TRANSPORT OF CARBON DIOXIDE IN BLOOD

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THE fitness of the element, carbon, to play a central role in living protoplasm is due, in part, to the properties of CO_2.[1] Most of these properties are important for mechanisms of CO_2 transport in the human body. It is significant that the final state of oxidation of each of the foodstuffs is a gas at body temperature which has a relatively high solubility in water. For example, at 0 C. and one atmosphere of pressure, one liter of water will dissolve 48.9 ml. of oxygen and 1,713 ml. of CO_2.[6] This high solubility of CO_2 is of great importance in the initial stages of photosynthesis and in providing efficient excretion of CO_2 in lower species of animals which exist without a discrete circulation. Although there is no significant human excretion of CO_2 which has not passed from the tissues via the circulation, the solubility of CO_2 in body fluids allows transport in human blood to be effective. The CO_2 content of blood at any given time represents a balance between tissue production and excretion by the lung. There exists for the CO_2 content of the blood a reserve capacity which can function along with increased circulation and ventilation to handle large increases in tissue production of CO_2 without serious compromise of homeostasis. An adult male in the basal state can be expected to contribute approximately 12 liters of CO_2 per hour to his blood stream. Dusk has observed that the capacity for sustained work by the normal human body is approximately 600 calories per hour.[2] This represents an increase of 800 per cent above basal levels, corresponding to 90 or 100 liters of CO_2 produced, transported, and excreted each hour.

MOVEMENT OF CARBON DIOXIDE

The movement of a gas through body fluids depends upon the diffusability of the gas as well as upon a pressure gradient. The intrinsic rate of diffusion of any substance is a function of its solubility, its molecular weight, and the permeability of the medium. Carbon dioxide is a larger molecule than O_2, but its solubility in body fluids is so much greater that it diffuses through the tissues twenty to thirty times as rapidly as does oxygen.[3]

The partial pressures of CO_2 in the tissues, the blood, and the alveolar air determine (a) the rapidity with which CO_2 is transferred across cell and capillary membranes, (b) the quantity of CO_2 held in physical solution, and (c) the extent to which certain reversible chemical reactions in the transport of CO_2 approach completion. Gases move from an area of high partial pressure to one of lower partial pressure, analagous to the way in which fluid runs downhill. Figure 1 illustrates the stepwise movement of oxygen from the air to the tissues over a course of decreasing partial pressure, while CO_2, which is produced in the tissues at a relatively high partial pressure, "flows downhill" to the atmosphere. The higher diffusability of CO_2 may account for the successful removal of CO_2 from the tissues with a lower pressure gradient than is necessary to move oxygen from the atmosphere to the tissues. This small gradient between the tissue P_{CO_2} and the alveolar P_{CO_2} emphasizes the readiness with which the CO_2 content of the intervening blood will rise with loss of

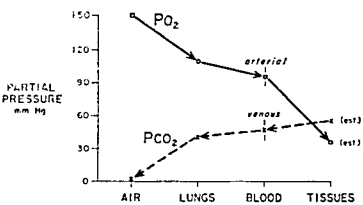

FIG. 1. The passage of oxygen from air to tissues, and of carbon dioxide from tissues to air, represents "downhill" gradients of decreasing partial pressure. Note that carbon dioxide, with a much higher diffusability than oxygen, requires a lower gradient for normal excretion than does oxygen for normal entry.

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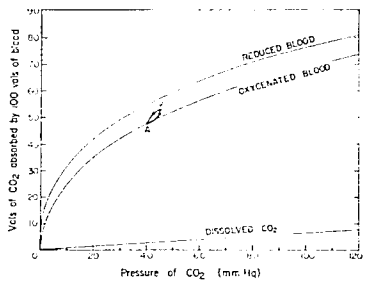

FIG. 2. The carbon dioxide dissociation curves for reduced and oxygenated blood. Points *A* and *V* indicate the values of arterial and mixed venous blood in a resting individual.[1, 5]

the gradient following relatively small increases in alveolar P_{CO_2}.

