Review Article

Mechanisms of Disease

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PROTECTION OF ACID–BASE BALANCE BY pH REGULATION OF ACID PRODUCTION

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UNDER normal physiologic conditions, acid–base balance is maintained by renal excretion of hydrogen ions generated during the metabolism of dietary protein and other metabolic processes. In normal subjects, these so-called fixed acids are produced at an average rate of approximately 1 mmol per kilogram of body weight, or 50 to 70 mmol per day, with a variety of organic acids accounting for half this amount and sulfuric and phosphoric acids for the remainder. When a disturbance in systemic pH occurs as the result of an excess or loss of acid or base, shifts in body buffers and ventilatory adjustment of the partial pressure of carbon dioxide promptly attenuate the change in pH until it can be corrected or at least stabilized by appropriate changes in renal acid excretion.

Lactic acid and the keto acids 3-hydroxybutyric acid and acetoacetic acid are produced when carbohydrate or fat is incompletely oxidized. These organic acids can be produced in large quantities, at times many hundreds of millimoles per day. Because they are dissociated at physiologic pH, in large quantities they pose a substantial threat to acid–base homeostasis. Under these circumstances, although renal acid excretion increases, it does not do so at a sufficiently rapid rate to dispose of the extra acid, and lactic acidosis or ketoacidosis develops.

We have postulated that systemic pH regulates the rate of endogenous acid production through a homeostatic mechanism (Fig. 1). This mechanism is particularly important when endogenous acid production is increased during lactic acidosis or ketoacidosis. Here, we review the evidence in support of this hypothesis and discuss its implications for clinically important acid–base disorders.

INFLUENCE OF pH ON KETO ACID METABOLISM

An increase in pH increases blood concentrations, urinary excretion, and net production of lactic acid and keto acids, and a decrease in pH has the opposite effect.[1-14] Recent studies have put this effect into a broader perspective, highlighting its role in the protection of acid–base homeostasis.

We initially studied the relation between systemic acid–base disturbances and keto acid metabolism in overweight subjects with fasting-induced ketogenesis,[9] because such persons generate substantial quantities of keto acids and their hydrogen-ion balance can be assessed without interference from food intake or stool loss. During three separate one-week fasts, the subjects were given sodium bicarbonate, sodium chloride, or ammonium chloride (2 mmol per kilogram of ideal body weight per day). Plasma bicarbonate concentrations and venous blood pH were lowest when the subjects received ammonium chloride, intermediate when they received sodium chloride, and highest when they received sodium bicarbonate (Fig. 2). Both blood concentrations and urinary excretion of keto acid anions were greater

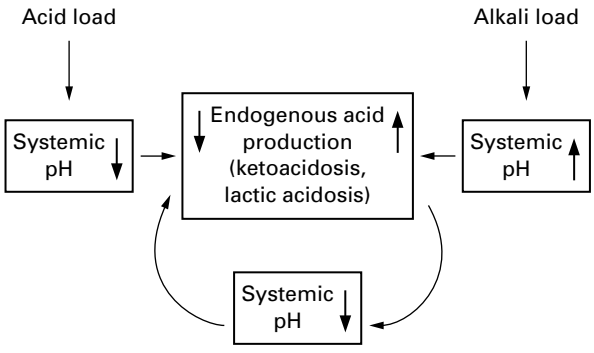

Figure 1. Negative Feedback Control of Endogenous Acid Production.

Increased production of lactic acid or keto acids reduces systemic pH, which in turn inhibits the rate of endogenous acid production. Other exogenous or endogenous acid loads also suppress endogenous acid production, whereas alkali loads enhance it. Alkali therapy accentuates the production of lactic acid or keto acids and thus interferes with this mechanism for regulating the acid–base balance.

