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Narrative Review

Pathophysiology of Metabolic Alkalosis: A New Classification Based on the Centrality of Stimulated Collecting Duct Ion Transport

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Metabolic alkalosis is a unique acid-base disorder because it can be induced and sustained by functional alterations in renal ion transport. This review summarizes more than 50 years of research into the pathophysiologic processes causing this disorder. The evidence reviewed supports the hypothesis that virtually all forms of metabolic alkalosis are sustained by enhanced collecting duct hydrogen ion secretion, induced by stimulation of sodium uptake through the epithelial sodium channel (ENaC). Enhanced collecting duct hydrogen ion secretion in metabolic alkalosis occurs most commonly secondary to changes in ion transport earlier along the nephron, but also can occur as the result of primary stimulation of ENaC. In both these settings, potassium secretion is stimulated, and abnormal potassium losses cause depletion of body potassium stores. Potassium depletion has a key role in sustaining metabolic alkalosis by stimulating renal hydrogen ion secretion, enhancing renal ammonium production and excretion, and downregulating sodium reabsorption in the loop of Henle and early distal tubule. A new classification of the causes of metabolic alkalosis is proposed based on these pathophysiologic events rather than response to treatment.
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INDEX WORDS: Acid-base disorders; metabolic alkalosis; collecting duct ion transport; pathophysiology; chloride; potassium; epithelial sodium channel.

Metabolic alkalosis is an enigmatic and unique acid-base disorder because it can be initiated and sustained by purely functional alterations in renal ion transport. In some instances, the pathophysiologic process is not completely understood. As a result, the causes often have been categorized based on response to treatment rather than on the specific pathophysiologic process. This review is an attempt to unify the seemingly disparate causes of this disorder based on our accumulated knowledge of the regulation of specific ion transporters and channels along the nephron. It is hoped that this analysis will provide new insights and simplify the approach to diagnosing and treating this common clinical disorder.

GENERAL CONSIDERATIONS

Metabolic alkalosis is generated by the primary addition of alkali to body fluids and is manifested by an increase in serum bicarbonate concentration. However, it becomes clinically evident as an acid-base disorder only when the abnormal increase is sustained by impairment of renal bicarbonate excretion (Box 1). In patients with no kidney function, alkali addition or acid losses increase serum bicarbonate levels, and the excess alkali is retained until it is consumed over time by endogenous acid production.[1,2] In individuals with adequate kidney function, in contrast, excess alkali is excreted rapidly, quickly restoring serum bicarbonate to normal levels. Persistent alkalosis occurs only when tubule ion transport is altered in a way that limits or prevents bicarbonate excretion.

Metabolic alkalosis in individuals with kidney function traditionally has been viewed as initiated and sustained by either chloride losses (usually but not always with associated hydrogen ion losses) or potassium losses. This view has proved useful in the approach to diagnosis and management, but it obscures the important interactions between potassium and chloride depletion in producing and sustaining most forms of metabolic alkalosis.[3] In this review, these interactions and their collective effects on collecting duct ion transport are emphasized. Changes in key ion transporters and their roles in inducing and sustaining metabolic alkalosis are discussed first, followed by an integrated view of these transport effects on steady-state serum bicarbonate levels.

EFFECTS OF CHLORIDE AND/OR POTASSIUM DEPLETION ON KEY ION TRANSPORTERS ALONG THE NEPHRON

Proximal Tubule Hydrogen Ion Secretion

Two transport proteins are responsible for hydrogen ion secretion into the proximal tubule, a sodium/hydrogen exchanger (NHE3), and a hydrogen ion–

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Box 1. Causes of Impaired Renal Bicarbonate Excretion in Metabolic Alkalosis

1. Kidney failure

2. Secondary stimulation of collecting duct ion transport

- Extrarenal Cl^- losses with secondary renal K^+ losses
- Renal Cl^- losses with secondary K^+ losses
  - ◇ Pharmacologic (diuretics)
  - ◇ Inactivating genetic mutations of Cl^--linked Na^+ cotransporters

3. Primary stimulation of collecting duct ion transport

- Mineralocorticoid induced
- Activating genetic mutations of ENaC or its signal pathway

Abbreviations: Cl^-, chloride; ENaC, epithelial sodium channel; K^+, potassium; Na^+, sodium.

transporting adenosine triphosphatase (H^+-ATPase). The hydrogen ion added to tubule fluid by these 2 apical membrane transporters removes ~70% of filtered bicarbonate from the tubule lumen. The activity of both transporters increases in direct relation to tubule fluid flow rate, so that bicarbonate reabsorption increases as the filtered load increases.[4-6] The same relationship occurs when filtered bicarbonate is increased in sustained metabolic alkalosis.[7,8] Potassium depletion stimulates proximal tubule hydrogen ion secretion, presumably by upregulating transport proteins involved in bicarbonate movement from cells to the peritubular interstitium.[9,10] This effect of potassium depletion appears to be mediated by an increase in endothelin secretion and is manifest both in the proximal and distal convoluted tubules.[11] Increases in bicarbonate delivery and potassium depletion contribute to sustaining an increased serum bicarbonate level, but they cannot be critical because substantial bicarbonate still is delivered to the distal nephron in metabolic alkalosis, and in addition, this anion can be secreted into the distal tubule and collecting duct, facilitating its rapid excretion.

