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Sodium Secretion as Part of the Formation of Gastric Juice

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ABSTRACT

Experiments with Heidenhain pouch dogs showed the well known high sodium concentrations at low secretion rates and low sodium concentrations at high ones after stimulation with a continuous intravenous injection of histamine. It was previously thought that the primary secretion did not contain any sodium, but that all the sodium present in the gastric juice appeared as a result of diffusion. A more detailed analysis of the experimental data showed, however, that there is in fact sodium present also in the primary juice in the small concentration of 3–5 mEq/l. The origin of the secreting volume containing this concentration of sodium is unknown.

INTRODUCTION

Due to the complexity of the anatomy of the gastric mucosa the composition of the gastric juice will depend on the type of stimulation and its effect on different types of cells. Histamine is thought to activate the parietal cells exclusively and to initiate a secretion of water and ions. The composition of this secretion is thought to be constant, as was first suggested by Pavlov in 1898 (21) (primary secretion, primary acidity, primary chloride concentration, etc.), but many well differ between different animal species. So far, figures are available for the composition of this primary secretion in dog (6, 11, 16, 17, 20) and man (19).

The primary secretion appears to contain H^+, K^+, Cl^- and water. The primary $[H^+]$ in man is lower (145–150 mEq/l) than in dog (160 mEq/l) whereas the $[K^+]$ shows correspondingly opposite values so that the sum of $[H^+]$ and $[K^+]$ seems to be the same in dog and man and equal to the Cl^--concentration.

Whether or not Na^+ is present in the primary juice is a matter of uncertainty. Before discussing this question a few words must be mentioned, however, about the methods used for determining the composition of the primary secretion.

The changes in the concentration of the primary juice are due to several factors, among which diffusion of the ions through the gastric mucosa is probably the predominant one. All these factors, however, lose in importance when the secretion rate (ml/min) reaches high values. Theoretically, if the secretion rate approaches infinity, all the ionic concentrations would approach their primary concentration values. Thus the extrapolated concentration values corresponding to infinitely high secretion rates are estimated. Linde & Öbrink (16) and Heinz & Öbrink (7) gave a complete picture of the relation between the H^+, K^+, Na^+ and Cl^- concentrations on the one hand and the secretion rate (v) in ml/min on the other, when a Heidenhain pouch dog was stimulated by histamine to steady-state secretions.

The hydrogen ion concentration increases with the secretion rate in a hyperbolic fashion from zero to the value of the primary acidity. The sodium ion concentration, on the other hand, shows a contrary pattern with the highest concentration at secretory rest. If sodium were entering the juice by diffusion only, the relation between its concentration and the secretion rate would follow the mathematical description given by Teorell (23) which will be discussed below.

This paper tries to analyse whether or not diffusion is the only route by which sodium enters the gastric lumen.

METHODS

Heidenhain pouch dogs were used and the results reported in this paper originate from experiments on one such dog. The animals were fasted overnight and were then stimulated by a continuous intravenous injection of histamine–dihydrochloride. Samples were usually taken every 10 minutes, but when the stimulation was weak and the secretion rate low the sampling time was extended accordingly. This was feasible as only the steady-state values were used.

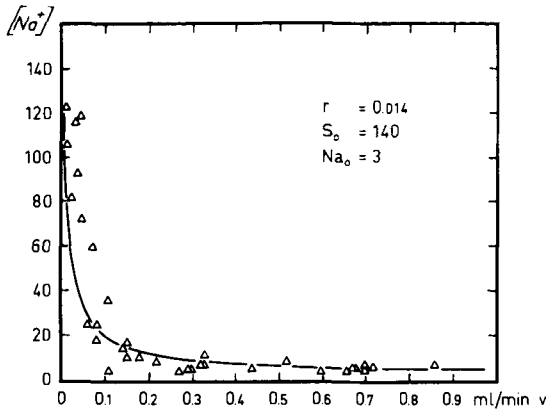

Fig. 1. The relationship between the sodium concentration and the secretion rate (v) under steady state conditions. The line is drawn according to Eq. (1) in the text with the following constants: S_0=140 mEq/l, Na_0=3 mEq/l and r=0.014 ml/min.

Volume and concentrations of H^+, K^+, Na^+ and Cl^- were recorded. For analytical procedures see Öbrink (20) and Linde & Öbrink (16).

