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J Clin Invest. 1970;49(3):548-556. <https://doi.org/10.1172/JCI106265>.

Research Article

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ABSTRACT Using a constant perfusion technique, sodium and bicarbonate absorption was studied in human subjects.

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Received for publication 9 January 1969 and in revised form 2 September 1969.

INTRODUCTION

Intestinal absorption of saline has been extensively studied in the past, but the mechanism of sodium chloride absorption, at least in vivo, is not clear. In a previous study in normal human subjects (1), we noted that jejunal absorption of sodium chloride appeared to be largely passive and greatly influenced by concentration gradients and by solvent drag. However, sodium was absorbed to a slight degree against an electrochemical gradient even when solvent flow was reduced to zero by addition of mannitol to the test solution. This observation suggested that some sodium absorption was active. The possibility that sodium movement from saline was a passive, rather than an active, process could not be excluded because of the presence of a chloride concentration gradient (lumen [Cl] = 140 mEq/liter, plasma [Cl] = 100 mEq/liter) which could have generated a small potential difference. In the present studies it was found that when the jejunum was perfused with a solution in which chloride concentration gradients were abolished by partial substitution with sodium sulfate, there was no net movement of sodium when water movement was zero. This observation suggests that sodium absorption from saline solutions is entirely passive.

In contrast to the apparently passive nature of sodium absorption from saline solutions, sodium can be absorbed against steep electrochemical gradients in the presence of bicarbonate (1). This bicarbonate mediated absorption cannot be explained by chemical concentration gradients of sodium chloride or by solvent drag and thus appears to be an active process. The second purpose of the present study was to explore the link between bicarbonate transport and the active component of sodium absorption. We found that bicarbonate absorption occurs against steep electrochemical gradients, is non-

electrogenic, is inhibited by acetazolamide, and generates high CO_2 tensions in luminal fluid. These observations suggest that bicarbonate absorption is mediated by active hydrogen ion secretion, rather than by bicarbonate ion transport per se, and that the link between sodium and bicarbonate transport is best explained by a sodium-hydrogen exchange process.

METHODS

Absorption in a 30 cm segment of intestine was studied by the Ingelfinger triple-lumen perfusion system that has previously been described in detail (2, 3). Briefly, the method involves perfusion of test solutions into the intestine and sampling gut contents 10 and 40 cm beyond the infusion point. Polyethylene glycol was the nonabsorbable volume marker. Experiments were started when the infusion site was at the ligament of Treitz as determined radiologically. Potential difference (PD) was measured between jejunal lumen and abraded skin with an intraluminal electrode as described earlier (1). To validate the use of abraded skin as a reference electrode, PD between skin and peritoneum was measured four times in patients undergoing peritoneal dialysis. With the skin as a reference, peritoneal PD was +2.0, +0.2, 0.0, and -0.2 mv in the four studies. Therefore, our results of PD measurements between skin and gut lumen should be approximately the same as between lumen and peritoneum.

In order to determine whether or not sodium is absorbed from saline when concentration gradients are not present, the jejunum was perfused with a salt solution in which part of the sodium chloride was replaced by sodium sulfate. In these experiments luminal sodium, potassium, and chloride concentrations were the same as plasma (140, 5, and 100 mEq/liter, respectively) with the additional anion being made up by sulfate. Water movement was manipulated by mannitol, as previously described (1). In order to compare these results with absorption from saline, subjects were restudied on a separate day using solutions containing 140 mM NaCl and 5 mM KCl.

In order to study bicarbonate absorption at different luminal bicarbonate concentrations, solutions containing 0, 37.5, 70, or 140 mEq/liter of bicarbonate (as the sodium salt) were perfused into the jejunum of normal subjects at a rate of 10 ml/min. The sodium concentration of each solution was maintained at 140 mEq/liter by the addition of appropriate amounts of sodium chloride. Potassium chloride, 5 mM, was also added to each solution.

The influence of acetazolamide on bicarbonate absorption was assessed in five subjects. Test solutions contained 70 mEq/liter of bicarbonate, 65 mEq/liter of chloride, 130 mEq/liter of sodium, and 5 mEq/liter of potassium. This solution was perfused three times in each subject, the first solution having zero, the second 250, and the third 500 mg/liter of acetazolamide.

