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Clinical Reviews

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The Alkaline Tide Phenomenon

Yaron Niv, M.D., and Gerald M. Fraser, M.D.

Abstract
The parietal cell is capable of secreting high concentrations of hydrochloric acid into the lumen of the stomach. The apical membrane of this cell contains K^+H^+ ATPase, which is responsible for proton transport into the lumen. Potassium and chloride channels are also present. The basolateral membrane of the parietal cell possesses transporters that maintain intracellular homeostasis. Specifically, large amounts of bicarbonate that are generated by carbonic anhydrase must be removed from the cell to prevent alkalinization. Efflux of bicarbonate into the blood after acid secretion can be detected and is known as the alkaline tide. Determination of the alkaline tide has been used to measure acid secretion. In this review, we summarize the published data.
Key Words: Alkaline tide—Acid secretion—Parietal cell.

The stomach is capable of secreting isotonic hydrochloric acid with a pH of 0.8 across the parietal cell apical membrane.[1] Activation of this process occurs when histamine and, to a lesser extent, acetyl choline and gastrin bind to their specific membrane receptors in the basolateral membrane. A complex system of secondary messengers and regulation mechanisms, involving both the cytoplasmic and membrane compartments, connects cell activation by hormone binding with activation of the transport proteins.

PARIETAL CELL APICAL MEMBRANE

Fundamental to understanding the mechanisms of epithelial secretion and absorption is the division of the cell membrane into apical and basolateral regions that are separated by intercellular tight junctions. These membrane regions function autonomously but in complimentary fashion to one another (Fig. 1). One of the two membrane areas characterizes the function of the cell, and the other region is responsible for homeostatic mechanisms that maintain intracellular concentrations of anions, cations, and pH within a narrow range.

From the Department of Gastroenterology, Rabin Medical Center, Beilinson Campus and Sackler School of Medicine, University of Tel-Aviv, Israel.

Address correspondence and reprint requests to Dr. Yaron Niv, Department of Gastroenterology, Rabin Medical Center, Beilinson Campus and Sackler School of Medicine, University of Tel-Aviv, Petach Tikvah 49100, Israel. E-mail: yniv@clalit.org.il

The parietal cell is characterized by a unique apical transport protein that is responsible for secreting protons. This K^+H^+ ATPase is found in the light microsomal fraction of oxyntic cells and is stimulated by K^+.[2] The protein is comprised of a 95-kd α-subunit and 55-kd β-subunit, both of which have been cloned and sequenced.[3] In the resting parietal cell, this enzyme is found in an inactive form in the cytoplasmic tubulovesicles; however, after stimulation (e.g., with cAMP), the tubulovesicles are incorporated into the apical membrane so that a large membrane area is exposed to the lumen. During secretion, protons are exchanged for K^+ ions in an electrically neutral process.

A prerequisite for extrusion of protons through the apical membrane is the presence of high concentrations of K^+ on the luminal side of the membrane. Possible mechanisms for K^+ secretion included a K^+Cl^- cotransporter and/or specific ion channels.[4] Using apical membrane vesicles, the presence of ion conductances for both K^+ and Cl^- was demonstrated.[5] Single channel recordings using patch clamp techniques confirmed the presence of Cl^- channels in amphibian oxyntic cells[1] and in HGT-1 cells, a cell-line with parietal cell properties.[6] Subsequently, a Cl^- channel with a conductance of 27 pS was demonstrated in membrane vesicles incorporated into planar lipid membranes, which was active at a pH of 3.0.[7] Single-channel recordings for apical membrane K^+ channels, in isolated parietal cells, have not been obtained, although the evidence points to the presence of parallel K^+ and Cl^- conductances in their apical membrane. However, the presence of a K^+Cl^- cotransporter has not been excluded.