RESULTS

Most of the experimental data have been reported elsewhere (16). The studies of the kinetics of the sodium ions were limited to the steady state conditions and the different steady state concentrations of the ion were plotted against their corresponding steady state values of the secretion rate as can be seen in Fig. 1. The well known pattern with high sodium values at low secretory rates (low H^+ concentration) and low values at high secretory rates (high H^+ concentration) is clearly demonstrated. From the figure it may be argued what value might be probable for the primary sodium concentration (Na_0), i.e. the sodium concentration at high secretory rates. Furthermore, it should be discussed whether or not the highest sodium values are attained before the secretion rate has fallen to zero.

DISCUSSION

In earlier presentations of the kinetics of the sodium ions it was assumed that the primary secretion did not contain any sodium. Yet sodium was obtained in the test tubes which was thought to be the result of a diffusion process. The steady-state relation between the sodium concentration and the secretion rate could then be described by the formula

$$Na=\frac{S_0}{\frac{v}{r}+1} \tag{1}$$

where S_0 is the concentration value to which the sodium would approach in a resting stomach, r is the permeability coefficient for sodium and v is the secretion rate (23). Eq. (1) describes a hyperbolic curve starting at S_0 for v=0 and approaching the v-axis as its asymptote for increasing v-values. As infinitely high v-values can never be experimentally obtained, no sodium-free samples have ever been analysed.

Consequently it has not been possible to prove with certainty that the primary juice completely lacks sodium.

For this reason it may be of interest to deduce the Na^+-v-relationship from the assumption of a primary sodium concentration of Na_0 mEq/l. If an experiment starts with a volume p ml in the stomach containing no sodium and we look upon the *changes* in the sodium concentration at time t, we would obtain the following equations:

$$\text{increment due to secretion}=\frac{vNa_0}{p+vt}dt \tag{2}$$

$$\text{increment due to diffusion}=\frac{r(S_0-Na)}{p+vt}dt \tag{3}$$

$$\text{decrement due to dilution}=-\frac{v\,dt}{p+vt}Na \tag{4}$$

The remaining symbols retain their meanings already mentioned.

The total changes of the sodium ion concentration will then be

$$\frac{dNa}{dt}=\frac{vNa_0+r(S_0-Na)-vNa}{p+vt} \tag{5}$$

The solution of this differential equation gives

$$Na=\left[\frac{S_0-Na_0}{\frac{v}{r}+1}+Na_0\right]\left[1-\left(1+\frac{vt}{p}\right)^{-\left(1+\frac{r}{v}\right)}\right] \tag{6}$$

In steady state condition, t approaches infinity or p can be considered to be zero. Then

$$Na=\frac{S_0\,Na_0}{\frac{v}{r}+1}+Na_0 \tag{7}$$

If Na_0=0, eq. (1) will appear.

Eq. (7) describes a hyperbolic curve starting at $Na=S_0$ for v=0 and approaching asymptotically

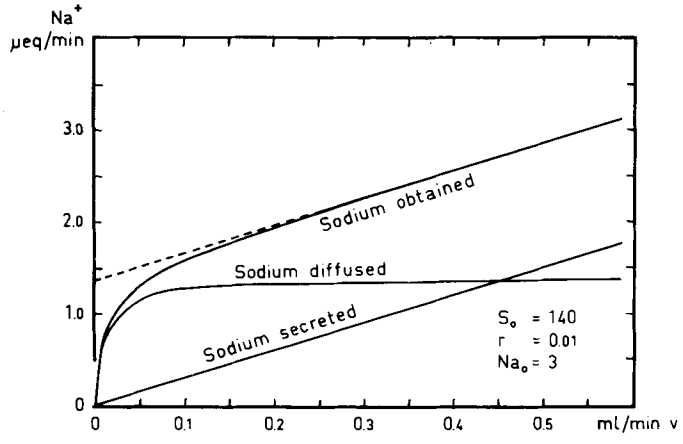

Fig. 2. The theoretical relationship between the output of sodium and the secretion rate (v). The output is the sum of the sodium secreted and the sodium which entered through a diffusion process. Cf. Eq. (9) in the text. The constants in the figure are $S_0=140$ mEq/l, $Na_0=3$ mEq/l and $r=0.01$ ml/min.

$Na=Na_0$ for $v\to\infty$ Eq. (7) is seen as the full line in Fig. 1. In this instance Na_0 was estimated to 3 mEq/l.

It is still difficult to judge from Fig. 1 whether there is a finite value of Na_0 or if the confidence limits are too wide to exclude zero. This problem may, however, be further elucidated if the amount of Na obtained is related to the secretion rate. We get the amounts by multiplying the sodium concentration figures by their corresponding v-values.