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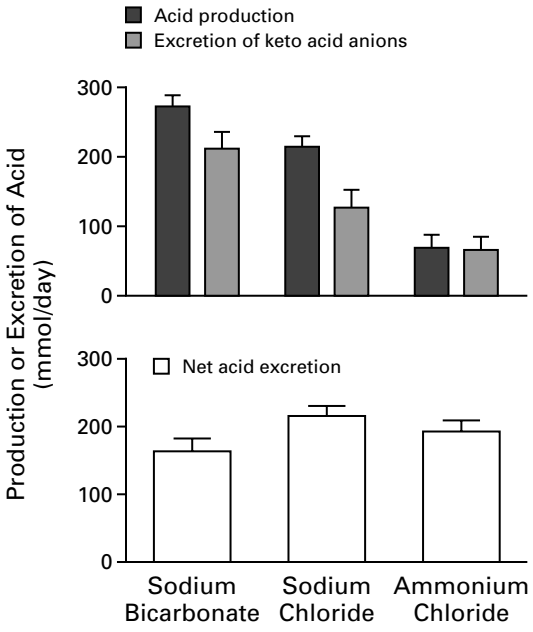

No. of Patients	7	5	6
Venous pH	7.35±0.01	7.32±0.01	7.30±0.01
Plasma bicarbonate (mmol/liter)	18.3±1.1	15.4±1.0	14.0±1.4

Figure 2. Mean (±SE) Steady-State Values of Acid Production, Excretion of Keto Acid Anions, and Net Acid Excretion during Days 5 to 7 of Fasting in Overweight Subjects.

Acid production was calculated as acid output (net acid excretion) minus acid intake (ingestion of ammonium chloride [acid], sodium chloride [control], or sodium bicarbonate [base] in a dose of 2 mmol per kilogram of ideal body weight per day).[9] The rates of net acid excretion (urinary ammonium plus titratable acid minus bicarbonate) were similar in the acid and base phases, despite a difference in acid intake of 238 mmol per day.

during the sodium bicarbonate phase than during the ammonium chloride phase, indicating that net keto acid production was considerably greater when the subjects ingested base (Fig. 2). The difference in the excretion of keto acid anions between the base and acid phases was 146 mmol per day. The conclusion that this change represented a pH-driven modification of net keto acid production was reinforced by the demonstration that the pattern of calculated acid production was similar (Fig. 2). Furthermore, when the subjects were in a steady state of acid–base balance, the acid-excretion rates were similar in the acid and base phases, even though the acid intake differed by 238 mmol per day. In addition, the difference in plasma bicarbonate concentrations between the acid and base phases was only 4 mmol per liter, whereas acid retention of this magnitude would be estimated to decrease plasma bicarbonate concentrations by approximately 24 mmol per liter over a three-day period (a difference of 4 mmol per kilogram per day in acid ingestion multiplied by three days, with the result divided by 0.5, on the assumption that the space of bicarbonate distribution is equal to 50 percent of body weight).

The role of reduced keto acid production in maintaining the acid–base equilibrium is emphasized by the changes in key acid–base values in response to an acid load in subjects in a high, low, or nonketogenic state (base-line excretion of keto acid anions, more than 68, 2 to 41, or less than 2 mmol per day, respectively) (Fig. 3). In the high ketogenic state, although there was no increase in acid excretion, the plasma bicarbonate concentration was only 2.0 mmol per liter lower than the control value (after equimolar ingestion of sodium chloride),[9,14] whereas a similar acid load in the nonketogenic state decreased the plasma bicarbonate concentration by 5.0 mmol per liter despite an increase of 80 mmol per day in net acid excretion[15-17] (and Fremont-Smith K, et al.: personal communication). Thus, the modification of keto acid production during a moderate acid load was the main factor that protected the acid–base equilibrium when keto acid production was substantial.

During the first week of starvation, many adaptive metabolic events occur, and keto acid production has not yet reached a steady state. To ascertain whether systemic acid–base disturbances modify the production of keto acids during a prolonged increase in endogenous acid production, we studied the effects of similar ammonium chloride, sodium chloride, and sodium bicarbonate loads on net keto acid production in subjects on a hypocaloric, ketogenic diet for two months.[10] During stable ketosis, which developed after four weeks, the ingestion of ammonium chloride decreased blood pH, plasma bicarbonate concentrations, and urinary excretion of organic acid and keto acid anions (Fig. 3 and 4). The changes in both acid–base values and excretion of organic and keto acids occurred within two days, were sustained while the acid ingestion continued, and were reversed with the substitution of an equimolar intake of sodium chloride. The response to the ingestion of sodium bicarbonate mirrored the findings with an acid load. Thus, systemic pH changes did not modify keto acid metabolism transiently but led to a new metabolic steady state with modified endogenous acid production.