$Na^+/K^+/Cl^-$ Cotransporter

This apical membrane cotransporter links sodium reabsorption with both potassium and chloride reabsorption in the loop of Henle. Impairment of its function by either diuretics[12] or one of several mutations in Bartter syndrome invariably leads to metabolic alkalosis by increasing sodium delivery to the collecting duct, where its reabsorption stimulates both hydrogen ion and potassium excretion (Fig 1). Chloride depletion results in hypochloremia, decreasing chloride delivery to this cotransporter, and this change in delivery in theory could impair its function. However, such an effect cannot be detected.[13] Potassium depletion decreases both activity of the $Na^+/K^+/2Cl^-$ cotransporter and messenger RNA levels for its synthesis.[14] Potassium depletion also promotes increased ammonium uptake through this cotransporter because ammonium competes with potassium for entry.[15] This effect facilitates the increase in ammonium excretion observed after induction of potassium depletion.

Na^+/Cl^- Cotransporter

This apical membrane cotransporter links sodium and chloride reabsorption in the early distal tubule. Blockade of its function by either thiazide diuretics or mutations in Gitelman syndrome causes metabolic

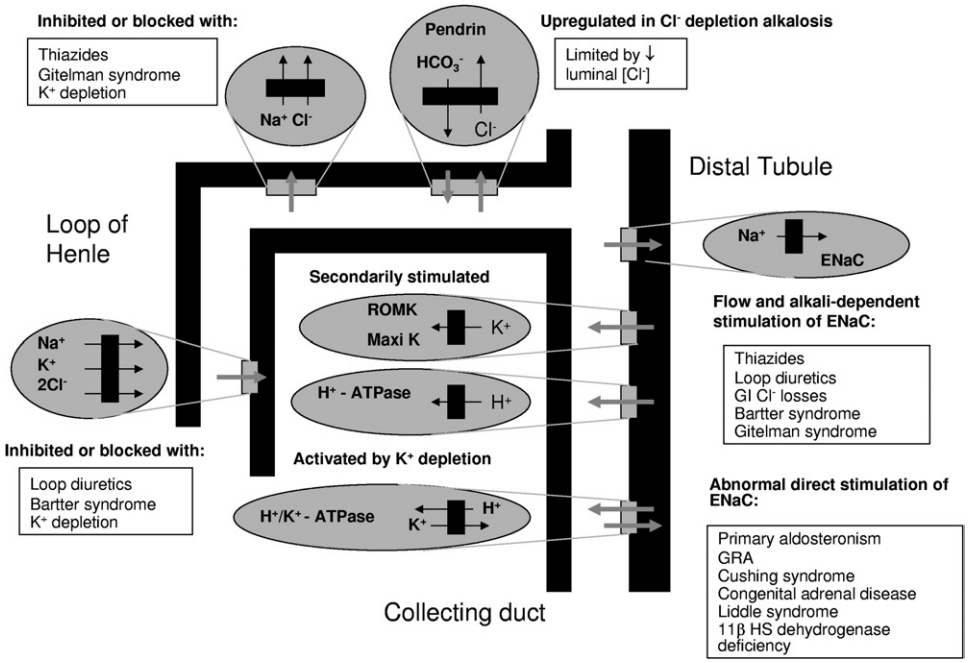

Figure 1. Schematic depiction of the key apical membrane ion transport proteins in the loop of Henle and distal nephron and the ways in which their function is altered to both impair excess bicarbonate (HCO_3^-) excretion and sustain potassium (K^+) losses in various forms of metabolic alkalosis. As shown in the figure, recent data strongly suggest that alkalemia (an increase in tubule fluid or interstitial [HCO_3^-]) directly stimulates the epithelial sodium channel (ENaC). Abbreviations: 11βHS, 11β-hydroxysteroid; Cl^-, chloride; GI, gastrointestinal; GRA, glucocorticoid-remediable aldosteronism; Na^+, sodium.

alkalosis by increasing sodium delivery to the collecting duct, where its reabsorption stimulates both hydrogen ion and potassium excretion.[16] The activity of this transporter and the messenger RNA for its synthesis also are downregulated by potassium depletion.[14] In chloride depletion states, it is proposed, but unproved, that a decrease in chloride delivery to this cotransporter impairs sodium uptake.