Thus

$$vNa=\frac{v(S_0-Na_0)}{\frac{v}{r}+1}+vNa_0 \qquad (8)$$

which can be re-written as

$$vNa=\frac{r(S_0-Na_0)}{1+\frac{r}{v}}+vNa_0 \qquad (9)$$

Theoretically this equation shows that the output of Na is the sum of a diffusion process (first term) and a secretion process (second term). This is illustrated in Fig. 2. The output curve (sodium obtained) will approach a line parallel to the vNa_0-line, the slope of which is equal to Na_0. If $Na_0=0$ the output curve will tend to become horizontal but if there is a primary secretion of sodium the output curve will show a slope. In Fig. 3 the actual output data are plotted and even if there is a good deal of scatter it can be clearly seen that there is a slope of approximately $Na_0=3$ to 5 mEq/l. As a matter of fact this plot gives a very sensitive estimation of the figures wanted. Thus a primary secretion of sodium at a concentration of 3 to 5 mEq/l seems quite probable.

The question whether or not the sodium ion is actively transported into the gastric juice has been a matter of dispute during the last decade. In his papers from 1951, 1952 and 1955, Hogben stated (8–10) that, at least in the isolated frog stomach, there is no active sodium transport. Instead he found an active chloride transport from the serosal to the mucosal side to be responsible for the electrical potential difference normally existing across the stomach mucosa. In short circuit experiments the short circuit current could be entirely accounted for by the difference in chloride and hydrogen ion transport. Lately, however, this view has been questioned by several authors who have observed an active sodium transport in some isolated gastric preparations (1, 2, 12–14, 22). The sodium was transported from the mucosal to the serosal side. Most authors assumed that there were species differences between their animals used and the frog.

Flemström & Öbrink (5) and Flemström (4) presented another explanation for the discrepancies among the findings. All the experiments showing an active transport of sodium were performed on isolated stomachs from mammals, where the risk of hypoxic conditions is known to be inevitable under the experimental conditions. Flemström showed that even an isolated frog stomach, that normally shows no sodium transport, during hypoxic conditions owed some of its short circuit current to an active sodium transport from the mucosal to the serosal side. Thus there is a possibility of simultaneous active transports of both chloride and sodium in opposite directions, but under normal conditions the sodium transport is almost completely suppressed.

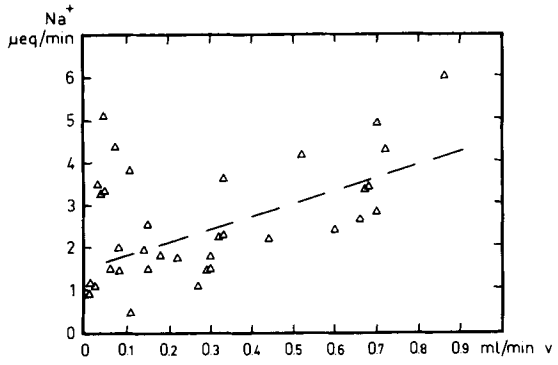

Fig. 3. The experimental relationship between the output of sodium and the secretion rate (v). The line in the figure has a slope corresponding to Na_o=3 mEq/l.

When it was believed that no sodium appeared in the primary secretion Linde and Öbrink (16) suggested that the water for the secretion came from a sodium-free compartment. The above-mentioned findings that the primary gastric juice contains Na^+ in a concentration of 3–5 mEq/l makes it possible that the secreted volume originates from some sodium-containing compartment. Whether there is a bulk flow from a compartment with a concentration of 3–5 mEq/l (such a compartment was actually found by Davenport (3) or whether the water comes from a compartment from which the sodium ions cannot escape due to sterical hindrance, cannot be decided from our present knowledge. Whether hypoxia leads to a change in the primary sodium concentration due to an active sodium transport remains to be investigated.

Sodium at low secretory rates

So far, the right tail of the curve in Fig. 1 reflecting the value of the primary sodium concentration has been analysed. The curve describes, however, the relation between Na^+ and v and according to Eq. (7) it depends on the values of S_o (which is the Na^+-concentration for v=0) and r in addition to Na_o, which has already been discussed.

To estimate the constants S_o and r the method of least squares could be used. The curve in Fig. 1 shows reasonable values, namely S_o=140 mEq/l, Na_o=3 mEq/l and r=0.014 ml/min. Another, and perhaps quicker, way would be to calculate the relation $1/Na=f(v)$.

