Does Aerobic Respiration Produce Carbon Dioxide or Hydrogen Ion and Bicarbonate?

Erik R. Swenson, M.D.

ABSTRACT

Maintenance of intracellular pH is critical for clinical homeostasis. The metabolism of glucose, fatty acids, and amino acids yielding the generation of adenosine triphosphate in the mitochondria is accompanied by the production of acid in the Krebs cycle. Both the nature of this acidosis and the mechanism of its disposal have been argued by two investigators with a long-abiding interest in acid–base physiology. They offer different interpretations and views of the molecular mechanism of this intracellular pH regulation during normal metabolism. Dr. John Severinghaus has posited that hydrogen ion and bicarbonate are the direct end products in the Krebs cycle. In the late 1960s, he showed in brain and brain homogenate experiments that acetazolamide, a carbonic anhydrase inhibitor, reduces intracellular pH. This led him to conclude that hydrogen ion and bicarbonate are the end products, and the role of intracellular carbonic anhydrase is to rapidly generate diffusible carbon dioxide to minimize acidosis. Dr. Erik Swenson posits that carbon dioxide is a direct end product in the Krebs cycle, a more widely accepted view, and that acetazolamide prevents rapid intracellular bicarbonate formation, which can then codiffuse with carbon dioxide to the cell surface and there be reconverted for exit from the cell. Loss of this "facilitated diffusion of carbon dioxide" leads to intracellular acidosis as the still appreciable uncatalyzed rate of carbon dioxide hydration generates more protons. This review summarizes the available evidence and determines that resolution of this question will require more sophisticated measurements of intracellular pH with faster temporal resolution. **(Anesthesiology 2018; 128:873-9)**

Dr. John Severinghaus and I have had a long-running intellectual difference in our understanding of the step(s) by which the several decarboxylase reactions in the mitochondria during aerobic metabolism lead to a buildup of hydrogen ions and carbon dioxide. I maintain the standard view that aerobic metabolism of carbohydrates, fats, and proteins proceeds with production of carbon dioxide from three mitochondrial decarboxylation reactions while he contends that hydrogen ion and bicarbonate are the immediate end products. The intracellular acidosis after carbonic anhydrase inhibition by acetazolamide observed by Severinghaus in the brain are claimed by both of us to be consistent with our understanding of the chemistry of these reactions and function of carbonic anhydrase. The editorial leadership of Anesthesiology suggested these viewpoints be published in detail with the larger aim of stimulating more work in this area of biochemistry and physiology. As in many instances during his long-storied career, Dr. Severinghaus has never shied from contesting conventional wisdom when data and solid physiologic arguments offer a logical and alternative explanation. I am pleased to present both our positions as a tribute to him and the large influence he has had in my career and thinking.

Three steps in the Krebs cycle are catalyzed decarboxylation reactions: pyruvate to acetyl-coenzyme A catalyzed by pyruvate dehydrogenase, isocitrate to α-ketoglutarate catalyzed by isocitrate dehydrogenase, and α-ketoglutarate to succinate by α-ketoglutarate dehydrogenase (fig. 1). All biochemists from Hans Krebs onward have considered carbon dioxide as the end product of these enzymic reactions, although they could not exclude hydrogen ion and bicarbonate, nor did they have the techniques to do so reliably. In later work, Krebs and Roughton[1] showed that carbon dioxide, and not bicarbonate, was the end product of two other decarboxylation reactions, urease and yeast pyruvate carboxylase, but these experiments were in purified simple systems and not the complex milieu of the mitochondria or cell. In the early twentieth century it was shown that carbon dioxide exists in three interchangeable forms: carbon dioxide itself, bicarbonate, and carbonic acid, in roughly the proportions of 10, 90, and 0.1%, respectively. Carbonic anhydrase, one of the fastest known enzymes, was discovered in 1932 and found to speed the interconversion of these three species by many orders of magnitude. While the left-hand side of the following reaction is virtually instantaneous, the right-hand side is very slow in physiologic terms (half time of roughly 7 s at 37°C) without catalysis. However, it is accelerated to completion within milliseconds by carbonic anhydrase (CA).

$$H^+ + HCO_{3^-} \leftrightarrow H_2CO_3 \xleftrightarrow{CA} CO_2 + H_2O \quad (1)$$

Figures were enhanced by Sara Jarret, C.M.I.