Pendrin

This chloride/bicarbonate (Cl^-/HCO_3^-) exchanger is located on the apical membrane of β intercalated cells in the connecting tubule and cortical collecting duct and secretes bicarbonate into the tubule lumen in exchange for chloride uptake.[17] Because of this configuration, pendrin is instrumental for excreting excess alkali when body bicarbonate levels are increased. The Cl^-/HCO_3^- exchanger is stimulated in metabolic alkalosis and thus potentially poised to facilitate bicarbonate secretion.[18,19] Removal of chloride from distal tubule fluid blocks bicarbonate secretion,[18,19] but this situation does not occur in vivo in metabolic alkalosis. In pendrin-null homozygous mice, no secretion of bicarbonate occurs; however, strikingly, metabolic alkalosis does not develop unless they also are placed on a chloride-restricted diet.[20] In the absence of chloride restriction, these mutant animals downregulate hydrogen ion–secreting transport proteins in the collecting duct, compensating for the lack of bicarbonate secretion.[21] Recent evidence suggests that the mechanism for this downregulation is a decrease in epithelial sodium channel (ENaC) activity induced by a decrease in bicarbonate delivery to the principal cells containing this ion channel.[22] In animals with metabolic alkalosis induced by chloride depletion, the Cl^-/HCO_3^- exchanger is fully functional and upregulated.[23] Because no bicarbonate appears in urine in these animals, increased bicarbonate secretion must be counterbalanced by high rates of hydrogen ion secretion in the distal tubule and collecting duct.[23,24] Stimulation of hydrogen ion secretion in the collecting duct likely is due to stimulation of ENaC, which in turn may be due to increased bicarbonate levels in both tubule fluid and the peritubular interstitium.[22] Pendrin also is upregulated when metabolic alkalosis is induced by mineralocorticoid administration,[25] but is downregulated in a mouse model in which potassium depletion is induced by dietary potassium restriction.[26] The role of pendrin in sustaining metabolic alkalosis and its functional linkage with collecting duct hydrogen ion secretion is an evolving story, but it seems likely that the balance between bicarbonate secretion through pendrin and hydrogen ion secretion in the collecting duct has a key role in determining the steady-state serum bicarbonate level.

ENaC

This sodium channel resides on the apical membrane of principal cells in the collecting duct and is regulated principally by flow rate (and thus sodium delivery) and aldosterone.[27-29] In addition, recent evidence suggests that the activity of this transporter is stimulated by alkalemia, an effect that is independent of aldosterone or sodium delivery.[22] Impairment of sodium uptake earlier in the nephron results in increased delivery and uptake of sodium through ENaC, increasing the electrochemical driving forces favoring both potassium and hydrogen ion secretion.[30,31] An increase in bicarbonate delivery to ENaC, as well as increased bicarbonate levels in tubule fluid and the peritubular interstitium, also may have an important role in stimulating this transporter in metabolic alkalosis,[22] but sufficient sodium delivery also is a necessary factor. Direct stimulation of this transporter by aldosterone and a variety of genetic and acquired disorders also causes potassium depletion and metabolic alkalosis when sodium delivery is sufficient.

Epithelial Potassium Channels

The ROMK (renal outer medullary potassium) channel resides on the apical membrane of epithelial cells in the loop of Henle and principal cells of the collecting tubule. Recycling of potassium through this channel in the loop of Henle is necessary for adequate function of the $Na^+/K^+/2Cl^-$ cotransporter. In the collecting duct, potassium secretion through this channel is driven by the electrochemical gradient generated by sodium reabsorption through ENaC. Potassium secretion is increased when sodium delivery and reabsorption are increased, even in the setting of overall potassium depletion.[30] The maxi-K channel also is located on the apical membranes of epithelial cells in the loop of Henle and principal and intercalated cells in the collecting duct. This channel is not open under normal conditions, but opens when flow is increased at either site and facilitates potassium secretion with higher conductance than ROMK.[32]

H^+-ATPase and H^+/K^+-ATPase

Hydrogen ion secretion in the collecting duct can occur through either H^+-ATPase or H^+-K^+-ATPase, both located on the apical membrane of α-intercalated cells. The first of these transporters is active under most conditions, although it requires aldosterone for optimal function.[33] Secretion of hydrogen ions through this transporter shows flow dependence, presumably due to flow-dependent sodium reabsorption creating a favorable electrochemical gradient.[34,35] In metabolic alkalosis induced by chloruretic diuretics and Bartter and Gitelman syndrome, hydrogen ion secretion is increased secondary to the increase in sodium deliv-

ery to the collecting duct and reabsorption through ENaC. In an experimental model of chloride-depletion metabolic alkalosis, distal nephron hydrogen ion secretion also is increased for any given level of luminal bicarbonate.[23,24] Two isoforms of an additional hydrogen ion–secretory transporter, the H^+/K^+-ATPase, are present in the collecting duct, and the activity of at least one of these is increased by potassium depletion,[36,37] providing an additional route for hydrogen ion secretion into the tubule in metabolic alkalosis.[11]

