Electrolyte quintet

Acid-base

Stephen L Gluck

Acid-base disorders are common clinical problems resulting from a wide variety of pathophysiological conditions, including newly recognised acquired and genetic causes. The history and physical examination and measurement of blood and urinary indices allow identification of the underlying cause of these disorders in most cases. Treatment directed at correction of electrolyte abnormalities and the underlying cause for the disorder is essential for preventing the acute and long-term metabolic consequences of acid-base derangements.

Acid-base homoeostasis

The extracellular fluid (ECF) contains about 350 mmol of bicarbonate buffer. Every day metabolism produces acid (as H^+) to a total of about 70 mmol (1 mmol/kg) as non-volatile sulphuric acid (25 mmol) from aminoacid catabolism, non-metabolised organic acids (40 mmol) and phosphoric and other acids. The kidney reabsorbs all of the filtered bicarbonate (HCO_3^-) and generates new bicarbonate in the collecting duct. The proximal tubule reabsorbs some 85% (3800 mmol) daily of filtered HCO_3^- and the thick ascending limb reabsorbs 10% (450 mmol).[1,2] In the collecting duct, proton secretion titrates the remaining luminal HCO_3^-, and buffering of secreted protons by non-bicarbonate buffers in the tubular lumen, mainly phosphate and ammonia, enables the cells to generate new HCO_3^-.[3] The rate of secretion of hydrogen ions (H^+, protons) is affected by several factors, including luminal pH, systemic pCO_2, mineralocorticoids, and the potential difference across the collecting duct.[4]

The renal cortical segment of the collecting duct normally has a potential difference of −30 to −60 mV, arising largely from sodium reabsorption, and this is an important driving force for H^+ secretion.[4] The amount of ammonium ion (NH_4^+) accumulating in the collecting duct increases as urinary pH becomes more acidic. Urinary ammonia is generated in mitochondria of the proximal tubule by deamination of glutamine.[5] Ammonia production is subject to physiological regulation, adding a mechanism for control of nett acid excretion independent of the rate of distal H^+ secretion; the rate of ammonia production per nephron is increased by metabolic acidosis, potassium (K^+) depletion, glucocorticoids, loss of functional renal mass, and other factors, and is suppressed by hyperkalaemia.[6] Under normal steady-state conditions, the nett quantity of acid secreted and the consequent renal generation of new bicarbonate equals the rate of metabolic proton generation, preserving H^+ balance). When that balance is disturbed the consequence is acidosis or alkalosis.

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Departments of Medicine and Cell Biology and Physiology, Washington University School of Medicine, St Louis, MO, USA
(Prof S L Gluck MD)

Correspondence to: Dr Stephen L Gluck, Renal Division, Washington University School of Medicine, 660 South Euclid Avenue, Box 8126, St Louis, MO 63110, USA
(e-mail: sgluck@imgate.wustl.edu)

Metabolic acidosis

Metabolic effects of H^+ retention

In metabolic acidosis non-volatile acid accumulates or HCO_3^- is lost at a rate that induces pathophysiological responses, and this can happen even when the plasma [HCO_3^-] is normal. "Non-volatile acid" refers to acids other than carbonic acid or CO_2, and I shall use the term acid interchangeably with non-volatile acid unless otherwise stated. Nett retention of H^+, which occurs either by increased intake or generation of acid or by loss of HCO_3^-, activates three adaptive physiological responses—namely, buffering, increased ventilation, and increased renal reabsorption and generation of HCO_3^-. Retained acid is titrated by both extracellular HCO_3^- and "cellular" buffers (mainly bone mineral[7] and skeletal muscle[8]). If the retention of acid is great enough, ventilation is stimulated within minutes, principally by increasing ventilatory volume (Kussmaul respirations). The kidney responds to nett accumulation of acid by increasing HCO_3^- reabsorption in the proximal tubule and thick ascending limb,[20] increasing H^+ secretion in the distal tubule and collecting duct, and increasing production of the urinary buffer ammonia, augmenting renal HCO_3^- generation through increased excretion of NH_4^+.[10,11] Under normal conditions, daily NH_4^+ excretion is about 30 mmol (0·5 mmol/kg); it can increase to 280 mmol (4 mmol/kg, or 1·5 μmol/mL glomerular filtrate) but that response requires several days.[12]