CARBON DIOXIDE DISSOCIATION CURVES

It is important to understand the manner in which the CO_2 content of the blood varies when there are changes in tension of the CO_2 to which it is exposed. Figure 2 presents the normal dissociation curves for CO_2.[1, 5] Certain important differences are noted when these are compared with the well-known oxygen dissociation curves. The content of dissolved CO_2 increases in linear fashion, with increasing partial pressures of CO_2 in the plasma, in essentially the same way in which dissolved oxygen increases with increasing partial pressures of oxygen. The total amount of dissolved CO_2 is greater than the dissolved oxygen for a given partial pressure of the corresponding gas, because of the higher solubility of CO_2. For each gas, however, the dissolved proportion represents only a small fraction of the total blood content. The total content of CO_2, as well as of oxygen, is strongly influenced by the partial pressure of the gas. But, unlike the sigmoid type of oxygen dissociation curve which characterizes hemoglobin, the plot of content against tension for CO_2 reveals a smooth curve which is nearly linear in physiological ranges. It is important to note that reduced blood has a greater capacity for taking up CO_2 than oxygenated blood, for any given CO_2 tension. In other words, when arterial blood gives up some of its oxygen to the tissues, its CO_2 carrying power will be increased. In figure 2 points *A* and *B* indicate the values for arterial blood (a P_{CO_2} of 40 mm. of mercury and a CO_2 content of 50 ml. per cent) and for mixed venous blood (a P_{CO_2} of 46 mm. of mercury and a CO_2 content of 55 ml. per cent) to be expected under resting conditions. Therefore the small arrows represent the normal exchange of CO_2 as blood moves through its physiologic circuit. In violent exercise, the CO_2 production of the tissues may temporarily outstrip the ventilatory excretion of CO_2. At such times, the oxygen saturation may drop and the CO_2 content of the blood may rise to 60 mm. of mercury or higher.

FORMS OF CARBON DIOXIDE IN BLOOD

Carbon dioxide originates in the tissues by the decarboxylation of organic acid intermediates. The CO_2 diffuses freely from its intracellular site of formation into interstitial fluid and blood. The quantity of dissolved CO_2 is the only portion of the total CO_2 content that contributes to the partial pressure of the gas. In view of solubility differences, it is appropriate that the role of physical solution in CO_2 transport be greater than in oxygen transport. Carbon dioxide also differs from oxygen in that it reacts chemically with the water in which it dissolves to form carbonic acid:

$$CO_2 + H_2O = H_2CO_3$$
$$\Delta F = 2.01 \text{ kg.-cal./mol.}$$

From the small value of ΔF, it is apparent that this is a readily reversible reaction.[1] Without a catalyst, this reaction is so slow that only an insignificant amount of carbonic acid is formed from CO_2 in the extracellular fluid. Within certain cells, particularly the red blood cells, CO_2 is rapidly hydrated under the influence of a specific zinc-containing enzyme, carbonic anhydrase.

Carbonic acid behaves as a weak acid, dissociating to form a bicarbonate ion:

$$H_2CO_3 = H^+ + HCO_3^-$$
$$\Delta F = 8.81 \text{ kg.-cal./mol.}$$

When base is present, as is generally the case, the reaction

$$BOH + H_2CO_3 = H_2O + B^+ + HCO_3^-$$

may be assumed to take place, in which B represents whatever basic radical or cation is present. The theoretical *p*K for the isolated dissociation of carbonic acid is 3.6. But under physiologic conditions, carbonic acid is always in equilibrium with CO_2, as well as undergoing dissociation (fig. 3). Since the equilibrium of the hydration of CO_2 forming carbonic acid strongly favors CO_2, the amount of carbonic acid undergoing dissociation is decreased by the competing reaction. Hence, the actually observed *p*K for the dissociation of carbonic acid is 6.11.

At the *p*H of blood, 7.4, the bicarbonate ion has a concentration twenty times that of undissociated carbonic acid. The bicarbonate ion, in addition to acting as the base of carbonic acid, is an acid in its own right, since it can ionize to form the carbonate ion $CO_3^=$. Since the *p*K of this ionization is 9.76, the concentration of carbonate ion in the blood has been assumed to be of no significance. But recent studies of Nichols[5] have suggested that the CO_2 stores in bone may be in equilibrium with the tiny amounts of carbonate ion in the plasma and the interstitial fluid.

For any given *p*H, oxyhemoglobin will dissociate to a greater extent than hemoglobin, and therefore behaves as a stronger acid:

$$HHb + O_2 = HbO_2 + H^+$$

This reaction is of importance in the maintenance of a stable *p*H in the red blood cells. When arterial blood perfuses the peripheral tissues, two opposing influences come into play within the red cell. The dissociation of the newly formed carbonic acid from the CO_2, which has just entered the red cell from the tissues, tends to lower the *p*H. But the transformation of oxyhemoglobin to reduced hemoglobin is one which converts a relatively strong to a relatively weak acid, and tends to raise the *p*H. As a consequence, hydrogen ions formed in the dissociation of carbonic acid are accepted by the imidazole groups of the reduced hemoglobin. The net result of these two events, termed the isohydric shift, is to maintain the *p*H of the erythrocyte essentially unchanged.

Figure 3 indicates that dissolved CO_2 (and not carbonic acid or bicarbonate ions) is the form in which it is thought to cross cell and capillary membranes. The exception to this concept appears to be the passage of the bicarbonate ion across the membrane of certain specialized cells such as the erythrocyte. Figure 3 emphasizes the critical influence which the CO_2 tension of plasma exerts upon the quantity and distribution of CO_2 in the various body compartments. The lightly drawn carbonate ion in plasma refers to the possible role in bone metabolism suggested above.