Summary of Tubule Ion Transport Changes in Metabolic Alkalosis

In sustained metabolic alkalosis, excretion of excess bicarbonate by the kidney is impaired by an abnormal increase in hydrogen ion secretion along the nephron. Proximal tubule bicarbonate reabsorption increases as a result of delivery-stimulated hydrogen ion secretion and the associated potassium depletion, but the key events maintaining alkalosis appear to reside in the distal nephron (Fig 1). Inhibition of chloride-linked sodium reabsorption in the loop of Henle or early distal tubule increases flow-dependent sodium reabsorption through ENaC in the collecting duct, and this increase in sodium reabsorption stimulates abnormal hydrogen ion and potassium secretion. ENaC also may be stimulated secondary to an increase in bicarbonate level in the collecting duct or surrounding interstitium.[22] Unregulated mineralocorticoid secretion or genetic abnormalities in ENaC or its signaling pathways lead to direct stimulation of its activity and stimulation of hydrogen ion and potassium secretion.

SECONDARY STIMULATION OF COLLECTING DUCT ION TRANSPORT

Gastrointestinal Chloride Losses

In humans who are given a diet containing very little chloride, nocturnal nasogastric suction for several days coupled with stimulation of gastric acid secretion induces sustained metabolic alkalosis.[38-40] Alkalosis develops rapidly during the period of suctioning, with plasma bicarbonate level increasing to ~40 mmol/L despite replacement of all losses except for the chloride that is linked to hydrogen ions. Generation of the alkalosis is associated with abnormal acid and potassium excretion into urine. After cessation of the drainage, metabolic alkalosis and potassium depletion persist despite normal dietary potassium intake until sufficient chloride is given to replete the losses induced.

The disorder is not corrected when supplemental potassium is administered without chloride.[40] In addition, induction and maintenance of the disorder is independent of either extracellular fluid (ECF) volume depletion or potassium losses[39,41] and is not mediated by increased aldosterone levels.[42] However, in the absence of potassium repletion, much larger amounts of chloride are required to correct the alkalosis.[39,43]

Diuretic-Induced Metabolic Alkalosis

Metabolic alkalosis induced by furosemide administration shows features identical to that induced by nasogastric drainage.[44] In healthy humans, 1-2 days of oral furosemide therapy plus a citrate supplement coupled with a diet restricted in chloride content produces sustained metabolic alkalosis. The alkalosis develops despite very modest potassium losses and with no measurable change in ECF volume or glomerular filtration rate (GFR). Correction is dependent on chloride repletion (induced by oral potassium chloride administration); potassium phosphate administration is ineffective. Aldosterone is not a contributing factor because levels increase during the correction phase.

Potassium Depletion

Potassium depletion independent of chloride depletion causes metabolic alkalosis in humans,[43] but the severity of alkalosis is dependent on dietary chloride intake. In patients with adequate chloride intake, serum bicarbonate levels increase significantly, by 2 mmol/L, after induction of moderate potassium depletion (Fig 2). However, when dietary chloride intake also is restricted, serum bicarbonate levels increase by a much greater amount, 7.5 mmol/L, emphasizing the interplay between potassium and chloride depletion in the pathogenesis of this disorder.

The specific effects of potassium depletion in sustaining metabolic alkalosis are: (1) a shift of hydrogen ions into cells, which increases ECF bicarbonate concentrations,[45] and (2) renal effects leading to an increase in hydrogen ion secretion throughout the nephron[8,46] and in ammonium production and excretion, facilitating acid excretion and sustaining the increase in ECF bicarbonate concentrations.[45,47] In addition, potassium depletion downregulates chloride-linked sodium reabsorption in the loop and early distal tubule,[14] ensuring sufficient sodium delivery to the collecting duct for continued stimulation of hydrogen ion and potassium secretion. Figure 3 shows the interactions between chloride and potassium depletion in sustaining the most common form of metabolic alkalosis and also illustrates the possible effects of alkalemia per se on sodium uptake through ENaC (Fig 3).