Furthermore, ingestion of methionine, a sulfur-containing amino acid from which sulfuric acid is produced, suppressed the production of keto acids to a degree similar to that with ammonium chloride (Fig. 4), indicating that acids with different anions as well as those generated endogenously have a sustained inhibitory effect on keto acid metabolism.[11]

In these studies of acute and chronic ketoacidosis, the degree of suppression or enhancement of keto acid output was similar with equivalent acid and base loads. However, the quantitative effect of these changes on the maintenance of an acid–base balance de-

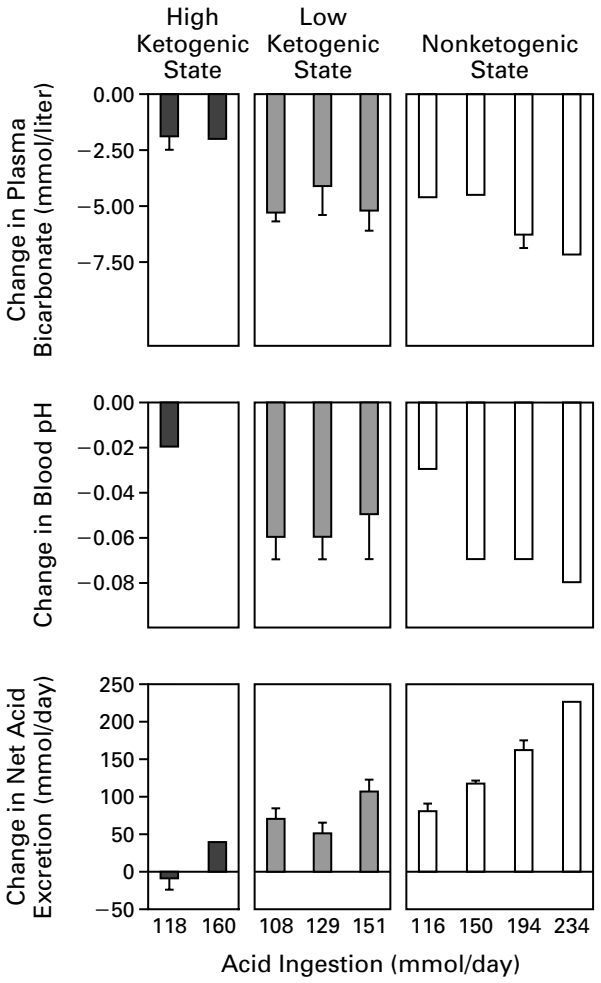

Figure 3. Influence of the Base-Line Rate of Keto Acid Production on the Response of Key Acid–Base Variables to Acid Ingestion.

Data for a high ketogenic state (base-line urinary ketone excretion, >68 mmol per day) were obtained during days 5 to 7 of total fasting,[9,14] data for a low ketogenic state (urinary ketone excretion, 2 to 41 mmol per day) were obtained during days 4 to 7 of the second month of a protein-sparing modified fast,[10,11] and data for a nonketogenic state (urinary ketone excretion, <2 mmol per day) were obtained after three to nine days of normal dietary intake[15,16] (and Fremont-Smith K, et al.: personal communication). The decreases in blood pH and plasma bicarbonate concentrations and the increase in net acid excretion in response to the acid load (as compared with equimolar ingestion of sodium chloride in the ketogenic states and the base-line value in the nonketogenic state) were substantially reduced in the high ketogenic state, indicating the effectiveness of reduced keto acid production in protecting the acid–base equilibrium in this setting. Values are means. The T bars indicate standard errors.

pended on the amount of keto acid produced. In the subjects who fasted for one week, in whom the average excretion of keto acid anions was 130 mmol per day, the decrease or increase in keto acid output offset 61 percent of the acid or base load that was being administered. On the other hand, in subjects