In addition to the dissolved CO_2 and bicarbonate which circulate in the blood, CO_2 can combine directly with hemoglobin to form carbaminohemoglobin. About one fifth of the total CO_2 in the blood is carried as carbaminohemoglobin.

$$R\text{-}NH_2 + CO_2 = R\text{-}NHCOO + H^+$$

This binding of CO_2 to the amino groups of the globin molecule does not require an enzyme, is mainly a function of the level of oxygen saturation of the hemoglobin, and is largely independent of the CO_2 tension. A small amount of CO_2 can be carried in the blood as the carbamino form with plasma proteins. But this form of transport is small compared with that in the red blood cell, because hemoglobin exists in far larger quantities than any other blood protein and also has a higher content of lysine, with its free amino group available for such binding.

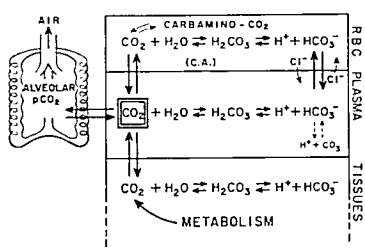

FIG. 3. Carbon dioxide transport reactions. The chemical reactions governing the transport of carbon dioxide are largely the same for peripheral tissues, plasma and red cells. The plasma carbon dioxide level is emphasized as the primary factor which, directly or indirectly, influences the amount of each form in which carbon dioxide occurs, regardless of location. The carbonic anhydrase activity of the red blood cell is indicated by "C.A."

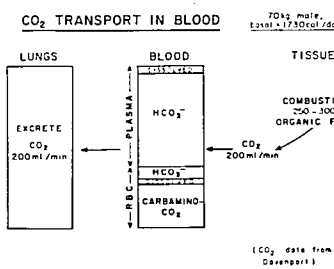

FIG. 4. The distribution in blood of the carbon dioxide arising each minute from the metabolism of an average adult resting male. See text for details.

Oxyhemoglobin does not form carbamino groups with the same facility that hemoglobin does. A given quantity of oxyhemoglobin can carry approximately one third as much CO_2 in the form of carbamino groups as hemoglobin. It has been calculated that hemoglobin is responsible, directly or indirectly, for the transport of 83 per cent of the total CO_2 carried by the blood.[5]

SUMMARY OF EVENTS IN CARBON DIOXIDE TRANSPORT

Arterial blood arrives at the tissue capillaries containing 50 ml. of CO_2 per cent at a P_{CO_2} of 40 mm. of mercury. This CO_2 is distributed approximately as follows: 3 ml. in physical solution, exerting a P_{CO_2} of 40 mm. of mercury, 3 ml. in carbamino form (because arterial blood has 95 per cent oxygen saturation), and 44 ml. as bicarbonate. In the tissues, CO_2 is constantly produced as an end-product of the oxidative processes of metabolism. The intracellular P_{CO_2} of the tissues is not readily determined, but is estimated at 46–50 mm. of mercury. Carbon dioxide passes by simple diffusion from the tissues into the blood, adding 5 ml. of CO_2 to each 100 ml. of blood. Venous blood thus leaves the capillary bed with a content of 55 ml. CO_2 and a P_{CO_2} of about 46 mm. of mercury. The additional 5 ml. CO_2 entering the blood from the tissues will be distributed approximately as follows: 0.5 ml. dissolved CO_2, 1 ml. in carbamino form (since the oxygen saturation has dropped from 95 to 70 per cent), and 3.5 ml. as bicarbonate. The distribution between red cells and plasma of the CO_2 which is added to the blood of a resting adult male each minute is shown in figure 4.

The largest segment of the CO_2 carried in the blood is present as bicarbonate in plasma. But very little carbonic acid is formed in the plasma, in contrast to the large amounts in the red cell resulting from the presence of carbonic anhydrase. The intracellular carbonic acid yields bicarbonate, with potassium as the chief intracellular cation. An increased bicarbonate concentration now exists within the cell, relative to the plasma. Therefore, some of the bicarbonate moves out of the cell and electrical neutrality is preserved by a corresponding movement of chloride ions from plasma into the cell. The net result of this migration is that a large fraction of the CO_2 which entered the red blood cell and was hydrated and then dissociated is now found in the venous plasma as bicarbonate. The combined result of the isohydric and chloride shifts just described is to increase the total number of anions and, thereby, the effective osmotic pressure within the cell. In consequence, water is redistributed between cells and plasma, so that the hematocrit of venous blood is appreciably higher than that of arterial blood, rising from 45 to 48 per cent.[5] This entire sequence is reversed in the pulmonary capillaries, to unload the three forms of CO_2 from the blood into the alveoli.

The ability to excrete CO_2 in amounts which correspond to over 12,000 mEq. of acid per day, while the *p*H of the blood remains constant within a few hundredths of a *p*H unit, while the tension of the blood CO_2 is stable within a few millimeters of mercury, and without major dislocations of water or electrolytes, represents one of the most impressive homeostatic accomplishments of the human body.

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