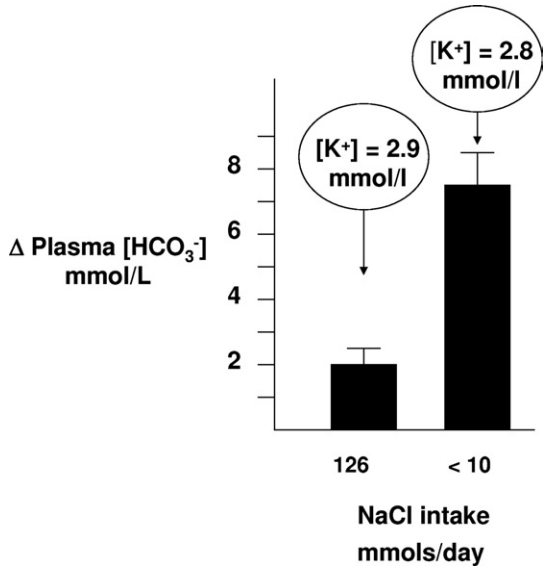

Figure 2. Effect of potassium (K^+) depletion (400-500 mmol, induced by dietary K^+ restriction for 2 weeks) on plasma bicarbonate levels ($[HCO_3^-]$) in healthy humans. The left-hand bar shows the increase with no dietary chloride (Cl^-) restriction. The right-hand bar shows the mean increase when dietary Cl^- intake also was markedly restricted. In both instances, the increase is significant ($P = 0.02$ in the normal-sodium-chloride [NaCl] group, $P = 0.001$ in the low-NaCl group). As indicated in the figure, plasma $[K^+]$ was essentially the same in both groups. Data from Hernandez et al.[43]

Role of GFR

Most forms of clinical chloride-depletion alkalosis are associated with a decrease in GFR, and this change was proposed to be instrumental in sustaining the disorder by limiting bicarbonate filtration.[48] Against this conclusion, GFR increases to greater than pre-alkalosis values in a rat model of sustained chloride-depletion alkalosis.[8,49] In addition, in one study of humans in which chloride-depletion alkalosis was induced by furosemide administration, careful measurement of GFR showed no significant decrease during induction and maintenance of metabolic alkalosis.[44]

Role of Aldosterone

It is unlikely that aldosterone has more than a facilitating role in sustaining chloride-depletion metabolic alkalosis. As discussed, aldosterone levels decrease in the alkalosis caused by chloride losses and increase during correction with potassium chloride treatment.[42,44] In addition, chloride-depletion alkalosis can be induced and sustained in adrenalectomized rats.[50] Although not essential, ample aldosterone is secreted in patients with sustained chloride-depletion metabolic alkalosis, particularly when associated with volume depletion, facilitating sodium uptake through ENaC.[42,44]

Role of Pco_2

The secondary increase in partial pressure of carbon dioxide (P_{CO_2}) that occurs in all forms of metabolic alkalosis paradoxically is an additional stimulus to increase hydrogen ion secretion in the kidney.[51] As a result, a small increment in serum bicarbonate level can be attributed solely to the increase in P_{CO_2} that normally occurs when metabolic alkalosis is induced. An increase in P_{CO_2} stimulates hydrogen ion secretion independent of changes in hydrogen ion levels.[52]

The Enigma of Chloride-Depletion Metabolic Alkalosis

When chloride depletion is induced by either induction of gastrointestinal losses or diuretic therapy, the disorder is sustained by dietary chloride restriction despite cessation of the initiating cause. In all models of metabolic alkalosis sustained by chloride depletion, both hydrogen ion and potassium secretion into the collecting duct are increased abnormally, but the mechanisms are incompletely understood. When assessed, sodium delivery to the collecting duct does not appear to be increased.[13,53,54] Several alternative hypotheses have been proposed. The first is that distal nephron bicarbonate secretion is limited by chloride delivery despite upregulation of the Cl^-/HCO_3^- exchanger, resulting in insufficient bicarbonate secretion to overcome the abnormal secretion of hydrogen ions in the collecting duct.[13] This proposal leaves unanswered the question of what is causing the abnormal hydrogen ion secretion in the first place. The second is based on a finding that collecting duct chloride reabsorption is increased in metabolic alkalosis.[55] The resultant decrease in collecting duct chloride levels has been proposed to create a milieu that favors hydrogen ion secretion coupled with chloride backflux in the inner medullary collecting duct. Against this proposal are experiments in perfused medullary collecting duct segments indicating that virtually all hydrogen ion secretion is linked to cation reabsorption, rather than chloride backflux.[56]

New evidence suggests another possible scenario. As discussed, ENaC activity appears to be stimulated by an increase in either basolateral or tubule fluid bicarbonate levels independent of other effects.[22] Given that the driving force for collecting duct hydrogen ion secretion is sodium uptake through ENaC, alkalemia-induced stimulation of ENaC coupled with just sufficient sodium delivery to the collecting duct may be the combination of events necessary to recapture all the filtered and secreted bicarbonate and sustain the metabolic alkalosis induced by chloride depletion. Repletion of body chloride stores may upset this delicate balance by causing a large enough increase in collecting duct bicarbonate delivery to