The normal range for excretion of the tricarboxylic anion citrate is 1–2 mmol (200–400 mg). Citrate excretion is greatly diminished by metabolic acidosis induced by administration of ammonia chloride.[13]

Evaluation of patient with low plasma [HCO_3^-]

Evaluation of a patient with a low [HCO_3^-] should begin with arterial blood gases to exclude primary hyperventilation and with calculation of the serum unmeasured anions, the "anion gap". The normal anion gap of 12 mmol/L arises primarily from serum albumin so the estimate has to be adjusted for albumin. Indeed the anion gap can be altered by several factors apart from unmeasured anions.[14] However, it does help to distinguish metabolic acidosis due to accumulation of unmeasured acid anions (chiefly organic acids) from metabolic acid due to loss of HCO_3^-.

Panel 1: **Fate of ingested or generated organic acids and effect on acid-base status**

Metabolism	$n \cdot NaHCO_3 + HA \rightarrow NaA + (n-1) \cdot NaHCO_3 + CO_2 + H_2O$ $NaA \rightarrow NaHCO_3$
Nett reaction	$HA \rightarrow CO_2 + H_2O$
Excretion	$n \cdot NaHCO_3 + HA \rightarrow NaA + (n-1) \cdot NaHCO_3 + CO_2 + H_2O$ $NaA \rightarrow$ Urinary excretion
Nett reaction	$HA + \cdot NaHCO_3 \rightarrow (n-1) \cdot NaHCO_3$
Accumulation	$n \cdot NaHCO_3 + HA \rightarrow NaA + (n-1) \cdot NaHCO_3 + CO_2 + H_2O$
Nett reaction	$n \cdot NaHCO_3 + HA \rightarrow NaA + (n-1) \cdot NaHCO_3$

Metabolic acidosis with increased anion gap

Ingested or metabolically generated organic anions have three posible fates (panel 1). The initial addition of the organic acid to plasma results in the titration of HCO_3^- and generation of the sodium salt of the anion in plasma. Some organic anions (such as the ketoacids acetoacetate and β-hydroxybutyrate or lactate) are readily metabolised to bicarbonate and there is no nett change in plasma $[HCO_3^-]$. Urinary excretion of the organic anion as sodium salt produces a nett loss of sodium bicarbonate, and consequent hyperchloraemic acidosis (see below). In all disorders causing metabolic acidosis with an increased anion gap, the organic acid is ingested or generated faster than it can be metabolised or excreted, resulting in both a nett loss of HCO_3^- and accumulation of the sodium salt of the acid in plasma. The three metabolic fates are not mutually exclusive. For example, in diabetic ketoacidosis, accumulation and excretion of ketoacid anions predominate but after treatment metabolism is the principal fate.

The most common of the endogenous organic acids are: β-hydroxybutyrate and acetoacetate, found in ketoacidosis; lactate in lactic acidosis; and organic acids that accumulate in severe renal insufficiency (eg, aliphatic dicarboxylic acids, phenolic aromatic acids, furanoic acid, 3-carboxy-4-methyl-5-propyl-2-furanpropionic acid, and hippuric acid). Retention of organic anions occurs only in very advanced renal disease and is nearly always preceded by a hyperchloraemic acidosis. The most common organic anions arising by ingestion and metabolism are salicylate, glycolate, glyoxalate, and oxalate, all from the metabolism of ethyleneglycol; and formate, from metabolism of methanol. Ketoacids, lactate, salicylate, methanol, and ethyleneglycol are readily assayed by most clinical laboratories. Ingestion of ethyleneglycol or methanol is usually associated with a raised plasma "osmolal gap",[15] and ethyleneglycol produces calcium oxalate crystalluria.