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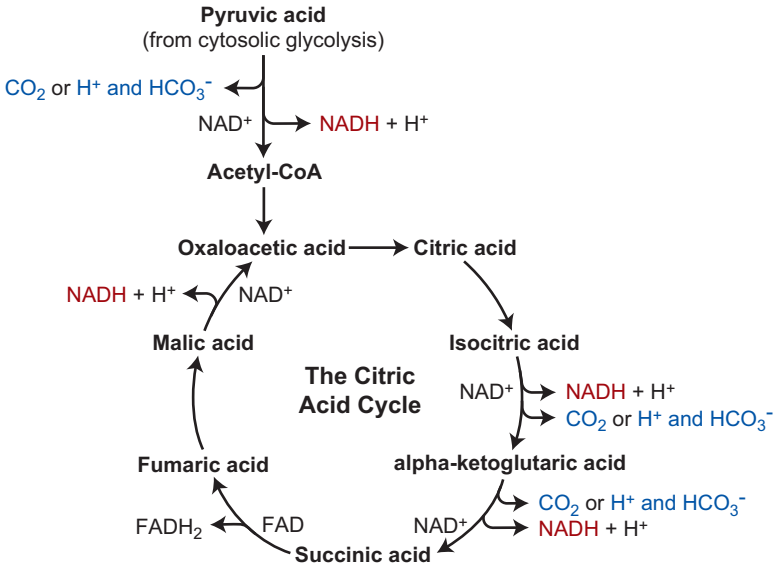

Fig. 1. The Krebs or citric acid cycle. The three decarboxylation reactions are shown with carbon dioxide (CO_2) or hydrogen ion (H^+) and bicarbonate (HCO_3^-) as the immediate end products as argued by Swenson and Severinghaus, respectively. CoA = coenzyme A; FAD = flavin adenine dinucleotide (oxidized form); $FADH_2$ = flavin adenine dinucleotide (reduced form); NAD^+ = nicotinamide adenine dinucleotide (oxidized form); NADH = nicotinamide adenine dinucleotide (reduced form).

In the 1950s, acetazolamide became clinically available as the first safe oral diuretic in heart failure and was subsequently found useful in treating many medical conditions from glaucoma to acute mountain sickness. It has no effect on metabolic rate, but by inhibiting carbonic anhydrase, it leads to carbon dioxide retention and a backup and increase of carbonic acid (hydrogen ion and bicarbonate), which can be exploited therapeutically in many clinical situations.[2]

Severinghaus's Thesis and Studies

In 1962, as part of studies on high altitude acclimatization, Severinghaus and his colleagues at the Cardiovascular Research Institute of the University of California, San Francisco, began research on the effects of acetazolamide on cerebral blood flow and brain acid–base balance in part to better understand how the drug benefits those going to high altitude. Acetazolamide had recently been shown to improve arterial oxygenation at high altitude by its stimulation of ventilation and by doing so could reduce acute mountain sickness, a syndrome of acute hypoxic intolerance characterized by headache, lassitude, fatigue, nausea, and anorexia. His studies revealed the possibility that the conventional view of aerobic metabolism producing carbon dioxide in the Krebs cycle could be interpreted differently.

Case Favoring Hydrogen Ion and Bicarbonate as the Initial Products in the Krebs Cycle Decarboxylation Steps

Cotev *et al.*[3] in 1968 reported that in anesthetized dogs with exposed cortical brain surface, acetazolamide administered intravenously within minutes reduced extracellular fluid pH from 7.22 to 7.12, but only increased cortical partial pressure of carbon dioxide from 45 to 48 mmHg. Acetazolamide more than doubled cerebral blood flow as measured by brain arterio-venous oxygen content difference and by 65% by a krypton clearance method. These blood flow changes increased cortical surface P_{O_2} from 42 to 62 mmHg. They suggested their findings proved that aerobic metabolism generates hydrogen ion and bicarbonate, rather than carbon dioxide. The hydrogen ion then combines with a bicarbonate ion to yield carbonic acid, which is then catalyzed rapidly by carbonic anhydrase to carbon dioxide and water (equation 1) and much more slowly when blocked by acetazolamide.

In 1969, to study this more directly, Severinghaus *et al.*[4] used the *in vitro* effect of sudden oxygenation of anoxic brain homogenates to initiate aerobic metabolism (figs. 2 and 3). Suddenly injected oxygen reduced pH by 0.04, but when acetazolamide was added to the homogenate, sudden oxygenation reduced pH by 0.10. This gave more credence to the concept that aerobic metabolism generates hydrogen ion and bicarbonate, which are transformed normally by carbonic anhydrase to carbon dioxide and water, thus blunting the acidosis.

The effects of acetazolamide were restudied in 1988 by Bickler *et al.*[5] in anesthetized rabbits using brain surface pH and PCO_2 electrodes. When brain surface PCO_2 was held constant by increasing ventilation sufficiently, after intravenous injection of acetazolamide, brain extracellular fluid hydrogen ion rose 20% (pH decreased 0.08) within 2 min (fig. 4), supporting again the thesis that aerobic metabolism generates hydrogen ion and bicarbonate from glucose and other metabolites of lipids and proteins that enter the Krebs cycle as pyruvate.