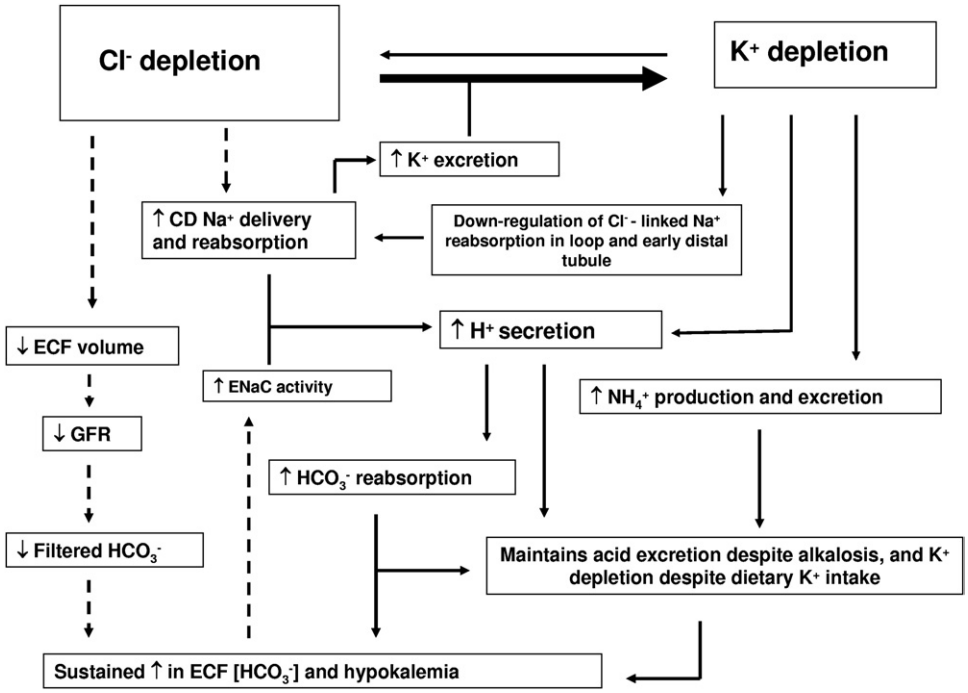

Figure 3. Schematic representation of the interactions between chloride (Cl^-) and potassium (K^+) depletion in sustaining the metabolic alkalosis associated with selective Cl^- depletion. Hatched arrows indicate suggested, but unproved, contributing effects. Depletion of Cl^- invariably leads to K^+ losses and sustained K^+ depletion, whereas primary K^+ depletion leads to Cl^- losses and depletion only when very severe. Depletion of K^+ stimulates collecting duct hydrogen ion (H^+) secretion, downregulates Cl^--linked sodium (Na^+) reabsorption, and increases renal ammonium (NH_4^+) excretion. Also shown in the figure, recent data strongly suggest that alkalemia (an increase in tubule fluid or interstitial bicarbonate level [HCO_3^-]) directly stimulates the epithelial sodium channel (ENaC). Abbreviations: CD, collecting duct; ECF, extracellular fluid; GFR, glomerular filtration rate.

overwhelm the increase in hydrogen ion secretion, thereby allowing serum bicarbonate levels to decrease and in turn decrease alkali-induced stimulation of ENaC. This novel hypothesis obviously requires further studies for verification. The effect of the associated potassium depletion to stimulate hydrogen ion secretion earlier in the nephron and cause a shift in sodium reabsorption from the loop and early distal tubule to the collecting duct, as well as alkali-induced stimulation of ENaC, may be the combination required for sustaining this common disorder.

Hereditary Disorders Producing Chloride Depletion and Metabolic Alkalosis

Congenital Chloridorrhea

This inherited disorder, manifested by watery diarrhea that is rich in chloride, is caused by a loss of function mutation in the DRA (downregulated in adenoma) gene, leading to a defect in the apical membrane Cl^-/HCO_3^- exchanger in the distal ileum and colon.[57] This defect leads to chloride depletion, metabolic alkalosis, and hypokalemia.

Bartter Syndrome

Bartter syndrome causes renal chloride wasting, metabolic alkalosis, and hypokalemia in infants and young children.[58,59] It is caused by one of several mutations that inactivate or impair the function of the $Na^+/K^+/2Cl^-$ cotransporter in the thick ascending limb of the loop of Henle.[59-62] The pathophysiologic process of the metabolic alkalosis in this disorder is identical to that induced by furosemide.

Gitelman Syndrome

Gitelman syndrome causes mild hypokalemia and metabolic alkalosis and is first manifest in young adults.[63,64] The disorder is caused by mutations that inactivate or interfere with the function of the Na^+/Cl^- cotransporter in the early distal tubule.[59,60,62] The pathophysiologic process of the metabolic alkalosis in this disorder is identical to that induced by thiazide diuretics.

PRIMARY STIMULATION OF COLLECTING DUCT ION TRANSPORT

Although the specific pathophysiologic process of this form of metabolic alkalosis differs notably from the form induced by chloride and potassium depletion, it shares the common theme of an increase in sodium delivery to the collecting duct coupled with stimulation of its reabsorption at this site in the nephron.