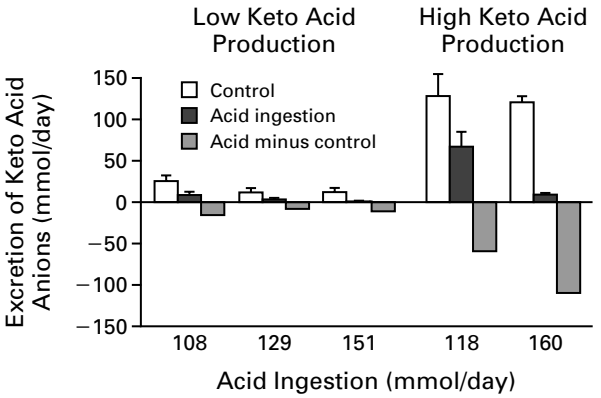

Figure 4. Rates of Steady-State Excretion of Keto Acid Anions (Representing Net Keto Acid Production) According to Base-Line Keto Acid Production in Overweight Subjects after Ingestion of Ammonium Chloride or Methionine[11] (Acid) or Equimolar Amounts of Sodium Chloride (Control).

Data for low base-line keto acid production (urinary ketone excretion, 2 to 41 mmol per day) were obtained during days 4 to 7 of the second month of a protein-sparing modified fast,[10,11] and data for high base-line keto acid production (urinary ketone excretion, >68 mmol per day) were obtained during days 5 to 7 of total fasting.[9,14] The degree of suppression of keto acid output varied with the acid load, whereas absolute suppression (acid minus control) varied with base-line keto acid production as well as with the acid load. Values are means. The T bars indicate standard errors. The negative numbers represent the decrease in keto acid anion excretion during acid ingestion.

adapted to a hypocaloric, ketogenic diet, who were excreting an average of only 13 mmol of keto acid anions per day, a similar decrease in keto acid output had a minimal effect on the response to the acid load.[10] In this case, acid excretion had a major role in maintaining an acid–base equilibrium, with changes in plasma acid–base values and net urinary acid excretion that were similar to those in the nonketogenic state (Fig. 3).

If pH modifications of keto acid production represent an acid–base regulatory mechanism, changes in pH resulting from respiratory and metabolic acid–base disorders should have similar effects. When acute metabolic and respiratory acid–base disturbances were induced in awake rats with chronic ketosis, a decrease in blood pH reduced the net keto acid output, whereas an increase in pH had the opposite effect.[12] Furthermore, all the changes occurred within two hours, persisted for the duration of acid or base loading, and were reversed when loading was terminated.

These results suggest that when endogenous acid production is increased, a reduction in the net endogenous production of acid regulates the acid–base equilibrium, whereas when endogenous acid production is minimal, other mechanisms of acid–base control are required to handle an acid or base load.

All these investigations have examined the influ-

ence of pH on the net production of keto acids but not the processes involved in their generation or metabolism. From the standpoint of acid–base homeostasis, only the net effect is important. However, as we have discussed in more detail elsewhere,[18] the predominant effect is mediated by changes in the generation of keto acids, with acidosis inhibiting and alkalosis stimulating lipolysis[19-22] and hepatic ketogenesis.[6,23,24]

INFLUENCE OF pH ON LACTIC ACID METABOLISM

Net lactic acid production can also be regulated by pH, with a low pH inhibiting glycolytic metabolism, and a high pH stimulating it.[25,26] Furthermore, in both humans and animals subjected to metabolic and respiratory manipulations of acid–base homeostasis, plasma lactate concentrations are usually increased during alkalemia and decreased during acidemia.[27-37] In the absence of stimulation, the changes in plasma lactate concentrations are small; during lactic acidosis, the administration of bicarbonate dramatically increases plasma lactate concentrations and net lactate production in both animals and humans.[38-45]

In rats with hypoxia-associated lactic acidosis, either mild respiratory acidosis (induced by increasing the partial pressure of carbon dioxide to approximately 60 mm Hg) or an equivalent degree of metabolic acidosis (induced by administering an intraarterial infusion of hydrochloric acid) abolished the progressive rise in plasma lactate concentrations that occurred in control rats with hypoxia (Fig. 5). A decrement in blood pH of 0.03 unit (similar to the small change in pH that alters keto acid production in obese humans in the fasting state[9]) virtually eliminated the rise in plasma lactate concentrations. Furthermore, respiratory alkalosis induced in rats with hypoxia-associated lactic acidosis resulted in increased plasma lactate concentrations, indicating that an increase in pH rather than the change in bicarbonate was responsible for the changes in lactate metabolism. These changes were rapidly reversible within one hour after the partial pressure of carbon dioxide had returned to normal. Although the rate of net lactate production was not measured, and lactate redistribution from the intracellular compartment to the extracellular compartment may have had a role, it seems highly likely that the changes in the plasma lactate concentration reflected an alteration in the generation of lactate.