To determine whether bicarbonate absorption was mediated by direct bicarbonate ion transport or by hydrogen secretion, studies were designed to determine whether the process generates a high CO_2 tension in luminal fluid. To avoid errors arising from contamination of the perfusate with gastric acid, the experiments were performed in patients with pernicious anemia. 11 such patients were studied and all had documented achlorhydria by maximum histamine test. These subjects were intubated with the triple-lumen tube and studied by the standard perfusion

technique. The three test solutions used were unbuffered saline, unbuffered bicarbonate, and buffered bicarbonate. The exact makeup of these solutions is described in Table I. Each pernicious anemia patient was perfused with at least two of these three solutions for a 90-120 min period. Test solutions were bubbled with 3% CO_2 at 25°C for 20 min before and during the perfusion; this yields a Pco_2 of approximately 40 mm Hg when the solutions were warmed to 37°C. Preliminary experiments showed that perfusion at 37°C through a similar length of polyvinyl tubing as used in the in vivo experiments did not measurably change the Pco_2 of solutions. Samples for Pco_2 and pH analysis were drawn into well-fitting all-glass syringes. In the first four subjects three 5-ml samples were withdrawn at 5-min intervals; samples from the distal aspiration site were collected 15 min after the proximal sampling. In all other subjects fluid from the proximal and distal sites was collected at a rate of 1 ml/min into 30-ml syringes. Two or three 30-min samples from each collecting site were analyzed for pH and Pco_2 between 15 and 30 min after their collection. Absorption rates for bicarbonate were measured as in a standard perfusion experiment after individual samples were appropriately pooled.

Pco_2 and pH of luminal fluid were measured with an Ultramicro pH/ Pco_2 meter (Instrumentation Laboratories Inc., Lexington, Mass.). Polyethylene glycol, electrolyte concentrations, and osmolality of intestinal perfusates were analyzed by methods previously described (1).

RESULTS

Sodium absorption from saline (bicarbonate-free) solutions. The results of these experiments are shown in Fig. 1. As previously noted (1), bulk water flow has a dramatic effect on jejunal sodium movement. With 140 mM NaCl solutions, sodium was absorbed at a rate of 2.5 mEq/hr per 30 cm when water flow was zero. On the other hand, when the chloride concentration gradient between lumen and blood was eliminated by partial substitution of sulfate for chloride in luminal fluid, sodium movement was approximately zero when water flow was zero.

As shown in Fig. 2, partial substitution of sodium bicarbonate or sodium sulfate for sodium chloride had no demonstrable effect on PD between abraded skin and jejunal lumen. Four other studies gave similar results.

These results provide evidence against active sodium or chloride absorption from saline solutions; when water flow was zero and when concentration gradients were obliterated, absorption rate was zero.

Characterization of bicarbonate transport. The rate of bicarbonate absorption at different bicarbonate concentrations is shown in Fig. 3. Bicarbonate absorption occurred at luminal concentrations as low as 3 mEq/liter; that is, against a lumen to plasma gradient of 22 mEq/liter. The PD between jejunal lumen and skin, measured in the same subjects during perfusion of the identical solutions, was approximately 2.5 mv (lumen positive to skin) and did not change when anion composition of test solutions was varied (Fig. 3). The PD

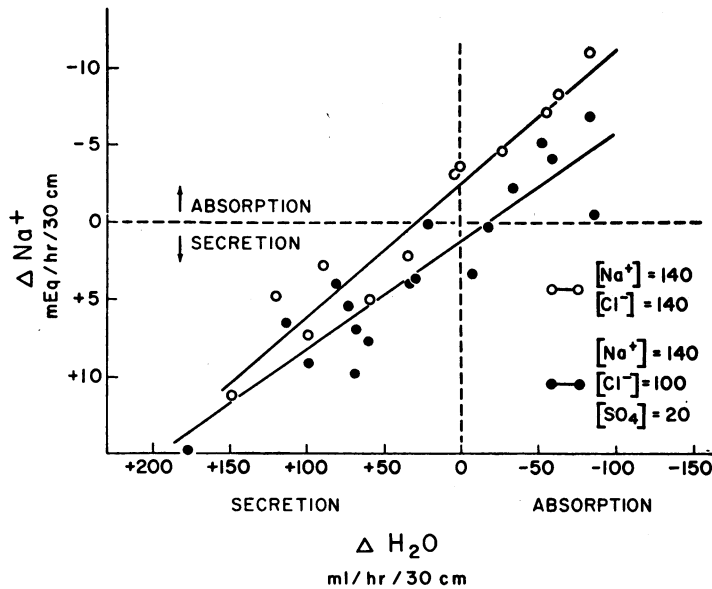


FIGURE 1 Effect of luminal chloride concentration on net sodium movement at varying rates of water movement. The rate and direction of water movement was manipulated by the amount of mannitol added to the test solutions. The sodium and chloride concentrations and the mean flow rate in the test segment were the same regardless of the rate or direction of water movement (see reference 1). The P value for the difference in ΔNa for the two test solutions was < 0.001 at zero water flow.

was much too small and of the wrong polarity to facilitate bicarbonate absorption. Thus, bicarbonate is absorbed against an electrochemical gradient.