Panel 2: **Evaluation of hyperchloraemic acidosis**

	Urinary solutes			
	NH_4^+	Cl^-	A^-	Na^+
GI tract HCO_3^- loss	↑ (*a*)	↓ (*b*)	↔	↓ (*c*)
Generated/ingested organic acids	↑ (*a*)	↔	↑ (*d*)	↑ (*c*)
HCl intake or equivalent*	↑ (*a*)	↑ (*f*)	↔	↑ (*e*)
Inadequate renal HCO_3^-	↓ (*g*)	↔	↔	↔
Renal HCO_3^- loss	↓ (*g*)	↔	↔	↔

*NH_4Cl, chloride salts of aminoacids or dilutional acidosis; ↔designates normal; (*a*) $NH_4^+ > 1$ mmol/kg daily; (*b*) $FE_{Cl} < 0{\cdot}5$; (*c*) $FE_{Na} < 0{\cdot}5$; (*d*) A>100 mmol/daily; (*e*) $FE_{Na} > 1{\cdot}0$; (*f*) $FE_{Cl} > 1{\cdot}0$; (*g*) $NH_4^+ < 1$ mmol/kg daily. FE=fractional excretion of a solute. Urinary unmeasured anion concentration (sum of urinary K^+, NH_4^+, and Na^+ less Cl^-) estimates sum of urinary sulphate and organic anion concentrations.

Glossary of equations

Anion gap $[Na^+]+[K^+]-[Cl^-]$

Total daily $U_{NH_4^+} = (U_{[NH_4^+]} \div U_{[Cr]} \times ([140-\text{age}]/50)^* \times$ lean body weight

*For men; multiply by 0·85 for women.

$U_{[NH_4^+]}$ (mmol/L)$=0{\cdot}5\{U_{osm}-[2(U_{Na^+}+U_K)+U_{urea}+U_{glucose}]$ where urinary (U) concentrations and osmolality are in molar units.

$FE_s = 100(U_S \times P_{Cr}) \div (P_S \times U_{Cr})$

In disorders ascribable entirely to accumulation of unmeasured anions, the reduction in the serum $[HCO_3^-]$ matches the anion gap. When this is not the case, a second acid-base disorder (such as hyperchloraemic acidosis or metabolic alkalosis) may be present, although this notion has been challenged.[16] When metabolic alkalosis and acidosis coexist, as in vomiting and ketoacidosis,[17] the plasma $[HCO_3^-]$ may be normal, and a raised anion gap may be the initial evidence of underlying acid-base disturbances.

Normal anion gap (hyperchloraemic acidosis)

Hyperchloraemic acidosis is a consequence of nett retention of HCl or metabolic equivalent (eg, NH_4Cl and chloride salts of aminoacids) or loss of $NaHCO_3$ or metabolic equivalent (eg, excretion of salts of organic anions in proportionate excess of chloride, panel 1). In normal plasma, the quotient $[HCO_3^-]/[Cl^-]$ is well above 0·25. Loss of bicarbonate may occur from the gastrointestinal tract via diarrhoea or a biliary fistula, for example, or from renal excretion of HCO_3^- or its equivalent, or from renal HCO_3^- generation insufficient to match acid intake or production.

Renal causes of HCO_3^- loss may be distinguished from non-renal causes by measurement of the urinary $[NH_4^+]$ excretion. In a setting of hyperchloraemic acidosis, a daily urinary $[NH_4^+]$ excretion of less than 1 mmol/kg is abnormal, indicating that the kidney is a primary cause of the abnormality. If urinary $[NH_4^+]$ measurement is not readily available it can be estimated from the urinary anion gap[18] (which may be misleading in the presence of large amounts of urinary organic anions), or from the urinary osmolal gap,[19] and the calculations are given in the glossary. If a 24 h urine collection is impracticable, a creatinine measurement on a random urine sample may be used to estimate the total daily excretion of NH_4^+ (or any other solute). A random urine sample may be used to distinguish among the causes of hyperchloraemic acidosis (panel 2).