These papers and the theoretical description of aerobic metabolism leading to production of carbon dioxide for elimination by the lungs from the initial production of hydrogen ion and bicarbonate have not been disproven by any experimental evidence. Severinghaus's argument, while based on his studies in the brain, would also apply to aerobic metabolism elsewhere, since some isozyme(s) of catalytically

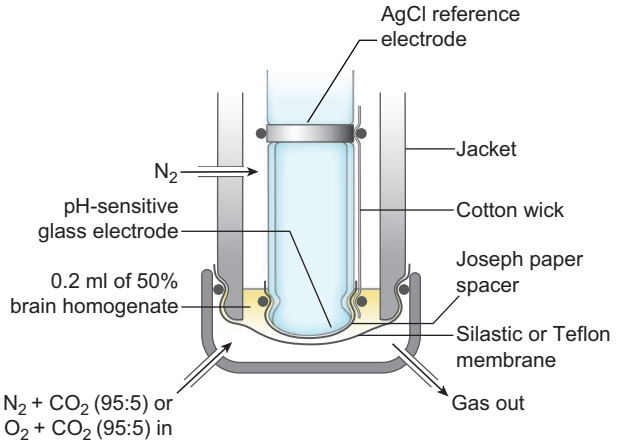

Fig. 2. Device for *in vitro* study of the effect of sudden oxygenation of brain tissue homogenate on tissue pH with and without acetazolamide. AgCl = silver chloride; CO_2 = carbon dioxide; N_2 = nitrogen gas; O_2 = oxygen. Reprinted with permission from Biochem J 1969; 114:703–5.

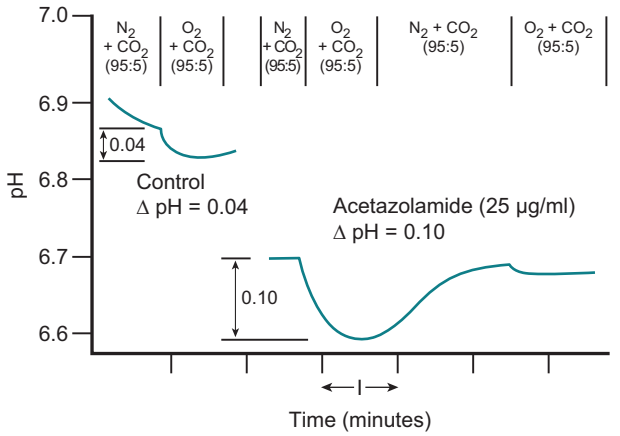

Fig. 3. The acid shift of an anoxic rat brain 50% homogenate with sudden oxygenation with and without acetazolamide. Acetazolamide blocks conversion of carbonic acid to carbon dioxide (CO_2) and water. N_2 = nitrogen gas; O_2 = oxygen. Reprinted with permission from Biochem J 1969; 114:703–5.

active carbonic anhydrase (now numbering 12) are present in all cells.

Swenson Antithesis: An Alternative View

I have taken for granted that the product of the oxidative decarboxylation steps in the Krebs cycle is carbon dioxide. My initial exposure to the contrary was in 1982 when I spent a memorable afternoon with Dr. Severinghaus during my interviews at the University of California, San Francisco, for pulmonary and critical care fellowship. I attempted from my junior status to explain his results by loss of carbonic anhydrase–mediated facilitation of intracellular carbon dioxide diffusion (more below, "Case Favoring Carbon Dioxide as the Initial Product in the Krebs Cycle Decarboxylation Steps"), this with some trepidation to a giant in the field of acid–base physiology and cardiopulmonary medicine. We had a spirited discussion, but neither was dissuaded by the other.