Bicarbonate absorption rate increased linearly with increasing luminal bicarbonate concentrations between 2 and 40 mEq/liter. On the other hand, absorption rate increased relatively slightly as luminal bicarbonate con-

centration was increased from 40 to 93 mEq/liter, suggesting partial saturation of the process.

As shown in Fig. 4, acetazolamide depressed the rate of bicarbonate absorption to values about one-half those in the control experiments when 500 mg/liter acetazolamide was included in the test solution.

Mechanism for bicarbonate absorption. These studies

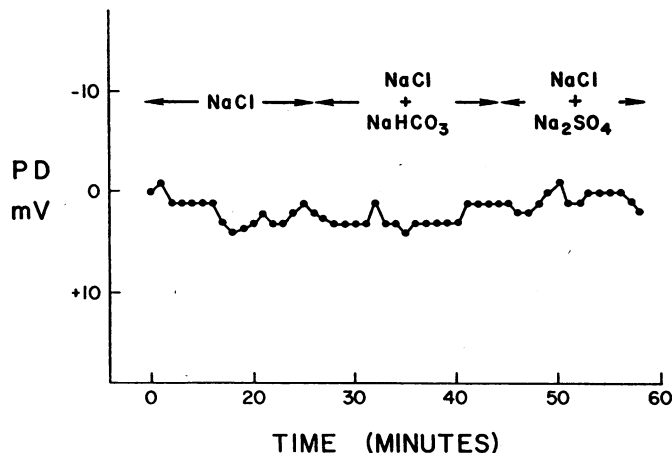


FIGURE 2 Effect of anion substitution of jejunal PD. A positive PD indicates lumen positive with respect to skin; a negative value means lumen negative with respect to skin. Partial substitution of $NaHCO_3$ or Na_2SO_4 for $NaCl$ had no demonstrable effect on PD.

were designed to determine whether bicarbonate absorption is mediated by hydrogen secretion. This process, in contrast to direct transport of bicarbonate ions, would generate a high P_{CO_2} in the luminal fluid. The first step in these studies was to determine the basal CO_2 tension of jejunal contents when bicarbonate is not being absorbed. To do this the jejunum of patients with pernicious anemia (chosen because they do not secrete gastric hydrochloric acid) was perfused with an unbuffered saline solution. These results are shown in Table I. The mean P_{CO_2} of the infused saline solution was 44.2 mm Hg. The P_{CO_2} in fluid collected 10 and 40 cm distal to the infusion site was 45.9 and 48.6 mm Hg, respectively. The P_{CO_2} of fluid collected from the distal sampling site was assumed to be fully equilibrated with the jejunal mucosa.

To see if bicarbonate absorption generates CO_2 , pernicious anemia patients were perfused with an unbuffered bicarbonate-containing solution. These results are shown in Table I and in Fig. 5. Compared to the P_{CO_2} during saline perfusion, perfusion of the bicarbonate solution was associated with a consistent rise in luminal P_{CO_2} .

To amplify the potential effect of hydrogen secretion on the change in P_{CO_2} , a nonbicarbonate buffer (phosphate) was added to the perfusate. As shown in Table I and Fig. 5, addition of the phosphate buffer to the bicarbonate-containing solution caused a further increment in the P_{CO_2} of jejunal fluid.

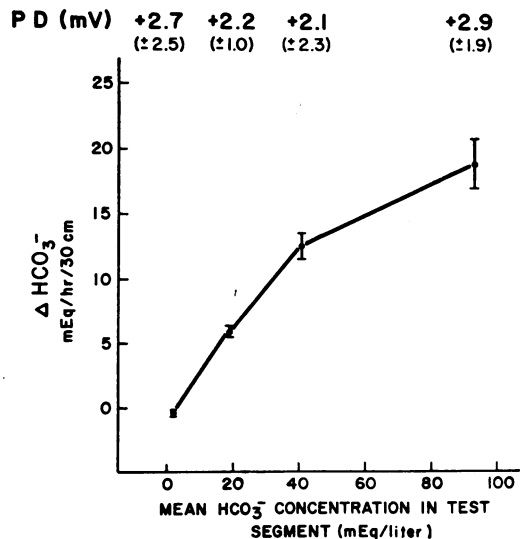


FIGURE 3 Effect of luminal bicarbonate concentration on bicarbonate absorption rate and on potential difference (PD) between jejunal lumen and skin. The number of patients studied was 14, 7, 8, and 8 for the four points, moving from left to right on the graph. PD measurements were made in six subjects at each of the bicarbonate concentrations.