Acidosis with abnormal urinary $[NH_4^+]$

Increased $[NH_4^+]$

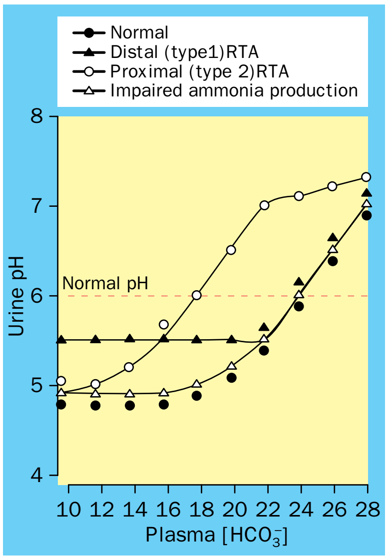
Gastrointestinal loss of HCO_3^- from drainage of gastrointestinal secretions or from diarrhoea produces a hyperchloraemic acidosis if the rate of loss exceeds the capacity for renal HCO_3^- generation. Effective bicarbonate loss may also result from ingestion of organic acids with subsequent loss of the sodium or potassium salt in the stool.

Generation of large amounts of organic anion produces a hyperchloraemic acidosis if anion excretion is rapid enough to prevent accumulation of the anion in plasma. Causes include ketoaciduria (as in recovery from diabetic ketoacidosis), hippuric aciduria from the metabolism of toluene (glue-sniffing), or D-lactate aciduria in short-bowel syndrome.

Administration of NH$_4$Cl or chloride salts of aminoacids produces a hyperchloraemic acidosis by metabolism to HCl. Administration of other chloride salts may produce a "dilutional acidosis", when there is a nett retention of Cl$^-$, as in ECF volume depletion and congestive heart failure[20] or with rapid intravenous saline.

Decreased [NH$_4^+$]

Abnormalities in the renal regeneration or reabsorption of HCO$_3^-$ are the principal causes of hyperchloraemic acidosis with reduced NH$_4^+$ excretion. This renal tubular acidosis (RTA) may be distinguished on the basis of the urinary pH in response to changes in the plasma [HCO$_3^-$] (figure).[21] The urinary pH is 6 or less at a normal plasma [HCO$_3^-$] of 24 mmol/L (point A), and lowering of the plasma [HCO$_3^-$] induces a progressive reduction in urinary pH.



Relation of urinary pH to plasma [HCO$_3^-$] in normal subjects and patients with different types of RTA

Renal tubular acidosis

Distal (type 1) RTA

In these disorders H$^+$ secretion in the collecting duct or the ability to lower urinary pH is impaired. Patients cannot reduce their urine pH below 5·5, even in the presence of a severe metabolic acidosis. Administration of furosemide reduces urinary pH below 5·5 in normal people but not in patients with type 1 RTA.[22] The urinary pCO$_2$ (or urine/blood pCO$_2$ difference) in alkaline urine is another index of [H$^+$] secretion in the collecting duct that is often abnormal in distal RTA.

Several subtypes have been identified (panel 3). Patients with a collecting duct that is excessivly permeable to H$^+$ (a "gradient" or "permeability" defect), as happens with amphotericin B administration, have a normal urinary pCO$_2$ in alkaline urine. Patients with an abnormally low rate of H$^+$ secretion ("secretory defect") have a urinary pCO$_2$ that is abnormally low, usually with profound hypokalaemia because Na reabsorption in the collecting duct is accompanied by K$^+$ secretion rather than H$^+$ secretion. Causes of this type of defect include type 2 carbonic anhydrase deficiency,[60] mutations in the anion transport protein AE1,[24] and deficiency of collecting-duct proton-transporting ATPase (as in Sjögren's syndrome[25]). Patients with an abnormally low collecting duct voltage ("voltage defect") also have a low urinary pCO$_2$, but the plasma [K$^+$] is usually normal or raised; urinary K$^+$ excretion is reduced after administration of furosemide. Voltage defect distal RTA is observed in urinary-tract obstruction,[26] interstitial nephritis associated with systemic lupus erythematosus,[27] and with potassium-sparing diuretics such as amiloride. In "incomplete" distal RTA the capacity to acidify the urine maximally is impaired but the plasma [HCO$_3^-$] is normal.[29] These patients usually come to the attention of the clinician because of kidney stones. Urinary citrate, an important inhibitor of calcium oxalate crystallisation in urine, is decreased in distal RTA, contributing to the nephrolithiasis.[30]