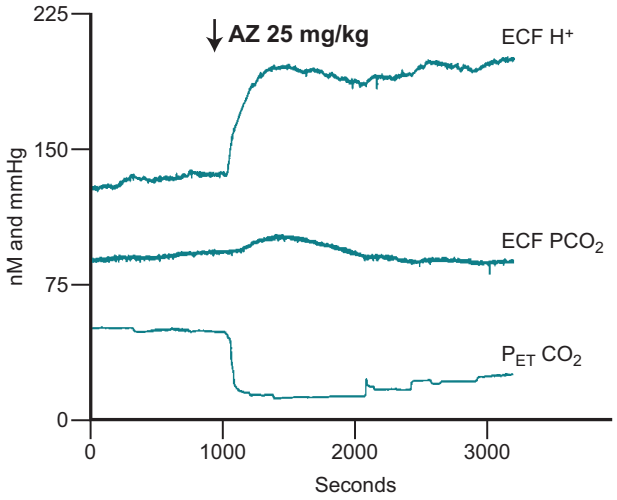

Fig. 4. After intravenous (IV) injection of acetazolamide (AZ) in anesthetized rabbit, effect on brain surface extracellular fluid (ECF) hydrogen ion (H^+) when partial pressure of extracellular fluid carbon dioxide (ECF P_{CO_2}) is held constant by increasing ventilation. ECF pH decreased 0.08 (recorded as hydrogen ion in nM) with accumulation of carbonic acid. $Paco_2$ decreased 8 mmHg. Previous studies showed that tissue P_{O_2} rose, excluding a hypoxic lactic acidosis. CO_2 = carbon dioxide; P_{ET} = end-tidal partial pressure. Reprinted with permission from J Appl Physiol 1988; 65:422–7.

In fact, my first introduction to him was as a young boy in the late 1950s, when my father, Edward Swenson, M.D., was a fellow in the newly established Cardiovascular Research Institute, to which Dr. Severinghaus had just been recruited by its founder, Julius Comroe, M.D. My father and Dr. Severinghaus coauthored several papers that definitively established the role of alveolar carbon dioxide as the stimulus that matches regional ventilation to changes in regional perfusion created by temporary balloon occlusion of a pulmonary artery.[6–8] They showed that changes in alveolar carbon dioxide alter airway tone and parenchymal compliance in analogy to hypoxic pulmonary vasoconstriction, which matches regional perfusion to changes in regional ventilation by altering pulmonary vascular tone. My father then went on to found the Pulmonary Division at the University of Florida in Gainesville. As I developed interests in medicine in high school and worked in his pulmonary function laboratory, I was inspired by stories he told of the Cardiovascular Research Institute and of the giants at its creation. Not straying too far from my roots, in my own studies I have continued to investigate this very much underrecognized mechanism of ventilation/perfusion ratio ($\dot{V}_A/\dot{Q}$) matching along with other mechanisms[9] by which carbon dioxide regulates $\dot{V}_A/\dot{Q}$ matching and recreating the experiments of my father and Dr. Severinghaus to show the importance of carbonic anhydrase in this response[10] and how the response acts to limit the $\dot{V}_A/\dot{Q}$ mismatch that develops during pulmonary embolism.[11] My laboratory is pursuing the cellular and molecular biology of the phenomenon along with its clinical implications in lung injury.

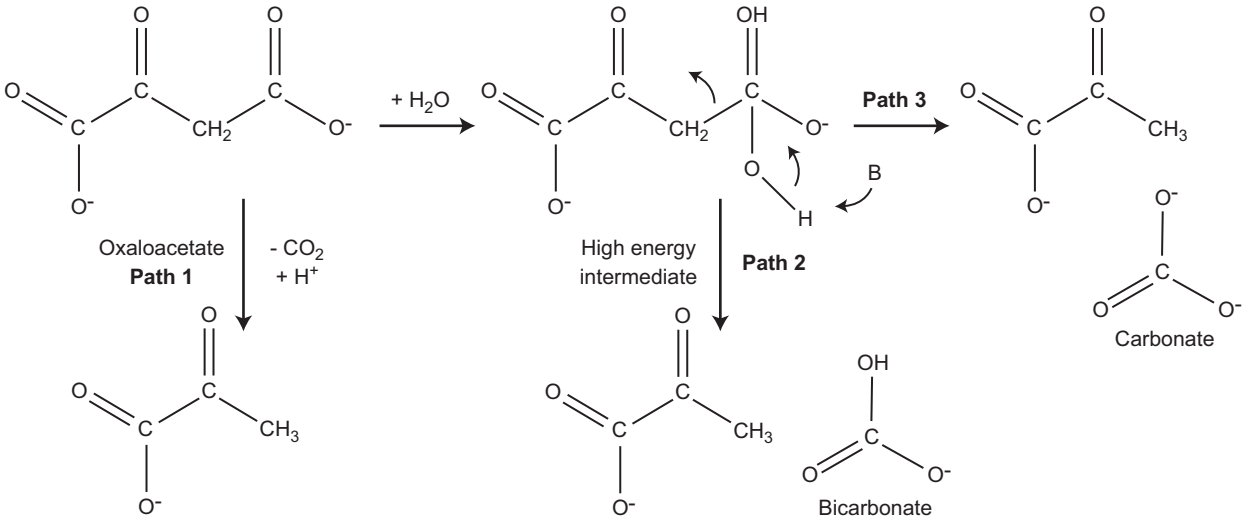

Fig. 5. Possible pathways of oxaloacetate decarboxylation. *Path 1* depicts immediate decarboxylation to carbon dioxide. *Paths 2 and 3* include first the addition of water to form a high energy intermediate that then yields bicarbonate or carbonate upon decarboxylation. Figure supplied by Ron Kluger, Ph.D., University of Toronto, Toronto, Canada.