Mineralocorticoid Excess

When the mineralocorticoid DOCA (desoxycorticosterone acetate) is injected into healthy humans ingesting a diet containing either 15 or 180 mmol of sodium a day, a notable difference in response is observed.[65] In patients ingesting the low-sodium diet, no change in potassium or sodium balance occurs and renal ammonium excretion and serum bicarbonate level do not change. In contrast, patients ingesting 180 mmol of sodium daily retained sodium and lost potassium and increased both renal ammonium excretion and serum bicarbonate concentration. These experiments show that a secondary increase in sodium delivery to the collecting duct is necessary to produce and sustain this form of metabolic alkalosis. In a subsequent study, aldosterone was administered to 3 patients ingesting normal salt intake for 90 days.[66] Surprisingly, this treatment caused only very mild metabolic alkalosis and decreased serum potassium levels only minimally. The investigators reviewed the reported cases of primary hyperaldosteronism and noted an inverse correlation between serum bicarbonate and serum potassium levels. They concluded that potassium depletion induced changes in renal hydrogen ion secretion that were central to inducing this form of metabolic alkalosis. In studies in animals, prior potassium depletion more than doubles the increase in serum bicarbonate level after DOCA administration.[67] Strikingly, in one such study in dogs, chloride reabsorption is attenuated after DOCA administration in potassium-depleted dogs, suggesting that potassium depletion is interfering with chloride reabsorption. This effect is consistent with downregulation of chloride-linked sodium reabsorption in the loop and early distal tubule, facilitating greater sodium delivery to the collecting duct.

Hereditary and Pharmacologic Activators of ENaC

Three hereditary diseases cause metabolic alkalosis as a result of primary stimulation of collecting duct ion transporters (Box 2).

Glucocorticoid-Remediable Aldosteronism

Glucocorticoid-remediable aldosteronism is caused by a genetic mutation that results in aldosterone being regulated by adrenocorticotropin rather than angiotensin, causing sustained high aldosterone levels and metabolic alkalosis.[68,69]

Liddle Syndrome

Liddle syndrome is caused by mutations that block removal of ENaC from the epithelial membrane, resulting in stimulated sodium reabsorption independent of aldosterone.[70-73] The pathophysiologic process of the disorder is identical to that caused by mineralocorticoid excess, except that serum aldosterone levels are low.

Box 2. Metabolic Alkalosis: Specific Causes

1. Secondary Stimulation of Collecting Duct Ion Transport

- Cl^- depletion syndromes (blood pressure normal or low)
  - ◇ Gastrointestinal and other nonrenal Cl^- losses
    - ▪ Vomiting, nasogastric drainage
    - ▪ Congenital chloridorrhea
    - ▪ Some villous adenomas
    - ▪ High-volume ileostomy drainage
    - ▪ Cystic fibrosis
  - ◇ Renal Cl^- losses
    - ▪ Chloruretic diuretic drugs[a]
    - ▪ Recovery from chronic hypercapnia
    - ▪ Genetic disorders (Bartter syndrome; Gitelman syndrome)
    - ▪ Severe K^+ depletion

2. Primary Stimulation of Collecting Duct Ion Transport

- Mineralocorticoid excess syndromes (blood pressure increased)
  - ◇ Primary aldosteronism
  - ◇ Glucocorticoid-remediable aldosteronism
  - ◇ Cushing syndrome
  - ◇ Congenital adrenal hyperplasia
  - ◇ Renin-secreting tumors
  - ◇ Medications
    - ▪ Fludrocortisone
    - ▪ 9 α fluoroprednisolone (inhaled)
- Apparent mineralocorticoid excess syndromes (blood pressure increased)
  - ◇ Liddle syndrome
  - ◇ 11β-hydroxysteroid dehydrogenase inhibition or deficiency

3. Alkali Intake or Administration

- Kidney failure
- Dietary Cl^- restriction

Abbreviations: Cl^-, chloride; K^+, potassium.
[a]Blood pressure may be increased in patients with associated hypertension.

11β-Hydroxysteroid Dehydrogenase Deficiency

The syndrome of apparent mineralocorticoid excess is caused by a mutation that inactivates 11β-hydroxysteroid dehydrogenase, the enzyme that removes cortisol before it can bind to the mineralocorticoid receptor in the collecting duct.[74-77] As a result, the receptor is activated by cortisol and ENaC is stimulated independent of aldosterone.

The same enzyme can be inhibited by glycyrrhizic acid, a component of natural licorice, allowing the more abundant cortisol to bind to and activate the receptor, continually stimulating sodium reabsorption independent of ECF volume.[74,78,79]

ALKALI INGESTION OR ADMINISTRATION

Ingested alkali or alkali precursors increase serum bicarbonate levels, but the increase is not sustained