As shown in Table I, bicarbonate absorption rate averaged 10.2 mEq/hr per 30 cm from the unbuffered bicarbonate solution and 8.1 mEq/hr per 30 cm in the presence of phosphate buffer. This difference is entirely

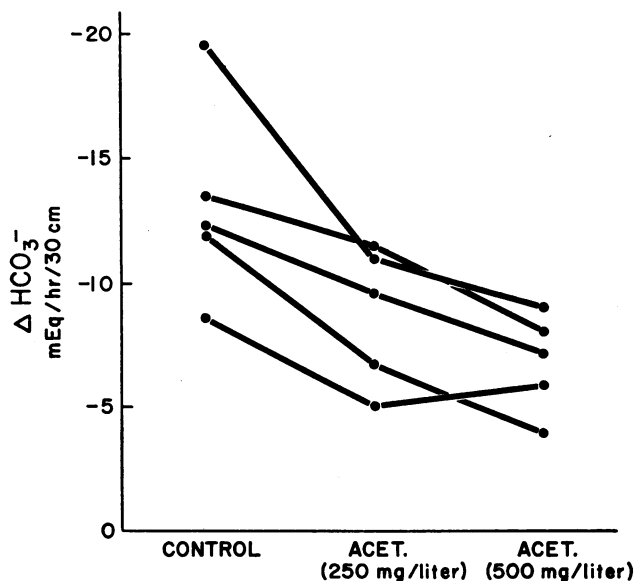


FIGURE 4 Effect of acetazolamide on bicarbonate absorption rate in the jejunum. The mean luminal bicarbonate concentration ± 1 SE was 40.9 ± 4.0 , 49.0 ± 3.2 , and 51.6 ± 3.2 mEq/liter for the control, and 250 and 500 mg/liter acetazolamide solutions, respectively.

due to patient selection, since when individual patients who had both buffered and unbuffered bicarbonate perfusions were compared, bicarbonate absorption rates were approximately equal. Table I also gives data for the pH of the test solutions and collected fluid.

In summary, the P_{CO_2} of jejunal fluid is higher when unbuffered bicarbonate solutions are infused than when saline is infused and higher still when a buffered bicarbonate solution is perfused, indicating that the

process mediating bicarbonate absorption generates a high CO_2 tension in the luminal contents.

DISCUSSION

These experiments, as well as previous studies (1), show that sodium absorption in the jejunum is markedly influenced by bulk flow of water. During isotonic saline perfusion, sodium is absorbed to a slight degree and this can be attributed to the chloride concentration

TABLE I
Jejunal Perfusion with Unbuffered Saline, Unbuffered Bicarbonate, and Buffered Bicarbonate in Patients with Pernicious Anemia*

	pH			P_{CO_2}			HCO_3^- absorption rate
	Infusion	Proximal	Distal	Infusion	Proximal	Distal	
Saline	4.95	6.22	6.21	45	48	51	
<i>n</i> = 9	5.85	6.60	6.77	46	48	61	
	5.73	6.32	6.25	47	61	60	
	6.11	6.50	6.50	47	53	55	
	6.30	6.15	6.10	31	39	46	
	5.16	5.90	5.89	40	42	39	
	4.91	6.29	6.29	39	35	36	
	5.35	5.75	6.06	58	40	41	
	5.62	6.35	6.32	45	47	48	
Mean \pm 1 SE	5.55 \pm 0.17	6.26 \pm 0.07	6.27 \pm 0.09	44.2 \pm 2.4	45.9 \pm 2.6	48.6 \pm 3.0	
Unbuffered bicarbonate	7.82	7.62	7.48	32	53	58	5.2
<i>n</i> = 7	7.60	7.42	7.21	51	58	58	7.4
	7.64	7.51	7.35	47	56	66	11.4
	7.63	7.46	7.23	53	62	57	11.7
	7.53	7.43	7.24	61	70	70	21.6
	7.59	7.50	7.37	54	59	65	10.8
	7.67	7.38	7.19	47	61	63	4.5
Mean \pm 1 SE	7.64 \pm 0.03	7.47 \pm 0.03	7.30 \pm 0.04	49.3 \pm 3.4	59.7 \pm 2.0	62.4 \pm 1.9	10.2 \pm 2.6
Buffered bicarbonate	7.76	7.55	7.38	50	64	80	4.2
<i>n</i> = 11	7.78	7.51	7.20	48	70	83	4.2
	7.66	7.33	7.22	39	70	71	
	7.85	7.66	7.40	32	50	68	5.0
	7.83	7.57	7.40	32	55	69	4.5
	7.85	7.41	7.11	29	62	72	8.4
	7.62	7.43	7.24	46	63	100	13.8
	7.60	7.36	6.92	47	76	90	11.5
	7.60	7.38	7.23	57	69	74	12.0
	7.50	7.42	7.33	73	73	72	5.4
	7.67	7.30	7.11	44	65	67	12.0
Mean \pm 1 SE	7.70 \pm 0.04	7.45 \pm 0.03	7.23 \pm 0.04	45.2 \pm 3.8	65.2 \pm 2.3	76.9 \pm 3.1	8.1 \pm 1.2