PARIETAL CELL BASOLATERAL MEMBRANE

Cells are able to normalize intracellular pH (pHi) when given an acid or alkali load. Potential mechanisms for these homeostatic corrections include Cl^--HCO_3^- and Na^+H^+ exchangers and the $Na^+HCO_3^-$ cotransporter. The presence of a Na^+H^+ exchanger was demonstrated in parietal cells using vesicles from the basolateral membrane.[8] In the presence of a proton gradient, there was $^{22}Na^+$ uptake by vesicles, which was inhibited by 0.5 mM of amiloride. Similarly, acidified whole parietal cells only corrected pHi in the presence of Na^+, which was blocked by amiloride. Similar experiments performed after loading of vesicles with $^{36}Cl^-$ or cells with

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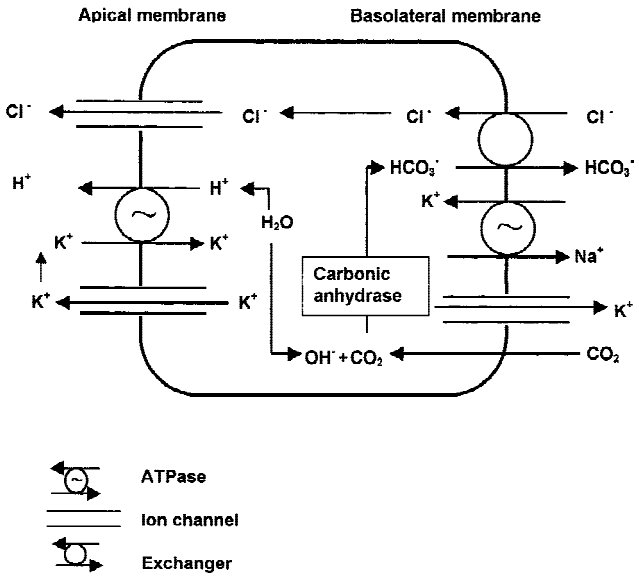

FIG. 1. The important ion transport mechanisms for acid secretion by parietal cells.

HCO_3^- showed that chloride and bicarbonate transport were interdependent and indicated the presence of a $Cl^-HCO_3^-$ exchanger.

Intracellular pH can be measured using pH-sensitive immunofluorescent dyes, such as BCECF.[9] The effect of blocking different transporters can give clues to the way they function in the resting and stimulated parietal cell. The secretion of H^+, K^+, and Cl^- has consequences for the parietal cell to maintain pHi and intracellular ion concentrations. In addition, the production of protons is paralleled by the equimolar production of bicarbonate, which must be removed from the cell.

It would be expected that pHi would rise after exposure to histamine. The pH rise was relatively small in two studies[10,11] and was unchanged in another study.[12] Inhibition of the $Cl^-HCO_3^-$ exchanger with a stilbene derivative (H_2DIDS) lead to a much faster increase in pHi in stimulated parietal cells, which indicates that HCO_3^- is removed by this mechanism. In addition, this exchanger supplies the Cl^- for secretion of HCl so that inhibition of the exchanger reduces acid secretion.[13]

The activity of the Na^+H^+ exchanger, which removes intracellular H^+ in exchange for Na^+ in the stimulated cell has been found to be both increased,[10] decreased,[11] and unchanged[12] in stimulated parietal cells. The increase in activity was explained as being important to increase intracellular Na^+, which in turn is supplied to the Na^+K^+ ATPase, which increases intracellular K^+ for secretion through apical K^+ channels. In contrast, the decrease in activity may be important to prevent increased alkalinization of the parietal cell in addition to the rise in pH caused by acid secretion. It appears that the important mechanism for maintaining pHi in the stimulated parietal cell is the $Cl^-HCO_3^-$ exchanger.[13]

When resting parietal cells are acidified and the Na^+H^+ exchanger is blocked by amiloride in the presence of bicarbonate, pHi is restored by a sodium/bicarbonate–dependent mechanism.[14] It was concluded that this $Na^+HCO_3^-$ exchange may be important for increasing intracellular bicarbonate. This in turn can be exchanged for Cl^- via the $Cl^-HCO_3^-$ exchanger so that the parietal cell can be charged with Cl^- in preparation for secretion of HCl. In contrast, no evidence for a bicarbonate-driven sodium uptake could be demonstrated in a study in which basolateral membrane vesicles were used.[15] Thus, the importance of this exchanger remains unclear.