Case Favoring Carbon Dioxide as the Initial Product in the Krebs Cycle Decarboxylation Steps

It has been argued that for carbonic acid or bicarbonate and hydrogen ion (since they are in virtual instantaneous equilibrium) to be the immediate decarboxylation products in these reactions would require first addition of water to form a high-energy intermediate that then releases the carboxyl group as bicarbonate or carbonic acid[12] as shown in figure 5 for oxaloacetate, another of the intermediate Krebs cycle carboxylic acids. Although evolution generally has sought and favored least-energy-demanding solutions, more recently it has been proven that some decarboxylation reactions generate bicarbonate rather than carbon dioxide,[12] but these compounds have little structural similarity to the Krebs cycle intermediates.

From the earliest work of Francis J. W. Roughton, Ph.D.,[13] who discovered carbonic anhydrase in 1932, it has been appreciated that inhibition causes carbon dioxide retention by denying to blood the ability of transporting carbon dioxide in large amounts as bicarbonate. As a consequence of complete carbonic anhydrase inhibition and to maintain a steady state of carbon dioxide elimination, the PCO_2 driving gradients across the tissues and lung must increase an order of magnitude from roughly 5 to 50 mmHg.[14]

This model of enhancement of carbon dioxide flux by carbonic anhydrase (*i.e.*, over small PCO_2 gradients), in which bicarbonate is effectively utilized as a transport form of carbon dioxide, was found to apply to the more microscopic level of thin fluid layers, lipid bilayer membranes, and

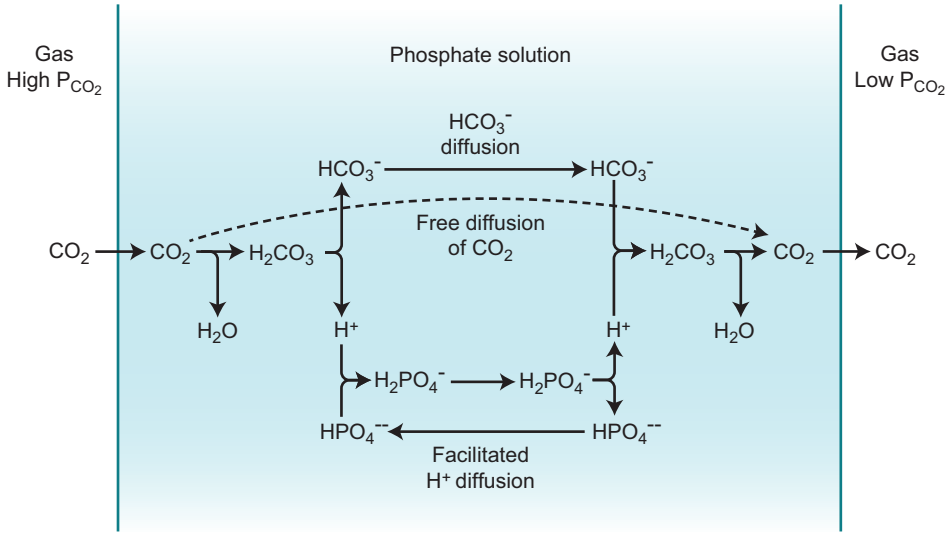

Fig. 6. In addition to free diffusion of carbon dioxide (CO_2), facilitated diffusion of carbon dioxide occurs based upon codiffusion of catalytically formed bicarbonate and facilitated proton transport by intracellular diffusion of buffer molecules such as phosphate and peptides. H_2CO_3 = carbonic acid; HPO_4^{--} = hydrogen phosphate; $H_2PO_4^-$ = dihydrogen phosphate; PCO_2 = partial pressure of carbon dioxide. Reprinted with permission from J Gen Physiol 1976; 67:773–90; doi: 10.1085/jpg.67.6.773.