* The unbuffered saline solution contained 140 mEq/liter of sodium, 5 mEq/liter of potassium, and 145 mEq/liter of chloride. The unbuffered bicarbonate solution contained 140 mEq/liter of sodium, 5 mEq/liter of potassium, 95 mEq/liter of chloride, and 50 mEq/liter of bicarbonate. The buffered bicarbonate solution contained, per liter, the following: $NaHCO_3$ 4.2 g; Na_2HPO_4 1.85 g; $NaH_2PO_4 \cdot H_2O$ 0.28 g; $NaCl$ 2.51 g; KCl 0.37 g. This resulted in a solution containing approximately 120 mEq/liter of sodium, 5 mEq/liter of potassium, 50 mEq/liter of bicarbonate, and 48 mEq/liter of chloride. The molar ratio of the phosphate buffer pair was 13 Na_2HPO_4 to 2 $NaH_2PO_4 \cdot H_2O$. The buffered bicarbonate solutions had a lower osmolality than the other test solutions to compensate for the presence of phosphate, which would be expected to increase the effective osmotic pressure of this solution. The rate of water absorption was almost exactly the same for the buffered and unbuffered bicarbonate solutions.

gradient between lumen and plasma. When this gradient is obliterated by partial substitution with sulfate, there is no net sodium movement at zero water flow. Since there is no significant potential difference across jejunal mucosa with either isotonic saline or isotonic saline partially replaced by sodium sulfate, these results indicate that there is no active absorption of sodium or chloride from saline solutions. All movement of sodium from saline solutions can be explained by either solvent drag or by chemical concentration gradients.

By contrast, when bicarbonate is present in luminal fluid, sodium is absorbed against electrochemical gradients (1). This suggests that there is in fact a mechanism for active transport of sodium by the jejunum but that it is obligatorily linked in some manner to the absorption of bicarbonate.

Because of its importance in conserving bicarbonate secreted into the proximal small bowel and because of its link to active sodium absorption, the mechanism by which the jejunum absorbs bicarbonate ions deserves careful scrutiny. On the basis of the present study and previous observations (1), bicarbonate absorption can be characterized as follows: (a) in contrast to sodium and chloride, bicarbonate absorption is not influenced by solvent drag; (b) bicarbonate absorption is not influenced by the presence or absence of glucose in the jejunal lumen (unpublished observations of the authors); (c) the bicarbonate absorption mechanism is at least partially saturable at high luminal concentrations; and (d) bicarbonate absorption can occur against steep electrochemical gradients. All these features are con-

sistent with an hypothesis that bicarbonate absorption is mediated by some active ion transport process.

There are two major active transport processes by which the jejunum might accomplish bicarbonate absorption, direct transport of bicarbonate ions or hydrogen secretion. The studies of McGee and Hastings, reported in 1942, are of interest in this regard (4). These workers collected juice from human jejunal segments that were isolated by two balloons of a Miller-Abbott tube. They found that jejunal fluid had a bicarbonate concentration about one-third that of plasma (8 mM/liter), a slightly acidic pH (6.5), and a calculated CO_2 tension about double that of blood (100 mm Hg). This composition corresponds to that which would result if about 15 mM of HCl per liter were added to an ultrafiltrate of blood, and it was concluded that the high CO_2 tension of jejunal juice was the result of a specific secretory (H^+) process. These findings have subsequently been verified by numerous other workers and their conclusions are generally accepted. However, the mechanism by which intestinal juice develops a CO_2 tension higher than blood plasma has recently been studied by Hamilton, Dawson, and Webb who convincingly showed that the high CO_2 tension of gut contents is not related to absorptive or secretory processes but rather is merely a reflection of high mucosal CO_2 tension (5). Thus, high Pco_2 values, which are characteristic of ileal as well as jejunal fluids, may not be used as evidence for H^+ secretion by the jejunum.