Proximal (type 2) RTA

Impaired proximal HCO$_3^-$ reabsorption results in delivery of bicarbonate to the collecting duct in excess of its capacity for reabsorption.[31] After the initial bicarbonaturia, plasma [HCO$_3^-$] and the amount of bicarbonate filtered both decrease, and a new steady state is reached within hours, with hyperchloraemic acidosis and urine free of bicarbonate. Although a random urinary pH may be above 5·5, the pH decreases appropriately in response to furosemide, except in combined distal and proximal acidification defects. Suspected proximal RTA is confirmed by significant bicarbonaturia (urine pH >6·5) in the presence of a low plasma [HCO$_3^-$]. This may be tested most easily by administering oral or intravenous bicarbonate, and drawing blood for plasma [HCO$_3^-$] measurement when urine pH is >6·5. A plasma [HCO$_3^-$] of 22 mmol/L or less (indicating a reduced "threshold" for HCO$_3^-$ excretion) confirms the diagnosis. Measurement of fractional excretion of HCO$_3^-$ may confirm proximal RTA too, but this measurement is not easy. The urinary pCO$_2$ in alkaline urine is usually >65 mm Hg in proximal RTA, but may be reduced in the presence of a coexisting distal RTA, as in type 2 carbonic anhydrase deficiency.[32]

Proximal RTA occurs most commonly as part of the Fanconi syndrome of multiple defects in proximal tubule transport that may be caused by myeloma light-chain nephropathy,[33] nephrotoxins,[34] and genetic diseases.[35] Proximal RTA may also occur as an isolated defect in HCO$_3^-$ transport.[36] Urinary citrate excretion may be normal in proximal RTA but is suppressed by NH$_4$Cl.[36]

Defective ammoniagenesis (type 4 RTA)

Defective ammonia production produces a type 4 RTA. The capacity to reabsorb HCO$_3^-$ and acidify the urine are preserved but the quality of acid excreted is reduced because of insufficient urinary buffer,[37] and collecting-duct HCO$_3^-$ generation is inadequate to preserve acid-base

Panel 3: **Evaluation of distal RTA**

Type of defect	**Urine pH**		**Plasma [K$^+$]**	**Urinary [K$^+$] increase after furosemide**	**Urine pCO$_2$ alkaline urine**
	Acidosis	Furosemide			
None (normal)	<5·3	<5·3	↔	Normal	>65
Permeability	>5·5	>5·5	↓	Normal	>65
Secretory	>5·5	>5·5	↓	Normal	<50
Voltage	>5·5	>5·5	↔ or ↑	Reduced	<50
Incomplete RTA (absence of acidosis)	NA	>5·5	↔ or ↓	Normal	<50

Panel 4: **Evaluation of metabolic alkalosis**

Condition	ECF	U [Cl^-]	U [Na^+]	TTKG	U pH
Primary increase in mineralocorticoid activity; pseudohyperaldosteronism syndromes	↑*	>20	>20	>2	<6
External alkali intake in renal failure	↑	>20	>20	. .	>6
External alkali intake in oedematous states	↑	<20	<20	. .	>8
Post-hypercapnia (active)	↔	<20	>20	>2	>8
Diuretics (active)	↓†	>20	>20	>2	<8
Bartter's syndrome	↓	>20	>20	>2	<6
Gastrocystoplasty	↓	>20	>20	>2	<5
Magnesium deficiency	↓	>20	<20	>2	<6
Nasogastric suction and vomiting (active)	↓†	<20	>20	>2	>6
Chloride diarrhoea	↓	<20	>20	<2	. .
Impermeable anion excretion	↓†	<20	>20	>2	5–6
Diuretics (prior), nasogastric suction and vomiting (prior), post-hypercapnia (prior)	↓†	<20	<20	<2	<6