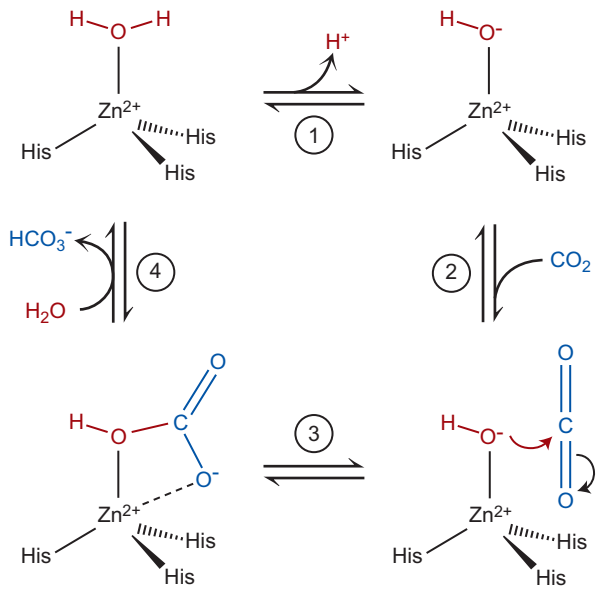

Fig. 7. The active site chemistry of carbonic anhydrase–mediated reversible catalysis of carbon dioxide (CO_2) hydration and bicarbonate (HCO_3^-) dehydration. A divalent zinc ion is activated by coordination to three histidine (His) molecules in a tetrahedral arrangement that permits binding of water, its hydrolysis to a zinc-hydroxide (*reaction 1*), nucleophilic attack on the carbonyl bond of carbon dioxide (*reaction 2*) to produce bicarbonate in the active site (*reaction 3*), and release of bicarbonate and regeneration of zinc-bound water (*reaction 4*). Reaction 1 is facilitated by rapid shuttling of the proton produced in reaction 1 to bulk water by hydrogen ion–titratable amino acid side chains leading out of the active site. Zn^{2+} = divalent positively charged zinc ion. Figure supplied by David Silverman, Ph.D., University of Florida, Gainesville, Florida.

cytosolic solutions in the late 1960s.[15–21] This augmentation of carbon dioxide flux by carbonic anhydrase in these various microscopic environments of the cell has been termed "facilitated diffusion of carbon dioxide."[14,15] Depending upon the concentrations of carbon dioxide/bicarbonate and diffusible buffer molecules such as phosphate and proteins, the enzyme in concentrations typical of most cells increases carbon dioxide diffusion by as much as fivefold. This facilitated codiffusion of carbon dioxide and bicarbonate by carbonic anhydrase with phosphate facilitating hydrogen ion buffering and diffusion is depicted in figure 6.[20]

The physical chemistry of carbonic anhydrase involves a tetrahedral-bound activated zinc ion in the active site that binds water and splits off a hydrogen ion (which is shuttled rapidly out to the surrounding solution), leaving a zinc-hydroxyl that in a nucleophilic attack on carbon dioxide forms zinc-bicarbonate, which then releases the bicarbonate to leave the zinc free to bind another water, as shown in figure 7.[22] By this chemistry, carbonic anhydrase permits the very rapid interconversion of carbon dioxide to bicarbonate and hydrogen ion, thus allowing carbon dioxide to move down its gradient in both forms. If this facilitated diffusion of carbon dioxide cannot take place, then carbon dioxide will build up, and by mass action hydrogen ion will accumulate as the still appreciable rate of uncatalyzed carbon dioxide hydration produces carbonic acid with a half time of 5 to 10 s at 37°C. In the cell or mitochondria consuming oxygen and generating carbon dioxide, the decrease in intracellular or intramitochondrial pH after carbonic anhydrase inhibition by acetazolamide measured by Dr. Severinghaus can therefore be explained by the buildup of carbon dioxide and its slower, but not insubstantial, uncatalyzed hydration to carbonic acid and thence to bicarbonate and protons. In his paper on brain cytosolic homogenates,[3] figure 3 shows the half time of the change in pH upon oxygen addition in the presence of acetazolamide is of the same magnitude, roughly 10 s. His argument would be more compelling if it were possible to show a much faster pH change than that of the kinetics and time course of the uncatalyzed carbon dioxide hydration reaction. The same difficulty of almost equal kinetics of the pH measurements and that of the uncatalyzed reaction applies also to the later *in vivo* experiments of Bickler *et al.*[5] seen in figure 4.

Since the decades of his experiments and those defining the concept of carbonic anhydrase–mediated facilitation of carbon dioxide diffusion, when enzyme inhibition was thought to be the only action of acetazolamide, the story has become more complicated by the fact that acetazolamide has other actions.[23] The one most pertinent is blockade of aquaporin-mediated carbon dioxide egress across cell membranes at concentrations thought only to inhibit carbonic anhydrase. Most cells, including the brain, have several membrane aquaporins that, in addition to allowing water movement across the cell wall, also allow passage of carbon dioxide gas.[24] An example of this is erythrocytes (fig. 8), where more than 90% of carbon dioxide movement occurs *via* aquaporin 1 and Rhesus proteins and not by simple diffusion across the lipid bilayer membrane. Any blockade of aquaporins by acetazolamide will lead to retention of carbon dioxide and intracellular acidosis independent of any aspect of mitochondrial metabolism.