It is still theoretically possible to distinguish bicarbonate absorption from hydrogen secretion; to do this,

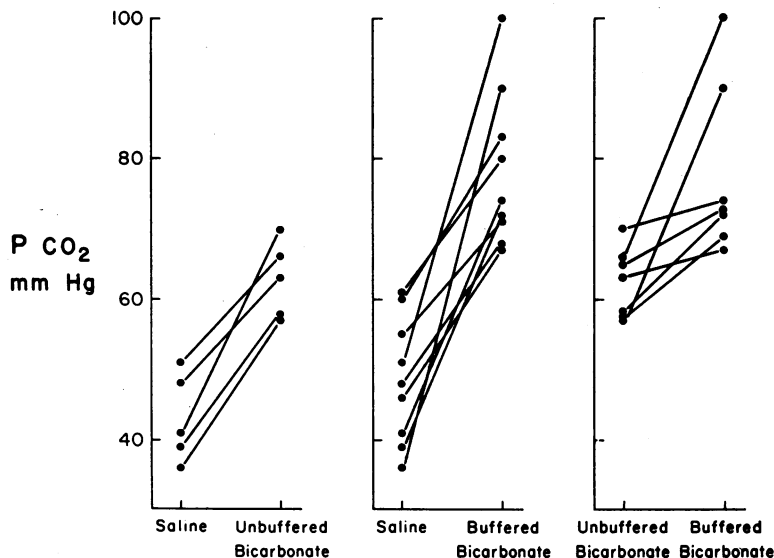


FIGURE 5 Pco_2 of fluid collected from distal aspiration site (40 cm from the infusion point) in patients with pernicious anemia. The data compare the Pco_2 of different perfusion solutions in individual patients.

the P_{CO_2} of jejunal fluid during bicarbonate absorption must be compared with the basal P_{CO_2} of jejunal fluid when bicarbonate is not being absorbed, rather than with blood plasma. During bicarbonate absorption secondary to hydrogen secretion, H_2CO_3 is generated from the reaction of H^+ with HCO_3^- in luminal fluid; since dehydration of H_2CO_3 is not instantaneous, the steady-state concentration of H_2CO_3 during H^+ secretion will be slightly higher than its concentration in a system in which the reactants are allowed to come to equilibrium (6, 7). Consequently, when jejunal fluid is removed from the site of acid secretion into a closed in vitro system, dehydration of the excess H_2CO_3 will cause the P_{CO_2} of this fluid to rise higher than the basal P_{CO_2} of jejunal contents. On the other hand, if bicarbonate ions are absorbed directly, H_2CO_3 is removed from the jejunal lumen and the P_{CO_2} of jejunal fluid after equilibration in vitro will be lower than the basal P_{CO_2} of jejunal contents (6).

Unfortunately, the absolute increase or decrease in steady-state H_2CO_3 concentration with hydrogen secretion or bicarbonate absorption is extremely small, and the net effect on final P_{CO_2} would theoretically be insufficient to permit experimental verification of the mechanism of bicarbonate removal from the jejunum. The change in P_{CO_2} can be magnified, however, if jejunal contents contained a nonbicarbonate buffer system such as phosphate. The theoretical effects of H^+ secretion on the one hand and bicarbonate transport on the other on P_{CO_2} in the presence of buffer is shown in Fig. 6.

As shown on the left side of Fig. 6, secreted hydrogen ions react with bicarbonate to form H_2CO_3 and with phosphate buffer to form NaH_2PO_4 . Since H_2CO_3 does not dissociate instantaneously, the steady-state concentration of H_2CO_3 during H^+ secretion is higher than its concentration in a system in which the reactants are allowed to come to equilibrium. By the same token, excess H_2CO_3 will cause the steady-state pH to be lower than predicted from the luminal bicarbonate concentration and P_{CO_2} by the Henderson-Hasselbalch equation (disequilibrium pH). After jejunal fluid is removed from the intestinal site of H^+ secretion and equilibrium occurs, CO_2 is generated from two sources. The first is the dehydration of excess H_2CO_3 , which elevates P_{CO_2} slightly. The second is the reaction of NaH_2PO_4 with sodium bicarbonate; the CO_2 produced by this reaction would be large enough to raise P_{CO_2} to a measureable extent.