Starting from Eq. (1) this leads to

$$\frac{1}{Na}=\frac{v}{rS_o}+\frac{1}{S_o} \qquad (10)$$

and from Eq. (7) to

$$\frac{1}{Na-Na_o}=\frac{v}{r(S_o-Na_o)}+\frac{1}{S_o-Na_o} \qquad (11)$$

As we now are interested in that part of the curve which has low v-values (low secretory rates) where both Na and S_o are much greater than Na_o, we may consider all the denominators in Eq. (11) to be very close to those in Eq. (10). This equation is represented by a straight line, where $1/rS_o$ is the differential factor for the function and $1/S_o$ is the intercept on the 1/Na axis. Fig. 4 depicts the function and furthermore shows that the v-intercept equals $-r$. Fig. 5 gives the actual experimental values presented in this way. That there is a large scatter for medium and high v-values should not surprise. This is expected when small figures are inverted. In the graph, a line similar to that in Fig. 4 is drawn corresponding to the values S_o=140 mEq/l and r=0.014 ml/min given in Fig. 1 (see above).

It must be admitted that although the slope seems correct, a line through the origin would have been a better fit.

One possible reason for this discrepancy may be the following: In deducing the differential equations (2) to (5) it was assumed that there is an instantaneous and complete mixing in the stomach. If, however, the newly formed gastric juice is incompletely mixed with the previously secreted volume the equations will be slightly different. In the extreme but possible case of no mixing, Eq. (3) will change to

$$\text{increment due to diffusion}=\frac{r(S_o-Na_o)}{p+vt}\cdot dt \qquad (12)$$

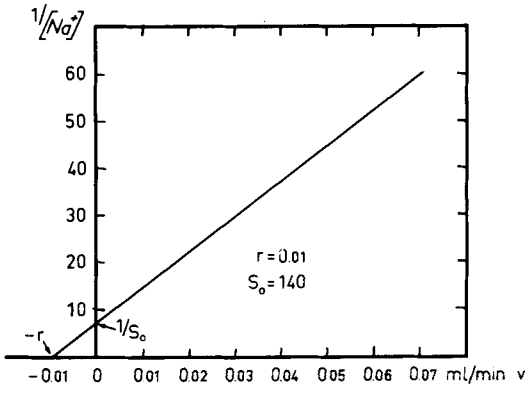

Fig. 4. The theoretical relationship between $1/Na^+$ and the secretion rate (v). The figure corresponds to Eq. (10) and approximately also to Eq. (11) in the text. The values of the constants are S_o=140 mEq/l and r=0.01 ml/min.

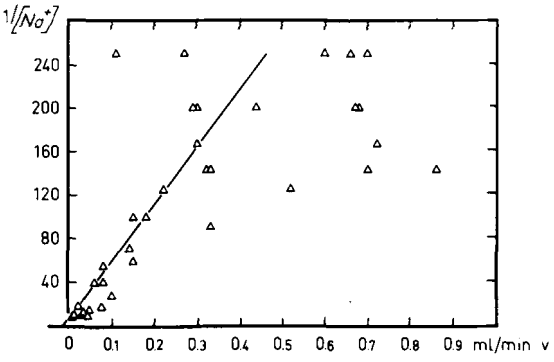

Fig. 5. The relationship between $1/Na^+$ and the secretion rate (v). For low v-values a straight line relationship should exist. The line in the figure drawn corresponds to the line in Fig. 4 and has the constants $S_o = 140$ mEq/l and $r = 0.014$ ml/min. A better fit would be a line through the origin corresponding to Eq. (15). See text.

and the complete differential equation will read

$$\frac{d\mathrm{Na}}{dt} = \frac{v\mathrm{Na}_o + r(S_o - \mathrm{Na}_o) - v\mathrm{Na}}{p + vt} \qquad (13)$$

Solving this equation gives for steady state conditions
($p = 0$ or $t = \infty$)

$$\mathrm{Na} = \frac{r}{v}(S_o - \mathrm{Na}_o) + \mathrm{Na}_o \qquad (14)$$

This curve is again a hyperbola but now $\mathrm{Na} = S_o$ when $v = r$. (The values for Na when $v < r$ have no physical meaning.)

Inverting Eq. (14) gives

$$\frac{1}{\mathrm{Na} - \mathrm{Na}_o} = \frac{v}{r(S_o - \mathrm{Na}_o)} \qquad (15)$$

Compare this with Eq. (11) and (10). The only difference is the disappearance of the intercept. The line expressed in (15) passes through the origin and would give a better fit if drawn in Fig. 5.

The curve in Fig. 1 would not change appreciably.

It should be remembered that similar treatment has been given acidity values when related to the secretion rate (19, 20).

There is no need to assume a non-parietal sodium secretion to explain the findings as was done theoretically in an elegant way by Makhlouf, McManus & Card (18) but adopted uncritically by Lee & Thompson (15). That is not to say, however, that a non-parietal secretion cannot exist, but the necessary assumption that this secretion is always constant while the parietal one changes is an obstacle to the hypothesis.

ACKNOWLEDGEMENT

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