Synthesis: Final Conclusions and Future Directions

The clinical relevance of whether carbon dioxide or hydrogen ion and bicarbonate are the immediate end product(s) of the mitochondrial decarboxylation steps in aerobic respiration that causes the pH of respiring mitochondria and cells to decrease and become more acidic with acetazolamide may seem rather remote. It is possible to speculate that under extreme circumstances, such as in severe ischemia, hypoxia, sepsis, extremely high rates of metabolism (such as during maximal exercise), or severe acid–base perturbations, one end product might be favored energetically over other.

Therefore, at this juncture, unless techniques with greater sophistication and faster temporal resolution can be brought to bear, we are left with two equally valid explanations for the change in intracellular pH caused by carbonic anhydrase inhibition by acetazolamide. Perhaps magnetic resonance spectroscopic measurements of pH with faster kinetics combined with addition of isotopic labeling of oxygen (^{18}O) or carbon (^{13}C) in pyruvate to follow the appearance by mass

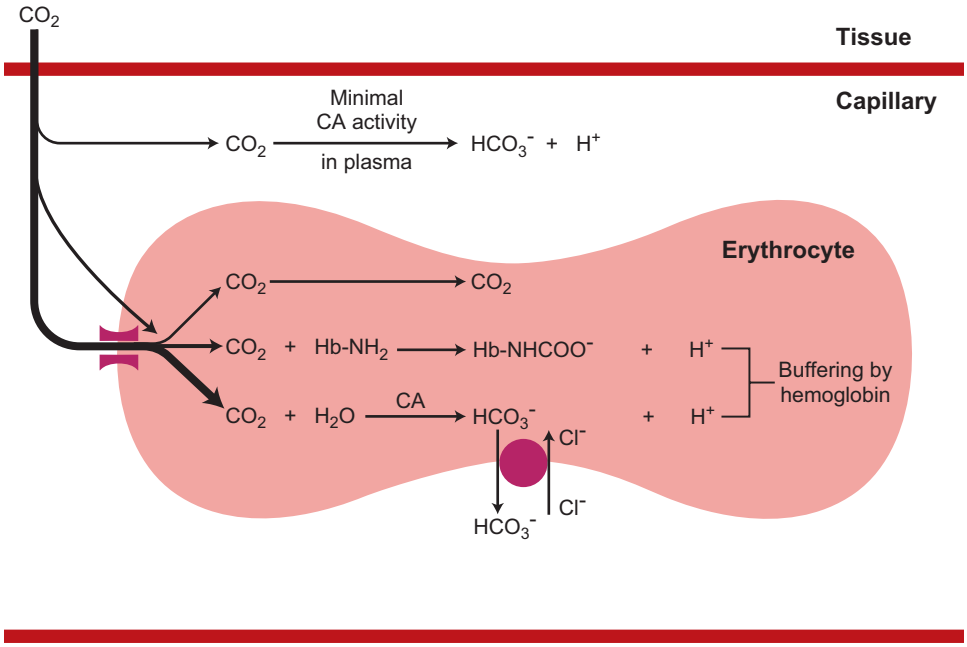

Fig. 8. Diffusion and reaction pathways for carbon dioxide (CO_2) movement from tissues into erythrocytes. The greatest part of carbon dioxide diffusion (⇉) across the erythrocyte membrane is *via* aquaporin (AQP)–1, the major protein permitting water permeability and rhesus antigen proteins. Erythrocytes lacking either aquaporins and Rhesus proteins or both show markedly reduced transmembrane carbon dioxide diffusibility. Neurons and astrocytes contain AQP4, another aquaporin that permits carbon dioxide flux and that, like AQP1, is blocked by acetazolamide. CA = carbonic anhydrase; Cl^- = chloride; H^+ = hydrogen ion; Hb-NH_2 = hemoglobin with free amine groups; Hb-$NHCOO^-$ = hemoglobin carbamate; HCO_3^- = bicarbonate. Figure supplied by Gerolf Gros, M.D., University of Hanover, Hanover, Germany.

spectroscopy of labeled oxygen or carbon in carbon dioxide and bicarbonate would be useful. Using the model of Severinghaus *et al.*,[4] it might be possible to determine whether labeled carbon dioxide or labeled bicarbonate appears first and in greater concentration relative to that predicted by equilibrium values when respiration is triggered by the introduction of oxygen to anoxic mitochondria.