The second mechanism for bicarbonate absorption is shown in Fig. 6 on the right. In this instance, HCO_3^- is absorbed directly and the steady-state concentration of H_2CO_3 in jejunal contents is slightly reduced. Hydrogen ions, made available after HCO_3^- absorption, react with the phosphate buffer pair and elevate the steady-state concentration of NaH_2PO_4 . After equilibration in vitro H_2CO_3 is regenerated which causes P_{CO_2} to fall below mucosal P_{CO_2} ; the concentration of NaH_2PO_4 is further increased.

From the foregoing analysis it is clear that acid secretion can be differentiated from bicarbonate absorp-

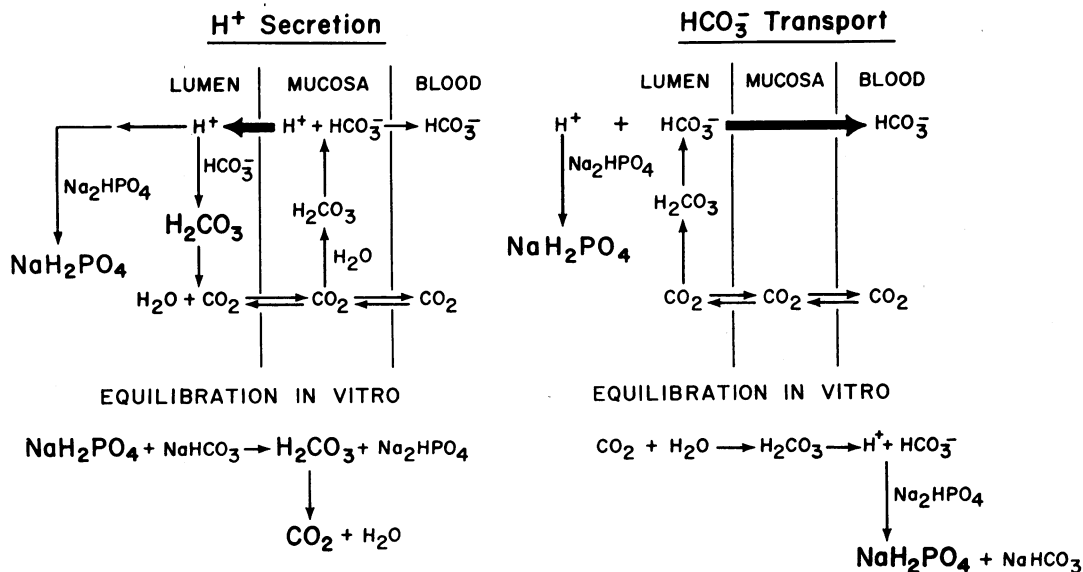


FIGURE 6 Two mechanisms for bicarbonate absorption in the jejunum. Hydrogen secretion, depicted on the left, generates a high CO_2 tension in luminal fluid. By contrast, HCO_3^- absorption acidifies luminal contents without generating excess CO_2 .

tion if three technical problems are solved. First, mixing with extraneous acid, such as that secreted by the stomach, must be avoided. This was obviated by studying patients with pernicious anemia who do not secrete gastric acid. Second, the basal CO_2 tension of jejunal contents, which presumably reflects the CO_2 tension of mucosal cells (5), must be measured. This was accomplished by measuring the Pco_2 of bicarbonate-free saline solutions that had been perfused through the jejunum. Finally, the Pco_2 of a buffered solution containing bicarbonate must be measured after it has been perfused through the jejunum and then allowed to equilibrate in vitro. This was accomplished by perfusing the jejunum with a phosphate buffered bicarbonate solution and measuring Pco_2 of the jejunal perfusate after its equilibration in an airtight glass system.

As shown in Table I and Fig. 5, the Pco_2 of buffered jejunal fluid containing bicarbonate was consistently higher than that of bicarbonate-free saline solutions or than that of unbuffered bicarbonate. This observation suggests that bicarbonate absorption is mediated by hydrogen secretion.

According to the preceding theoretical discussion, a nonbicarbonate buffer is essential in order for H^+ secretion to measurably increase CO_2 tension. There are two possible explanations for the observation that the unbuffered bicarbonate solutions develop a higher Pco_2 than unbuffered saline. First CO_2 generated within the lumen may not equilibrate with mucosal cells instantaneously and a delay in CO_2 diffusion might cause some elevation in luminal Pco_2 . Second, some nonbicarbonate buffer (phosphate and others) probably enters the intestinal test segment during perfusion, even though the test solution was initially free of such buffers.