*Without oedema and hypertension present. †May be increased in oedematous states such as congestive heart failure.

balance. Ammoniagenesis may be impaired by physiological suppression from hyperkalaemia or glucocorticoid insufficiency. Hyperkalaemia probably suppresses renal ammonia production by inhibiting HCO_3^- exit from the proximal tubule cell and raising the cell pH. The type 4 RTA of mineralocorticoid deficiency is a result of hyperkalaemia and suppression of ammonia production.[37] Glucocorticoid is required both for the increase in skeletal muscle protein catabolism and in glutamine synthesis and for the enhanced renal ammoniagenesis observed in metabolic acidosis.[38] Loss of functional renal mass impairs ammoniagenesis by decreasing the number of proximal tubule cells generating ammonia. Type 4 RTA is usually not apparent until 70–80% of nephrons have been lost, but hypercatabolic states in which H^+ generation increases (eg, fever, severe illness, glucocorticoid administration, and hyperalimentation) may induce overt acidois. In some renal diseases, such as urinary-tract obstruction, renal ammonia production is suppressed even though there is no loss of renal mass.

Metabolic alkalosis

Mechanisms

In normal acid-base homoeostasis two factors defend against metabolic alkalosis—the capacity of the kidney to excrete large amounts of HCO_3^- and the metabolic production of non-volatile acid. The kidney is highly efficient in excreting infused HCO_3^-, and administration of Na_2CO_3 causes little or no increase in plasma [HCO_3^-]. Even if 100% of the filtered HCO_3^- is reabsorbed, metabolic acid production consumes 1 mmol HCO_3^- daily for every kilogram of body weight. The generation of metabolic alkalosis thus requires both an increase in alkali addition (HCO_3^- generation) to the ECF and an impairment in renal HCO_3^- excretion.

Alkali addition

Alkali addition may occur from sources outside the kidney or from the kidney itself. Extrarenal sources include loss of gastric secretions (which removes HCl) through vomiting or nasogastric suction; redistribution of alkali from intracellular stores to the ECF, as happens in potassium or chloride depletion; and oral or parenteral administration of alkali as, for example, acetate salts of aminoacids in intravenous alimentation, citrate from transfusions,[39] or via absorption of alkali from antacid and oral ion-exchange resing given together, the milk-alkali syndrome,[40] or oral or intravenous HCO_3^-.

Excessive generation of alkali in the kidney collecting duct occurs in response to sustained elevation of the pCO_2, increased mineralocorticoid activity, increased sodium delivery to the collecting duct, potassium deficiency, and delivery of impermeant anions to the collecting duct. Collecting duct H^+ secretion is increased in response to hypercapnia,[41] and may persist after return of the pCO_2 to normal. Mineralocorticoids, sodium delivery, and impermeant anions increase collecting-duct acidification by increasing sodium reabsorption and augmenting the lumen-negative potential. Mineralocorticoids also stimulate H^+ secretion directly.[42] Potassium deficiency stimulates H^+ secretion in the distal nephron, increases the production of the urinary buffer ammonia,[42] and may stimulate HCO_3^- generation by increasing collecting duct expression of an H^+-K^+-ATPase that reabsorbs K^+ in exchange for H^+ secretion.[44]

Impaired HCO_3^- excretion

The primary defence against metabolic alkalosis is HCO_3^- excretion caused by a decrease in proximal tubule HCO_3^- reabsorption.[1] In metabolic alkalosis, factors that can impair ability to excrete HCO_3^- include decreased glomerular filtration and stimulation of proximal tubule HCO_3^- reabsorption (eg, by a raised pCO_2 and hormonal agents such as angiotensin II and norepinephrine, and K^+ deficiency). K^+ deficiency appears to act by increasing the inside-negative potential difference of the proximal tubule cells, stimulating cellular HCO_3^- exit.[45]