These findings with lactic acidosis, in combination with the prior reports that pH can modulate plasma lactate concentrations, strongly support the notion that a low pH impedes lactic acid formation under conditions of lactic acidosis. How this alteration in lactic acid production occurs remains unclear. As with ketoacidosis, the most compelling explanation is that pH regulates the generation of lactic acid.

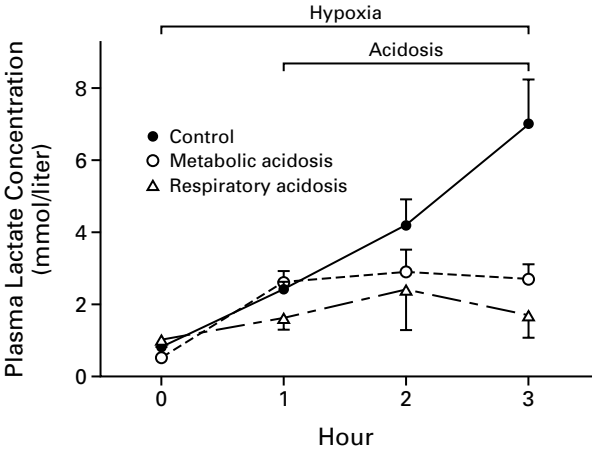

Figure 5. Effect of Metabolic Acidosis and an Equivalent Degree of Respiratory Acidosis on Lactic Acidosis Caused by Hypoxia (8 Percent Inspired Oxygen) in Rats.[46]

Metabolic acidosis, induced by administering an infusion of hydrochloric acid that decreased the plasma bicarbonate concentration by 1.8 mmol per liter, caused the pH to decrease by 0.03 unit. A similar degree of respiratory acidosis, induced by increasing the partial pressure of carbon dioxide from 41 to 59 mm Hg, caused the pH to decrease by 0.04 unit. Both metabolic acidosis and respiratory acidosis significantly attenuated the rise in the plasma lactate concentration. Values are means ±SE.

The best evidence that pH modulates lactic acid generation comes from studies of muscle during exercise. In both human and animal muscles, the heightened lactic acid production during exercise decreases in the presence of either metabolic or respiratory acidosis.[21,47-52] Although alkalemia may increase the rate of lactic acid generation, the data are less clear-cut than with acidemia.[21,47-52] Measurements of key glycolytic intermediates indicate that a low pH decreases muscle lactate generation by inhibiting glycolysis,[47] at least in part through the effect of pH on the enzyme phosphofructokinase. The acidemia-induced decrease in glycolytic flux is accompanied by a decrease in muscle performance.[21,51] These pH-induced alterations in muscle lactate generation are mirrored by concurrent changes in plasma lactate concentrations.[50,51] Therefore, it seems clear that pH, at least in part, modifies net lactate production and plasma lactate concentrations as a result of changes in the generation of lactate. Studies of muscle with the use of phosphorus-31 nuclear magnetic resonance spectroscopy have not established whether intracellular pH is the signal for altered lactate production.[50]

OTHER ENDOGENOUS ACIDS

Changes in urinary excretion of organic anions may serve as an acid–base regulatory mechanism in rats during dietary acid or base challenges, since total organic acid excretion increases with bicarbonate

loading and decreases in response to ammonium chloride.[53] Systemic alkalosis in rats is accompanied by substantial increases in citrate excretion.[54] These findings have been interpreted to mean that increased excretion of citrate and other organic anions in response to bicarbonate loading or systemic alkalosis represents a loss of base, since if these organic anions were not excreted, their oxidation would generate bicarbonate.[54] However, the metabolism of organic anions results in a net gain of bicarbonate only if they are ingested or produced with a cation other than a hydrogen ion (or as a salt, not an acid).

Furthermore, in these studies it was assumed that a renal tubular mechanism governing the excretion of organic anions protected acid–base homeostasis. However, if plasma concentrations of citrate or organic anions (neither of which were measured in these studies) increased in response to alkalosis (and decreased in response to ammonium chloride), this would suggest that endogenous acid production resulting from the metabolism of other organic acids is analogous to the production of keto acid and lactic acid and that increased urinary excretion results solely from an increase in the filtered load. Even if plasma organic-anion concentrations fell in response to alkalosis, as long as plasma concentrations remained stable despite increased renal excretion, the data would still be consistent with an increase in net organic acid production. In this case, the presence of an additional systemic, pH-mediated effect on renal tubular transport of organic anions would be required.