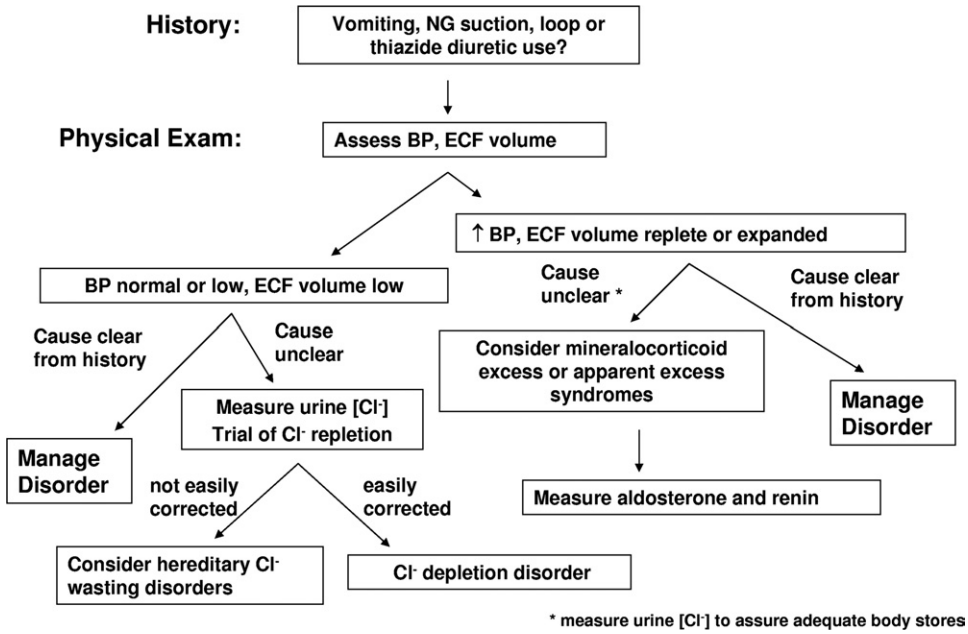

Figure 4. Diagnostic approach to metabolic alkalosis and steps in identifying the cause of the disorder. Abbreviations: BP, blood pressure; Cl^-, chloride; ECF, extracellular fluid; NG, nasogastric.

because the excess alkali is excreted rapidly. However, in patients placed on a diet that contains very little chloride (<20 mmol/d), daily alkali supplementation causes a sustained increase in serum bicarbonate levels.[80] In patients with pre-existing chloride or potassium depletion, alkali ingestion or administration also results in a sustained increase in serum bicarbonate levels. In patients with kidney failure, ingested or administered alkali is retained independently of body chloride or potassium stores.[1]

A NEW CLASSIFICATION OF METABOLIC ALKALOSIS

Based on this analysis, 3 pathophysiologic processes encompass all causes of metabolic alkalosis (Box 2). The most common pathophysiologic process is secondary stimulation of collecting duct ion transport, induced in most instances by an increase in sodium delivery and reabsorption through ENaC. Examples include diuretic-induced inhibition of sodium reabsorption in the loop of Henle and early distal tubule and hereditary disorders that impede chloride-linked sodium uptake. When induced, this form of metabolic alkalosis is sustained by chloride depletion. The precise mechanism by which chloride depletion sustains alkalosis remains to be elucidated, although recent evidence suggests that a key factor may be alkali-induced stimulation of ENaC coupled with both a limitation in bicarbonate delivery and sufficient sodium delivery to the collecting duct to recapture all filtered and secreted bicarbonate. As listed in Box 2, potassium depletion itself is a cause of secondary stimulation of hydrogen ion secretion, likely by inhibiting sodium reabsorption in the loop of Henle and early distal tubule.

The second pathophysiologic process is primary stimulation of ion transporters in the collecting duct. This form of metabolic alkalosis is almost always associated with hypertension due to sodium retention and attendant ECF volume expansion. The most common example of this type of alkalosis is primary hyperaldosteronism. The third and different pathophysiologic process is alkali intake or administration in the setting of impaired renal bicarbonate excretion. This form most commonly occurs in patients with kidney failure.

Box 2 provides a comprehensive list of the causes of metabolic alkalosis. This classification provides the basis for a new diagnostic approach that centers on the history and physical examination, rather than response to chloride administration (Fig 4). A history of gastrointestinal losses or diuretic use points to the most common causes of metabolic alkalosis. Obtaining a good history is coupled with assessment of ECF volume and blood pressure. Complementing this assessment is measurement of plasma aldosterone and renin when necessary. In some cases, measurement of urine chloride excretion or a diagnostic trial of saline or potassium chloride administration may be necessary to make the diagnosis.

SUMMARY

Metabolic alkalosis is caused by the ingestion or generation of new alkali in body fluids and sustained by changes in kidney function that prevent

the normally rapid excretion of this excess alkali. In patients without kidney disease, combined chloride and potassium depletion are responsible for most cases of clinically significant metabolic alkalosis. Depletion of body stores of these ions induces changes in renal ion transport that limit bicarbonate excretion, primarily by stimulating hydrogen ion secretion into the collecting duct in a setting in which sufficient sodium is delivered to this segment of the nephron. The same syndrome is induced by direct abnormal stimulation of sodium transport through ENaC in the collecting duct.

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