A second renal mechanism in the defence against metabolic alkalosis is HCO_3^- secretion by Cl^-/HCO_3^- exchange in the luminal membrane of the cortical collecting duct. In states of chloride depletion, with or without depletion of ECF volume, a reduction of chloride delivery to the collecting duct impairs HCO_3^- secretion. Chloride depletion also stimulates release of organic acids from stores. At first this lowers extracellular HCO_3^- but because K^+ is also lost from cellular stores subsequent K^+ depletion may perpetuate the alkalosis.[46]

Evaluation of patient with metabolic alkalosis

Assessment of ECF volume, urinary electrolytes, and transtubular K^+ gradient (TTKG, an index of K^+ secretion) allow the underlying causes of metabolic alkalosis to be distinguished (panel 4). Common settings are conditions associated with primary increase in mineralocorticoid activity or with ECF depletion.

Increased mineralocorticoid activity

Mineralocorticoid (or mineralocorticoid-like) activity increases in primary hyperaldosteronism, Cushing's syndrome, and congenital adrenal hyperplasia with 11β and 17β hydroxylase defects,[47] and by ingestion of compounds with mineralocorticoid activity. Primary mineralocorticoid excess produces alkalosis by inducing K^+ deficiency and stimulating distal nephron Na^+ reabsorption and H^+ secretion. Not all patients with primary hyperaldosteronism have hypokalaemia,[48] and the plasma-aldosterone/renin quotient may be used as a screening test in patients without renal insufficiency.[49] Glucocorticoids in the physiological range do not have mineralocorticoid activity because of selective metabolism in collecting duct epithelial cells by 11β-hydroxysteroid dehydrogenase (11β-HSDH). When the capacity of that metabolic system is exceeded, as in Cushing's syndrome or with steroid therapy, glucocorticoids do also exert significant mineralocorticoid activity. The drug carbenoxolone and glycyrrhetinic acid (the active compound in liquorice) have mineralocorticoid-like properties and act by inhibiting renal 11β-HSDH.[51]

Simple volume depletion raises angiotensin II and mineralocorticoid levels but seldom causes metabolic alkalosis because renal HCO_3^- generation is not increased. Distal flow rates and sodium delivery, two of the major factors affecting K^+ secretion, will both decrease but the distal nephron undergoes an adaptive response that sustains K^+ secretion. Nor does volume depletion increase the non-bicarbonate buffer required to generate more HCO_3^-. Although angiotensin II does stimulate proximal ammoniagenesis this is probably counterbalanced by increased proximal tubule reabsorption. Isolated K^+ deficiency produces little or no metabolic alkalosis[52] because hypokalaemia inhibits aldosterone secretion.

In the clinical conditions that produce metabolic alkalosis, mineralocorticoid excess is accompanied by continued sodium delivery to the distal nephron, by potassium depletion, or both. Diuretics maintain high distal nephron flow rates and sodium delivery concomitantly with high aldosterone levels, which sustain a large potential difference in the distal nephron, promoting K^+ excretion and H^+ secretion. Bartter's and Gitelman's syndromes arise from genetic defects in salt transporters in the thick ascending limb and distal tubule, respectively;[53] they are the physiological equivalents of regular high-dose loop or thiazide diuretics.

Nasogastric suction generates alkali by removing HCl; the Na_2CO_3 generated is partly excreted until the resulting volume depletion stimulates distal sodium reabsorption, resulting in loss of K_2CO_3 rather than sodium. Bladder reconstructive surgery using gastric tissue produces similar systemic electrolyte abnormalities, but with different urinary electrolyte changes.[54] Inhibitors of gastric acid secretion may prevent these complications. Congenital[55] or acquired chloride diarhoea produces both Cl^- and K^+ depletion, inducing alkalosis.[46] Impermeant anions stimulate distal H^+ secretion and K^+ losses by increasing the potential difference of the collecting duct.