Excretion of citrate is governed by pH-mediated changes in its transport and metabolism by renal proximal tubules.[55-58] In animals and humans, the ingestion of alkali and metabolic alkalosis result in increased excretion of citrate, and acute and chronic metabolic acidosis and acute respiratory acidosis result in decreased excretion of citrate.[55-58] Citrate excretion is not altered by chronic respiratory acidosis, because the intracellular pH of renal proximal tubules, which influences both the metabolism and the excretion of citrate, is apparently reduced to a greater extent by metabolic acidosis and by acute respiratory acidosis than by chronic respiratory acidosis.[56]

Under normal conditions, the rate of urinary citrate excretion in humans is 3 to 6 mmol per day (0.04 to 0.08 mmol per kilogram), and the rate of total organic acid excretion is 0.5 mmol per kilogram, whereas both rates are approximately 10 times as high in rats. Therefore, alterations in the metabolism of citrate and other urinary organic anions are likely to contribute less to acid–base homeostasis in humans than in rats. In our studies with fasting[9] and with a ketogenic diet[10,11] in humans, all the differences in the excretion of organic anions could be explained by changes in the excretion of keto acid anions.

In summary, small (physiologic) changes in systemic pH as a result of metabolic or respiratory acid–base perturbations lead to predictable changes in keto acid and lactic acid metabolism that occur promptly, can be sustained, are readily reversible, and result in an increase or decrease in net endogenous acid production. This change may make an important contribution to the maintenance of an acid–base equilibrium, especially if the rate of endogenous acid production is high. This phenomenon represents a negative feedback system for acid–base homeostasis that allows changes in systemic pH to regulate acid production (Fig. 1).

CLINICAL AND PATHOPHYSIOLOGIC IMPLICATIONS

The acid–base regulatory mechanism described above has several important clinical consequences. As in the experimental studies we have described, the effects are most pronounced in clinical settings in which the net production of endogenous acid is increased.

Effect on Energy Metabolism

As intermediates or end products, endogenous acids serve important metabolic functions. Modification of their production can have serious implications for the optimal use of fuel. This effect is most apparent during prolonged fasting and exhaustive exercise, when other sources of energy have been consumed or their metabolic pathways blocked.

Prolonged Fasting

In a state of prolonged fasting, glucose is produced through gluconeogenesis at the expense of a breakdown in protein and loss of nitrogen. Keto acids provide an alternative to glucose as a source of energy for the brain, which is the main consumer of glucose in a state of prolonged fasting. By inhibiting ketogenesis, acidosis reverses the nitrogen-sparing effect of fasting-induced ketogenesis. The administration of sodium bicarbonate during short-term starvation has been shown to decrease urea and ammonium excretion while increasing the output of keto acids.[59]

Exercise

During exercise-induced stimulation of lactic acid production, the administration of ammonium chloride decreases plasma lactate concentrations and limits endurance, whereas the administration of sodium bicarbonate has the opposite effect.[21] During exhaustive forearm exercise, when oxidative metabolism is inhibited and phosphocreatine stores are depleted, metabolic acidosis diminishes lactic acid production and thus limits the only remaining source of ATP.[50] During starvation, exercise with increased blood lactate concentrations results in decreased blood keto acid concentrations, despite the increased availability of free fatty acids.[60]

Acute and Chronic Acid–Base Disturbances and Increased Organic Acid Production

Pregnancy

Because of the demands of the fetus for glucose and amino acids, fasting during pregnancy results in an accelerated fall in maternal blood glucose concentrations and more pronounced ketogenesis than that associated with fasting in the absence of pregnancy. The mild respiratory alkalosis accompanying pregnancy[61] may act as a buffer for transient ketoacidosis or may enhance the ketotic state if fasting is prolonged. If there is also metabolic alkalosis due to vomiting or injudicious use of diuretics, ketoacidosis or lactic acidosis may develop.