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Competing Interests

The author declares no competing interests.

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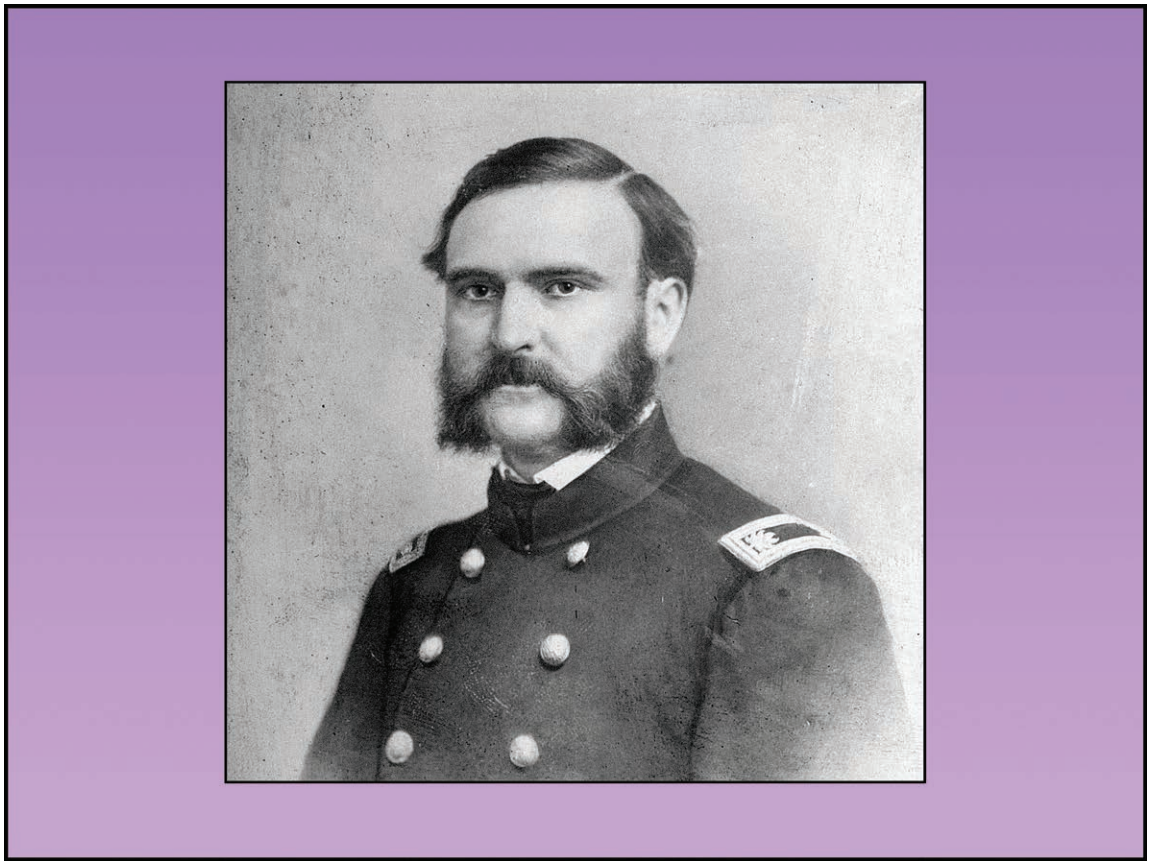
Charles Halpine or How Chloroform Killed Simultaneously a General and a Private



Born in Oldcastle, County Meath, Ireland, Charles Graham Halpine (1825 to 1868) emigrated to the United States in 1851. He worked as a journalist and editor in Boston, Washington, D.C., and then New York City, before joining the Union's 69th New York Volunteer Infantry. During the Civil War, he penned poetry and prose for periodicals and eventually books under the pseudonym of "Miles O'Reilly," a hapless Irish private in the "47th Regiment New York Volunteers." Progressively reassigned and promoted through the ranks, Halpine was photographed (*above*) as a lieutenant colonel. By the time Halpine resigned his commission, he had been breveted to brigadier general for merit. In August of 1868, while self-administering his own remedy for insomnia and migraines, 43-yr-old Halpine accidentally overdosed on undiluted chloroform. And that is how chloroform killed simultaneously a general (Halpine) and a private (O'Reilly). (Copyright © the American Society of Anesthesiologists' Wood Library-Museum of Anesthesiology.)

George S. Bause, M.D., M.P.H., Honorary Curator and Laureate of the History of Anesthesia, Wood Library-Museum of Anesthesiology, Schaumburg, Illinois, and Clinical Associate Professor, Case Western Reserve University, Cleveland, Ohio. UJYC@aol.com.