An alternate explanation for the finding that unbuffered bicarbonate solutions develop a higher Pco_2 than unbuffered saline solutions is that CO_2 is generated within the mucosal cells during bicarbonate absorption or that the addition of absorbed NaHCO_3 into blood generated a high venous Pco_2 with which the luminal fluid would equilibrate. However, the observation that the jejunal fluid Pco_2 is higher with buffered than with nonbuffered bicarbonate perfusion cannot be explained by back diffusion of CO_2 . Only H^+ secretion would be expected to cause the Pco_2 of a buffered bicarbonate solution to be higher than that of a poorly buffered bicarbonate solution.

One other possible interpretation of our data needs consideration. If bicarbonate absorption takes place from a peripheral compartment that is sequestered from the main stream of fluid flowing through the jejunal lumen, bicarbonate concentration gradients might be set up between these different luminal compartments. For in-

stance, if all bicarbonate was absorbed from a small sequestered compartment, the bicarbonate concentration in this compartment would fall markedly while that in the central core would not decrease at all. Mixture of two such solutions of different pH would generate CO_2 , and the Pco_2 of the mixture would be enhanced by the presence of buffer (8, 9). This possibility seems unlikely for three reasons. First, using in vitro techniques, we have shown by trial and error (unpublished observations) that the bicarbonate concentration in the peripheral compartment would have to be lower than 5 mEq/liter in order to raise Pco_2 significantly when mixed with a core solution having a bicarbonate concentration of 35 mEq/liter. Second, the mobility of bicarbonate salts is high, and it is likely that diffusion of sodium bicarbonate from core to periphery would be rapid and prevent development of large concentration gradients between the two compartments. Finally, it is difficult to imagine how the core and peripheral solutions would ever become mixed if sequestration were great enough to allow high concentration gradients to become established in the first place.

In summary, these studies on pernicious anemia patients suggest that acid secretion mediates bicarbonate absorption in the human jejunum. If so, it would be anticipated that development of hydrogen ion concentration gradients would be the major factor which limits the rate of bicarbonate absorption. Acid secretion lowers the pH of jejunal contents by consuming HCO_3^- , and this effect is accentuated by the acid disequilibrium pH. High luminal bicarbonate concentrations would mitigate this effect considerably and should be associated with higher rates of H^+ secretion and HCO_3^- absorption. As shown in Fig. 3, the rate of bicarbonate absorption was in fact markedly dependent on bicarbonate concentration in the range of 2–40 mEq/liter, but raising the luminal bicarbonate concentration to 93 mEq/liter had relatively little additional effect. These findings suggest that secretion of acid in the jejunum is limited by pH gradients only when luminal bicarbonate falls below approximately 40 mEq/liter; above this level the pH of jejunal contents is sufficiently alkaline to insure near maximum rates of acid secretion.

In most H^+ secretory systems, the enzyme carbonic anhydrase is thought to provide a plentiful supply of H^+ at the H^+ secretory site by catalyzing the hydration of CO_2 to H_2CO_3 . Inhibition of this enzyme might thus be expected to inhibit the rate of jejunal H^+ secretion and HCO_3^- absorption. As shown in Fig. 4, acetazolamide did inhibit HCO_3^- absorption by approximately 50%. However, two facts make interpretation of this effect of acetazolamide difficult. First, carbonic anhydrase is present in only very small and perhaps insignificant amounts in the small intestinal mucosa of animals (10).

Second, acetazolamide has been shown to exert effects other than on carbonic anhydrase (11). Thus, acetazolamide may inhibit acid secretion and bicarbonate absorption through mechanisms not involving carbonic anhydrase.

Finally, in what form is the hydrogen secreted? Three possibilities are a neutral HCl pump, an electrogenic hydrogen pump (chloride secretion or sodium absorption would follow passively), and a sodium-hydrogen exchange process. Whatever the mechanism of hydrogen secretion, it is clear that it somehow enhances sodium absorption as well as mediates bicarbonate absorption. A neutral HCl pump would not enhance sodium absorption, so this form of acid secretion seems unlikely. The two remaining possibilities cannot be definitely distinguished from the data on hand. The fact that PD does not change with increasing rates of H⁺ secretion (as bicarbonate concentration rises) favors an electrically neutral sodium-hydrogen exchange. On the other hand, a slight change in PD, perhaps undetectable by our method, might enhance sodium absorption in a tissue which is so highly permeable to sodium ions. Thus, electrogenic H⁺ secretion cannot be entirely excluded.

ACKNOWLEDGMENTS

This work was supported under U. S. Public Health Service Training Grant 5 TO1 AM 5490 and Research Grant 5 RO1 AM 06506.

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