Alcohol-Associated Ketoacidosis

Ketoacidosis and lactic acidosis associated with alcohol consumption is a complex disorder.[62,63] Ketosis usually occurs after periods of binge drinking, inadequate food intake, or protracted vomiting or during withdrawal. Metabolic alkalosis induced by vomiting and volume depletion or respiratory alkalosis due to hyperventilation may enhance keto acid production, which is already increased because of hypoinsulinemia-induced mobilization of free fatty acids.[62] In addition, increased plasma lactate concentrations have been associated with metabolic alkalosis induced by vomiting.[64]

Salicylate Intoxication

Salicylate intoxication is accompanied by respiratory alkalosis and usually an increased-anion-gap metabolic acidosis. The latter results from the accumulation of salicylate as well as lactic acid and keto acids.[65] The increase in organic acid production is likely to be the result of the respiratory alkalosis, because salicylate-induced lactic acidosis in animals can be prevented by preventing hypocapnia[66] and because the highest anion gaps have been noted in patients with alkalemia.[65]

Treatment of Ketoacidosis and Lactic Acidosis

Diabetic Ketoacidosis

Diabetic ketoacidosis is the result of severe insulin deficiency, which leads to increased lipolysis with uncontrolled production and decreased metabolism of keto acids. Treatment with insulin reverses the acidosis as well as the other metabolic defects. Before insulin was available, an acid (ammonium phosphate) load was shown to decrease ketonuria in subjects with diabetes,[3] whereas a base (sodium bicarbonate) load increased it.[1] Treatment with sodium bicarbonate delays the correction of ketonemia.[67,68] In addition, a randomized, prospective, controlled trial of treatment with sodium bicarbonate in patients with severe diabetic ketoacidosis (pH, 6.90 to 7.14) showed no benefit of bicarbonate over standard therapy with respect to any of the usual measures of recovery.[69] Thus, bicarbonate is usually not required for the treatment of acidosis in patients with diabetic ketoacidosis.

Fasting and Hypocaloric Ketogenic Diets

Modifications of fasting, commonly used for weight reduction, induce mild ketoacidosis. Data on the benefits or risks of supplementing such diets with alkali are scarce. The output of keto acids is increased[9] and loss of protein may be decreased,[59] but these changes are not likely to be quantitatively important over a short period.

Lactic Acidosis

Although sodium bicarbonate has been considered the mainstay of therapy for patients with lactic acidosis, in both animals and humans with lactic acidosis, bicarbonate therapy increases net lactate production and plasma lactate concentrations.[47,70] The importance of this effect in managing the clinical condition is unclear, and the overall benefit of bicarbonate therapy remains controversial.[71-73] Nevertheless, in the absence of clear evidence of harm, we concur with the view that judicious administration of bicarbonate to maintain a blood pH of 7.15 to 7.20 — values presumably sufficient to mitigate the adverse hemodynamic effects of acidosis — represents a reasonable therapeutic approach.

Reduced Renal Acid Excretion

Renal Tubular Acidosis

Whether acid–base balance is maintained in patients with reduced renal acid excretion continues to be debated. In patients with stable renal tubular acidosis, acid–base balance may be maintained by reduced production of endogenous acids.[74] There is no evidence of a similar process in patients with stable metabolic acidosis due to various renal disorders.[75]

End-Stage Renal Disease

Despite the efficient transfer of bicarbonate from dialysate to patient during hemodialysis, plasma bicarbonate concentrations never equilibrate with dialysate bicarbonate concentrations, and in some patients, the plasma concentrations decrease during dialysis, suggesting that the delivery of bicarbonate may be accompanied by increased acid production.[76]

CONCLUSIONS

There is convincing evidence that small changes in systemic pH modify the rate of endogenous acid production in a direction and amount that can attenuate the effect of an acid challenge in a variety of physiologic and pathologic situations. The changes occur rapidly, can be sustained, are reversible, and are most important when lactic acid or keto acids are

being generated in large quantities. In such states, the change in acid production can be an essential mechanism for maintaining acid–base equilibrium. Because keto acids and lactic acid serve as important alternative sources of energy as well as metabolic intermediates, modification of their production or metabolism through changes in pH can have deleterious effects on energy metabolism. Therefore, in patients with acid–base disorders and increased organic acid production, decisions about treatment should take into consideration both acid–base and metabolic outcomes.

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