172, 1931.