Respiratory acid-base disorders

Under normal conditions, the blood pCO_2 is maintained at 39–41 mm Hg by alveolar ventilation under the control of respiratory centres in the pons and medulla oblongata. Changes in the production of CO_2 are accompanied by corresponding alterations in alveolar ventilation, resulting in little or no change in pCO_2. Ventilation is regulated by brainstem chemoreceptors for pCO_2, pO_2, and pH, by neural impulses from arterial chemoreceptors and lung-stretch receptors, and by impulses from the cerebral cortex. Respiratory acidosis or alkalosis arise from a primary increase or decrease in blood pCO_2. They may coexist with other primary acid-base disorders.

Acute hypercapnia has many causes, including airway obstruction, respiratory-centre depression (as from drugs or brainstem injury), neuromuscular weakness (drugs, myasthenia, Guillain-Barré), restrictive pulmonary disease (pneumothorax, severe pneumonia), inadequate mechanical ventilation, and severe circulatory impairment. Within minutes of an acute rise in pCO_2, there is a small increase in the plasma $[HCO_3^-]$ (about 1 mmol/L for every 10 mm Hg), due largely to intracellular buffering of carbonic acid protons and cellular loss of the bicarbonate in exchange for chloride. The increase in $[HCO_3^-]$ is not accompanied by an increase in renal bicarbonate secretion, indicating an adaptive increase in bicarbonate reabsorption. Hyperphosphataemia usually occurs in acute hypercapnia. Patients manifest anxiety and shortness of breath, which may progress to delirium, encephalopathy, myoclonus, and seizures in severe hypercapnia. Treatment should be directed toward increasing ventilation, by mechanical ventilation if necessary, and correcting the underlying cause.

Sustained hypercapnia, or chronic repiratory acidosis, can be caused by disorders such as chronic obstructive lung disease, respiratory centre disorders (eg, obesity-hypoventilation syndrome), neuromuscular disorders (eg, amyotrophic lateral sclerosis), and restrictive defects (interstitial fibrosis, thorax deformities). The pCO_2 of the CSF changes rapidly to match the arterial blood pCO_2. Hypercapnia that persists for more than a few hours induces an increase in CSF $[HCO_3^-]$ that reaches a maximum by 24 h and partly restores the CSF pH. Prolonged hypercapnia also stimulates renal nett acid secretion, causing the blood $[HCO_3^-]$ concentration to increase to a new steady state after 3–5 days (figure). Caution must be exercised in reducing the pCO_2 in these patients. Sudden correction of hypercapnia (eg, by mechanical ventilation) alkalinises the CSF which may cause seizures, and induces an acute systemic metabolic alkalosis that can persist for days.

The causes of acute hypocapnia include hypoxia, anxiety, pain, sepsis, hepatic failure, CNS disorders (such as stroke and infections), pulmonary disorders (eg, infections and interstitial lung disease), drugs (salicylate intoxication), and pregnancy. Acute reduction in pCO_2 produces a small but immediate decrease in $[HCO_3^-]$ due to cellular uptake of bicarbonate in exchange for chloride Acute hypocapnia also induces cellular uptake of potassium and phosphate, causing blood levels to fall, and increases the binding of ionised calcium to serum albumin. Patients with acute hypocapnia may experience cardiac arrhythmias, cerebral vasoconstriction, facial and peripheral paraesthesias, muscle cramps, and syncope or seizures. Treatment should be directed toward decreasing hyperventilation, by sedation if necessary, and correcting the underlying cause.

Several disorders, such as high-altitude hypoxia, chronic hepatic failure, chronic pulmonary disease, CNS trauma, and pregnancy, can produce a chronic respiratory alkalosis. Sustained hypocapnia produces a corresponding reduction in CSF pCO_2 and a fall in the CSF $[HCO_3^-]$, correcting the pH toward normal. Within minutes to hours of sustained hypocapnia, there is an inhibition of proximal tubule bicarbonate reabsorption, and a subsequent bicarbonaturia. A new steady state is reached in 2–3 days, with a reduced plasma [HCO_3^-] concentration (figure). The [HCO_3^-] may require several days to return to normal after correction of chronic hypocapnia, resulting transiently in a hyperchloraemic metabolic acidosis.

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