There are K^+ channels in the basolateral membrane, which are stimulated early in the process of secretion.[16] These large conductance, inwardly rectifying channels hyperpolarize the cell membrane and, therefore, increase the driving force for exit of Cl^- at the apical membrane. There appear to be differences in the control of thesis channels between mammalian species in which cAMP and carbachol had no effect[16] and amphibian species in which two types of channels were found to respond to carbachol or cAMP, respectively.[17]

ALKALINE TIDE

To prevent alkalinization of the parietal cell concomitantly with acid secretion, bicarbonate extrusion must occur to prevent cell death.[18] It was thought teliologically that for every proton secreted, a HCO_3^- ion enters the bloodstream. This process, with physiologic consequences, was first recognized in the 1960s as alkalinization of the blood and urine after a meal and was termed the "alkaline tide."[19,20] We have incorporated that expression to denote the increment in total body HCO_3^- that accompanies the acute increase in the rate of acid secretion.

The alkaline tide can be calculated by multiplying the change in blood base excess (in meq/L) by the initial volume of distribution of added bicarbonate. The latter has been studied by several methods[21] and has been found to be related to body weight (in kg) by a mean "coefficient of distribution" constant of 0.3. This factor is valid for up to 1 hour after the acute event[20] according to the following equation:

$$\text{alkaline tide (meq)} = \{\Delta BE(\text{meq/L}) \times f60 \times w(\text{kg})\} + U(\text{meq})$$

where ΔBE indicates the change in base excess; $f60$, coefficient of volume distribution (the subscript indicating the 60 minutes time-dependence of the coefficient); w, body weight; and U, net urinary excretion of base during the same interval. Because U accounted for a negligible fraction of the alkaline tide, it can be omitted.

In studies by Rune[19,20] and ourselves,[22] it was shown that when alkaline tide and acid secretion are measured simultaneously after histamine or pentagastrin stimulation, the bicarbonate accumulation in arterial or arterialized venous blood augments in a linear fashion and the peak value is equivalent to the amount of acid recovered.

We have studied the applicability of the alkaline tide as a clinical measure of acid secretion in arterial blood and arterialized venous blood[23] and have established a method for estimation of gastric acid output rate. The development of a reliable and reproducible technique, in which arterialized venous blood is obtained after immersion of the hand in a water bath at 45°C, has made this possible.[22,24] We also found that cimetidine or vagotomy lead to the abolition of postprandial alkaline tide in arterialized venous blood from duodenal ulcer patients. The practical importance of the measurement of alkaline tide may be the demonstration of incomplete vagotomy, after vagotomy and pyloroplasty, in symptomatic patients.

There have been 17 studies of alkaline tide (Table 1),[22,24–38] with confirmation of this phenomenon in all but two of them.[37,38] These studies have been performed in experimental animals, in human volunteers, in patients with duodenal ulcer disease, and in children in whom the loss of alkaline tide was a marker for infection. Increased base has been found in arterial and venous blood, in arterialized venous blood obtained from peripheral veins after warming of the hand in a water bath at 45°C, and in urine. Various methods of stimulating acid secretion have been used, including a protein-rich meal, gastrin, pentagastrin, histamine, and betazole. In some of the studies, it was found that surgical vagotomy or antisecretory agents lead to the disappearance of alkaline tide. A reverse phenomenon to alkaline tide was demonstrated after stimulation of pancreatic secretion with secretin.[34] Microelectrode studies showed that there was acidification of pancreatic tissue under these conditions.

Two studies did not confirm the existence of the alkaline tide phenomenom.[37,38] The lack of effect of cimetidine, ranitidine, or omeprazole provided the main evidence. Johnson et al.[38] failed to demonstrate an increase in carbon dioxide in expired air after a meal, with or without omeprazole. Because they were unable to detect either renal or pulmonary compensatory phenomena, it was concluded that alkalinization (if it occurs) was of no physiologic significance. Further support for this study was obtained from microscopic examination of blood flow in capillaries in gastric glands at the base of the parietal cells.[37] It was found

TABLE 1. *Association between alkaline tide and gastric acid output*

Series	Setting	Source	Association	Stimulus	Antagonist
Rune,[19] 1965	Volunteers	Arterial blood	+	Histamine, meal	NT
Rune,[20] 1966	Volunteers	Arterial blood	+	Histamine, meal	NT
Hughes,[26] 1977	Volunteers	Venous blood	+	Meal, gastrin, betazole	NT
Weber,[28] 1986	Eligator	Venous blood	+	Meal	NT
Ahmad,[29] 1986	Volunteers, postvagotomy	Urine	+	Meal	Vagotomy
Vaziri,[27] 1987	Volunteers	Urine	+	Insulin	NT
Langbroek,[30] 1990	Dogs	Arterial blood	+	Meal	NT
Johnson,[31] 1990	Volunteers, postvagotomy	Urine	+	Meal	Vagotomy
Niv,[23] 1992	Ulcer patients	Urine	+	Pentagastrin, meal	NT
Niv,[22] 1993	Ulcer patients	Arterial blood, arterialized venous blood	+	Pentagastrin	NT
Thomas,[33] 1993	Children	Urine	+	Meal	Ranitidine
Ashley,[34] 1994	Volunteers	Pancreatic parenchima*	+	Secretin	NT
Niv,[24] 1995	Ulcer patients, postvagotomy	Arterialized venous blood, urine	+	Meal	Vagotomy, cimetidine
Niv,[25] 1995	Ulcer patients	Arterialized venous blood	+	Pentagastrin	Verapamil
Secor,[35] 1995	Snakes	Venous blood	+, Accompanied with chloride depletion	Meal	NT
Vaziri,[37] 1980	Volunteers	Urine	–	Meal	Cimetidine
Johnson,[38] 1995	Volunteers	Urine, expired air	–	Meal	Ranitidine, omeprazole

*Alkaline tide after pancreatic stimulus.
NT indicates not tested.

that the blood flowed in the direction of the lumen. Thus, it is not clear how bicarbonate reaches the systemic blood circulation.

In the past, we showed that the calcium channel blocker verapamil inhibited the alkaline tide after stimulation with pentagastrin by 65%.[25] Because calcium is the secondary messenger for gastrin in the parietal cell, this demonstrates the importance of extracellular calcium influx in gastrin-stimulated acid secretion. In additional studies, a reduction of 5.4% in ionized calcium in serum was demonstrated, together with a rise in pH, after a protein meal or the administration of gastrin or betazole.[26] The gastric mucosa, when stimulated to secrete acid by histamine, is less sensitive to damage by externally administered acid.[39] It was concluded that the alkaline tide was important in the protection from mucosal damage. When rats were depleted of chloride by treatment with diuretics and equimolar bicarbonate was used to replace the chloride, only 0.4% of the bicarbonate was recovered in the urine after 4 hours.[40] The explanation was that the conservation of sodium, and thus intracellular volume, probably prevented the bicarbonate from being excreted. Elevation of urinary bicarbonate may serve as a protecting mechanism against uric acid stone formation. In patients with nephrolithiasis, the alkaline tide phenomenon disappeared.

CONCLUSION

Alkaline tide is the physiologic counterpart of stimulated acid secretion. During acid secretion the parietal cell uses the basolateral membrane $Cl^-HCO_3^-$ exchanger to remove intracellular bicarbonate and to maintain pHi. At the same time, chloride enters the cell ready for acid secretion. The extrusion of bicarbonate leads to the alkaline tide phenomenon, which can be accurately determined by changes in base excess in arterialized venous blood. Vagotomy and H_2-receptor antagonists inhibit the alkaline tide response to histamine and pentagastrin. The measurement of alkaline tide may be useful as an alternative to that of the rate of gastric acid output.

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